

March 4, 2021

By Electronic Submission On www.regulations.gov

Food and Drug Administration
Department of Health and Human Services
Compounding of Human Drug Products Under
Sections 503A and 503B of the Federal Food,
Drug, and Cosmetic Act; Establishment of a
Public Docket
Docket No. FDA-2015-N-0030

RE: Supplement to August 17, 2020 Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded “Bioidentical Hormone Replacement Therapy”

To Whom It May Concern:

On behalf of a coalition of traditional compounding pharmacies and FDA-registered outsourcing facilities (the “Coalition”), we are hereby submitting this supplement to our August 17, 2020 comment to the Food and Drug Administration (“FDA” or “Agency”) regarding The National Academies of Sciences, Engineering, and Medicine (“NASEM”) Report addressing the clinical utility of compounded bioidentical hormone replacement therapy (“cBHRT”).¹ As set forth below, materials recently produced by FDA in response to a lawsuit filed by Reed Smith LLP (“Reed Smith”) demonstrate that FDA was in stark violation of the Federal Advisory Committee Act (“FACA”) in FDA’s management and control of the NASEM Committee. The documents produced by FDA thus far provide further support for the Coalition’s position that **FDA cannot, in any way, adopt or rely on any of the conclusions or recommendations** published by NASEM in its Report, and should FDA adopt or rely on any of the conclusions or recommendations in the Report in crafting policy on cBHRT, FDA will threaten the health of the millions of patients across the U.S. who rely on this medication.

As illustrated in our initial comment, the Report is merely a conduit through which FDA is baselessly attempting to discredit critical and life-sustaining compounded therapies in favor of FDA-approved hormone medications. The Report itself is rife with bias in favor of such FDA-approved hormone therapies, and in order to get a comprehensive understanding of just how deep this bias went, on July 31, 2020, Reed Smith submitted an extensive Freedom of Information Act (“FOIA”) request to FDA requesting communications between FDA (including FDA’s Center for Drug Evaluation and Research),

¹ We hereby incorporate by reference our comment to FDA submitted on August 17, 2020, including all defined terms set forth therein. See enclosed as Exhibit 1.

NASEM, and other relevant individuals and entities within a specified timeframe.² FDA had 20 working days to respond to the FOIA request—yet, the statutory response deadline came and went, and FDA still withheld the Agency’s records.³ Ultimately, Reed Smith filed a FOIA Complaint against FDA on October 1, 2020, requesting that FDA produce all records responsive to the FOIA request.⁴

Nearly two months after filing the Complaint, FDA proposed to Reed Smith that the Agency produce responsive documents on a rolling basis, starting with documents from two allegedly primary FDA custodians, i.e., Ms. Gabrielle Cosel and Ms. Elizabeth Hankla. Reed Smith agreed to this process, while reserving the right to identify additional custodians after review of FDA’s initial production from Ms. Cosel and Ms. Hankla.⁵ Based off this initial production, it is abundantly clear that the bias present throughout the Study and the Report was no coincidence—the initial production revealed that FDA steered the NASEM Committee in violation of FACA.

Therefore, as it stands, in the interest of time and due to the threat the Report *presently* poses to the health of millions of Americans should FDA adopt it in its current state, we are submitting this supplemental comment now urging FDA to reject the conclusions and recommendations proffered in the Report, because FDA violated FACA in at least the following ways:

- Before the Study even began, FDA provided one-sided information to NASEM on compounded medications, particularly hormone medications, that profoundly shaped the NASEM Committee’s position on cBHRT;
- As the Study began to materialize, FDA played a role in determining who should serve on the NASEM Committee and who NASEM should rely on as cBHRT subject-matter “experts”;
- During the course of the Study, FDA and the NASEM Committee consistently collaborated over substantive aspects of the Study; and

² Specifically, the FOIA request asked for responsive documents concerning the following subjects: (1) The National Academies of Sciences, Engineering, and Medicine or NASEM; (2) Bioidentical hormones; (3) Compounded bioidentical hormone therapy (otherwise known as “cBHT” or “cBHRT”); (4) Difficult to compound; (5) Clinical Utility; (6) Pharmacy Compounding Advisory Committee (otherwise known as “PCAC”); (7) Jane Axelrad; and (8) Axelrad Solutions, LLC. *See* FOIA request, submitted July 31, 2020, enclosed herein as Exhibit 2.

³ 5 U.S.C. § 552(a)(6)(A).

⁴ *See* Complaint For Injunctive Relief, enclosed herein as Exhibit 3.

⁵ *See* Joint Status Report, enclosed herein as Exhibit 4. Further, on February 9, 2021, Reed Smith identified four additional custodians with responsive documents: (1) Gail Bormel; (2) Sara Rothman; (3) Amy Akparewa; and (4) Lesley-Anne Furlong. FDA agreed to release responsive non-exempt records from Ms. Bormel and Ms. Akparewa by March 26, 2021, and responsive non-exempt records from Ms. Rothman and Ms. Furlong by May 31, 2021. This email is enclosed herein as Exhibit 5. We therefore reserve the right to submit a second supplemental comment upon receipt of additional responsive records from FDA. We would also like to further note that, should we deem it necessary, we will be pursuing litigation under FACA in order to participate in the kind of discovery permitted in FACA litigation. *See Alcresta Therapeutics, Inc. v. HHS*, Civil Action No. 18-243 (Aug. 2018) (order permitting discovery on a plaintiff’s FACA count).

- Finally, FDA was given the opportunity to review and comment on the Report before it was published—a Report that was supposed to be advice independent from FDA.

Overall, despite FDA’s stated goal of commissioning a study that would deliver the “independent advice of unparalleled objectivity of the highest quality,” the actual Study and corresponding Report were anything but independent and objective. Rather, the materials that FDA has produced thus far under FOIA demonstrate that FDA effectively inserted itself as a voice in the NASEM Committee, as a presenter throughout the Study, and as a writer of the Report. This Study was never independent of FDA, and FDA’s management and control of the NASEM Committee violated FACA.

I. FDA Took Steps To Steer The NASEM Study From Its Inception By Providing One-sided Information To NASEM On Compounded Medications, Particularly Hormone Medications, That Inevitably Shaped The NASEM Committee’s Position On cBHRT.

The initial materials produced by FDA thus far under FOIA demonstrate that FDA steered the NASEM Study from its inception in direct violation of FACA. As set forth in our initial comment to FDA, FACA is the legal foundation that defines and sets parameters for how federal advisory committees operate. As such, FACA prohibits a federal agency from managing or controlling an advisory committee and, in essence, prohibits that agency from manipulating the advisory committee while the committee develops its advice or recommendations.⁶

Despite FDA’s tacit acknowledgement of FACA’s applicability, FDA’s manipulation of the Study was rampant. FDA went to great lengths from the start of the Study to manage and control the NASEM Committee and thereby steer the Study toward the conclusions and recommendations FDA desired—which is peculiar, given the emphasis FDA initially placed on a need for Study independence. That is, before the Study even began, in order for FDA to obtain federal funding from the Department of Health and Human Services (“HHS”) to award the Study contract to NASEM, FDA had to submit a Department of Health and Human Services Acquisition Plan (the “*Acquisition Plan*”) to HHS, which set out, among other things, FDA’s goals for the Study, reasons why NASEM was the appropriate committee to engage the Study, and anticipated costs.⁷ FDA stated in its Acquisition Plan to HHS that, due to the nature of the Study:

[I]t is *in the public interest to receive the independent advice of unparalleled objectivity* of the highest quality that provides an inherent degree of acceptability. Considering the volunteer nature of committee members as well as the *independence, objectivity, quality and acceptance of [NASEM] recommendations*, [NASEM] represents a cost effective means for examining the critical issues of this project.⁸

⁶ In pertinent part, FACA states that “[a]n agency may not use any advice or recommendation provided by the National Academy of Sciences . . . that was *developed by use of a committee created by that academy under an agreement with an agency*, unless . . . the committee was not subject to any *actual management or control by an agency* or an officer of the Federal Government . . .” 5 U.S.C. app. 2 § 15(a)(1) (emphases added).

⁷ See HHS Acquisition Plan, at FDACDER_002307, enclosed herein as Exhibit 6.

⁸ HHS Acquisition Plan, at FDACDER_002308, Exh. 6 (emphasis added).

Thus, in order to even obtain the federal funding to contract the Study out to NASEM (which, at \$1,345,719.00, was no small price for federal taxpayer dollars to cover) FDA had to explain to HHS that this Study needed to reflect independence and objectivity because that was in the best interest of the public.

Yet, FDA destroyed any semblance of Study independence almost immediately. Notwithstanding FDA's professed need for independence, FDA inserted dangerous bias and mischaracterizations into its Acquisition Plan, essentially telling NASEM how the Study should go and which conclusions should be made, especially as they relate to the regulation of cBHRT and pellets. Specifically, FDA stated in its Acquisition Plan that "compounded drugs are subject to a **lower regulatory standard** than FDA-approved drugs,"⁹ and stated that one of the reasons the Study was needed was because FDA had:

recently became aware of many **adverse events associated with compounded implantable hormone pellets**. For example, during an inspection FDA discovered that one marketer collected more than 4,000 reports of adverse events associated with these products over approximately four years. These adverse events concerned endometrial cancer, prostate cancer, stroke, heart attack, deep vein thrombosis, breast cancer, cellulitis, and pellet extrusions. FDA is currently reviewing these cases.¹⁰

This means that before the NASEM Committee had a chance to review any relevant materials or form its own opinion or even **initiate** the Study, FDA had already told NASEM that all compounded medications were less safe than FDA-approved drugs and that hormone pellets, in particular, were problematic. FDA offered no variety in opinions besides its own regarding the regulation of compounded medications. And, with respect to the inspection referred to above, **none** of the information collected actually reflected serious complications or unexpected adverse events associated with cBHRT. The "adverse events"¹¹ FDA referred to were either coincidental randomly occurring events or possible secondary reactions from treatment with cBHRT (e.g., acne, rashes, etc.)—they were **not** serious and/or unexpected adverse events.

These unfounded claims profoundly shaped NASEM's outlook on these issues, which is evidenced in part by the fact that NASEM wrote a White Paper echoing FDA's opinions on compounded medications and pellets shortly after FDA prepared its Acquisition Plan and nearly **nine months** before the Study began.¹² In other words, NASEM seemingly formed its opinion on cBHRT based **only on** FDA's Acquisition Plan and nine months before the NASEM Committee held its first open session to hear from any other industry stakeholders besides FDA, the Study sponsor. And NASEM understood the importance of independence, as NASEM conceded in its White Paper that it had developed policies to implement certain portions of FACA, and therefore NASEM "must provide **independent, unbiased advice** without actual or perceived interference or management of the outcome (findings and recommendations)" during

⁹ HHS Acquisition Plan, at FDACDER_002320, Exh. 6 (emphasis added).

¹⁰ HHS Acquisition Plan, at FDACDER_002319, Exh. 6 (emphasis added).

¹¹ The marketing company FDA referred to is unable to determine where FDA obtained the number of allegedly adverse events referenced in its Statement. This company's records do not reflect 4,202 separate events.

¹² "Clinical Utility of Treating Patients With Compounded 'Bioidentical Hormone Replacement Therapy,'" hereinafter referred to as NASEM's White Paper, at FDACDER_002255, FDACDER_002262 (emphasis added), enclosed herein as Exhibit 7.

the Study and in the Report.¹³ However, nearly a year before the Study opened its doors to public input, the NASEM Committee had already spent at least nine months listening to only one biased voice—FDA.

II. FDA Provided Recommendations To NASEM On Who Should Serve On The NASEM Committee And Who NASEM Should Rely On As cBHRT Subject-Matter “Experts.”

Once the Study parameters were finalized, FDA began making recommendations to NASEM as to who should serve on the NASEM Committee, i.e., who should be the judges of the Study and ultimate writers of the Report,¹⁴ and who it should hear from as subject-matter “experts” on cBHRT. First, FDA sent an entire list of individual recommendations to NASEM setting out who should serve on the NASEM Committee to analyze the clinical utility of cBHRT. One of the individuals recommended by FDA, Adel H. Karara, actually served on the NASEM Committee. Another individual, Nanette Santoro, published literature that was considered by the NASEM Committee in forming its conclusions and recommendations. And, two other individuals that FDA proffered to NASEM, James H. Liu and Jane Axelrad, actually served as Report reviewers and were able to provide substantive comments and revisions to drafts of the Report before it was published.

FDA’s attempt to have Ms. Axelrad serve on the NASEM Committee was particularly surprising given FDA’s stated assertion in its Acquisition Plan that it wanted a committee of “independence” and “objectivity.”¹⁵ Despite the wealth and variety of non-FDA industry stakeholders from which FDA could have chosen, FDA initially sought out Ms. Axelrad, the Agency’s former lead on compounding for over two decades. Although Ms. Axelrad operates her own consulting firm now, her perspectives and voice cannot be separated from FDA—and FDA knew this and tried to capitalize on it. However, when asked, Ms. Axelrad disclosed that she had a client conflict of interest that prohibited her from participation on the NASEM Committee, as reflected in the following timeline of email communications:

**November 9, 2018, 6:35 AM
FDA to Ms. Axelrad** “NASEM have asked us to recommend people for their consideration for their expert committees for the [the Study]. Among other experts, they are looking for people with knowledge of regulatory matters. *If you are open to it, we’d like to include your name in our recommendations to them.*”¹⁶

**November 9, 2018, 10:00 AM
Ms. Axelrad to FDA** “I don’t think I can do it as *I have a client interested in bioidentical hormones*. I nominated 5 people for that, 5 outside doc experts and one I would think that would be a conflict. Maybe I could do pain creams?”¹⁷

¹³ NASEM’s White Paper, at FDACDER_002255, FDACDER_002262 (emphasis added), Exh. 7.

¹⁴ See FDA recommendations for NASEM Committees, at FDACDER_000010, enclosed herein as Exhibit 8.

¹⁵ HHS Acquisition Plan, at FDACDER_002308, Exh. 6.

¹⁶ E-Mail Correspondence between FDA and Ms. Axelrad, at FDACDER_000006, enclosed herein as Exhibit 9.

¹⁷ E-Mail Correspondence between FDA and Ms. Axelrad, at FDACDER_000007, Exh. 9.

However, despite this apparent conflict, FDA still made sure Ms. Axelrad was on NASEM's radar from the get-go:

**November 9, 2018, 6:49 PM
FDA to NASEM**

“Ms. Axelrad was formerly the associate director for Policy, Center for Drug Evaluation and Research, Food and Drug Administration for 25 years. Following the fungal meningitis outbreak, Axelrad was the agency lead on drug compounding. ***We are recommending Ms. Axelrad for the Committee on compounded topical pain medications, as she has indicated she may have a current business conflict with regard to hormone therapy.***”¹⁸

Conflicts aside, FDA wanted Ms. Axelrad's voice to be part of the Study. So, once Ms. Axelrad said “no” to committee participation, her involvement pivoted to presenting to the NASEM Committee, participating in the Study, and serving as a Report reviewer, which allowed her to have substantive influence over the Report's conclusions and recommendations. One such recommendation published in the Report was that the Pharmacy Compounding Advisory Committee (“PCAC”) review certain bioidentical hormone therapies and pellets as candidates for FDA's Difficult to Compound List—a recommendation that came ***directly*** from Ms. Axelrad's presentation to the NASEM Committee, and an assertion that was identical to the position she took as FDA's compounding lead during meetings with PCAC in 2015.¹⁹

FDA cannot assert that Ms. Axelrad's presentation that hormones are too difficult to compound—the same position she took while at FDA—was in any way independent from FDA. And, given Ms. Axelrad's decades-long tenure with FDA, there is truly no way to separate her opinions from those of the Agency when even her presence in a room implies that FDA has arrived. Because her opinions and

¹⁸ FDA recommendations for NASEM Committees, at FDACDER_000014, Exh. 8. We also note that even though FDA formally recommended Ms. Axelrad for inclusion on a committee for a different NASEM study on pain creams, FDA provided committee recommendations to NASEM for both the cBHRT Study and the pain cream study in the same single email, thereby ensuring that NASEM would know Ms. Axelrad's name and experience while NASEM reviewed the recommendations for the NASEM Committee on cBHRT.

¹⁹ In a 2015 presentation by FDA to PCAC, on behalf of FDA, Ms. Axelrad asserted that compounders are not equipped to compound certain medications based on their alleged level of difficulty. Specifically, she stated: “[W]e have seen drugs and categories of drugs that even drug manufacturers have difficulty getting right . . . So I think that there may be certain drugs on the list that we don't think that even a highly skilled compounding operation could do successfully . . . [W]e want to eliminate risks to public health that might be associated with compounding difficult-to-compound drugs that we don't think, in most cases, can be compounded safely or provide a safe and effective product.” Thursday, June 18, 2015 PCAC meeting, pages 67-92. The medications Ms. Axelrad was referring to in the 2015 meeting were substances that had already been submitted to FDA's public docket FDA-2013-N-1523 (which was seeking nominations for FDA's Difficult to Compound List) and thus were already on FDA's radar. Among the nominations received by the Agency through this docket, ***nine*** were hormones or categories of hormones that the NASEM Committee, in its Report, suspiciously recommended PCAC to review. That is, of the 11 hormones or categories of hormones the NASEM Committee recommended PCAC to review, ***nine were already nominated for FDA's Difficult to Compound List in 2014 when Ms. Axelrad served as the FDA lead on compounding.*** See Nominations to the Difficult to Compound List or comments submitted in response to FDA's December 4, 2013 Federal Register notice were submitted to docket FDA-2013-N-1523.

the issues about which she presented are all intrinsically and undeniably tainted by FDA, FDA in effect recommended *itself* for the Study, which is an alarming violation of FACA.

In addition to NASEM Committee member recommendations, FDA also told NASEM who the subject-matter experts for cBHRT were and provided scientific literature to the NASEM Committee from these alleged “experts.” FDA’s cBHRT “expert” recommendations included: The North American Menopause Society; American College of Obstetricians and Gynecologists; Endocrine Society; American College of Physicians; National Association of Nurse Practitioners in Women’s Health; HealthyWomen; and National Women’s Health Network.²⁰ Not a single “expert” represents an active prescriber of cBHRT, nor are any of these groups considered specialists in the intricacies of prescribing and treating with cBHRT—they merely offer opinions without the expertise of actual prescribers. Notably, at one point FDA even acted as its own “subject-matter expert” by presenting to the NASEM Committee on compounding and, specifically, the differences between compounding according to Section 503A and Section 503B of the Federal Food, Drug, and Cosmetic Act. It is of course important for a committee like the NASEM Committee to work with experts in the field, but NASEM was supposed to act as an “independent advisor” to FDA and to “partner with experts, representing *various areas of expertise* in medical product development, ethics, clinical investigation, clinical care, law, and patient perspectives.”²¹ FDA was not supposed to intervene in the Study and steer the NASEM Committee toward the groups only FDA deemed to be “experts.” Moreover, at no time does it appear that FDA ever suggested to the NASEM Committee that it should hear from active clinical cBHRT prescribers or other compounding industry stakeholders.²²

III. As The Study Progressed, FDA And The NASEM Committee Consistently Collaborated Over Substantive Aspects Of The Study.

As the Study progressed, the documents produced by FDA reveal that FDA and the NASEM Committee frequently collaborated over substantive aspects of the Study, steadily chipping away at the independent advice the NASEM Committee was initially called upon to give and blurring the lines as to who was actually running the Study. For example, when the NASEM Committee asked FDA for guidance on the regulatory oversight of compounding, it was FDA who presented on and discussed the subject.²³ And, FDA consistently forwarded FDA resources to the NASEM Committee for its consideration. Moreover, as it relates just to adverse events, FDA actually told NASEM, directly and indirectly, on *three* separate occasions that it was FDA’s belief that there were significant adverse events associated with pellets. Recall that prior to the Study’s inception, FDA had already told NASEM through FDA’s

²⁰ See FDA recommendations for NASEM Committees, at FDACDER_000015, Exh. 8.

²¹ FDA Justification for Other than Full and Open Competition, at FDACDER_002340, FDACDER_002341, enclosed herein as Exhibit 10 (emphasis added).

²² We note that, when the Coalition became involved in the Study, FDA balked at the idea of other industry opinions. Email correspondence between FDA and the Study coordinator indicated concern over stakeholder involvement late in the Study. Specifically, the Study coordinator told FDA that the Study had a “substantial amount of late stakeholder interest and we’re not exactly sure as to why . . . only in the last few months have these stakeholders expressed interest in providing comments to the committee.” To which FDA replied, “I’m not sure why some of those stakeholders were late in expressing interest, one of the speakers as you may know is a well-known attorney (in our wonky world, haha) who represents compounders so perhaps she had a hand in organizing the outreach to you.” See February 6-7, 2020 Email Correspondence, at FDACDER_001801, FDACDER_001802, enclosed herein as Exhibit 11.

²³ See April 2019 Email correspondence, at FDACDER_000889, enclosed herein as Exhibit 12.

Acquisition Plan that FDA had become aware of “adverse events associated with compounded implantable hormone pellets.”²⁴ Then in July 2019, which was approximately halfway through the Study, FDA told the NASEM Committee that cBHRT in pellet form was a particular problem by stating that it is FDA’s “understanding that most if not all of the [adverse] events relate to drugs formulated as *pellets*”²⁵ Then, to make sure that the NASEM Committee had not forgotten FDA’s position on pellets, in September 2019, right in the middle of the Study, FDA published a press release that grossly mischaracterized cBHRT and pellets as unsafe and/or ineffective and implied that the compounding of cBHRT is inherently risky.²⁶

IV. FDA Was Handed The Pen To Revise The Report Before It Was Published—A Report That Was Supposed To Be Advice Independent From FDA.

FDA’s influence over the NASEM Committee did not cease when the Study ended—rather, FDA continued to exercise broad management and control over the NASEM Committee even as it was drafting its ultimate Report. FDA did so by proposing revisions to a Report that was supposed to represent “independent advice of unparalleled objectivity” from an institution that provided the public “an inherent degree of acceptability.”²⁷ Given FDA’s involvement throughout the Study and given that FDA was offered the pen in writing the Report, it frankly begs the question of, what is the worth of this Study?²⁸ It appears that FDA merely wanted to mask its longstanding opinions on cBHRT and pellets under the guise of NASEM—a well-known public institution that is inherently trusted by the public. Regardless of FDA’s true intentions with this Study, there is absolutely no way that the Report can be considered independent of FDA’s management and control.

We are continuing to receive and review materials from FDA under FOIA. Nevertheless, from what we have received so far, we have seen enough to conclude that it is abundantly clear that FDA had actual management and control over the NASEM Committee, which made it impossible for the NASEM Committee to publish an independent, unbiased Report. Therefore, FDA must disregard this Report in its entirety—FDA *cannot* adopt *any* of the conclusions or recommendations in the NASEM Report because FDA’s interference with the Report violated FACA.

²⁴ HHS Acquisition Plan, at FDACDER_002319, Exh. 6.

²⁵ July 2019 Email correspondence, at FDACDER_001378, enclosed herein as Exhibit 13 (emphasis added).

²⁶ FDA Statement on improving adverse event reporting of compounded drugs to protect patients, September 9, 2019, enclosed herein as Exhibit 14.

²⁷ FDA Justification for Other than Full and Open Competition, at FDACDER_002340, Exh. 10.

²⁸ FDA also steered the definition of “clinical utility” by providing literature to NASEM on what constitutes “clinical utility.” “What Is Clinical Utility and Why Should We Care?” Dr. Granley. Further, NASEM’s Policies explicitly state that, “[s]ponsors are not given an opportunity to suggest changes in reports,” i.e., NASEM’s Policies forbid sponsors from serving as reviewers to NASEM’s reports. Our Study Process <https://www.nationalacademies.org/about/our-study-process> (last visited March 4, 2021).

V. Conclusion.

In conclusion, FDA violated FACA by inserting itself into the NASEM Committee and steering the Study from its inception. Therefore, ***FDA must reject the NASEM Committee's Report*** and all the conclusions and recommendations therein, in favor of keeping cBHRT, a critical, life-saving therapy, available for the millions of patients that rely on this therapy.

Very truly yours,

/s/ Rachael G. Pontikes

Rachael G. Pontikes
For Reed Smith LLP

RGP:rl

EXHIBIT 1

August 17, 2020

By Electronic Mail

U.S. Food & Drug Administration
Department of Health and Human Services
Compounding of Human Drug Products Under
Sections 503A and 503B of the Federal Food,
Drug, and Cosmetic Act; Establishment of a
Public Docket
Docket No. FDA-2015-N-0030

RE: The National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded “Bioidentical Hormone Replacement Therapy”

To Whom It May Concern:

We hereby submit this comment to the U.S. Food & Drug Administration (“*FDA*” or “*Agency*”) on behalf of a coalition of traditional compounding pharmacies and FDA-registered outsourcing facilities (the “*Coalition*”) and request that FDA reject the conclusions and recommendations published by The National Academies of Sciences, Engineering, and Medicine (“*NASEM*”) in its report titled *The Clinical Utility of Compounded Bioidentical Hormone Therapy: A Review of Safety, Effectiveness, and Use* (the “*Report*”). FDA cannot adopt the Report or rely on it in any way, because the Report patently fails to represent an independent perspective and is rooted in striking biases. As such, the adoption thereof not only threatens to violate the statutory requirements for federal advisory committees set forth in the Federal Advisory Committee Act (“*FACA*”), but will also prohibit *millions* of men and women across the U.S. from receiving the treatment they need.¹

This Report is evidence of yet another public attempt by FDA to discredit critical and life-sustaining compounded hormone therapies in the eyes of the public in favor of FDA-approved hormone therapies. FDA’s disdain for compounded hormone therapies appears to have begun in 2002, after a finding by the Women’s Health Initiative that FDA-approved hormone medications raised the risk of heart disease, blood clots, and certain cancers.² To overcome the negative press, FDA engaged in a series of

¹ The NASEM Committee acknowledges four times throughout its Report that compounded hormone therapy is used by millions of men and women. See National Academies of Sciences, Engineering, and Medicine, *The clinical utility of compounded bioidentical hormone therapy: A review of safety, effectiveness, and use*, pages 1, 18, 219, 227, (2020) (hereinafter referred to as the “*Report*”).

² See Hormone Therapy Trials (HT), Women’s Health Initiative, <https://www.whi.org/about/SitePages/HT.aspx> (last visited August 17, 2020) (“The WHI Hormone Therapy Trials (HT) were designed to test the effects of postmenopausal hormone

public endeavors designed to discredit compounded bioidentical hormone replacement therapy (“cBHRT”), which included initiating enforcement action against seven pharmacies that compounded cBHRT in 2008.³ Two days after initiating such enforcement actions, FDA responded favorably to a Citizen’s Petition submitted by a commercial manufacturer of FDA-approved hormone replacement therapy products asking that FDA take action against compounders of cBHRT.⁴ In addition, FDA published press releases and participated in a press conference touting its position against cBHRT. In doing so, FDA garnered cross-country news headlines such as, “*FDA Warns Against Bio-Identical Hormone Therapy*,”⁵ “*FDA cracks down on makers of ‘bioidentical’ hormones*,”⁶ and “*FDA Warns Pharmacies On Hormone Claims*,”⁷ among so many others.

Notwithstanding FDA’s attempts to discredit cBHRT, physicians across the country continued to see the benefits of cBHRT and its positive effects on their patients, particularly with women suffering from a broad range of menopause symptoms. Over the next ten years, more and more physicians around the country began treating their patients with cBHRT. As a result, in fall 2018, FDA commissioned NASEM to appoint an ad hoc committee (the “*NASEM Committee*”) to examine the clinical utility of treating patients with cBHRT. The NASEM Committee held a series of open and closed sessions from March 2019 to April 2020, to examine data, research, and stakeholder input in order to form conclusions and recommendations regarding the clinical utility of cBHRT (the “*Study*”). On July 1, 2020, the NASEM Committee published its Report, wherein it concluded that there is a lack of high-quality clinical evidence to demonstrate the safety and effectiveness of cBHRT and, accordingly, that there is insufficient evidence to support the overall clinical utility of cBHRT as treatment for menopause and male hypogonadism symptoms.⁸ In light of this supposed dearth of evidence to support the marketed claims for the clinical utility of cBHRT, the NASEM Committee recommended restricted use of cBHRT, assessments of their difficulty to compound, and additional education, state and federal regulatory oversight, and research.⁹

therapy on women’s risk for coronary heart disease (primary analyses) and on hip and other fractures and breast cancer (secondary analyses). The effects of hormone therapy on endometrial cancer was also evaluated in women with a uterus.)

³ On January 7, 2008, FDA issued Warning Letters to seven compounding pharmacies (Panorama Compounding Pharmacy, Saint John’s Medical Plaza Pharmacy, Murray Avenue Apothecary, Pharmacy Compounding Specialties, Reed’s Compounding Pharmacy and Pacifica Pharmacy) based on the Agency’s determination that these pharmacies were providing false and misleading information about compounding with estriol.

⁴ On January 9, 2008, two days after initiating enforcement action against seven compounding pharmacies, FDA responded to Wyeth Pharmaceuticals’ Citizen Petition.

⁵ Steven Reinberg, *FDA Warns Against Bio-Identical Hormone Therapy*, The Washington Post, January 9, 2008.

⁶ Liz Szabo and Julie Appleby, *FDA Cracks Down On Makers Of ‘Bioidentical’ Hormones*, USA Today, January 10, 2008.

⁷ Anna Wilde Mathews and Sarah Rubenstein, *FDA Warns Pharmacies On Hormone Claims*, Wall Street Journal, January 10, 2008.

⁸ Report, at 9. Please note that despite the dozens of disease states that physicians prescribe cBHRT to address, the NASEM Committee only considered two disease states to be of “substantial patient interest:” menopause and male hypogonadism symptoms.

⁹ In total, the NASEM Committee made six recommendations to FDA: (1) Restrict the use of compounded bioidentical hormone therapy (cBHRT) preparations; (2) Review select bioidentical hormone therapies and dosage forms as candidates for the U.S. Food and Drug Administration (FDA) Difficult to Compound List; (3) Improve education for prescribers and pharmacists who market, prescribe, compound, and dispense compounded bioidentical hormone therapy (cBHRT) preparations; (4) Additional federal and state-level oversight should be implemented to better address public health and clinical concerns regarding the safety and effectiveness of compounded bioidentical hormone therapy (cBHRT); (5) Collect and disclose conflicts of interest;

The Report is just the latest chapter in a long battle initiated by FDA against compounders that specialize in cBHRT and the physicians and patients they serve. From its inception, the Study was not independent and demonstrated extraordinary bias, including gender bias. Accordingly, as set forth in greater detail below, FDA must reject the Report in its entirety for the following reasons:

- **FDA stacked the deck against the compounding industry by steering the NASEM Committee to conclude that cBHRT has no clinical utility and may be too difficult to compound.** FDA unfairly and inappropriately influenced the NASEM Committee's conclusions and recommendations to discredit cBHRT because it is not FDA-approved. The Federal Food, Drug, And Cosmetic Act ("*FDCA*") via the Drug Quality Security Act ("*DQSA*") exempts compounds like cBHRT from the new drug approval process, meaning FDA cannot evaluate compounded medication for its perceived clinical utility (i.e., for safety and effectiveness). FDA cannot therefore circumvent its governing federal statute and effectively force cBHRT through new drug approval via this commissioned Study.
- **The Study was predicated on multiple forms of bias.** In a review of who comprised the NASEM Committee, the materials the NASEM Committee chose to consider, and the organizations that provided data for the Study, it is clear that the scales were tipped far in favor of Big Pharma. The NASEM Committee also heavily relied on studies that it claimed demonstrated "methodologic rigor," which have traditionally used the male body as the default and excluded women, and are therefore rooted in striking gender bias. These multiple forms of bias seriously call into question the credibility of the Report and the NASEM Committee's conclusions and recommendations.
- **FDA's adoption or use of the Report violates FACA.** FACA requires membership of an advisory committee to be fairly balanced, and it also prohibits a federal agency from managing or controlling an advisory committee. In this case, FDA so heavily influenced the NASEM Committee and its conclusions and recommendations that FDA, in essence, managed and controlled the NASEM Committee. Jane Axelrad's involvement, as well as the active measures FDA took to control the outcome of the Study, demonstrate FDA's undue influence over the NASEM Committee and its results. Accordingly, FDA may not adopt the Report without violating FACA.

Nonetheless, even if FDA accepts the Report at face value and considers adopting the recommendations therein, we strongly discourage FDA from engaging the Pharmacy Compounding Advisory Committee ("*PCAC*") for any evaluation of whether a bioidentical hormone in any form, including pellet form, should be a candidate for FDA's Difficult to Compound List. It appears that PCAC itself is in violation of FACA for failing to be fairly balanced in the points of view represented and the functions it performs and is therefore in no position to be evaluating whether hormone therapies or categories thereof should be included on FDA's Difficult to Compound List. Further, should PCAC place

and (6) Strengthen and expand the evidence base on the safety, effectiveness, and use of compounded bioidentical hormone therapy (cBHRT) preparations. Report, at 5.

certain bioidentical hormones and pellets on the Difficult to Compound List, this will have devastating effects on the health and wellbeing of the *millions* of patients treated with cBHRT.

We therefore urge FDA to disregard the Report in its entirety, as FDA cannot follow any of the NASEM Committee's recommendations without running afoul of FACA, acknowledging its undue influence over the Study, and endorsing the Report's clear gender and other biases.

I. FDA Stacked The Deck Against The Compounding Industry By Steering The NASEM Committee To Conclude That cBHRT Has No Clinical Utility And May Be Too Difficult To Compound.

FDA can neither accept the NASEM Committee's conclusions nor adopt its recommendations because FDA unfairly influenced the NASEM Committee in order to achieve its goals of discrediting cBHRT. FDA steered the NASEM Committee to conclude that cBHRT has no clinical utility and may be too difficult to compound. FDA did so in the following key ways: (1) by influencing the NASEM Committee's definition of "clinical utility" in such a way that it effectively forces compounds through the new drug approval process, a process from which compounds are statutorily exempt; (2) by furthering its public campaign designed to discredit cBHRT; and (3) by indirectly encouraging the dominance of presenter and Report reviewer Jane Axelrad—who, as the former FDA lead on compounding for 21 years, *is* FDA on compounding issues.

First, FDA's influence over the NASEM Committee's definition of "clinical utility" holds compounded cBHRT to new drug approval standards that compounds were never designed to meet and effectively allows FDA to inappropriately practice medicine. As a result of the *FDA*-submitted literature, including peer-reviewed articles, consumer surveys, and formal position statements and guidelines, the NASEM Committee chose to define "clinical utility" as, "a multidimensional construct that reflects evidence about *safety, effectiveness*, therapeutic need, and patient preference concerning benefit-risk balance."¹⁰ This definition mirrors the language in Section 355 of the FDCA, which sets out requirements for drugs that go through FDA's new drug approval process. Specifically, Section 355 states that an application for new drug approval must contain, among other things, "full reports of investigations which have been made to show whether or not such drug is *safe for use and whether such drug is effective in use . . .*" 21 U.S.C. § 355(b)(1)(A) (emphasis added). In other words, both the Committee's definition of "clinical utility" and FDA's threshold for new drug approval require the same evidence of *safety and effectiveness*.

Compounded medication is not just a poor fit for new drug approval but is, in fact, wholly exempt from FDA's new drug approval requirements. Drugs compounded in compliance with Section 503A and Section 503B of the FDCA are statutorily exempt from compliance with Section 355. 21 U.S.C. § 353a(a); 21 U.S.C. § 353b(a). As a result, compounded medications need not, do not, and *cannot*, provide the kind of "safety and effectiveness" data normally expected for FDA new drug approval. FDA, the industry, and the Courts have long acknowledged that compounded medications are not designed to go through FDA's new drug approval process, as "it would not make sense to require compounded drugs created to meet the unique needs of individual patients to undergo the testing required for the new drug approval process."

¹⁰ Report, at x (emphasis added).

Thompson v. W. States Med. Ctr., 535 U.S. 357, 369 (2002).¹¹ Nevertheless, in defining “clinical utility” as it did, and in using that definition as the guiding principle throughout the Report, the NASEM Committee, under clear direction from FDA, fashioned a threshold that compounded preparations, and cBHRT in particular, ***cannot meet***. It can come as no surprise then that the NASEM Committee reached the conclusions that it did—namely, that there is a lack of high-quality clinical evidence, akin to studies submitted in the new drug approval process, to demonstrate the safety and effectiveness of cBHRT.

Additionally, the NASEM Committee’s definition of “clinical utility” allows FDA to practice medicine—which the Agency is well aware it cannot do. As set out above, at FDA’s influence, the NASEM Committee defined “clinical utility” as a construct that reflects evidence about, among others, “***therapeutic need***.”¹² The NASEM Committee clarified that, “[i]n the context of this report, therapeutic need relates to the treatment of menopausal and male hypogonadism symptoms.”¹³ In other words, at the request and sponsorship of FDA, the NASEM Committee is evaluating whether a certain medication (i.e., cBHRT) treats two specific disease states—***this is the practice of medicine***, and the practice of medicine lies wholly outside the scope of FDA’s purview. Physicians—not FDA—are to determine which medication is appropriate to prescribe to best treat their patients. In commissioning NASEM to examine the “clinical utility” of treating patients with cBHRT, FDA effectively inserted itself into the decision-making process between a physician and his or her patient and called into question physicians’ judgement as to the use of cBHRT for treatment.

Numerous courts have held that ***FDA does not have the legal authority to regulate the practice of medicine*** and even FDA has, in the past, acknowledged that it has no such authority.¹⁴ During FDA’s 2008 challenge to cBHRT, Kathleen Uhl, then Assistant Commissioner, Office of Women’s Health at

¹¹ See also *Med. Ctr. Pharmacy v. Mukasey*, 536 F.3d 383, 398 (5th Cir. 2008); *United States v. Franck’s Lab, Inc.*, 816 F. Supp. 2d 1209, 1243 (M.D. Fla. 2011), order vacated, appeal dismissed, No. 11-15350 (11th Cir. Oct. 18, 2012).

¹² Report, at x (emphasis added).

¹³ *Id.* at 4.

¹⁴ “In the legislative debates that led up to the enactment of the Food, Drug, and Cosmetic Act of 1938 (FDCA), Congress expressed a concern that the statute not interfere with the practice of medicine. In the course of passing the Drug Amendments of 1962, Congress reiterated this point.” Lars Noah, *Ambivalent Commitments to Federalism in Controlling the Practice of Medicine*, 53 U. Kan. L. Rev. 149, 173 (2004) (citing Ch. 675, 52 Stat. 1042 (codified as amended at 21 U.S.C. §§ 301-397 (2000)); S. Rep. No. 87-1552, at 1998 (1962) (“[T]he ... [Act] should not interfere with the professional function of the physician. FDA clearance would assure physicians that a drug effectively produces certain physiological actions, but the physician, not the FDA, would determine whether these specific physiological effects would be useful or beneficial with respect to particular patients.”); 78 Cong. Rec. 2728 (1934) (statement of Sen. Copeland) (responding to fears that the proposed legislation would interfere with the “prerogatives of the doctor” by emphasizing that the revised bill “makes certain that the medical practitioner shall not be interfered with in his practice”)). Further, FDA has also stated in proposed rulemaking that, “[t]hroughout the debate leading to the enactment [of the FDCA], there were repeated statements that Congress did not intend the Food and Drug Administration to interfere with medical practice and references to the understanding that the bill did not purport to regulate the practice of medicine as between the physician and the patient.” *United States v. Evers*, 643 F.2d 1043, 1048 (5th Cir. 1981) (quoting 37 FR 16503). FDA has acknowledged during the course of proposing a rule to address labeling of prescription drugs that “it is clear that Congress did not intend the Food and Drug Administration to regulate or interfere with the practice of medicine” 37 FR 16,503, 16,504 (Aug. 15, 1972). And, Dr. Janet Woodcock, former Director of FDA’s Center for Drug Evaluation and Research, testified before Congress that “FDA does not generally regulate the practice of pharmacy or the practice of medicine—the States traditionally have regulated both the prescribing and dispensing of drugs.” *Drugstores on the Net: The Benefits and Risks of On-Line Pharmacies: Hearing Before the Subcomm. on Oversight & Investigations of the House Comm. on Commerce*, 106th Cong. 99 (1999) (statement of Dr. Janet Woodcock, Director of the FDA’s Center for Drug Eval. & Research).

FDA, stated that “the discussion is really between the woman and her health care provider to make a decision what the appropriate therapy for treatment of her menopausal symptom” and “what’s the appropriate therapy for each individual women is really a conversation between her and her doctor.”¹⁵ So, even in the context of prescribing cBHRT, FDA *knows* it must step out of the room. Physicians are free to prescribe cBHRT if, in their professional medical judgment, they determine that it is appropriate to treat their patients. By commissioning the Study, FDA is circumventing its defined authority and calling into question physicians’ endorsement of cBHRT for the treatment of their patients.

Further, FDA continued its targeted public media campaign designed to influence the Report as well as the public’s perception of cBHRT. FDA has been critical of cBHRT for many years and, as stated above, prior to commissioning the Study, had engaged in a concerted campaign *against* compounders of cBHRT. At least as early as 2008, FDA, without any report of adverse events related to cBHRT, began such campaign by initiating enforcement actions against pharmacies compounding cBHRT on a seemingly arbitrary basis.¹⁶ With no reports of adverse events related to cBHRT, many industry stakeholders easily concluded that FDA took action against compounders not because there were issues with the actual compounded medication, but because of the citizen petition filed by Big Pharma giant, and manufacturer of FDA-approved hormone replacement therapies, Wyeth Pharmaceuticals, which requested that FDA halt the compounding of estrogen medications that contain estriol. Nearly 77,000 comments were submitted in response to this petition, almost all in opposition to Wyeth Pharmaceutical’s requests, yet FDA sided with Big Pharma and issued Warning Letters to seven compounding pharmacies. The industry was left with the impression that FDA’s actions were triggered by a pharmaceutical company with a commercial interest in suppressing compounding.

Then most recently, in September 2019, FDA published a press release in the middle of the Study that mischaracterized adverse event reporting for cBHRT and implied that the compounding of cBHRT is inherently risky. This press release highlighted FDA’s concern over 4,202¹⁷ allegedly adverse events associated with cBHRT that had never been reported to FDA, yet the press release grossly mischaracterized these so-called “adverse events” in order to suggest that cBHRT was unsafe and/or ineffective. Even assuming all 4,202 alleged adverse events were serious and/or unexpected, there remains no evidence that these events were not previously reported and since fully addressed by the offending company. Rather, there seems to be no other explanation for these very public, mischaracterized allegations and their timing other than to perpetuate an unfounded view in the public arena that cBHRT is unsafe. That is, FDA used the press release to reference its own Study, stating that it had contracted with NASEM to “conduct a Study on the *risks* associated with compounded hormone products.” Right in the middle of its own commissioned and supposedly independent Study, FDA publicly announced its position that cBHRT is risky, complete with mischaracterizations masquerading as evidence to back it up. As FDA was the sponsor of the Study, with several current and former FDA members continually weighing in during the Study presentations or via press releases, what choice did the NASEM Committee have but to

¹⁵ Transcript of FDA Press Conference on FDA Actions on Bio-Identical Hormones, FTS HHS, FDA, January 9, 2008.

¹⁶ In response to the question of whether FDA received adverse event reports or reports of harm to patients as a result of cBHRT, Kathy Anderson, Deputy Director, Division of New Drugs and Labeling Compliance of FDA responded, “[w]ith respect to your answer about whether we received any adverse event reports, we have not.” *Id.*

¹⁷ Please note that the medical marketing and training company FDA associated with this number of alleged adverse events was unable to verify how or where FDA obtained this number, as this company’s records do not reflect 4,202 events in its tracking system.

conclude that there is a public health concern regarding the prescribing, compounding, dispensing, and use of cBHRT?

Finally, the dominance of Jane Axelrad, FDA's lead on pharmacy compounding from 1991-2016, as a presenter, participant in Study meetings, and Report reviewer, evidences that FDA drove the Report's conclusions.¹⁸ Although Ms. Axelrad retired from FDA after 25 years in April 2016, she launched her own consulting firm Axelrad Solutions and has since used her platform to continue to call for tighter restrictions on the compounding industry. Her participation in and influence over the Study are problematic and strain credulity on the entire Report. Specifically, Ms. Axelrad's presentation advocated for the NASEM Committee to find certain cBHRT and pellet therapies too difficult to compound—an assertion that was at the time, and remains, wholly outside the scope of the Study's charge.

Public information about the NASEM Committee meetings does not indicate who requested that Ms. Axelrad present information claiming cBHRT is too difficult to compound, why she introduced this topic into the Study, and/or why the NASEM Committee found it appropriate for the topic to be considered, despite it being outside of the Study's directive.¹⁹ Nevertheless, Ms. Axelrad's presentation resulted in the NASEM Committee's second recommendation that PCAC should evaluate estradiol, estrone, estradiol cypionate, estriol, dehydroepiandrosterone, pregnenolone, progesterone, testosterone, testosterone cypionate, testosterone propionate, and all compounded bioidentical hormone therapy preparations formulated in pellet dosage form as candidates for FDA's Difficult to Compound List.²⁰

Ms. Axelrad's view that cBHRT should be deemed "too difficult to compound" cannot be considered independent. Her opinion cannot be separated from FDA because it is identical to the position she took as FDA's compounding lead during meetings with PCAC. During public PCAC meetings, on behalf of FDA, Ms. Axelrad asserted that compounders are not equipped to compound certain medications based on their alleged level of difficulty.²¹ The medications she had to be referring to were substances that had already been nominated to the public docket FDA had opened in 2013, and thus already on FDA's, and Ms. Axelrad's, radar.²² Among the nominations received by the Agency, *nine* were hormones or categories of hormones that the NASEM Committee suspiciously recommended PCAC to review. That is, of the 11 hormones or categories of hormones the NASEM Committee recommended PCAC to review, *nine were already nominated for FDA's Difficult to Compound List in 2014 when Ms. Axelrad served*

¹⁸ In joining a Compounding Expert Committee meeting with the United States Pharmacopeia on October 23-24, 2013, Ms. Axelrad was introduced by the Chair of the Compounding Expert Committee as "the FDA lead on pharmacy compounding."

¹⁹ To ascertain the full scope of the communications between FDA and Ms. Axelrad regarding the NASEM study and positions she held about cBHRT while at the Agency, we have served FDA with a FOIA request, enclosed herein as Exhibit 1. We will supplement this Comment as we receive additional information.

²⁰ Report, at 239.

²¹ In presenting to PCAC in 2015, less than one year before she left FDA, Ms. Axelrad stated the following: "[W]e have seen drugs and categories of drugs that even drug manufacturers have difficulty getting right So I think that there may be certain drugs on the list that we don't think that even a highly skilled compounding operation could do successfully [W]e want to eliminate risks to public health that might be associated with compounding difficult-to-compound drugs that we don't think, in most cases, can be compounded safely or provide a safe and effective product." Thursday, June 18, 2015 PCAC meeting, pages 67-92.

²² Nominations to the Difficult to Compound List or comments submitted in response to FDA's December 4, 2013 Federal Register notice were submitted to docket FDA-2013-N-1523.

*as the FDA lead on compounding.*²³ Ms. Axelrad cannot tell the NASEM Committee that hormones are too difficult to compound—the same position she took while at FDA—and maintain any kind of independence from the Agency.

Ms. Axelrad’s participation, as an extension of FDA, also violated NASEM rules. Not only was she a presenter and active participant in Study meetings, but she was also chosen as a Study reviewer, a role in which she reviewed the Report and suggested changes. NASEM’s Policies explicitly state that, “[s]ponsors are not given an opportunity to suggest changes in reports,” i.e., NASEM’s Policies forbid sponsors from serving as reviewers to NASEM’s reports.²⁴ Here, FDA clearly served as a reviewer of this Report (and presenter and participant in the Study), via Ms. Axelrad. Ms. Axelrad’s role (or, more accurately, FDA’s inappropriate role in its Study) standing alone completely invalidates the Report.

II. The Report Is Heavily Rooted In Bias And, As Such, Presents Faulty Conclusions Upon Which The Agency Cannot Rely.

Notwithstanding FDA’s influence, the NASEM Committee’s makeup, the materials it considered, and the organizations from whom it sought data weighed heavily in favor of Big Pharma. Moreover, the materials the NASEM Committee considered, and the data of which the NASEM Committee claims to need more, are rooted in striking gender bias. As a result, the Report lacks credibility and the NASEM Committee’s conclusions and recommendations must be disregarded.

(a) The NASEM Committee Was Comprised Of Individuals Biased Against The Compounding Industry, Which Caused Them To Rely On The Wrong Data.

First, the NASEM Committee lacked the expertise and clinical experience necessary to evaluate cBHRT, and this caused the NASEM Committee to analyze data and literature that fell far outside of the scope of, and which was sometimes irrelevant to, the Study’s charge.²⁵ The NASEM Committee was comprised of 12 members with a shared goal to assess the *clinical utility* of *compounded* hormone medications. However, despite their impressive resumes, not a single member of the NASEM Committee had any stated first-hand expertise or experience in studying, compounding, *or* prescribing compounded

²³ Of the hormones and categories thereof recommended for PCAC review, estradiol, estrone, estradiol cypionate, dehydroepiandrosterone, pregnenolone, progesterone, testosterone, testosterone cypionate, and all compounded bioidentical hormone therapy preparations formulated in pellet dosage form were already nominated to the Difficult to Compound List in 2014.

²⁴ Our Study Process <https://www.nationalacademies.org/about/our-study-process> (last visited August 17, 2020).

²⁵ Although compliance with United States Pharmacopeia (“USP”) general chapters is not the focus of this section, we wanted to highlight another example of where the NASEM Committee relied upon faulty data. The NASEM Committee alleged in its Report that there was inconsistent oversight of compounding pharmacies with respect to USP compliance. To make this claim, the NASEM Committee relied upon outdated and incorrect information from The Pew Charitable Trusts and the National Association of Boards of Pharmacy. Report, pages 64-65. For example, the Report includes a map that claims that New Hampshire law contains no data with respect to USP <795> compliance, yet New Hampshire regulations currently state, “[t]he board shall require all compounders engaging in compounding in all situations to adhere to and comply with the current edition of the United States Pharmacopeia including but not limited to Chapters 795 (USP 795) and 797 (USP 797)” N.H. Code Admin. R. § 404.01(b). Similarly, the Report’s map also claims that Utah law contains no data with respect to USP <795> compliance, yet the Utah Pharmacy Practice Act states, “[f]acilities shall follow USP-NF Chapter 795, compounding of non-sterile preparations” Utah Admin. Code r. R156-17b-614a(3)(a). These are only two small examples that demonstrate that NASEM Committee relied on false data to form its conclusions.

medications, much less cBHRT. However, a strong majority of the members had some explicit connection to Big Pharma. For example:²⁶

- **Lesley H. Curtis, Ph.D.:** Dr. Curtis is a health services researcher who oversees a portfolio of products that use observational data to address questions related to, among others, pharmacoepidemiology, which studies the utilization and effects of drugs in large numbers of people. Dr. Curtis is a Professor and Chair of Population Health Sciences and Interim Director of the Duke Clinical Research Institute at Duke University, which **has a number of professional connections with pharmaceutical companies**, but it has **not conducted trials on bioidentical hormone replacement therapy products**;
- **Susan S. Ellenberg, Ph.D.:** Dr. Ellenberg is a Professor of Biostatistics, Medical Ethics, and Health Policy at the University of Pennsylvania Perelman School of Medicine who **works closely with several pharmaceutical companies, including Merck, Bristol-Myers Squibb, and Marinus Pharmaceuticals**;
- **Adel H. Karara, Ph.D., FCP:** Dr. Karara is a Professor of Pharmaceutical Sciences at University of Maryland, Eastern Shore, where he teaches in the areas of pharmaceuticals, biopharmaceuticals, and pharmacokinetics. Prior to joining academia, Dr. Karara **held senior positions in the pharmaceutical industry, including positions at Roche, Berlex, and Novartis**. While at Berlex, Dr. Karara **provided new drug approval support FDA-approved hormone therapies such as Yasmin, ClimaraPro, Menostar, and Angeliq**;
- **Robert B. MacArthur, Pharm.D., M.S.:** Dr. MacArthur is the **only Doctor of Pharmacy on the NASEM Committee** and the only member to potentially have any compounding experience, though not first-hand experience. Dr. MacArthur is currently the Pharmacy Director at The Rockefeller University Hospital and the President of Orphan Drug Services, Inc., which provides drug development and statistics services to pharmaceutical companies. **His work experience includes large pharma (Sandoz and Novartis), small to mid-size pharma (Systems Medicines, CTI, Aeson Therapeutics, Cancer Prevention Pharmaceuticals, and others), commercial phase 1 units (LAB, Inc., others), and GMP drug manufacturing (Pii Inc. US, PharmMaterials UK, and others)**. In academia, his work enabled studies, which includes compounding novel oral and injectable products for first-in-human/phase I/ II/III studies; and
- **David R. Rubinow, M.D.:** Dr. Rubinow is the Meymandi Professor and Chair of the Department of Psychiatry at the University of North Carolina at Chapel Hill's School of Medicine. **Dr. Rubinow has professional and financial interests in Sage Therapeutics**, a pharmaceutical company that primarily manufactures and distributes medications to treat central nervous system disorders.

Despite their long lists of personal achievements, the Committee members lacked the requisite experience in prescribing, preparing, and dispensing compounded medications. Further, not a single Committee

²⁶ For complete biographies of all 12 NASEM Committee members, see Report at 269–76.

member is a current physician that treats patients with any compounded hormone therapies. Experience in compounding and prescribing hormone therapies is **crucial** to understanding the clinical utility of compounded bioidentical hormone therapies. The Committee's lack of appropriate expertise, in and of itself, is enough to raise serious questions regarding the conclusions and recommendations reflected in the Report.

Nevertheless, even if the NASEM Committee members were appropriately qualified to oversee the Study, their shared experience in and ties to Big Pharma inherently caused the NASEM Committee to seek out data and studies akin to those conducted by Big Pharma, skewing the results of the Study and the conclusions reached by the NASEM Committee. Despite stakeholders submitting *thousands* of research articles and observational data points for the NASEM Committee's review, the NASEM Committee only "identified a total of **13 studies** related to cBHRT that were of adequate **methodologic rigor** for inclusion in its review of safety and effectiveness of these preparations."²⁷ These 13 studies, which formed the basis of the NASEM Committee's analysis of the clinical utility of cBHRT, **only focused on five compounded bioidentical hormone variations**.²⁸ Such a narrow focus on only 13 studies, which only consider a small fraction of the therapies that are needed to treat patients, blatantly ignores the variability inherent in compounding bioidentical hormones. For example, one compounding pharmacy that presented to the NASEM Committee has "compounded over 149,000 unique hormone formulations using fewer than 10 hormones."²⁹ There is no way that 13 studies can act as a representative sample of the **hundreds of thousands** of compounded bioidentical hormone variations.

Moreover, in cherry-picking the 13 studies, the NASEM Committee inexplicably ignored the medical judgment of a series of reputable physicians who routinely treat their patients with cBHRT for a myriad of conditions.³⁰ Rebecca Glaser, M.D., David Rosensweet, M.D., and Pamela Smith, M.D., M.P.H., M.S. all provided insightful presentations rooted in scientific evidence to the NASEM Committee regarding their decisions to treat their patients with cBHRT. Further, seventeen physicians, many of whom are Fellows of The American Congress of Obstetricians and Gynecologists, also submitted statements that they regularly, and **safely**, exercise their medical judgment to prescribe cBHRT for their male and female patients to treat a variety of life-threatening medical conditions, such as decline in brain function, depression, heart disease, heart failure, fibrocystic breast disease, ovarian cysts, autoimmune disorders, bone health, neurodegenerative diseases, breast cancer, insulin resistance, cholesterol issues, Alzheimer's, and dementia, among others. Yet, the NASEM Committee completely disregarded medical experts in this very field, and, in the face of a wealth of observational data, chose to somehow conclude that there is no clinical utility to cBHRT.

²⁷ During the NASEM Committee's Q&A on the Report on July 1, 2020, when asked what it would like to see with respect to evidence to support the clinical utility of cBHRT products, the NASEM Committee stated it wanted more observational studies and evidence to support safety and efficacy, despite the thousands of articles and observational studies that were already submitted during the study's course. *See also* Report, at 140 (emphasis added).

²⁸ It is important to note that none of the 13 studies reported adverse events.

²⁹ Report, at 95.

³⁰ We hereby incorporate all arguments and all exhibits contained in our letter to the NASEM Committee submitted on November 7, 2019. This letter is enclosed herein for reference as Exhibit 2.

(b) *The Data Relied Upon By The NASEM Committee, And The Additional Data It Seems To Be Seeking, Are Rooted In Gender Bias.*

It is perhaps even more troubling that the NASEM Committee appears to have overlooked the gender bias that impedes the independent and credible nature of the very studies the NASEM Committee determined it needed in order to evaluate the clinical utility of cBHRT. The NASEM Committee claimed that it needed well-designed, double-blind, randomized, placebo-controlled trials—that is, studies like those required in FDA’s new drug approval—in order to evaluate the safety and effectiveness of cBHRT, and that the lack of such studies hindered its ability to evaluate cBHRT’s clinical utility. But even if a plethora of such studies existed for the NASEM Committee’s review, that information still would not allow it to make an informed decision on the safety and effectiveness of cBHRT. This is because these kinds of controlled studies frequently exclude women, and women are the very patient population at the heart of this Study and are the very patient population that will be most severely impacted if FDA adopts the Report. In only considering 13 studies and asking for more controlled trials, the NASEM Committee made conclusions and recommendations for women’s health based on data and information that left women out of the conversation.

Based on the Coalition’s limited engagement with the NASEM Committee during its Study, it was clear that there was a dearth of understanding of the difference between male and female hormones, which is critical to determining which trials (e.g., observational versus controlled) will be most informative for the Study. In this case, due to the highly individualized nature of hormones and compounded hormone therapies, cBHRT is a poor fit for controlled trials (as are all compounds, as Congress recognized when it exempted compounds from these trials via the DQSA) and, accordingly, observational data fills this gap.³¹ Female hormones are particularly idiosyncratic and are fundamentally more complicated and misunderstood than male hormones—biological facts that make women a poor fit for double-blind, randomized, placebo-controlled trials.³² Big pharmaceutical companies that can afford these trials often see female candidates for their studies as risky—women can get pregnant and the risk of fetal concern is often too much to bear for the Study sponsor. In a 2014 report, researchers at the Brigham and Women’s

³¹ We would like to reiterate that stakeholders submitted *thousands* of research articles and observational data points for the NASEM Committee’s review throughout the course of the Study, which were largely ignored.

³² For example, there is a common misconception that female bodies do not produce much, if any, testosterone, but this is far from the truth. Testosterone is the most abundant and biologically active hormone throughout a woman’s lifespan. Testosterone levels drop in the years prior to, and during, menopause, which causes similar symptoms of deficiency for women as it does in men (yet, it occurs earlier in a woman’s life compared to a man’s). This can lead to new onset mood disorders (or worsen existing ones), apathy, impaired glucose metabolism (which leads to weight gain), insulin resistance/diabetes, fatigue, muscle wasting, bone loss, cognitive impairment, migraine headaches, low libido, and other sexual function disorders. See Rebecca Glaser and Constantine Dimitrakakis, *Testosterone therapy in women: Myths and misconceptions*, *Maturitas* 74(3), P230-234 (2013) (“[Testosterone] is the most abundant biologically active female hormone, [Testosterone]T is essential for physical and mental health in women . . .”). See also Amy Westervelt, *The medical research gender gap: how excluding women from clinical trials is hurting our health*, *The Guardian*, 30 April 2015 (“According to the Institute of Medicine, every cell in our bodies has a sex, which means men and women are different at a cellular level. That also means that diseases, treatments, and chemicals might affect the sexes differently. And yet there’s a long and storied tradition of ignoring gender when it comes to health research. For several reasons, female subjects have historically been excluded from toxicology or biomedical research . . .”).

Hospital in Boston chronicled the exclusion of women from health research and its impact on women's health:

The science that informs medicine – including the prevention, diagnosis, and treatment of disease – ***routinely fails to consider the crucial impact of sex and gender***. This happens in the earliest stages of research, when ***females are excluded from animal and human studies or the sex of the animals isn't stated in the published results***. Once clinical trials begin, researchers frequently do not enroll adequate numbers of women or, when they do, fail to analyze or report data separately by sex. This hampers our ability to identify important differences that could benefit the health of all.³³

Thus, these hormone studies are more often conducted with male candidates, and the data is later extrapolated to female patients.³⁴ The individualized, complicated, inherently idiosyncratic nature of female hormones is completely disregarded in these scenarios in favor of the “easier” male model. Caroline Criado Perez, author of *Invisible Women: Data Bias in A World Designed For Men*, specifically notes the presence of the male-default data bias in FDA drug trials. One issue that has gone utterly unaddressed, Perez states, is whether the drugs are tested in women at different stages of their menstrual cycles, which can impact the drug's effectiveness.³⁵ It is ironic, to say the very least, for the NASEM Committee to determine cBHRT lacks studies of adequate methodologic rigor when these types of studies routinely exclude women, and when they do include women, utterly fail to take into account the impact of hormone fluctuations on a drug's effectiveness.

As a result, women and their physicians have been utterly excluded from NASEM's evaluation of what is best for women's bodies.³⁶ The NASEM Committee relied on methodologies of data evaluation that exclude women and their unique hormonal make up, and ignored the medical judgment of reputable leading physicians that routinely prescribe cBHRT to treat scores of patients. Then, when it came to patients, the NASEM Committee actively disregarded patient choice—dismissing women's opinions of their own well-being as “preference” and rendered this “preference” as non-instrumental to forming its conclusions. Specifically, the Study concluded, “[b]ased on a limited number of studies, patients (largely women) taking cBHRT are thought to be simultaneously ‘pushed away’ from FDA-approved [bioidentical hormone therapy] and ‘pulled toward’ cBHRT by conflicting psychosocial forces.”³⁷ Instead of validating the physician's recommended treatment for the patient and the patient's right to follow the advice of her physician, the NASEM Committee made the gendered assertion that women are too influenced by social

³³ Sex-Specific Medical Research Why Women's Health Can't Wait, A Report of the Mary Horrigan Connors Center for Women's Health & Gender Biology at Brigham and Women's Hospital, 2014, page 5.

³⁴ Mark Glezerman, *Women are dying because most medical research is done on men*, New York Post, August 16, 2016 (“Yet the vast majority of clinical research on diseases and medications is performed on men, which means that half of the population is treated based on data that doesn't necessarily apply to them.”); Caitlin Hoff, *Taking on Gender Bias in Clinical Trials*, National Women's Health Network, February 26, 2019 (“For decades, health research was done on men and the results were assumed to apply to women. Women were treated as if they were just smaller versions of a male body.”).

³⁵ Caroline Criado-Perez, *Invisible Women: Exposing Data Bias in a World Designed for Men* 203–04 (2019).

³⁶ Holdercroft, Anita, *Gender bias in research: how does it affect evidence based medicine?*, Journal of the Royal Society of Medicine vol. 100,1 (2007): 2-3. (“The evidence basis of medicine may be fundamentally flawed because there is an ongoing failure of research tools to include sex differences in study design and analysis. The reporting bias which this methodology maintains creates a situation where guidelines based on the study of one sex may be generalized and applied to both.”).

³⁷ Report, at 8.

factors to make an informed decision about *their own healthcare*. The fact that the NASEM Committee is advocating for safety and effectiveness data akin to new drug approval funded by Big Pharma is merely another way for FDA to ignore and gloss over the unique needs of women and make the male body the default model—a way that represents a dismissive and patronizing attack on women’s health and women’s right to their quality of life.

III.If FDA Adopts The Conclusions And Recommendations In The Report, FDA Will Be In Violation Of The Federal Advisory Committee Act.

As set forth above, FDA so heavily influenced the NASEM Committee and its conclusions and recommendations that FDA, in essence, managed and controlled the NASEM Committee. Ms. Axelrad’s involvement, as well as the active measures FDA took to control the outcome of the Study, demonstrate FDA’s undue influence over the NASEM Committee and its results. Accordingly, FDA may not adopt the conclusions and recommendations in the Report without violating FACA.

It is through the enactment of FACA in 1972 that Congress formally recognized the importance and value of federal advisory committees. For years, federal advisory committees have played a critical role in shaping policies for and providing advice to the federal government. Thanks to the role that advisory committees play, the public is given an opportunity to engage in important governmental issues and the government, as well as the public, are given access to expertise on a broad range of issues affecting federal policies and programs. Federal agencies that engage advisory committees must adhere to the requirements established by FACA. In particular for our purposes here, FACA requires membership of an advisory committee to be fairly balanced and prohibits a federal agency from managing or controlling a committee created by NASEM. Specifically, “[a]n agency may not use any advice or recommendation provided by the National Academy of Sciences . . . that was *developed by use of a committee created by that academy under an agreement with an agency*, unless (1) the committee was not subject to any *actual management or control by an agency* or an officer of the Federal Government . . .” 5 U.S.C. APP. 2 § 15(a)(1) (emphasis added). In other words, FDA cannot use any conclusions or recommendations provided by NASEM if they are the result of a NASEM Committee that was unduly influenced by FDA.

It is abundantly clear that FDA had management and control over the NASEM Committee. First, the involvement of Ms. Axelrad, former FDA lead on pharmacy compounding, in the Study evidences that FDA had a strong command over the outcome it wanted. She participated in and presented during the Study and reviewed the Report in violation of NASEM’s own policies, and likely suggested articles for the NASEM Committee’s review.³⁸ Second, FDA on its own submitted data, such as articles and references, for the Study’s consideration and influenced the definition the NASEM Committee used for “clinical utility.” FDA forced the NASEM Committee to evaluate cBHRT under a new drug approval standard knowing full well that cBHRT, as compounded medication, was neither suited for nor could ever meet such a standard. Finally, FDA submitted data on alleged adverse events involving cBHRT in order to unduly influence the NASEM Committee’s perception that cBHRT is inherently risky and that its use should be restricted. The adverse event information was, as stated above, heavily mischaracterized and gave a false impression about the prevalence of incidents involving cBHRT and their severity. FDA

³⁸ “Furthermore, during the National Academies’ external review process, additional articles were suggested by reviewers of the report.” Report, at 257.

pumped the NASEM Committee with one-sided information in order to ensure that the NASEM Committee came to the conclusions it did.

In sum, as a result of FDA's involvement, the NASEM Committee fell subject to severe management and control by the very agency that commissioned what should have been an independent Study. Therefore, FDA's adoption of any of the conclusions or recommendations in the Report is a violation of FACA.

IV. We Strongly Caution FDA Against Adopting The NASEM Committee's Recommendation That PCAC Review Certain Bioidentical Hormone Therapies And Pellets As Candidates For FDA's Difficult To Compound List.

Even if the Report is taken at face value and FDA considers adopting its conclusions and recommendations, we strongly discourage FDA from adopting the NASEM Committee's recommendation that PCAC review certain bioidentical hormone therapies and pellets as candidates for FDA's Difficult to Compound List. PCAC is an advisory committee that operates in violation of FACA and is therefore in no position to evaluate whether hormone therapies or categories thereof should be included on FDA's Difficult to Compound List. Further, PCAC's involvement threatens to remove viable hormone treatment options for millions of patients who cannot be treated by FDA-approved bioidentical hormone therapies, which will have a devastating impact on the health and well-being of these patients.

To start, PCAC is a federal advisory committee that operates in violation of FACA. FACA requires that "membership of the advisory committee . . . be *fairly balanced in terms of the points of view represented* and the functions to be performed by the advisory committee . . ." 5 U.S.C. APP. 2 § 5(b)(2) (emphasis added). For a *compounding* committee whose purpose is to provide "advice on scientific, technical, and medical issues *concerning drug compounding* under sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act, and, as required, any other product for which the Food and Drug Administration has regulatory responsibility, and make appropriate recommendations to the Commissioner of Food and Drugs," only *two of its 12 voting members* actually have compounding listed as their expertise, yet PCAC claims in the FACA database that "[m]embers are *authorities in the fields of pharmacy compounding*, pharmaceutical manufacturing, pharmacy, medicine, and related specialties."³⁹ This is clearly not the case.

PCAC needs to adequately represent the interests and needs of providers and patients who use and depend on compounded medications. Compounding is often practiced in community settings, and it is therefore vital that voting members of PCAC have a thorough understanding of compounding in a community setting in order to appropriately advise FDA. As PCAC stands, this advisory committee is *not* "fairly balanced in terms of the points of view represented" and is therefore in stark violation of FACA. 5 U.S.C. APP. 2 § 5(b)(2).

The implications of an imbalanced advisory committee are that the individuals who comprise the committee may not be in the best position to properly evaluate whether certain bioidentical hormone

³⁹ HHS 5220 Pharmacy Compounding Advisory Committee, Committee Detail, <https://www.facadatabase.gov/FACA/apex/FACAPublicCommittee?id=a10t0000001gzugAAA> (last visited August 17, 2020).

therapies and pellets should be candidates for FDA's Difficult to Compound List. As a result, critical bioidentical hormone therapies are at risk of being placed on a list that removes them as treatment options for the millions of patients across the U.S. who rely on them. Not only that, but if compounders cannot prepare certain bioidentical hormone therapies, they run the risk of going completely out of business, which will have a devastating impact on the compounding industry and the patients they serve.

Moreover, to the extent FDA is considering a way to further evaluate the safety of estradiol, estrone, estradiol cypionate, estriol, dehydroepiandrosterone, pregnenolone, progesterone, testosterone, testosterone cypionate, and testosterone propionate, we want to emphasize that the NASEM Committee *did not* conclude that these substances are not *safe*. This distinction is critical because not only do these bioidentical hormones not belong on the Difficult to Compound List, but they do not have identified safety risks that would require them to be placed in Category 2 of FDA's 503B Bulks List.⁴⁰

V. Conclusion.

In conclusion, we request that FDA *reject* the NASEM Committee's Report and all the conclusions and recommendations therein, in favor of keeping cBHRT, a critical, life-saving therapy, available for the *millions* of patients that rely on this therapy.

Very truly yours,

/s/ Rachael G. Pontikes

Rachael G. Pontikes
For Reed Smith LLP

RGP:rl

⁴⁰ Category 2 of the 503B Bulks List represents bulk drug substances that were nominated with sufficient supporting information for FDA to evaluate them, but FDA identified significant safety risks relating to the use of these substances in compounding pending further evaluation. FDA has stated it would consider taking action against an outsourcing facility for compounding drug products with this bulk drug substance under its general enforcement policies.

EXHIBIT 1

July 24, 2020

Via Online Access Portal

Food and Drug Administration
Division of Freedom of Information
Office of the Executive Secretariat, OC
5630 Fishers Lane, Room 1035
Rockville, MD 20857

RE: Freedom of Information Act Request

To Whom It May Concern:

We are submitting the following Freedom of Information Act (“FOIA”) request to the U.S. Food & Drug Administration (“FDA”).

A. Requestor's name, address, and telephone number.

Rachael Pontikes
10 South Wacker Drive
40th Floor
Chicago, IL 60606
(312) 207-2857

B. A description of the records being sought. The records should be identified as specifically as possible. A request for specific records that are releasable to the public can be processed much more quickly than a request for "all information" on a particular subject. Also fees for a more specific and limited request will generally be less.

I request the following records:

- All communications* between FDA (including, but not limited to, FDA’s Center for Drug Evaluation and Research (“CDER”)) and the National Academies of Sciences, Engineering, and Medicine (including, but not limited to, Leigh Jackson), from January 1, 2016, to the present regarding the following subjects:

* For purposes of this FOIA request, the term “communications” includes, but is not limited to, e-mail messages, letters, memoranda, and calendar invitations and notations.

- Bioidentical hormones;
 - Compounded bioidentical hormone therapy (otherwise known as “cBHT” or “cBHRT”);
 - Difficult to compound;
 - Clinical utility ;
 - Pharmacy Compounding Advisory Committee (otherwise known as “PCAC”);
 - Jane Axelrad; or
 - Axelrad Solutions LLC.
- All communications between FDA (including, but not limited to, FDA’s CDER) and Jane Axelrad from May 1, 2016, to the present regarding the following subjects:
 - National Academies of Sciences, Engineering, and Medicine (otherwise known as “NASEM”);
 - Bioidentical hormones;
 - Compounded bioidentical hormone therapy (otherwise known as “cBHT” or “cBHRT”);
 - Difficult to compound;
 - Clinical utility; or
 - Pharmacy Compounding Advisory Committee (otherwise known as “PCAC”).
- All communications between FDA (including, but not limited to, FDA’s CDER) and Axelrad Solutions LLC from December 6, 2016, to the present regarding the following subjects:
 - National Academies of Sciences, Engineering, and Medicine (otherwise known as “NASEM”);
 - Bioidentical hormones;
 - Compounded bioidentical hormone therapy (otherwise known as “cBHT” or “cBHRT”);
 - Difficult to compound;
 - Clinical utility; or
 - Pharmacy Compounding Advisory Committee (otherwise known as “PCAC”).
- All communications between FDA (including, but not limited to, FDA’s CDER) and the Pharmacy Compounding Advisory Committee, from November 27, 2013, to the present regarding the following subjects:
 - Bioidentical hormones;
 - Compounded bioidentical hormone therapy (otherwise known as “cBHT” or “cBHRT”);
 - Difficult to compound;
 - Clinical utility;
 - National Academies of Sciences, Engineering, and Medicine (otherwise known as “NASEM”);
 - Jane Axelrad; or
 - Axelrad Solutions LLC.

Food and Drug Administration
July 24, 2020
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ReedSmith

C. A statement concerning willingness to pay fees, including any limitations.

I will pay all fees associated with this request. If the agency estimates that those fees will exceed \$1,000.00, please contact me before proceeding further.

Very truly yours,

Rachael G. Pontikes

Rachael G. Pontikes
For Reed Smith LLP

RGP:rl

EXHIBIT 2

November 7, 2019

VIA EMAIL
VIA UPS

Ms. Leigh Miles Jackson
Study Director
The National Academies of Sciences,
Engineering, and Medicine
Keck Center
Keck 765
500 Fifth St. NW
Washington, DC 20001

**Re: Study on the Clinical Utility of Treating Patients with Compounded
“Bioidentical Hormone Replacement Therapy”**

Dear Ms. Jackson:

We write on behalf of a coalition of six compounding facilities that serve thousands of patients and physicians throughout the United States every month (the “*Coalition*”). We understand that the National Academy of Sciences, Engineering, & Medicine (“*NASEM*”) has been engaged by the Food & Drug Administration (“*FDA*”) to conduct a study on the *Clinical Utility of Treating Patients with Compounded “Bioidentical Hormone Replacement Therapy”* (the “*Study*”). The purpose of the Study is three-fold:

- (1) review the current and historic uses of compounded Bioidentical Hormone Replacement Therapy (“*BHRT*”) to treat patients;
- (2) understand the physical and chemical characteristics of compounded BHRT preparations; and
- (3) review and assess the available evidence regarding the safety and effectiveness of compounded BHRT preparations.

Ultimately, we understand that the committee comprised to conduct the Study (the “*Committee*”) will summarize the aforementioned information and issue a report containing recommendations regarding the clinical utility of compounded BHRT preparations; the safety and effectiveness of compounded BHRT preparations; and the patient populations that would benefit from compounded BHRT preparations in lieu of FDA-approved drug products.

In an effort to aid the Committee, the Coalition seeks to present information targeting the three-fold purpose of the Study. In order to assess the overall clinical utility of compounded BHRT, the

Coalition will present an overview of the current and historic uses of compounded BHRT to treat patients, and the reasons why FDA-approved BHRT preparations cannot adequately meet patient need. In addition, the Coalition will present evidence demonstrating that compounded BHRT preparations are safe, effective, and do not present demonstrable difficulties to compound consistently.

In light of the information below, the Coalition believes the Committee should find that: (1) compounded BHRT preparations are clinically necessary to treat the patient population; and (2) compounded BHRT preparations are safe, effective and do not present demonstrable difficulties to compound. Although we understand that the Committee will be conducting a hearing on the Study on November 12, 2019, we respectfully request that the Coalition be granted a separate meeting with the Committee to present our key experts and answer any questions the Committee may have.

I. Compounded BHRT Preparations Are Critically Necessary For The Treatment Of A Variety Of Conditions.

The Committee recognizes that in order to assess the overall clinical utility of compounded BHRT, it is first important to understand the current and historic uses of compounded BHRT to treat patients, and the reasons why FDA-approved BHRT drug products cannot adequately meet patient need. Accordingly, in order to assist the Committee in preparing its report, we have first set forth below a brief history of compounding in general and where compounding sits in the overall regulatory scheme for drug products. We further provide an overview of the current and historic uses of compounded BHRT and then, finally, we explain why FDA-approved BHRT drug products cannot adequately meet patient need.

The Coalition has provided a representative sample of statements from physicians and a nurse practitioner who regularly prescribe compounded BHRT preparations to their patients.¹ These physicians and nurse practitioner support compounded BHRT preparations being made available to their patients. We have summarized these statements in this submission; however, we encourage the Committee to read these statements and reach out to the practitioners for further comment. And, we must also make the Committee aware that there are scores of other physicians and prescribers eager to provide further informative statements like the ones enclosed herein.

As set forth below, physicians recognize that the available FDA-approved BHRT drug products are not offered in the variety of dosage forms and strengths necessary to treat a patient population that needs personalized hormone therapies. Compounded BHRT preparations fill the gaps left by FDA-approved drug products but, due to the nature of hormone therapy, these compounded BHRT preparations cannot go through the new drug approval process. In addition, there are certain patients and patient populations that simply cannot be treated with the current slate of FDA-approved BHRT drug products. Accordingly, compounded BHRT preparations are medically necessary for the treatment of a variety of conditions and patient access to this medication must be preserved and protected.

¹ See Group Exhibit 1, which comprises signed statements from the following: Jeffrey R. Baker, MD, MS; George Benson Branning, MD; David A. Brownstein, MD; Angela DeRosa, DO, MBA, CPE; Bruce Dorr, MD, FPMRS; Christine Farrell, MSN, FNP-C; Laura Grant, MD; Arlene Jacobs, MD; Steven A. Komadina, MD; Daniel Elias Melville, MD; John Joseph Peet, MD, FACOG; John J. Pierce, DO; Cory Stephen Rice, DO; Ann Elizabeth Stanger, MD; G. DeAn Strobel, MD, FACOG; Allan Warshowsky, MD, FACOG, ABIHM; and David Watson, MD, FACOG.

(a) Compounded Medication Is A Traditional Component Of The Practice Of Pharmacy.

Pharmacy compounding is a vital, medically necessary, longstanding, and integral part of the delivery of health care in the United States. Compounded drugs have historically filled the interstitial spaces where, in the physicians' judgment, there is no suitable commercially manufactured drug product available to treat a patient. This unavailability occurs for many reasons. For example: (1) there is no manufactured product to accomplish a desired or preferred medical objective; (2) a commercially available product, while available, is nonetheless not suitable because of patient allergies; drug delivery format, e.g., tablet, injectable, patch, suppository, etc.; flavoring; combination with other drugs, etc.; and (3) a manufactured drug also may not come in the dosage appropriate for a particular patient, e.g., pediatric versus adult dosage.

Without compounding, physicians run the risk that a patient's specific and unique medical need will go untreated. Pharmacies compound and dispense drugs pursuant to prescriptions to treat cancer, autism, premenstrual syndrome, menopause, andropause, infertility, pain management, and every other conceivable condition or illness. Without compounded drugs to treat conditions for which no manufactured drugs exist (or for which manufactured drugs exist, but for patient-specific reasons are unsuitable), certain drug therapies or regimens would be unavailable altogether. Therefore, after physicians determine that there is no suitable commercially manufactured drug available, these physicians prescribe pharmacy compounds.

As a traditional component of pharmacy practice, the States—and more specifically, State boards of pharmacy—have historically had oversight of most aspects of pharmacy compounding practices through State laws regulating the practice of pharmacy. All 50 States address compounding in some form and impose rigorous registration, inspection, and safety requirements. State pharmacy laws have registration requirements for resident and non-resident pharmacies or pharmacists; set forth the professional standards for pharmacies and pharmacists; establish labeling and purity requirements for drugs, including compounded drugs; establish licensure procedures for pharmacists and resident and non-resident pharmacies; and establish certain training and education requirements for pharmacists and other pharmacy providers.

While States have historically regulated compounding as a traditional part of pharmacy practice, the federal government has historically regulated commercial drug manufacturing and distribution. When enacted in 1938, the Food, Drug, and Cosmetic Act (“*FDCA*”) did not address drug compounding. Rather, while FDA was given authority to regulate drug manufacturing, the historic practice of traditional pharmacy compounding remained regulated by State law. Under the *FDCA*, drug manufacturers are required to comply with a series of conditions appropriate for the production of one-size-fits-all drugs, like new drug approval (“*NDA*”) requirements, labeling requirements, and the requirement that drugs be prepared in facilities that comply with current Good Manufacturing Practices (“*cGMPs*”). Compounding pharmacies, on the other hand, prepare unique medications for the particularized medical need of a patient or patient population when a physician determines a commercially available drug is not suitable for treatment. The *FDCA* requirements for manufactured drugs were not designed for these specialized medications.

In 2013, however, Congress, through a series of legislative measures, exerted limited federal oversight over traditional compounding pharmacies and created a new registration for a certain type of compounding facility called an “outsourcing facility.” These legislative actions culminated in the Drug Quality and Security Act (“*DQSA*”) of 2013. Under Section 503A of the *DQSA*, traditional compounding pharmacies, or Section 503A compounding pharmacies as they are commonly called, remain primarily regulated by the States but are required to meet certain limited criteria under the statute. They need not register with FDA, but can be subject to FDA inspection. Section 503B of the *DQSA*, in turn, requires compounding facilities that choose to operate as outsourcing facilities to register with FDA and comply with certain conditions. Section 503B outsourcing facilities are subject to risk-based inspections by FDA and must comply with cGMP standards as well as other requirements set forth in the *DQSA*.

Section 503A compounding pharmacies and Section 503B outsourcing facilities play a vital role in ensuring that patient needs are met in those cases where FDA-approved drug products cannot meet patient medical need. Without access to the compounded medications prepared by these facilities, public health would suffer.

(b) Current And Historic Uses Of Compounded BHRT Preparations To Treat Patients.

The need for compounded forms of hormone medication cannot be understated. This is especially true for compounded BHRT preparations, which have played an important role in treating a wide variety of medical conditions and symptoms in male and female patients for decades. Bioidentical hormones are plant-derived hormones that, when used by the human body, are molecularly and structurally identical to those hormones endogenously produced by the human body and circulated in the human bloodstream.² Treatment with compounded BHRT has consistently proven to be a safe and effective alternative to the one-size-fits-all approach of FDA-approved bioidentical hormone therapies, as they can be custom compounded to match each patient’s unique needs and body chemistry.

Compounded bioidentical hormone therapy was first introduced in the 1980s to treat menopause symptoms. Dr. Jonathan Wright researched alternatives to commercially available conjugated estrogens by analyzing the estrogens he found were naturally produced by female bodies: estradiol, estrone, and estriol. He then compounded a product known as “Triest,” which combined those three estrogens into a topical cream.³ Subsequent hormone testing revealed that estrone may not be needed—thus, “Biest” was formed, which is a compounded topical cream made of estradiol and estriol and remains one of the most popular and effective compounded bioidentical hormone therapies today.

However, the real catalyst to the increase in treatment with compounded BHRT is attributed to the early termination and results of the Women’s Health Initiative (“*WHI*”) trials on estrogen and progestin. Designed in 1991 and completed between 1993 and 2005, *WHI* conducted two parallel studies (estrogen plus progestin and estrogen only) of hormone therapies to assess the effects of hormone therapy on

² Santoro N, Braunstein, et al., Compounded Bioidentical Hormones in Endocrinology Practice: An Endocrine Society Scientific Statement, *J Clin Endocrinol Metab.* 2016 Apr; 101(4):1319 (defining the term “bioidentical” to mean hormones that have “the same molecular structure as a hormone that is endogenously produced and circulates in the human bloodstream . . .”).

³ For further information, see Jonathan V. Wright, *Natural Hormone Replacement: The Safe and Natural Menopause Treatment Alternative*, 41 (1997).

cardiovascular disease and breast cancer.⁴ Media coverage of the initial results of the estrogen plus progestin trial indicated that the risks of cardiovascular disease, breast cancer, and venous thromboembolism, among others, were not outweighed by the benefits of this treatment. In response to these results, many female patients and physicians sought alternative hormone treatments.⁵

Thus, in 2004, BHRT therapies re-emerged into the market as an alternative to synthetic, conjugated estrogen therapies.⁶ Compounded forms of BHRT soon followed as an effective way to individualize symptom management and optimize the clinical experience for patients. Today, compounded BHRT is used by physicians and other medical professionals around the country to treat at least the following conditions and symptoms:⁷

Male and Female Patients	Male Patients Only	Female Patients Only
1. Adrenal dysfunction	1. Andropause	1. Cervical dysplasia
2. Anxiety	2. Erectile dysfunction	2. Chronic pain
3. Autoimmune diseases (thyroid, arthritis)		3. Endometriosis
4. Bone density/bone health		4. Fibrocystic breast disorder
5. Brain dysfunction		5. Fibroids
6. Cardiometabolic disease		6. Fibromyalgia
7. Cardiovascular disease		7. Heavy vaginal bleeding
8. Chronic pain		8. Inadequate luteal phase in infertility patients
9. Coronary heart disease		9. Interstitial cystitis
10. Depression		10. Menopause symptoms (vaginal dryness, low libido, hot flashes, night sweats, vaginal atrophy)
11. Diabetic control		
12. Heart disease/failure		
13. Incontinence		
14. Insomnia		
15. Joint pain		
16. Low testosterone/low hormone levels		
17. Mental illness		

⁴ For further information on the two trials conducted by the Women’s Health Initiative, *see* Hormone Therapy Trials (HT), Women’s Health Initiative, <https://www.whi.org/about/SitePages/HT.aspx> (last visited November 7, 2019) (“The WHI Hormone Therapy Trials (HT) were designed to test the effects of postmenopausal hormone therapy on women’s risk for coronary heart disease (primary analyses) and on hip and other fractures and breast cancer (secondary analyses). The effects of hormone therapy on endometrial cancer was also evaluated in women with a uterus.”).

⁵ Garnet L. Anderson, Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women’s Health Initiative randomized controlled trial, *JAMA* 291(14) (2004) (“The WHI estrogen plus progestin trial was halted in July 2002 after a mean 5.2 years of follow-up because health risks exceeded benefits. Coronary heart disease (CHD), stroke, and venous thromboembolic disease were all increased in women assigned to active treatment with estrogen plus progestin. Breast cancer was also increased while colorectal cancer, hip fracture, and other fractures were reduced. The lack of benefit for CHD was supported by the Heart and Estrogen/progestin Replacement Study (HERS), which also tested CEE plus MPA in women with known coronary artery disease at baseline.”).

⁶ Ravdin PM, et al., The Decrease in Breast-Cancer Incidence in 2003 in the United States, *N Engl J Med* 2007; 356:1670-1674 (describing the negative impact the WHI trials had on prescriptions for commercially available hormone replacement therapies).

⁷ For further information, *see* the physicians’ and nurse practitioner statements attached hereto as Group Exhibit 1.

18. Neurodegenerative diseases (Alzheimer's, Parkinson's)		11. Musculoskeletal issues
19. Obesity		12. Ovarian cysts
20. Osteopenia/osteoporosis		13. Perimenopausal hormone deficits
21. Sexual health		14. Perimenopause
		15. Phase related to estrogen dominance and progesterone deficiency
		16. PMDD
		17. PMS
		18. Polycystic ovarian disease
		19. Post-TAH/BSO patients with estrogen dominant side effects
		20. Vaginal health

(c) FDA-Approved BHRT Drug Products Cannot Meet The Needs Of Every Patient.

FDA-approved BHRT drug products cannot meet the needs of every patient while compounded BHRT preparations are better suited to meet patient needs. As a threshold matter, it is important to understand that the nature of hormone therapy is idiosyncratic and, therefore, requires frequent blood test monitoring and symptom evaluation to ensure that patients are not only getting dosed correctly, but are absorbing the medication in the most effective way possible. All patients are different and, therefore, each patient has different sensitivities, tolerances, and reactions to hormone therapy that must be monitored throughout treatment so that dosages and/or combinations of hormones can be adjusted appropriately.⁸

FDA-approved BHRT drug products cannot accommodate the individualized nature of hormone therapy. Commercially available hormone therapies are not available in all dosage forms, strengths, and combinations required for treatment and, accordingly, many patients experience inconsistencies in treatment and unwanted side effects from these drugs. In addition, there are certain patient populations

⁸ Statement from Dr. Watson, Exhibit 1-Q (“All patients are different, and therefore each patient has different sensitivities, tolerances, and reactions to hormone therapy that must be monitored throughout treatment so that the dosages and/or combinations of hormones can be adjusted appropriately. The commercially available BHRT does not, in my experience and medical judgment, allow me to effectively treat my patients the same way and to the same degree to that of compounded BHRT.”); Statement from Dr. Strobel, Exhibit 1-O (“In my professional medical judgment, I prefer to treat my patients with compounded BHRT instead of the commercially available BHRT because hormone therapy requires a constant reassessment and adjustment of the hormone dose and the medication. It is impossible to treat patients with a one-size-fits-all hormone therapy treatment.”).

that simply cannot be treated by an FDA-approved BHRT drug.⁹ Physicians recognize the clinical utility of compounded BHRT to fill the gaps in treatment left by FDA-approved BHRT, and to provide for a more consistent, tailored manner of hormone treatment that significantly reduces, if not eliminates, common side effects.

(i) *Compounded BHRT Preparations Can Be Prepared In A Wider Variety of Dosage Forms, Strengths and Combinations.*

Compounding offers patients a variety of dosage strengths, forms, and combinations that would not otherwise be available to them if patients were relegated to only the commercially available hormone therapies. The following chart sets forth the dosage forms available in an FDA-approved BHRT drug product, compared to the dosage forms that can be prepared by a Section 503A compounding pharmacy or Section 503B compounding facility:

Dosage Form Available	Commercially Available BHRT Drug Products	Compounded BHRT Preparations
Oral	<ul style="list-style-type: none"> • Capsules (powder filled) • Capsules (oil based) • Tablets 	<ul style="list-style-type: none"> • Capsules (powder filled) • Capsules (lactose free) • Capsules, semi-solid filled • Capsules, oil-filled • Tablet triturates • Troches and mini-troches, soft • Troches and mini-troches, hard • Buccal tablets • Soft linguets • Liquids (syrups, suspensions, emulsions) • Sublingual drops (oil)
Vaginal	<ul style="list-style-type: none"> • Gel • Creams • Inserts • Rings • Tablets 	<ul style="list-style-type: none"> • Suppositories/inserts <ul style="list-style-type: none"> - Water-soluble - Lipid-soluble • Creams • Solutions (Poloxamer, etc.)
Topical/Transdermal	<ul style="list-style-type: none"> • Gels • Patches • Mini-patches (dots) • Topical emulsion • Spray solution 	<ul style="list-style-type: none"> • Creams • Gels • Microemulsion gels • Lotions, clear • Lotions, opaque • Lotions (aqueous, nonaqueous) • Suspensions
Injection	<ul style="list-style-type: none"> • Aqueous 	<ul style="list-style-type: none"> • Aqueous

⁹ Statement from Dr. Grant, Exhibit 1-G (describing how commercially available bioidentical micronized progesterone is contraindicated in patients with a peanut allergy because it contains peanut oil); Statement from Dr. Jacobs, Exhibit 1-H (describing how there is no commercially available bioidentical testosterone approved for treatment in women).

	<ul style="list-style-type: none"> Oils (sesame, castor) 	<ul style="list-style-type: none"> Nonaqueous (e.g., sesame oil, castor oil, grapeseed oil, CoSolvents)
Nasal	No commercially available option.	<ul style="list-style-type: none"> Drops Sprays Solutions Suspensions
Rectal	No commercially available option.	<ul style="list-style-type: none"> Enema <ul style="list-style-type: none"> - Gels - Suspensions - Emulsions

As is abundantly clear from the chart, patients can obtain compounded BHRT preparations in a much wider variety of dosage forms and combinations than those available to them from an FDA-approved BHRT drug product. Compounded BHRT preparations permit more choice, and can be prepared in a much more effective manner to better treat the patient population.

Moreover, with compounded BHRT preparations, medical providers are able to adjust and optimize a patient’s medication dosage forms and strengths rather than relegating their patients to cookie-cutter, commercially available BHRT drug products that do not work for them. For example:

- Progesterone** – FDA-approved bioidentical progesterone only comes in two dosage forms—an oral peanut oil-filled gel cap that cannot be titrated, or vaginal gel—whereas compounded progesterone can be prescribed in any strength and in any form needed to best treat the patient.¹⁰ Patients often require slight adjustments in strength of hormone therapy in order to receive the optimal benefits of therapy—the two commercially available progesterone products do not allow physicians to make these precise adjustments to the dosage strengths that are required in order to optimize treatment.¹¹ This is especially necessary because, in physicians’ experience, only approximately half of the patient population being treated with commercially available progesterone can tolerate the hormone because the side effects are so severe that they cause patients to discontinue treatment.¹² The side effects of commercially available progesterone include mood changes, headaches, nausea, bloating, menstrual cramps, fluid retention and irritability.¹³

¹⁰ Statement from Dr. Brownstein, Exhibit 1-C (describing the limitations in dosage form and strength of FDA-approved bioidentical progesterone and explaining a medical professional preference to treat patients with bioidentical progesterone compounded in a gel, cream, or troche depending on which form is best absorbed by the specific patient).

¹¹ Statement from Dr. Baker, Exhibit 1-A (“Safe and effective use of hormone therapy is idiosyncratic and requires ongoing reassessment of patient health, readjustment of hormone combinations, and readjustment of dosage strengths to effectively treat the patients that need this therapy.”).

¹² Statement from Dr. Peet, Exhibit 1-K (“Only approximately half of the patients treated with commercially available progestins can tolerate the hormone because the side effects are so severe that they cause patients to discontinue the treatment.”).

¹³ Statement from Dr. Peet, Exhibit 1-K (“The side effects of commercially available progestins include mood changes, headaches, nausea, bloating, menstrual cramps, fluid retention, and irritability.”); Statement from Dr. Grant, Exhibit 1-G (“Oral micronized progesterone in doses potent enough to protect the uterine endometrium, can give many patients CNS side effects, such as dizziness and fatigue.”); Statement from Dr. Strobel, Exhibit 1-O (describing the risks and side-effect profile of

Prometrium, in particular, is a commercially available progesterone medication available as an oral capsule. It contains sensitive oils that can denature the progesterone during shipping and delivery of the medication. Additionally, the capsule contains peanut oil, so those patients with peanut allergies cannot be treated with it.¹⁴ Finally, only approximately 80% of the patient population treated with Prometrium can tolerate the medication because of the side effects. If left to only Prometrium, approximately 20% of patients needing progesterone treatment would be left untreated without the availability of compounded forms of progesterone. On the other hand, compounded progesterone sublingual troches and oral capsules can be tolerated by the overwhelming majority of patients with no side effects.¹⁵

- **Estrogens** – There are a limited number of FDA-approved bioidentical hormone therapies containing estrogens and they are only approved in a few dosage strengths and forms. Women need estrogen doses adjusted constantly depending on life events and health changes. Oral estrogens represent the most frequently used route of administration but can produce wide ranges in serum levels due to the large variation in intestinal absorption and liver metabolism.¹⁶ As a result, medical providers cannot optimize patients’ estrogen status without the availability of compounded bioidentical estrogens, which allows them to tailor the dosage strength and dosage form. For example, many physicians prefer to treat their patients with estrogen compounded into a cream, gel, drops, troche, or a vaginal suppository, depending on what the individual patient can best absorb. Compounded Estrogen allows for changes in dosage forms while FDA-approved estrogen drug products cannot.¹⁷
 - **Estradiol** – One form of estrogen, Estradiol, is necessary for the treatment of postmenopausal patients. There are several options for Estradiol if the patient is under 60 years of age and healthy. However, in physician

commercially available progestin therapy); Statement from Dr. Warshowsky, Exhibit 1-P (describing how patients with a peanut allergy cannot tolerate commercially available progesterone).

¹⁴ Statement from Dr. Peet, Exhibit 1-K and Statement from Dr. Warshowsky, Exhibit 1-P (describing how the heat-sensitive oils in Prometrium can denature the progesterone).

¹⁵ Statement from Dr. Peet, Exhibit 1-K (“[O]nly approximately 80% of the patient population treated with Prometrium can tolerate the medication because of the progestin-type side effects.”); Statement from Dr. Jacobs, Exhibit 1-H (describing how commercially available progesterone is “not as well absorbed by patients and often cause negative side effects, such as abnormal bleeding and inadequate improvement of symptoms,” and how many patients better tolerate progesterone taken in different dosage forms); Statement from Dr. Baker, Exhibit 1-A (“Compounded progesterone in topical creams or oral troches are able to bypass many of these side effects.”).

¹⁶ J.P. Devogelaer et al., Long-term effects of percutaneous estradiol on bone loss and bone metabolism in postmenopausal hysterectomized women, 28 *Maturitas Journal of the Climacteric & Postmenopause* 243 (1998).

¹⁷ Statement from Dr. Grant, Exhibit 1-G (describing how, although bioidentical estrogens are commercially available in several dosage forms, these products are sometimes not absorbed or tolerated well by patients, which make the product ineffective with respect to that patient); Statement from Dr. Brownstein, Exhibit 1-C (“There are a limited number of FDA-approved bioidentical hormones therapies and they are only approved in a few dosage strengths. Women need estrogen doses adjusted constantly depending on life events and health changes.”); Statement from Dr. Stanger, Exhibit 1-N (describing how bioidentical estriol is not commercially available and therefore must be compounded in order to treat certain conditions like vaginal dryness).

experience, only approximately *half* of patients are able to absorb transdermal formulations.¹⁸ If the patient desires to continue transdermal administration, often a compounded, stronger version of the BHRT is required in order to appropriately treat the patient. Oral estradiol increases the risk of blood clotting disorders. Compounded transdermal estradiol and compounded estradiol in subcutaneous pellets reduce this risk as well as the risk of heart attack and stroke.¹⁹

Estrogel, in particular, is an FDA-approved bio-identical Estradiol topical gel that is typically prescribed to female patients in doses of one pump (1 gram) per day; however, most female patients require more than one pump to effectively treat their symptoms. Most patients cannot absorb two pumps (2 grams) of Estrogel in a consistent manner because of the amount of surface area on the body that the topical cream needs to cover. In these instances, physicians prescribe compounded bio-identical Estradiol in a more concentrated dose. With double the strength in one pump, patients get a better treatment that is tailored to what they actually need and their compliance with the prescribed dose is higher than if patients had to use two pumps of Estrogel each day.²⁰

- **Testosterone** – There are only a limited number of FDA-approved bio-identical testosterone dosage strengths, and there is no FDA-approved bio-identical testosterone for treatment in women alone, or in *both* men and women. Compounded testosterone allows physicians to not only effectively treat male and female patients, but allows them to adjust the dosage strength or combination of hormones slightly depending on the health status of the patient.²¹

Physicians prescribe compounded testosterone for women in creams, sublingual troches, and subcutaneous pellets. Compounded testosterone as a subcutaneous pellet, in particular, delivers more constant serum levels with fewer peaks and troughs compared to creams and troches. The vast majority of female patients being treated with compounded testosterone pellets for androgen deficiencies have all androgen deficiencies resolved without any side effects.²²

¹⁸ Statement from Dr. Strobel, Exhibit 1-O (“[O]nly approximately *half* of patients are able to absorb the transdermal formulations which means that the available strengths often are not sufficient.”).

¹⁹ Statement from Dr. Peet, Exhibit 1-K (describing the risks of blood clotting disorders such as deep vein thrombosis and risk of pulmonary embolism with oral estradiol).

²⁰ Statement from Ms. Farrell, Exhibit 1-F (describing the issues many patients experience with Estrogel).

²¹ Statement from Dr. Grant, Exhibit 1-G (“Currently, there are no bio-identical testosterone products available for women commercially. Therefore, custom compounded testosterone products are the only option available.”); Statement from Dr. Stanger, Exhibit 1-N (“[C]ompounded bio-identical testosterone is very important for women, as there is currently no bio-identical testosterone FDA-approved for treatment in women.”); Statement from Dr. Brownstein, Exhibit 1-C (“There are only a limited number of FDA-approved testosterone dosage strengths, and there is no FDA-approved testosterone for treatment in both men and women.”).

²² Statement from Dr. Peet, Exhibit 1-K (“prefer to prescribe compounded testosterone as a subcutaneous pellet because pellets deliver more consistent serum levels with less peaks and troughs compared to the creams and troches. The more peaks in serum levels cause more side effects (acne, abnormal hair growth, oily skin, fluid retention); the more troughs in serum levels means

Moreover, Androgel, the commercially available testosterone for men, does not absorb as well in male patients—rather, the serum levels spike too high and cause side effects or drop too low and are ineffective. The serum level spikes and troughs both occur within 24 hours of application of the gel. Similar risks are associated with commercially available injectable testosterone for men—the serum level spikes are too high and cause acne, hair loss, fluid retention, and elevated red blood cell count; or the serum level troughs are too low and are less effective. Accordingly, physicians prescribe compounded testosterone for men in creams and subcutaneous pellets, which deliver more consistent results with less side effects.²³

There are myriad other instances where the FDA-approved product does not adequately meet patient needs and compounded BHRT preparations are better suited for certain patient populations. Physicians recognize that compounded BHRT preparations more effectively treat their patients and, accordingly, consistently prescribe compounded BHRT preparations as part of their overall treatment regimen.

In addition to obtaining a more tailored approach, compounded BHRT preparations also promote patient compliance. It is worth considering that patients treated with the synthetic hormones contained in FDA-approved drug products suffer severe side effects such as weight gain, cognitive issues, and acne, which often leads to patient non-compliance with hormone therapy. Patients will often simply not refill their prescription once they experience these side effects.²⁴ With compounded BHRT preparations, physicians can perform blood tests on their patients and adjust their medications over time during the course of treatment to ensure that patients receive the most precise dosage forms and strengths tailored to their needs and current circumstances.²⁵ Compounded BHRT preparations tailored to the patient eliminate the side effects associated with synthetic hormones and, accordingly, ensure patient compliance with treatment protocols.²⁶

(ii) *Compounded BHRT Preparations Cannot Go Through New Drug Approval*

It is important to note that compounded BHRT preparations cannot go through new drug approval. As set forth in the attached physician statements, in order to appropriately treat patients with hormone medications, a physician will first perform a blood test on a patient, and then, once those results are

the treatment is less effective.”); Statement from Dr. Jacobs, Exhibit 1-H (describing how having the ability to treat patients with compounded pellet therapy avoids the peaks and troughs of absorption often caused by treatment with transdermal creams and troches).

²³ Statement from Dr. Peet, Exhibit 1-K (describing the serum level issues he has observed in patients being treated with Androgel).

²⁴ Statement from Dr. Rice, Exhibit 1-M (“When patients were treated with synthetic hormones, they suffered severe side effects such as weight gain, cognitive issues, and acne, which often led to patient noncompliance with the hormone therapy. Specifically, patients would return often having never refilled their prescription after the first prescription fill.”); Statement from Dr. Stanger, Exhibit 1-N (“The more tolerable the medication, the greater the patient compliance with the treatment regimen.”).

²⁵ Statement from Dr. Jacobs, Exhibit 1-H (“With compounds, I am able to perform blood tests on my patients every 5-6 weeks to evaluate and reevaluate how the patients is responding to the hormone therapy.”); Statement from Dr. Stanger, Exhibit 1-N (describing how her standard of practice is to evaluate blood tests on patients every three months to once a year, which allow her to consistently monitor hormone levels of patients and adjust hormone treatment dosages accordingly); Statement from Dr. Brownstein, Exhibit 1-C (describing how compounded BHRT is necessary to be able to make “precise adjustments to the dosage strengths that are required in order to optimize treatment.”).

²⁶ Statement from Dr. Rice, Exhibit 1-M (describing side effects associated with synthetic hormone treatment).

obtained, prescribe compounded BHRT in the dosage form and strength tailored to the patient's needs. That patient is then monitored throughout the course of treatment and the physician will make tweaks to the compounded BHRT preparation based upon the patient's continued progress. As a result, compounded BHRT preparations are prescribed in a myriad of different combinations, dosage forms and strengths.

There is no way, accordingly, that all of the different dosage forms, strengths and combinations of compounded BHRT preparations can go through new drug approval. New drug approval takes millions of dollars and years of clinical study before a new drug makes its way to market. New drug approval does not allow for incremental changes in medication over the course of treatment. Each change to a compounded BHRT preparation is in a small amount and may be different depending on what a patient's blood test shows. Physicians are, in essence, responding in real time to the patient's needs. The new drug approval process does not allow for this kind of real-time changes in personalized treatment. As a result, the only way for most patients in need of hormone therapy to obtain the appropriate medication to fit their needs is through compounding.

(iii) *FDA-Approved BHRT Drug Products Cannot Treat All Patients And Patient Conditions*

Finally, there are not enough FDA-approved BHRT drug products on the market today to address the myriad patient populations and disease states that would benefit from hormone therapy. First, we note that FDA-approved hormone therapies are designed for, and approved to, treat certain disease states and are not, in fact, manufactured for hormone replacement therapy. Thus, the nature of compounded BHRT medications are fundamentally different than those of FDA-approved drug products and the hormone treatment protocol they achieve serves a fundamentally different medical purpose.

Thus, not only do compounded BHRT preparations allow for more choice with respect to the nature, dosage form and strength of the drug product, but compounded BHRT preparations are vital to treat conditions that are not addressed by the FDA-approved BHRT products on the market today. For example:

- **Testosterone** – There is no commercially available bioidentical testosterone approved for women. Women with low bone density, weight gain, loss of energy, hot flashes, night sweats, depression, and sleep issues benefit from testosterone treatment. Many women must resort to self-treatment with their husband's testosterone, which is not appropriately dosed for female patients. As a result, physicians regularly prescribe compounded bio-identical testosterone to resolve low libido, sleep issues, and bone mass deficiency in female patients. The compounded bio-identical formula is safer for female patients than using the commercially available testosterone for men.²⁷
- **Combination Testosterone + Progesterone + Estrogen** – There is no FDA-approved combination testosterone, progesterone, and estrogen product, therefore, the only way a patient may be treated with this combination is via a compounded form of the

²⁷ Statement from Dr. Dorr, Exhibit 1-E (“In my professional medical experience, I have witnessed many female patients that require testosterone treatment and, as a result, are relegated to self-treating with their husbands’ testosterone, which is dosed as male ranges and is unsafe for self-treatment by women.”); *see also* Statement from Dr. Jacobs and Statement from Dr. Strobel, Exhibits 1-H and 1-O respectively, discussing the issues prevalent with no commercially available bioidentical testosterone approved for treatment in women.

medication. Physicians prescribe this combination of bioidentical hormones to treat menopausal symptoms, depression, anxiety, bone health issues, urinary problems, and andropause (in men only).²⁸

- **Combination Progesterone + Testosterone** – There is no FDA-approved combination testosterone and progesterone product. Therefore, the only way to obtain this combination is via a compounding facility. Physicians prescribe combination testosterone and progesterone in creams or gels depending on how their patients absorb the therapy. Such compounded combinations are prescribed to treat menopause, depression, anxiety, bone health issues, and brain dysfunction.²⁹

In fact, there are entire patient populations that can only be treated with compounded BHRT preparations. These include (1) patients with allergies; (2) patients who cannot use specific dosage forms (*i.e.* cannot swallow, pediatric, skin conditions, gut issues, etc.) and (3) patients who cannot tolerate side effects of commercially available hormone therapies.³⁰ Without the availability of compounded BHRT preparations, thousands of patients will needlessly suffer simply because they cannot be effectively treated by the commercially available BHRT drug products available today.

II. Compounded BHRT Preparations Are Safe, Effective And Do Not Present Demonstrable Difficulties For Compounding Consistently.

The Coalition understands that one of the primary concerns the Committee must consider is not simply that compounded BHRT preparations are necessary for treatment, but also that they are safe and effective. The Coalition wishes to assure the Committee that compounded BHRT preparations are indeed safe and effective, and do not present demonstrable difficulties to compound consistently.

(a) Compounded BHRT Preparations Are Known To Be Safe and Effective.

As is evident from the physicians' and nurse practitioner's statements accompanying this submission, and contrary to the narrative put forth by certain presenters to the Committee, compounded BHRT preparations have been shown to be consistently safe and effective for patients in a wide variety of circumstances that require hormone therapy. There is, in fact, no evidence of a pattern of "adverse events" associated with compounded BHRT preparations, nor is there a basis to assert that they are unsafe or an ineffective treatment for a variety of conditions.

²⁸ Statement from Dr. Brownstein, Exhibit 1-C (describing the forms in which he prescribes compounded combinations of bioidentical testosterone, progesterone, and estrogen and for which conditions in his female patients because there is no commercially available bioidentical combination of these hormones).

²⁹ *Id.* (describing the forms in which he prescribes compounded combinations of bioidentical testosterone and progesterone and for which conditions in his female patients because there is no commercially available bioidentical combination of these hormones).

³⁰ See Statements from Dr. Grant, Dr. Jacobs, Dr. Peet, Dr. Warshowsky, Exhibits 1-G, 1-H, 1-K, and 1-P respectively, which discuss how commercially available bioidentical progesterone is contraindicated in patient populations that suffer from a peanut allergy, and how many side effects of commercially available bioidentical hormone therapies cannot be tolerated by patients.

As a threshold matter, Section 310.305(b) defines a “serious adverse drug experience” to mean: Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity, or
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include

- allergic bronchospasm requiring intensive treatment in an emergency room or at home;
- blood dyscrasias or convulsions that do not result in inpatient hospitalization; or
- the development of drug dependency or drug abuse.

21 U.S.C. § 310.305(b). The Coalition is not aware of serious adverse drug experiences associated with compounded BHRT preparations that would fall within the definition above.³¹ Many purported risks associated with compounded BHRT preparations, moreover, are misleading or completely false.³²

Nevertheless, to the extent there is ever an event that falls within “serious adverse drug experience,” it will be reported to FDA. Section 503B outsourcing facilities must, pursuant to statute, submit adverse event reports to FDA. 21 U.S.C. § 353b(b)(5). Failure to report such events is a violation of the FDCA. Likewise, although Section 503A of the FDCA does not expressly require traditional compounders to report serious adverse drug experiences to FDA, FDA is required to have enhanced communications with the States and state regulatory bodies about concerns raised, or actions taken, against compounding pharmacies. 21 U.S.C. § 105. One of the ways FDA intends to pursue this communication is through the *Memorandum of Understanding Addressing Certain Distributions of Compounded Drug*

³¹ We note that recently FDA reported that during a routine inspection in 2018 of BioTE Medical, FDA investigators uncovered information about 4,202 alleged adverse events that had *never* been reported to the Agency. See Sept. 9, 2019 FDA Statement *On Improving Adverse Event Reporting of Compounded Drugs to Protect Patients*, <https://www.fda.gov/news-events/press-announcements/statement-improving-adverse-event-reporting-compounded-drugs-protect-patients>. These “adverse events” were not events that fell within the definition of “serious, life threatening or unexpected adverse drug experience” that would have required reporting to FDA. Rather, these “adverse events” were physicians’ feedback to BioTE- which is a training organization. The overwhelming majority of this feedback described predictable and expected outcomes such as extrusions, cellulitis and hematomas and should not be construed as an indication that there is a public health risk associated with compounded BHRT.

³² Statement from Dr. Pierce, Exhibit 1-L (discussing certain example of treatment with hormone therapy and how the treatment’s alleged links to health risks are patently false).

Products Between the States and the Food and Drug Administration wherein States will agree to notify FDA of any complaint relating to a compounded preparation distributed outside the State involving a serious adverse drug experience or serious product quality issue and provide information about those events and issues. In addition, many States have similar adverse event reporting requirements, and both consumers and physicians are able to file MedWatch reports with FDA at any time with respect to a complaint about a compounded BHRT preparation. Thus, there are ample ways in which FDA will remain apprised of adverse events associated with compounded BHRT preparations.

Finally, even beyond the general lack of evidence to suggest that compounded BHRT preparations are unsafe or ineffective, both physician and patient experiences demonstrate that compounded BHRT preparations are safe and improve peoples' lives:

- **Allan B. Warshowsky, M.D., FACOG, ABIHM³³** – Dr. Warshowsky is a board certified OBGYN who treats his patients with compounded BHRT instead of commercially available BHRT because compounded BHRT has proven to be a more effective treatment option for his patients. Many of Dr. Warshowsky's female patients come to him already being treated with commercially available BHRT that does not work for them – that is, they are not being fully treated, they are not able to tolerate the side effects, and they do not feel like they are getting better. In Dr. Warshowsky's experience, when he switches his patients from commercially available BHRT to compounded BHRT, these patients' health improves, their symptoms resolve, and they suffer far less negative side effects;
- **Gennell DeAn Strobel, M.D., FACOG³⁴** – Dr. Strobel is a board certified OBGYN who treats many of her patients safely and successfully with compounded BHRT in ways that she is not able to do with commercially available BHRT. In Dr. Strobel's medical opinion, "one-size-fits-all" commercially available BHRT cannot relieve many of her patients' symptoms in the way that compounded BHRT can and does.

Dr. Strobel has witnessed huge improvements in patient conditions when using compounded BHRT—for example, one patient told her that, "she had not been able to have intercourse or even wear panties or slacks for over 9 years and was able to resume these activities happily after 6 months of therapy!"³⁵ Once Dr. Strobel began treating the many breast cancer survivor patients with compounded BHRT, Dr. Strobel "quickly realized the impact of this treatment when women (and their spouses) literally cried tears of joy when they 'felt like a woman again' because they were able to enjoy intimacy again. Women would also tell [her] that their sleep, energy, hot flashes, moods, and many other aspects of life were improved as well."³⁶

Dr. Strobel has treated thousands of menopausal and perimenopausal patients and, in her medical experience, very few women have complete resolution of their menopausal and perimenopausal symptoms with commercially available hormone therapy. This data is drastically different with compounded BHRT which, in Dr. Strobel's

³³ See Statement from Dr. Warshowsky, Exhibit 1-P.

³⁴ See Statement from Dr. Strobel, Exhibit 1-O.

³⁵ *Id.*

³⁶ *Id.*

experience, resolves over 80% of these symptoms, and over 90% if sterile subcutaneous compounded pellets are used;

- **David Watson, M.D., FACOG**³⁷ – Dr. Watson is a board certified OBGYN who treats many of his patients with compounded BHRT because he witnesses “near immediate improvement in these patients’ overall health”—a degree of treatment effectiveness he did not see with conventional, commercially available hormone therapies.³⁸ For example, Dr. Watson routinely witnesses severe osteopenia and osteoporosis completely reversed in patients after appropriate treatment with compounded BHRT. Dr. Watson also routinely sees his patients using less and less additional medication after being treated with compounded BHRT. That is, once taking compounding BHRT, these patients no longer need to rely on mood stabilizers, erectile dysfunction medication, or diabetes medication.

Moreover, in Dr. Watson’s medical experience, compounded BHRT reduces the risks associated with commercially available BHRT and, therefore, is a safer alternative. Specifically, when treating a patient with compounded BHRT testosterone pellets, in Dr. Watson’s experience, the hormone is absorbed into the bloodstream and bypasses the liver, which results in a 70% reduction in breast cancer risk in patients where pellet therapy was the right dosage form. It is Dr. Watson’s medical opinion that “compounded BHRT is real, it is effective, and it should be here to stay;”³⁹

- **John Joseph Peet, M.D., FACOG**⁴⁰ – Dr. Peet is a board certified OBGYN who treats over 5,000 patients effectively with compounded BHRT. In Dr. Peet’s medical experience, compounded BHRT is an effective hormone treatment option and “[a]pproximately 90-95% of [his] male and female patients treated with some form or combination of compounded BHRT have their symptoms completely resolved.”⁴¹

Further, compounded BHRT is a safe, and often safer, alternative to commercially available BHRT. In Dr. Peet’s medical experience, compounded transdermal estradiol and compounded estradiol in subcutaneous pellets actually reduce the risk of heart attack and stroke when compared to the commercially available form. Similarly, compounded progesterone sublingual troches and oral capsules can be tolerated by 99% of his patients with absolutely no side effects—a sharp contrast, in his medical experience, to the side effects suffered by his patients when being treated with the commercially available form;

- **Laura Grant, M.D., NCMP**⁴² – Dr. Grant is a board certified OBGYN who has specialized in menopausal hormone therapy for the past 12 years. In Dr. Grant’s medical experience, her patients treated with compounded BHRT describe the therapy

³⁷ See Statement from Dr. Watson, Exhibit 1-Q.

³⁸ *Id.*

³⁹ *Id.*

⁴⁰ See Statement from Dr. Peet, Exhibit 1-K.

⁴¹ *Id.*

⁴² See Statement from Dr. Grant, Exhibit 1-G.

as “life saving,” because “their quality of life would be so poor that it would not be worth living” if they were not treated with compounded BHRT.⁴³

It is Dr. Grant’s medical opinion that commercially available BHRT does not adequately treat her patients due to “ineffectiveness, non-toleration of side effects, insufficient dosages options to relieve symptoms, lack of variety in dosage and routes of administration, and complete non availability of testosterone.”⁴⁴ Dr. Grant states, “my medical practice will be significantly hindered without the compounded hormone option, and female patients will be very poorly served to see this option removed. When the patient . . . returns to her ob/gyn or PCP for a better solution than the commercial product given, and the doctor responds, ‘That’s your only choice, take it or leave it.’ I believe that we, as professionals entrusted with the care of midlife women experiencing life altering menopausal symptoms, can do a better of job, and we must not be hobbled in trying to do so.”⁴⁵

- **Bruce Dorr, M.D., FPMRS**⁴⁶ – Dr. Dorr is a board certified OBGYN who treats his patients with compounded BHRT because it is an effective hormone therapy treatment option for his patients. Dr. Dorr finds that “it is effectively impossible to treat patients with a one-size-fits-all hormone therapy treatment.”⁴⁷ Compounded BHRT is also a safer alternative to commercially available BHRT—for example, compounded BHRT in pellet form is much safer for patients with a history of blood clotting, such as deep vein thrombosis or pulmonary embolus;
- **Steven A. Komadina, M.D.**⁴⁸ – Dr. Komadina is a board certified OBGYN and New Mexico State Senator who switched to treating his patients with compounded BHRT because he witnessed the health of his patients significantly and quickly improve at rates that he had not previously seen with commercially available BHRT. In Dr. Komadina’s experience, his patients better tolerate compounded BHRT and demonstrate more consistent results from treatment with compounded BHRT. In Dr. Komadina’s medical judgement, if he had to return to treating patients with only commercially available BHRT, “I know that I would witness a decline in my patients’ health and wellbeing.”⁴⁹
- **Arlene Jacobs, M.D.**⁵⁰ – Dr. Jacobs is a board certified OBGYN whose patients simply feel better on compounded BHRT. In Dr. Jacobs’ medical opinion, compounded BHRT “is a safer treatment as there is no risk of clotting and compounded BHRT carries far less side effects.”⁵¹ Further, compounded bioidentical hormone therapies

⁴³ *Id.*

⁴⁴ *Id.*

⁴⁵ *Id.*

⁴⁶ See Statement from Dr. Dorr, Exhibit 1-E.

⁴⁷ *Id.*

⁴⁸ See Statement from Dr. Komadina, Exhibit 1-I.

⁴⁹ *Id.*

⁵⁰ See Statement from Dr. Jacobs, Exhibit 1-H.

⁵¹ *Id.*

bypass the liver and are safer for patients who have suffered a stroke or some form of blood clot; and

- **Christine Farrell MS.N, F.NP.-C**⁵² – Ms. Farrell is a credentialed nurse practitioner who successfully treats approximately 90-95% of her patients with compounded BHRT. It is Ms. Farrell’s professional opinion that compounded BHRT “is safer and more effective for patients requiring hormone therapy” than the commercially available BHRT options.⁵³

As is evident from the above, and the other physicians’ statements attached hereto, compounded BHRT preparations are safe and effective, and patients experience better health outcomes when using compounded BHRT preparations than they do when taking commercial BHRT drug products.

(b) Compounded BHRT Preparations Do Not Present Demonstrable Difficulties For Compounding.

The Coalition understands that Jane Axelrad of Axelrad Solutions, LLC has suggested that the Committee consider whether compounded BHRT preparations are demonstrably difficult to compound in order to inform its assessment of whether compounded BHRT preparations are safe and effective. As a threshold matter, the purpose and scope of this Study does not contemplate an analysis of whether compounded BHRT preparations are demonstrably difficult to compound. That is for FDA to determine in accordance with the parameters set forth in the FDCA. Accordingly, the Committee should not consider this issue for purposes of its Report.

Nevertheless, to the extent the Committee wishes to tackle the demonstrably difficult analysis, the Coalition maintains that compounded BHRT preparations do not present demonstrable difficulties for compounding such that the difficulties are reasonably likely to lead to an adverse effect on the safety or effectiveness of that drug product. The Coalition has a wealth of data to demonstrate that compounded BHRT is not demonstrably difficult to compound—and will provide it upon request. To the extent that the Committee does believe this analysis is integral to whether compounded BHRT is safe and effective, it should examine this data before coming to any conclusion. Without this data, the Report would be incomplete. The Coalition further notes that if the Committee is truly considering a detailed analysis on this subject, then a separate meeting is necessary to fully address this issue.

By way of background, both Section 503A and Section 503B of the FDCA require compounded drugs to satisfy several conditions in order to be entitled to certain statutory exemptions under the FDCA. Section 503A prohibits traditional compounders from compounding a drug product if it “presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product.” 21 U.S.C. § 353a(b)(3)(A). Similarly, one of the conditions for compounding under Section 503B is that the drug cannot be on a list published by the Secretary of drugs or categories of drugs “that present demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs, taking into account the risks and benefits to patients,” and that the drugs are compounded in accordance with “conditions that are necessary to prevent the drug or category of drugs from presenting [such]

⁵² See Statement from Ms. Farrell, Exhibit 1-F.

⁵³ *Id.*

demonstrable difficulties.” 21 U.S.C. § 353b(a)(6). Both Section 503A and 503B require FDA to develop a list of difficult to compound drugs through regulations, which means notice and comment rulemaking.

FDA has solicited nominations for the difficult to compound list(s), and several nominations submitted so far include hormone products, namely: estradiol (oral and topical); progesterone (oral and topical); progesterone with estradiol (oral and topical); testosterone pellets; and estriol (dosage form not specified).⁵⁴ FDA intends to consider a set of six criteria when considering whether a drug product is demonstrably difficult to compound. As set forth below, the six criteria do not support the conclusion that compounded BHRT preparations, including those already nominated, are demonstrably difficult to compound.

(i) *Complexity of the Formulation.*

One of the first considerations in determining whether a compound presents demonstrable difficulties is whether the formulation of the compound is complex. FDA has stated that a complex formulation refers to formulations in which the ingredients (both active and inactive) “are required to have certain physicochemical characteristics or properties that are necessary to achieve or maintain the proper performance of the drug product.”⁵⁵ In addition, “the compatibility and/or stability (physical and chemical) of the API(s) and/or excipients in the final dosage unit may be evaluated to determine if the compounded drug product has a complex formulation.” FDA has particularly focused on particle size and the concern that, if particle size distribution is not maintained, there will be changes in absorption both topically and orally.

First, with respect to compounded BHRT preparations, both Section 503A and Section 503B facilities that compound BHRT preparations have a wealth of stability and potency data demonstrating that compounded BHRT preparations are consistently stable over time. Compounders understand the importance of BHRT formulations that enable proper performance of the drug product, which must include optimal absorption within patients.⁵⁶

Second, compounders understand that particle size in the context of hormone therapy is critical. There will always be variability in the particle size of a drug product. However, compounders have many tools available to them to deal with particle size distribution. For example, compounders can use a mortar and pestle to grind bulk ingredients into more uniform distributions. This is a traditional method that effectively reduces the particle size. Compounders also have mixers, blenders, and milling devices that can increase particle distribution while ensuring consistency of particle size. For example, an Unguator is a mixer that can be used for various preparations based upon time and RPM settings. An Unguator prepares uniform particle distribution consistently and repeatedly, ensuring uniform particle distribution that can aid in performance of the compound. A Ram or Resodyn Acoustic mixer delivers formulations within the FDA RSA value, actual results 3%. Compounders also use SpeedMixers and Mazerustar®

⁵⁴ Please note that Abraham Morgentaler, M.D., who originally nominated testosterone pellets for the difficult to compound list, has expressed his intention to withdraw the nomination. His statement regarding his decision to withdraw compounded testosterone pellets from the difficult to compound nomination process is attached hereto as Exhibit 2.

⁵⁵ See PDF of Presentation by Jane Axelrad to NASEM: Understanding the List of Difficult to Compound Drug Products, June 27, 2019.

⁵⁶ The Coalition has access to a wealth of data demonstrating stability and can provide the same to the extent the Committee wishes to review the data.

planetary mixers, which provide fast and thorough mixing and deaeration simultaneously. Finally, an ointment mill can reduce particle size of a compounded preparation to under 20 microns using sheer force to reduce particle size. This equipment can be calibrated to ensure consistency over time. Overall, pharmacists can rely on equipment to aid in the particle distribution, prohibit agglomerate formation and employ particle size reduction with equipment at their disposal.⁵⁷

As a result, the complexity of the formulation for compounded BHRT does not render them too difficult to compound.

(ii) *Complexity of the Drug Delivery Mechanism.*

FDA has stated that the complex drug delivery mechanism “refers to the way in which the drug is released from the dosage form or targeted for delivery in the body to achieve the desired therapeutic effect, such as passing through the stomach without dissolution and absorption or achieving permeation through the skin at a specific rate.” Arguments suggesting that compounded BHRT preparations have a complex drug delivery mechanism include that estradiol, progesterone and testosterone must be administered using specific dosage forms to enable complex drug delivery and absorption mechanisms for GI transport, or for transdermal or vaginal transport. In addition, it is purported that since reproductive hormone API is highly lipophilic, formulations employing hard and soft gelatin capsules, which contain water, need to be carefully characterized to ensure water migration into fill material does not result in API precipitation, from conversion or particle size growth to the extent it changes the product performance, and safety and efficacy, over the shelf-life of the product.

These characterizations are inaccurate. Hormone pellets, for example, are compounded in a mechanism that has been around since the 1950s. Compressed pellets have been clinically shown to absorb at a rate consistent with clinical data being presented to the Committee. In addition, there is an approved drug with this mechanism in a singular strength that does not meet all patient needs. Likewise, with respect to micronized powder capsules, De Lignières found in 1999 that administration of oral progesterone micronized powder capsules as part of an HRT regimen in post-menopausal women is effective at preventing estrogen dependent endometrial stimulation.⁵⁸ Several pharmacokinetic studies have shown relatively consistent AUC, Cmax, and Tmax values.

In addition, proponents of placing compounded BHRT preparations on a difficult to compound list argue that many of the same concerns also apply to the oral and vaginal dosage forms which require sophisticated knowledge of the various delivery and absorption mechanisms and their designs, including the thickness, surface area, and water content of the dosage form, and the chemical structure of the mechanism of release from hard-gelatin capsules, tablets and soft gel capsules, or other lipid and crystalline based vehicles, such as pellets or suppositories. In a study carried out in 1999 by Ken Burry, “[s]ignificant increases in serum concentrations of progesterone were observed in all of the women studied.”⁵⁹ Furthermore, in a study at the University of Sao Paulo, researchers found that compounded

⁵⁷ The Coalition can provide the Committee with supportive data if so desired.

⁵⁸ De Lignières B. Oral micronized progesterone. *Clin Ther.* 1999;21(1):41-60. doi:10.1016/S0149-2918(00)88267-3; Maxson WS, Hargrove JT. Bioavailability of oral micronized progesterone. *Fertil Steril.* 1985;44(5):622-626. doi:10.1016/S0015-0282(16)48977-6.

⁵⁹ *Am J Obstet Gynecol* 1999;180:1504-11.

vaginal progesterone prophylactically reduced the frequency of uterine contractions and the rate of preterm delivery in women at high risk for prematurity.⁶⁰

Accordingly, the Coalition maintains that the complex delivery systems (e.g., oral capsules compounded without allergenic oils or pelleted hormones) affirmatively do not present demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product.

(iii) *Complexity of the Dosage Form.*

The third factor FDA intends to consider is whether the physical dosage units of the compounded BHRT preparations present characteristics that are difficult to consistently achieve and maintain. In doing so, it intends to consider the “container closure systems that may interact with the compounded drug and affect its intended use, either through physical (inconsistent dose administration) or chemical interactions between the compounded drug and the container closure system.”

As set forth in the chart provided in Section I(c)(i) above, compounded BHRT preparations can be prepared in a wider range of dosage forms than the commercially available alternatives. Nevertheless, while compounding allows for bioidentical hormones to be available to patients in a variety of physical dosage units, the characteristics of these dosage units are not too difficult to consistently achieve or maintain when performed in an appropriate environment and with equipment that can ensure consistency and safety.

Arguments that compounded BHRT preparations have complex dosage forms appear to lean towards water absorption from capsules causing degradation. First, the Coalition is not aware of any compounders that use water progesterone capsules dosed orally. Second, while this can be an issue for manufacturers where the drug products have expiration dates, but not for compounded products which employ beyond use dates. Compounding pharmacies employ lab services to test preparations to ensure stability and potency. Hormone pellets, for example, are made with dry active pharmaceutical ingredients (no water) compressed with only two ingredients. Full stability indicating stability studies ensure analytical testing identifies degradants and other parameters consistent with GMP level stability methods.

Accordingly, the variety of dosage forms available for compounded BHRT preparations does not make compounded BHRT too difficult to compound

(iv) *Complexity of Achieving Bioavailability.*

It is possible to ensure bioavailability of compounded BHRT preparations. FDA states that bioavailability refers to “the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.” The Coalition understands that compounded preparations may be considered too difficult to compound if bioavailability is too challenging to achieve because of certain characteristics of the API or of the compounded formulation, such as low permeability and/or low solubility. However, that is not the case with compounded BHRT

⁶⁰ If the Committee wishes to see the underlying data, the Coalition will make that data available for review.

preparations. Numerous studies show that progesterone micronized powder capsules show appropriate bioavailability.⁶¹ Hormone pellets show bioavailability from actual patient results achieved in well over a million pellet insertions and can be verified through the thoughts of physicians utilizing the therapy and from clinical studies. In addition, please see the enclosed synopses of studies with regard to absorption and bioavailability for compounded BHRT preparations.⁶²

Moreover, sometimes systemic absorption bioavailability is not something that is desired in treatment. Estriol vaginal cream preparations can take care of vaginal dryness and atrophy without endometrial lining build up or systemic elevation by dosing at 0.5mg daily and then reducing to 0.5mg twice weekly. A review of data from 1950 to 1994 Voojis determined that single daily intravaginal estriol treatment dosages clearly and consistently demonstrate that endometrial proliferation does not occur. They further concluded that single-day estriol treatment binding to the endometrial estrogen receptor is too short to induce proliferative effect.

Finally, there is recent data to support that hormone pellets have achieved bioavailability.⁶³

Accordingly, as the data shows, it is possible to ensure bioavailability of compounded BHRT preparations.

(v) *Complexity of the Compounding Process.*

As described by FDA, “[c]ompounding process complexity refers to whether compounding the drug requires multiple, complicated, or interrelated steps and/or specialized facilities and/or equipment to achieve the appropriate drug product.”

Compounding performed by the members of the Coalition, which is performed according to the conditions set out in Section 503A and Section 503B of the FDCA, is done within specialized facilities using specialized equipment. For example, Section 503A compounders use SpeedMixers and Section 503B outsourcing facilities use Mazerustar® planetary mixers, which provide fast and thorough mixing and deaeration simultaneously. Achieved through continually revolving and rotating the container concurrently, the unique dual rotation action eliminates the need for mixing rods, blades or media, or an evacuation device and can dramatically reduce processing times.⁶⁴ Likewise, compounders can use a mortar and pestle, mill, blender, and/or automated sieving device to grind bulk ingredients into more

⁶¹ Maxson WS, Hargrove JT. Bioavailability of oral micronized progesterone. *Fertil Steril.* 1985;44(5):622-626. doi:10.1016/S0015-0282(16)48977-6; Handelsman D, Machev MA, Howe C, Turner L, Conway AJ. An analysis of testosterone implants for androgen replacement therapy. *Clinical Endocrinology.* 1997; 47, 311-315; Handelsman D, Conway AJ, Boylan L. Pharmacokinetics and Pharmacodynamics of Testosterone Pellets in Man. *Journal of Clinical Endocrinology and Metabolism.* 1990; 70, 216-221; De Lignières B. Oral micronized progesterone. *Clin Ther.* 1999;21(1):41-60. doi:10.1016/S0149-2918(00)88267-3.

⁶² Synopses of studies regarding absorption and bioavailability for compounded BHRT preparations, enclosed herein as Exhibit 3.

⁶³ F. Jockenhovel, E. Vogel, M. Kretzer, W. Reinhardt, S. Lederbogen and D. Reinwein, Pharmacokinetics and pharmacodynamics of subcutaneous testosterone implants in hypogonadal men, *Clinical Endocrinology* (1996) 45, 61-71.

⁶⁴ Dual Action Revolution & Rotation Mixers, Technic, <https://www.technic.com/equipment/parts-supplies-accessories/mazerustar-planetary-mixers> (last visited November 7, 2019).

uniform distributions. Compounder also has mixers, such as Unguator, Ram or Resodyn Acoustic mixers, and ointment mills.

Overall, there is nothing about the compounding process for BHRT that is too complex such that it is reasonably likely to lead to an adverse effect on the safety or effectiveness of the preparation.

(vi) *Complexity of the Physicochemical or Analytical Testing.*

Finally, there is sufficient release testing conducted that proves that compounded BHRT preparations are what they purport to be. FDA has stated that the physicochemical or analytical testing complexity “refers to the challenges presented with confirming the drug product will perform as expected with regard to certain characteristics.” It is possible to test compounded BHRT preparations to ensure that they will perform as they are expected to perform, and many compounding facilities have the testing and data to support this.

USP and FDA set guidelines for testing compounded preparations. For Section 503A compounding pharmacies, these guidelines are set forth in USP quality assurance Chapter <1163> and Chapters <795> and <797>. FDA, in turn, has established cGMP requirements for 503B outsourcing facilities. According to analytical labs testing hormones, there is simplicity in testing due to hormones being small molecules with a good chromophore that allow for easy HPLC-UV detection. HPLC-UV is the most commonly used instrument in lab testing for small molecule drugs. No specialized instruments such as nuclear magnetic resonance, mass spectrometry, or x-ray powder diffraction are required in the testing of hormone substances. Compounders, whether they are Section 503A or 503B facilities, have access to independent lab services for microbial identification, potency/purity, sterility, particulate matter, and bioburden testing, including ARL Laboratories, DynaLabs, Eagle Labs, James River Labs, and Avomeen Laboratory.

In addition, with respect to Section 503A compounding pharmacies, underlying testing data supports the conclusion that compounded BHRT preparations are stable over time and are not too difficult to compound. Topical hormone studies, for example, show stability. Studies demonstrate that the compounding preparations are stable at the outset, and that the stability is maintained over time even in combination with multiple BHRT active ingredients. Compounded BHRT preparations prepared by Section 503B outsourcing facilities, in turn, are not too difficult to compound under cGMP. As shown by Product Annual Reviews (a requirement to comply with cGMP), important characteristics of stability, container closure, and related data demonstrates the safety and efficacy of compounded BHRT preparations. Studies show that compounded BHRT can be prepared safely and effectively, again and again over time.⁶⁵

In sum, although the Committee *should not* consider this issue for purposes of its Report, the Coalition maintains that compounded BHRT preparations do not present demonstrable difficulties for compounding such that the difficulties are reasonably likely to lead to an adverse effect on the safety or effectiveness of that drug product.

⁶⁵ If the Committee wishes to see the underlying data, the Coalition will make that data available for review.

III. Conclusion

The Coalition appreciates the attention of the Committee and hopes that this submission has contributed to the discussion regarding the clinical utility of compounded BHRT preparations. As set forth herein, the evidence supports finding that:

- (1) compounded BHRT preparations are clinically necessary to treat the patient population;
and
- (2) compounded BHRT preparations are safe, effective and do not present demonstrable difficulties to compound.

As stated, although we understand that the Committee will be conducting a hearing on the Study on November 12, 2019, we respectfully request that the Coalition be granted a separate meeting with the Committee to present key experts and answer any questions the Committee may have. We look forward to hearing from you soon.

Very truly yours,

/s/ Rachael G. Pontikes

Rachael G. Pontikes

RGP:rl

Enclosures

Group Exhibit 1

Exhibit 1-A

IMMANUEL CLINIC

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Springdale, AR 72762

(P) 479-756-3251 (F) 479-756-9186

Statement from Jeffrey R. Baker M.D. M.S.

Qualifications

My name is Jeffrey R. Baker, M.D., M.S. My professional background is as follows. I received my Bachelor of Arts in Chemistry and Biology from Point Loma College in San Diego, California in 1978. I received my Masters of Science in physiology and immunology in 1980 and my Doctor of Medicine from Oral Roberts University School of Medicine in 1984. I completed my residency in Family Practice at the University of California Irvine Memorial Medical Center from 1984 to 1987, where I also served as Chief Resident of Family Practice in 1987. During residency, I practiced at Kaiser-Harbor City, California Urgent Care and Promptcare Urgent Care in Huntington Beach, California. My up to date CV is enclosed for reference.

I received certifications from the National Board of Medical Examiners and the American Board of Family Practice. I received the ABFP-Certificate of Added Qualification in Sports Medicine from 1993-2003. I have been licensed to practice medicine in Arkansas since 1997.

I have held numerous organization leadership positions. I was the Resident Physician Member of the American Academy of Family Physicians National Board of Directors from 1986-1987, the Delegate to the AAFP National Congress of Delegates from 1985-1987, the California AAFP Board of Directors in 1987, the San Diego AAFP Board of Directors from 1989-1994, the President of the San Diego County AAFP from 1992-1993, the Executive Committee Graybill Medical Group from 1989-1995, the Executive Committee Palomar Medical Center from 1991-1994, the Chairman-Steering Committee for the Formation of the Department of Family Practice at Palomar Medical Center from 1991-1993, and the Board of Directors Palomar-Pomerado Medical Associates (IPA) from 1993-1994.

I have been in continuous private practice from 1987-present. During that time, I worked at Graybill Medical Group in Escondido, California in family practice, specifically inpatient care including ICU and surgery, and I worked in outpatient primary care and sports medicine from 1987-1997. I have also practiced Emergency Medicine and in-patient hospitalist duties at the V.A. Medical Center in Fayetteville, Arkansas from 1998 to present.

Presently, I work in outpatient primary care and integrative medicine at the Immanuel Clinic in Springdale, Arkansas, a position I have held since 1997.

Experience With Treatment Of Compounded Bio-Identical Hormone Therapy

I treat approximately 900 patients annually in settings where compounded Bio-Identical Hormone Therapy (“BHRT”) for male and female patients is a part of therapy, and the large majority of these patients are successfully prescribed and treated with BHRT using a compounded therapy solution.

Medical Conditions and Patient Populations Treated with Compounded BHRT

I prescribe compounded BHRT to treat male and female patients of all ages depending on their individual symptoms. I prescribe compounded BHRT to treat andropause in male patients, and I prescribe compounded BHRT to treat various conditions and symptoms in teen through adult female patients. Specifically, I prescribe compounded topical creams, oral troches, oral capsules, vaginal creams, injectable testosterone and implantable pellets to treat the following conditions:

- Phase-related estrogen dominance and progesterone deficiency
- Perimenopausal hormone deficits
- Menopausal and post-menopausal hormone support therapy
- Disease-specific therapy for PCOS, fibrocystic breast disorder, endometriosis, ovarian cysts, fibroids, and cervical dysplasia

I prescribe compounded bioidentical hormone therapy to treat the above conditions in female patients because routinely available pharmaceutical options either lack necessary ingredients, or more commonly, do not have the manufactured dosage ranges required to individualize therapy.

Additionally, I prescribe individualized compounded progesterone in topical or oral forms for the management of post total abdominal hysterectomy with bilateral salpingo-oophorectomy (“TAH/BSO”) patients with estrogen dominant side effects.

When applicable, compounded BHRT is prescribed to achieve normal peri and post-menopausal ranges of progesterone and androgen levels and can add to the comprehensive management strategy when fibromyalgia, chronic pain, and/or musculoskeletal issues are present.

Why is Compounded BHRT Preferred Over Commercially Available BHRT?

In my professional medical judgment, the primary reason I choose to treat my patients with compounded BHRT instead of commercially available BHRT is the ability to individualize treatment, which is critical in hormone therapy. It is my professional medical opinion that the treatment needs of the patient population I see are too diverse to be treated by the current dosing forms of commercially available hormone therapies. Even if FDA were to approve more BHRT dosing forms in the future, these treatments would still not be tailored enough to meet the variety of hormone treatment needs of the majority of my patients. Safe and effective use of hormone therapy is idiosyncratic and requires ongoing reassessment of patient health, readjustment of hormone combinations, and readjustment of dosage strengths to effectively treat the patients that

need this therapy. Commercially available BHRT simply cannot be individualized to the extent it would need to be in order to treat these patients.

Additionally, non-enteral forms of delivery can be especially important for hormone therapy. Hormone metabolites are a common etiology for side effects and complications of oral therapy. Compounded progesterone in topical creams or oral troches are able to bypass many of these side effects. The use of compounded estriol can moderate the side effects of estradiol only therapy and can significantly reduced the estrogen dominant side effects that contribute to patient non-compliance with prescribed hormone therapy as well as some of the immediate to long term therapy complications, which can include fibrocystic breast disorder, fibroids, endometriosis and also the exaggeration of the 16 (OH) estrone/2 (OH) estrone ratios which have been proposed to promote pro-proliferative effects related and possibly predisposing to female reproductive cancers.

Finally, compounded BHRT allows me to properly address and resolve androgen deficiencies in female patients. The only available testosterone for treatment in women is found in one of two fixed estradiol/methyltestosterone formulations, which I avoid because: (1) oral forms of testosterone delivery promote adverse liver metabolites and (2) having only two dosing formats essentially negates appropriate individualized therapy for the majority of patients, making compounded testosterone the only reasonable option for treating androgen deficiencies in female patients.

Thank you for the opportunity to represent the medical concerns regarding continued availability of individually compounded BHRT for the many thousands of patients nationwide for whom these forms of therapy has been life changing.

Sincerely,

/s/ Jeffrey R. Baker, M.D., M.S.

Jeffrey R. Baker M.D. M.S.

Born: December 24, 1955

Married: Penne Baker Five children: 21-30 years of age

Undergraduate degree:

Point Loma College San Diego, CA

Double major Chemistry and Biology B.A 1974-78

Postgraduate Degrees:

Oral Roberts University-School of Medicine Tulsa OK

M.S. Physiology and Immunology 1978-80

M.D. Doctor of Medicine 1980-84

Residency Training

University of California Irvine Memorial Medical Center

Family Practice Residency 1984-87 Chief Resident-Family Practice 1987

Certifications:

National Board of Medical Examiners 1984

American Board of Family Practice 1987, 1993 and 2000

ABFP-Certificate of Added Qualification in Sports Medicine 1993-2003

Licensed in California 1985-1997

Licensed in Arkansas 1997-present

Organizational Medicine

American Academy of Family Physicians (AAFP) 1984-2007

Fellow of the AAFP 1991

California Chapter AAFP 1984-1997

Arkansas AAFP 1998-2000

California Medical Association 1987-1997

Arkansas Medical Society 1998-2000

San Diego County Medical Association 1987-1997

Washington County. AR Medical Society 1998-2000

American College of Sports Medicine 1990-2003

American College for the Advancement of Medicine 1990-present

Organizational Leadership:

-Resident Physician Member of the American Academy of Family Physicians
National Board of Directors 1986-87

-Delegate to the AAFP National Congress of Delegates 1985-87

-California AFP Board of Directors 1987

-San Diego AFP Board of Directors 1989-94

-President San Diego County AFP 1992-93

-Executive Committee Graybill Medical Group 1989-1995

-Executive Committee Palomar Medical Center 1991-94

-Chairman-Steering Committee for the formation of the Department of
Family Practice at Palomar Medical Center 1991-93

-Board of Directors Palomar-Pomerado Medical Associates (IPA) 1993-94

Occupational Experience

During residency:

-Kaiser-Harbor City, CA Urgent Care 1985-87

-Promptcare Urgent Care Huntington Beach, CA 1985-87

During private practice years 1987-2017:

-Graybill Medical Group Escondido, CA

-Family Practice, inpatient care including ICU and surgery 1987-1995

-Family Practice, outpatient primary care and sports medicine 1995-1997

-Immanuel Clinic Springdale, AR Outpatient primary care and Integrative
Medicine 1997-present

-V.A. Medical Center Fayetteville, AR

-ER physician and in-patient hospitalist 1998-2015

-ER physician 2016-present

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Exhibit 1-B



Statement From Dr. George Benson Branning, M.D.

Qualifications

My name is Dr. George Benson Branning, M.D. My professional background is as follows. I received my Bachelor of Arts in biology and microbiology from the University of Texas at Austin in 1983. I received my Doctor of Medicine at the University of Texas Southwestern Medical Center of Dallas in 1989. I completed my residency in obstetrics and gynecology at Baylor University Medical Center Dallas from 1989 to 1993, and I was Chief Resident from 1992 to 1993.

After residency, I worked as an attending physician at Baylor University Medical Center, Dallas from 1993 to 2008. In 2009 I moved my practice to Baylor Medical Center at Frisco (now Baylor, Scott and White Medical Center of Frisco), where I worked as the Chief of Staff from 2011 to 2012, and I worked as the Medical Director of Obstetrics from 2016 to 2017. Currently, I am a board-certified OBGYN in my solo practice, Texas Gynecology. I predominantly practice at Baylor, Scott and White Medical Center of Frisco. I no longer practice obstetrics and have dedicated my practice of medicine to gynecology, minimally invasive surgery, hormone balancing and aging, nutrition, sexuality, and overall human wellness.

I have numerous professional memberships. I am a fellow of the American College of Obstetrics and Gynecology and a Diplomate of the American Board of Obstetrics and Gynecology. I am a member of the Texas Medical Association, the Society of Laparoendoscopic Surgeons, the American Association of Gynecologic Laparoscopy, the Collin County Medical Association, the Dallas Ft. Worth Obstetrics and Gynecology Society, the Southwestern Gynecologic Assembly, and the Institute of Functional Medicine. For further information on my clinical interests and practice, please see my enclosed CV.

Experience With Treatment Of Compounded Bio-Identical Hormone Therapy

As stated above, I have dedicated my practice in part to hormone therapy, which includes treating my patients with compounded bioidentical hormone replacement therapy (“BHRT”). I treat approximately 100 patients per month and all of them are being treated with some form of compounded BHRT. Approximately 90-95% of my patients being treated with compounded BHRT experience symptoms resolution, and patient compliance is near 100% with compounded BHRT options.

Medical Conditions and Patient Populations Treated with Compounded BHRT

I prescribe compounded BHRT to treat a variety of medical conditions and symptoms in my male and female patients. Specifically, I prescribe compounded BHRT to treat the following:

Male Patients

- ADD-like symptoms
- Cognition fog
- Gain of fat mass
- Hypogonadism
- Loss of muscle mass
- Low libido
- Profound lack of energy
- Suboptimal testosterone levels

Female Patients

- ADD-like symptoms
- Cognition fog
- Loss of muscle mass
- Low libido
- Menopause symptoms (e.g., profound and abrupt drop of hormone levels, hot flashes, vaginal dryness, sexual dysfunction, and increase weight, among others)
- Problems with lipids
- Profound lack of energy
- Suboptimal testosterone levels (prior to menopause)
- Weight gain

Why is Compounded BHRT Preferred Over Commercially Available BHRT?

In my professional medical judgment, I choose to treat my patients with compounded BHRT, where appropriate, instead of the commercially available BHRT, because compounded BHRT allows me to tailor critical hormone therapy to the individual needs of my patients. Compounded BHRT is important therapy because it mimics the way the ovary or the testicle makes the hormone. In my professional opinion, the biggest issue with FDA-approved BHRT is the inadequate nature of the dosing, and the unacceptable variance allowed in generics. In addition, some patients have issues with the adhesives with patches and as a result experience contact dermatitis, or will show significant absorption variability from one patient to the next with creams. These dosage forms may be the only option commercially available. Compounding allows me to treat the patient with both the dosage *strength* and dosage *form* that is best tolerated and best absorbed by the individual patient. In other words, I can trust the modern compounding pharmacy with dose, purity, and quality control that most optimally treats my patients for the conditions from which they suffer.

- **Testosterone**

I prescribe compounded bioidentical testosterone, typically in pellet form, for my male and female patients. Again, pelleted delivery mimics the gonad's delivery of testosterone. The commercially available bioidentical testosterone that is available as a cream is an issue for patients because each patient absorbs a cream differently, and the biochemistry is difficult to gauge. Additionally, patients must be careful with cross-contamination of testosterone creams, as touching or hugging partners, children, or pets, can unintentionally spread the medication to them. In my professional medical opinion, FDA-approved commercially manufactured testosterone is provided in too small a dose for optimization.

Creams also do not correspond with the same consistent serum absorption levels that are achieved with compounded pellet therapy. Compounded pellet therapy avoids the daily or weekly

rollercoaster of absorption that comes with testosterone creams, gels, patches, or injections. However, I want to note that depending on the specific patient needs (for example, in premenopausal women), compounded testosterone in cream form may be most appropriate and effective for that patient. I have found that pelleted delivery of the appropriate dose of compounded testosterone is preferred by the majority of my patients because of the success rate in treatment of the patient's symptoms and medical conditions.

Compounded testosterone is absolutely necessary to treat my female patients because there is no commercially available bioidentical testosterone approved for treatment in women. When I treat my female patients, I use a compounding pharmacy to compound bioidentical testosterone and bioidentical estradiol into a single dose consisting of their custom amount of compounded bioidentical testosterone in pellet form, and there is no commercially available option for this treatment for women.

- **Estradiol**

I prescribe compounded bioidentical estradiol in pellet form because of the sustained absorption levels that can be achieved that are not available in FDA-approved bioidentical estradiol options. Because of the sustained estradiol level, I am able to reduce patients' FSH levels to below menopausal levels, thus protecting them from, and often reversing, osteopenia or osteoporosis. This reduces the significant amount of fracture injuries found in osteoporosis patients. Only compounded estradiol pellets give the patients sustained levels of estradiol for months at a time, which is preferred by the body.

- **Progesterone**

I prescribe compounded bioidentical progesterone to female patients who still have a uterus and who are receiving estrogen in some form. In my professional medical opinion, female patients are most successfully treated with progesterone in a compounded oral pill. In my professional medical opinion, the increased risk of DVT and breast cancers with synthetic oral progestins (to be distinguished from the molecule progesterone) is unacceptable. Commercially available bioidentical generic progesterone creates too great of a variance in my patients. Generics are allowed 20% variance in the active ingredient by the FDA. In my professional medical experience, I saw too much vaginal bleeding when using generic micronized progesterone to offset the estradiol in patients with a uterus. However, when I prescribe the same dose of compounded bioidentical progesterone, these patients experience far less bleeding in the same situation.

Sincerely,

/s/ Dr. George Benson Branning, M.D.

George Benson Branning, M.D.

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Profile

Born in Miami, Florida February 12, 1960

Dr. Branning has three children: Caroline, Addison and Benson

Practice Experience

Baylor Medical Center at Frisco 2005-Present

Baylor Medical Center at Frisco 2016-2017
Medical Director, Obstetrics

Baylor Medical Center at Frisco
Chief of Staff 2011-2012

Baylor University Medical Center, Dallas 1993-2008
Attending Physician

Managing Partner of Texas Obstetrics and Gynecology Associates, PLLC

Residency

Baylor University Medical Center Dallas 1989-1993
Department of Obstetrics and Gynecology
Chief Resident 1992-1993

Medical Education

Medical Doctor 1985-1989
University of Texas Southwestern Medical Center of Dallas

Undergraduate Education

The University of Texas at Austin 1980-1984
Bachelor of Arts in Biology and Microbiology

Memberships

Fellow of the American College of Obstetrics and Gynecology
Diplomate of the American Board of Obstetrics and Gynecology
Texas Medical Association
Society of Laparoendoscopic Surgeons
American Association of Gynecologic Laparoscopy
Collin County Medical Association
Dallas Ft. Worth Obstetrics and Gynecology Society/Past President
Southwestern Gynecologic Assembly
Institute of Functional Medicine

Clinical Interests

Advanced Endoscopic Surgical Techniques
Minimally Invasive Surgery
Advancements in Contraception and Sterilization
daVinci Robotic Surgical Systems
Hormone Balancing and Aging
Human Sexuality as it pertains to Wellness

Dr. Branning no longer practices Obstetrics. He has dedicated his practice of medicine to gynecology, minimally invasive surgery, hormone balancing and aging, nutrition, sexuality, and overall human wellness.

Exhibit 1-C

**Center for Holistic Medicine
6089 W. Maple Rd. Ste. 200
West Bloomfield, MI 48323**

Statement From David A. Brownstein, M.D.

Qualifications

My name is David A. Brownstein, M.D. My professional background is as follows. I received my Bachelor of Science in Psychology from the University of Michigan in 1989 and received my Doctorate of Medicine degree from Wayne State University School of Medicine in 1989. I conducted my residency at Providence Hospital Family Practice Residency in Southfield, Michigan from 1989 to 1992, during which time I also received a diploma from the National Board of Medical Examiners. Following my residency, I became a Diplomate of the American Board of Family Practice in 1992, 1998, 2006, and 2016. In 2006, I graduated from the Desert Institute School of Classical Homeopathy in Phoenix, Arizona. I am currently a Board-Certified family physician at the Center for Holistic Medicine in West Bloomfield, Michigan.

I have served as the Medical Director of the Center for Holistic Medicine since 1999. Prior to that, I served as a staff physician at the Detroit Medical Center from 1993-1999 and the staff physician for the Specialists in Family Practice from 1992-1993. I worked in the Emergency Room at Providence Hospital from 1991-1994. I have had numerous other affiliations, such as with the Center for Holistic Medicine, the American Academy of Preventive Medicine, the Omni Care Physician Ad Hoc Committee for Preventative Medicine, the American Academy of Medical Acupuncture, the American Academy of Family Physicians, and the Journal of Comprehensive Integrative Medicine, among many others. For a full list of all affiliations, please see my enclosed CV. I received the 2005 American College for the Advancement in Medicine Norman E. Clarke Sr. Award for Science and Practice and the 2005 ARC Excellence Award for Distinguished Clinician for his "Advancement in the Diagnosis and Treatment of Chronic Diseases" from the American Academy of Integrative Medicine.

Presently, I am a Clinical Assistant Professor of Medicine at the Wayne State University School of Medicine. I have been appointed to that position since 2016 and will remain in that role until 2021. Previously, I was appointed as a Clinical Assistant Professor of Internal Medicine at Wayne State University School of Medicine from 1999 to 2004.

Throughout the years, I have lectured internationally to physicians and other industry members about my success in using natural hormones and nutritional therapies in my practice. For example, I have served as a lecturer for the NAET Annual Symposium, PCCA Functional Endocrinology Symposium, Women's International Pharmacy, International College of Integrative Medicine, the American Holistic Medical Association, Thyroid Support Group, and Innovative Therapy Services. I am the author of 15 books including *The Miracle of Natural Hormones*, *Overcoming Arthritis*, *Overcoming Thyroid Disorders*, and *Iodine: Why You Need It, Why You Can't Live Without It*. For a full recitation of all presentations given and publications authored, please see my enclosed CV.

Experience with Treatment Of Compounded Bio-Identical Hormone Therapy

I am one of the foremost practitioners of holistic medicine. I have over 25 years of experience treating my patients with compounded Bio-Identical Hormone Therapy ("BHRT"). Of

all the patients I treat, approximately 80% of them are being treated with compounded BHRT because, in my professional medical judgment, commercially available BHRT is not an effective treatment option for these patients. My medical experience has proven that when compounded BHRT is prescribed appropriately and when patients comply with the treatment plan, not only is the treatment effective, but it also has an excellent safety record.

Medical Conditions and Patient Populations Treated with Compounded BHRT

I treat a variety of medical conditions in my male and female patients with compounded BHRT. Of the 80% of my patients that I treat with compounded BHRT, approximately 70% are female patients and approximately 30% are male patients. The table below represents some of the medical conditions that my patients present with and that are effectively treated by compounded BHRT.

Male Patients

- Adrenal dysfunction
- Adrenopause
- Anxiety
- Cardiovascular Disease / Coronary Heart Disease
- Decline in brain dysfunction and complaints of being “unable to think”
- Depression
- Heart disease/failure
- Insomnia

Female Patients

- Adrenal dysfunction
- Anxiety
- Cardiovascular Disease / Coronary Heart Disease
- Decline in brain dysfunction and complaints of being “unable to think”
- Depression
- Heart disease/failure
- Insomnia
- Menopause symptoms (e.g., hot flashes, low libido)

Why is Compounded BHRT Preferred Over Commercially Available BHRT?

In my professional medical judgment, I prefer to treat my patients with compounded BHRT instead of the commercially available BHRT because hormone therapy requires individualized treatment and a constant reassessment and adjustment of the hormone dose and the medication—it is effectively impossible to treat patients with a one-size-fits-all hormone therapy treatment.

First and foremost, the commercially available BHRTs do not contain all the bioidentical hormones and in enough of a variety of dosage strengths and forms necessary to optimize treatment for patients. Specifically, as set out below, I utilize compounding pharmacies to compound certain bioidentical hormones and certain combinations thereof because there is no commercially available bioidentical option to treat my patients.

• Progesterone

FDA-approved progesterone only comes in two dosage strengths and is only available in an oral pill or vaginal gel, whereas compounded progesterone can be prescribed in any strength and in any form needed to best treat the patient. I prescribe progesterone compounded in a gel,

cream or troche, depending on what works best for my patients. Some patients absorb better from a cream while others do best with a gel. I prescribe compounded progesterone to treat menopausal symptoms, bone health issues, brain disorders including depression and anxiety, fatigue, chronic fatigue syndrome, and fibromyalgia. My patients often require slight adjustments in strength of hormone therapy in order to receive the optimal benefits of therapy—the two commercially available progesterone products do not allow me to make these precise adjustments to the dosage strengths that are required in order to optimize treatment.

- **Estrogens**

There are a limited number of FDA-approved bioidentical hormones therapies and they are only approved in a few dosage strengths. Women need estrogen doses adjusted constantly depending on life events and health changes. I am not able to optimize my patient's estrogen status without the availability of compounded bioidentical estrogen. I prefer to treat my patients with estrogen compounded into a cream, gel, drops, troche, or a vaginal suppository, depending on what the individual patient can best absorb. Often, in my professional experience, I have patients switch from a cream to a gel or a suppository, as their health and medical conditions change—the FDA-approved estrogens do not allow me to treat patients in this way. I prescribe compounded estrogens to treat menopause, vaginal dryness, urinary tract problems, depression, anxiety, and bone health.

- **Testosterone**

There are only a limited number of FDA-approved testosterone dosage strengths, and there is no FDA-approved testosterone for treatment in both men and women. Compounded testosterone allows me to not only effectively treat my male and female patients, but allows me to adjust the dosage strength or combination of hormones slightly depending on the health status of my patients. I typically prescribe compounded testosterone in creams, gels, or injectables depending on how my patient best absorbs the therapy. I prescribe compounded testosterone to treat menopausal symptoms, muscle disorders, depression, anxiety, bone health, fibromyalgia, chronic fatigue syndrome, and andropause (in men only).

- **Combination Testosterone + Progesterone + Estrogen**

There is no FDA-approved combination testosterone, progesterone, and estrogen product, therefore, the only way I can get this product to treat my patients is from a compounding facility. I prescribe compounded testosterone, progesterone, and estrogen in creams, gels, and oral troches depending on what my individual patient best absorbs. I prescribe this combination of bioidentical hormones to treat menopausal symptoms, depression, anxiety, bone health issues, urinary problems, and andropause (in men only).

- **Combination Progesterone + Testosterone**

There is no FDA-approved combination testosterone and progesterone product. Therefore, the only way I can get this product to treat my patients is from a compounding facility. I prescribe combination testosterone and progesterone in creams or gels depending on how my patients absorb the therapy. I prescribe this combination of hormones to treat menopause, depression, anxiety, bone health issues, and brain dysfunction.

Finally, it has been my experience that patients prefer the individualized treatment they receive from compounded BHRT treatment. Patients cannot obtain a personalized treatment plan using commercially available BHRT. As stated above, hormone therapy requires a constant reassessment of a patient's hormone levels, which requires patients to frequently have their blood tested so that the prescriber can evaluate how effective the medication is on each individual patient. This may then require me to write a new prescription for a different dose or a different combination of therapies to be compounded by a compounding pharmacy. My medical opinion is clear: the readjustment of the dose and therapies cannot be done with commercially available BHRT, and therefore without compounded BHRT, thousands of patients will be forced to go without the medication that best treats their individual medical conditions and they will suffer.

Sincerely,

A rectangular box containing a handwritten signature in black ink. The signature is written in a cursive style and appears to read "Dr. [unclear]".

CURRICULUM VITAE

David A. Brownstein, M.D.
6890 W. Maple Rd. Suite 200
West Bloomfield, MI 48322
(248) 851-1600 (P)
(248) 851-0421 (F)

EDUCATION:

Graduate: Desert Institute of Classical Homeopathy. 1.16.06. Phoenix, Az.
Diplomate, American Board of Family Practice –July, 1992, July 1998, July, 2006
Providence Hospital Family Practice Residency - July, 1989 - June, 1992
Diplomate, National board of Medical Examiners - July, 1990
Wayne State University School of Medicine - M.D., June, 1989
University of Michigan - B.S., psychology, May, 1985. Graduated with distinction.
Graduate, Desert Institute School of Classical Homeopathy. Phoenix, Arizona. 2005-2006.
Diplomate. American Board of Family Practice. July, 2006
Diplomate American Board of Family Practice July, 2016

PUBLICATIONS:

Author: ***The Miracle of Natural Hormones***, 1998. 152pp. Medical Alternatives Press.
Author: ***The Miracle of Natural Hormones 2nd Edition***, 1999. 204pp. Medical Alternatives Press.
Author, The Physician's Page Newsletter for the Road Back Foundation, Vol. 4, No. 3, Hormones and Chronic Disease, August, 1999
Principal Investigator in Research study: The Effect of a Gamma Oryzanol Formulation on insulin-like Growth Factor-1 in Volunteers, by David Brownstein et al. To be published.
Principal Investigator in Research study: The Effects of Flax Seed Oil and Glucobalance on Lowering Triglyceride Levels, by David Brownstein et al. To be published.
Principal Investigator in research study: NAET, A Novel Treatment for Allergies, By David Brownstein, et al. Submitted for publication.
Author: ***Overcoming Arthritis***, 2000. 252 pp. Medical Alternatives Press.
Author: ***Overcoming Thyroid Disorders***, 2002. 276pp. Medical Alternatives Press.
Author: ***The Miracle of Natural Hormones 3rd Edition***, 2003. 282 pp. Medical Alternatives Press
Article for Thyroid News, December, 2003.
Author: ***Iodine, Why You Need It, Why You Can't Live Without It***. 2004. Medical Alternatives Press.
Author: ***Salt Your Way To Health***. 2005. Medical Alternatives Press.
Article: Smart Life Forum Newsletter. November, 2005.
Article: <http://www.bellaonline.com/site/thyroidhealth>. Salt: Dietary Villain or Foundation of Health?

Author: The Saliva/Serum Iodide Ratio as an Index of Sodium Iodide Symporter Efficiency. The Original Internist. Vol. 12., No. 4. Winter 2005.
Author: Validation of the Orthiodosupplementation Program: A Rebuttal of Dr. Gaby's Editorial on Iodine. The Original Internist. Vol. 12., No. 4. Winter 2005.
Quoted in article "Sorting Out Salt". Better Nutrition. June 2007.

Author: *Iodine, Why You Need It, Why You Can't Live Without It, 2nd Edition.* 2006. Medical Alternatives Press.

Author: *Guide to Healthy Eating.* Medical Alternatives Press. 2006.

Author: The Saliva/serum iodide ratio as an index of sodium iodide symporter efficiency. The Original Internist. Vol. 12, No. 4 . Winter, 2005.

Author: Celtic Sea Salt: Shattering the Myths of One of Nature's Most Helpful Nutrients. VRP Newsletter. Feb, 2006. Vol. 20, No. 2. VRP.com

Author: Iodine; The Final Story. VRP News. Vol. 20, No.4. April, 2006.

Interviewed for Newsletter article in Health Letter, Japan. May 2006.

Interviewed for article "Shake It Up" in Alternative Medicine. September. 2006.

Author: Health Letter, Japan. October, 2006

Author: *Drugs That Don't Work and Natural Therapies That Do.* Medical Alternatives Press. 2007

Author: Refined vs. Unrefined Salt. Well Being Journal. Vol. 16, No. 3. May/June 2007

Author: Iodine Why You Need It Why You Can't Live Without It, 3rd Edition. Medical Alternatives Press. 2007

Overcoming Thyroid Disorders, 3rd Edition. Medical Alt. Press. 2008

Editor: Dr. Brownstein's Natural Way to Health Newsletter. First Edition May, 2008

Interviewed for Crusader Magazine Issue 45 Nov/Dec 2008. Iodine Article

Interview for Crusader Magazine Issue 46 Jan/Feb 2009 Salt Article

Author: Iodine Why You Need It, Why You Can't Live Without It, 4th Edition, 2009

Author: Iodine Deficiency. VRP News. March, 2009.

Author: Whole Blood Concentrations of Elemental Silver. The Original Internist. Vol. 16, No.1. March 2009.

Co-Author, Op-Ed in Wall Street Journal, "The Truth about Hormone Therapy". 3.16.09

Author: *The Guide to a Dairy-Free Diet.* Medical Alternatives Press. 2009

Author: Drugs That Don't Work and Natural Therapies That Do, 2nd Edition. Medical Alternatives Press. 2009.

Article for Newsmax Magazine, March 2010. "No To Low-Salt Diets."

Author of Monthly Newsletter, *Dr. Brownstein's Natural Way to Health.* 2008-present

Author: Are you salt deficient? Caduceus. Issue 79. 2010

Author: **The Soy Deception**, 2011

Author: **Vitamin B12 for Health**, 2012

Author: **The Skinny on Fats**, 2014

Author: **The Statin Disaster** 2015

Author: **Ozone: The Miracle Therapy.** 2016

Author: **Heal Your Leaky Gut.** 2017

FACULTY APPOINTMENT:

Clinical Assistant Professor of Internal Medicine, Wayne State University School of Medicine, 1999-2004

Clinical Assistant Professor of Medicine, Wayne State University School of Medicine, 2016-2017, 2018-2021

AFFILIATIONS:

Medical Director, Center for Holistic Medicine, 1999

Research Committee, Nambudripods Allergy Relief Foundation, 1998

Nambudripods Allergy Relief Foundation, member 1996- present

Member Board of Examiners for American Academy of Preventive Medicine - 1996

American Academy of Preventive Medicine member - 1996-present

Physician Reviewer for Physician's Review Organization of Michigan- 1995-present

American Academy of Medical Acupuncture associate member, 1993 - present

Member Joint Family Practice Advisory Committee for credentialing family physicians

Detroit Medical Center 1995-present

Member expert panel for Omni Care Physician Ad Hoc Committee for preventative medicine - 1996

Acupuncture Society of Michigan member 1995 - present. **Board of Trustees** 1995. **Vice President** 1996, **President**, 1997.

American Academy of Medical Acupuncture member, 1995-present

American Academy of Family Physicians member, 1985 – present

Peer Review of Michigan (PROM) reviewer: 2001-present

Editorial Board: Journal of Comprehensive Integrative Medicine. 2014-present

AWARDS:

2005 American College for the Advancement in Medicine Fall 2005 Norman E. Clarke Sr. Award for Science and Practice. Long Beach, California. December, 2005

2005 ARC Excellence Award for Distinguished Clinician for his "Advancement in the Diagnosis and Treatment of Chronic Diseases." From American Academy of Integrative Medicine. West Palm Beach, FL. December, 2005

PRESENTATIONS:

Guest lecture for NAET Symposium for Doctors, Buena Park, CA. 1997

Guest lecture for NAET Symposium for Doctors, Buena Park, CA. 1998

Guest lecture, American Holistic Medical Association, Sterling Heights, MI, April, 1998

Guest lecture for Fairview Hospital Women's Health Day. Cleveland, Ohio, September, 1998

Featured guest on Adrienne Selko radio show, Cleveland, OH, October, 1998

Guest lecture for Broda O. Barnes, M.D. Research Foundation, Stamford, CT, October 1998.

Guest lecture for Selko Communications Holistic Medicine for the 21st Century, Cleveland, OH, February, 1999

Lecture to Wayne State University School of Medicine, April, 1999

Guest lecture for Carrot Country GNC, Brandon, FL, May 1999

Guest lecture for American Association of Podiatric Physicians and Surgeons Annual Seminar, May, 1999

Guest lecture, Holistic Medicine for the 21st Century, West Bloomfield, MI, June 1999

Guest lecture for NAET Symposium for Doctors, Buena Park, CA, July 1999
Guest lecture for Thyroid Support Group, Plymouth, MI, September 1999
Guest lecture for Temple Beth El Health and Fitness Wellness 2000, November 1999
Guest lecture for Michigan Holistic Nurses' Association, January, 2000
Guest lecture for Wellness Seminar, Maumee, Ohio, February, 2000
Guest lecture for Michigan Chiropractic Society annual Meeting, Lansing, Michigan, February, 2000
Guest lecture for Innovative Therapy Services, Indianapolis, IN, March, 2000
Guest Lecture for The Road Back Foundation, Los Angeles, CA, March, 2000
Guest Lecture for Hadassah, West Bloomfield, MI April, 2000
Lecture to Wayne State University School of Medicine 4th Year Medical Students, April 7, 2000
Radio Interview for AM WKHB 600 AM Impact on Health, Pittsburgh, PA, May 24, 2000
Guest Lecture Gilda's Club, Royal Oak, MI, May 25, 2000
Guest Lecture Pituitary Disorder and Endocrine Support Group, West Bloomfield, MI , Nov, 2001
Lecture Broda O. Barnes, M.D. Research Foundation, Stamford, CT February, 2002
Lecture Wayne State University School of Medicine 4th Year Medical Students, April, 2002
Lecture Michigan Society of Infection Control Spring Conference, Lansing MI, April, 2002
Interview Mary Shomon, About.Com Web site, July, 2002
Lecture for Women's International Pharmacy, Madison, Wisconsin. Sept, 2002
Lecture Broda Barnes M.D. Research Foundation, Stamford, CT, Sept, 2002
Lecture Scleroderma Foundation, Troy, Michigan, Sept., 2002
Lecture: International College of Integrative Medicine, Dallas, Tx. April, 2003
Lecture: NAET Annual Symposium, Kauai, Hawaii, July 2003
Lecture: Broda Barnes, M.D. Research Foundation. Stamford, CT. September, 2003.
Lecture Nutraceutical Group, San Francisco, CA. April 2004
Lecture: Medical Alternatives Press, Novi, MI April, 2004
Lecture: Henry Ford Community College, Dearborn, MI April, 2004
Lecture: Orlando, Fl. National Advanced Practice Conference. April 15, 2004
Testimony to Human Rights and Wellness Subcommittee, Wash. D.C. July 22, 2004
Broda O. Barnes, M.D. Research Foundation, Sept, 2004. Stamford, CT.
Lecture to NFWL, Sarasota, Fl. Nov, 2004
Lecture to ProServ. Orlando, FL, Jan. 2005
Institute for Health Resources, Marquette, Michigan. April, 2005. Marquette, MI
Lecture: PCCA Functional Endocrinology Symposium. August, 2005. Houston, TX.
Lecture: Genesis Health Systems. October, 2005, Grand Blanc, MI.
Lecture: Novi Sheraton Hotel. Natural Therapies That Work. October, 2005. Novi, MI.
Lecture: Greensborough, NC. October 15, 2005. Biotics Research.
Lecture: Broda O. Barnes, M.D. Research Foundation. October 21-22, 2005. Stamford, CT.

Lecture: ACAM. November 11, 2005. Anaheim, CA.
Lecture: American Academy of Anti-Aging Medicine. December 10, 2005. Las Vegas, NV.
Lecture: Smart Life Forum. January 19, 2006. San Francisco, CA.
Lecture: Wayne State University School of Medicine 4th Year Medical Students Elective. April, 2006
Lecture: PCCA Functional Endocrinology Symposium. April, 2006. Houston, TX.
Radio Interview: Dr. Stephen Hotze. May 5, 2006
Radio Interview: Healthy Talk Radio with Debra Ray. May 12, 2006.
Lecture: NAET Annual Symposium. Buena Park, CA. July, 2006
Lecture: PANLA Annual Lecture. Indiana, PA. August, 2006
Lecture: Genesys Learning Institute. September, 13, 2006. Flint, MI.
Lecture: Growing Connections 2006 Conference. Davisburg, MI. Oct. 2006
Lecture: North Carolina Chiropractic Association. November, 2006. Greensborough, N.C.
Lecture: PCCA Functional Endocrinology Symposium. November, 2006. St. Louis, MO.
Lecture: Age Management Medicine Group. November, 2006. Las Vegas, NV.
Lecture: PCCA Canada Functional Endocrinology Symposium. November 2006. Vancouver, Canada.
Interview: Healthmyths.net. December, 2006
Lecture: American Academy of Orthopedic Medicine. Boulder, CO. January, 2007
Lecture: Recent Advances of the Use of Iodine in Medicine. Scottsdale, AR. February, 2007
Lecture: Yoga Shelter. West Bloomfield, MI. February, 2007
Guest on Ron Hoffman's Healthy Talk Radio. www.wor710.com. 2.28.07
Guest on Debra Ray's Healthy Talk Radio. 3.4.07
Guest on The Power Hour with Joyce and Dave. 3.16.07
Guest on Temple of Health Radio Show. 4.20.07. www.templeofhealth.ws
Lecture Viotron International. Novi, MI. 3.17.07
Lecture Healthy Eating, Healthy Choices. 5.4.07. Novi, MI
Lecture NOHA, Inc. Morton Grove, IL. 5.3.07
Lecture to Institute for Functional Medicine: 5.25.07, Tuscon, AZ.
Lecture ZRT Conference on Bioidentical Hormones, Portland, OR. 7.29.07
Lecture: PCCA BHRT Conference. Denver, CO. 08/2007
Lecture: Cancer Control Society, Los Angeles, CA. 9.1.07
Lecture: PCCA Nutritional Seminar. Houston, TX. 9.6.07
Lecture: Broda Barnes M.D. Research Foundation, Stamford, CT. 9.7-9.9.07
Radio Interview. Power Hour. 9.21.07
Lecture Iodine Conference. San Diego, CA. 10.5.07
Lecture. Viotron International. Indianapolis, IN. 10.13.07
Lecture ZRT Labs. Orlando, FL. 10.26.07
Lecture Viotron International. Cleveland, OH. 11.3.07
Dr. David Biles Radio Show. 12.16.07. California
Lecture: ZRT BHRT Symposium. 1.18.08 San Diego, CA

Lecture: Growing Connections. Troy Michigan. 2.2.08
Lecture: Biotics Research. Baltimore, MD. 2.23.08
Lecture: BHRT International Symposium. Las Vegas, NV. 2.29.08-3.1.08
Lecture: Colorado Functional Medicine Forum. Boulder, CO. May 8, 2008
Lecture: PCCA BHRT. Detroit, MI 5.16.08
Lecture: ZRT Annual BHRT Update: Portland, OR, July 11, 2008
Lecture: Genesys Regional Medical Center. August 13, 2008
Lecture: NAET Annual Symposium. Buena Park, CA. August 29, 2008
Lecture: Biotics Research. Atlanta, GA. September 6, 2008
Lecture Biotics Research, Tampa, Fl. October 4, 2008
Lecture ZRT Laboratory, Tuscon, AZ. October 24, 2008
Lecture: International Academy of Compounding Pharmacists. January, 2009
Lecture National Chiropractic College, Chicago, IL. 3.20.09
Lecture: Biotics Research. Chicago, IL 3.21.09
Lecture: Biotics Research: Massachusetts, 3.28.09
Lecture: Biotics Research: Houston, TX. 4.4.09
Lecture Biotics Research. Albuquerque, NM. 7.9.09
Lecture: Florida Chiropractic Association, Orlando, Fl. 8.29.09
Lecture: American Academy of Anti-Aging Medicine. San Jose, CA. 9.11.09
Lecture: Biotics Research: Los Angeles, CA. 9.26.09
Lecture: Amarillo Health Initiative. Amarillio, TX. 10.10/09
Lecture: Biotics Research, N.Y., N.Y. 11.13.09
Lecture: Providence Hospital Dept. of Cardiology. Southfield, MI 12.4.09
Lecture: National Institute for the Clinical Application of Behavioral Medicine. Hilton Head, S.C., 12.11.09
Lecture: Royal College of Medicine, London, England. January 20, 2010
Lecture Newsmax Cruise, March, 2010
Lecture: University of Miami Integrative Medicine Symposium, 2010. Miami, FL. 4.23-4.24.10
Lecture: Orthomolecular Medicine Annual International Conference April 30, 2010. Vancouver, Canada.
Webinar to Agribus on Salt Your Way to Health. July 16, 2010
Lecture: Florida Chiropractic Association. August 27-28 2010. Orlando, Fl.
Lecture: Biotics Research. Los Angeles, CA. 9.25.10
Lecture: Florida Chiropractic Association. Naples, Fl. 11.19-20, 2010.
Lecture to NICABM, Hilton Head, SC. 12.8.10
Lecture to Fordham Page Nutritional Study Group March 4-5, 2011 Herndon, VA
Lecture Rebekah's Pure Living, Lapeer, MI March 26, 2011
Lecture Fellowship for American Academy of Anti-Aging Medicine, Orlando, Fl April 7, 2011
Guest on Dennis Courtney Radio Show April 15, 2011
Lecture to American Chiropractic Association Council on Nutrition. April 29, 2011 Orlando, FL
Lecture American Nutrition Association. May 6, 2011. Skokie, IL

Lecture to Metabolic Management Group, Schaumburg, IL May 7, 2011
Guest on Dennis Courtney Radio Show, May 13, 2011
Lecture to Biotics Research, N.W., Seattle, WA. May 21, 2011
Lecture to Florida Chiropractic Association, Boca Raton, FL. June 17-18, 2011
Radio Interview John Wycoff Radio, East Lansing, MI. 6.25.11
Radio Interview Dennis Courtney, Pittsburg, PA. 7.8.11
Lecture NAET Annual Symposium. Buena Park, CA. 7.29.11.
Lecture Fordham-Page Nutrition Study Group. Roanoke, VA. 8.26-8.27.11
Radio Interview Dennis Courtney Radio. Pittsburg, PA. 9.16.11
Radio Interview Power Hour. 9.30.11
Lecture Biotics Research. NY, NY. 10.22.11
Radio Interview Dennis Courtney Radio. Pittsburg, PA. 10.28.11
Lecture Big Lick Study Club. Roanoke, VA. 11.4.11
Lecture Biotics Research. Colorado. 11.12.11
Lecture Synergy Group. Calgary, CA. 11.18.11
Lecture NICABM. Hilton Head, SC. 12.8.11
Lecture Biotics Research, Houston, TX. 12.10.11
Lecture Webinar, Biotics Research, Houston, TX. January 9, 2012
Radio Interview Natural News Talk Hour, February 2, 2012
Lecture Kansas Pharmacy Association, Kansas City, MO. March 3, 2012
Lecture DSD International, Phoenix, AZ March 31, 2012
Lecture Biotics Research, San Francisco, CA. April 14, 2012
Lecture Halleluiah Acres, Shelby, NC. April 20, 2012
Lecture Biotics Research, Bedford, MA. May 12, 2012
Lecture Biotics Research, Falls Church, VA. May 19, 2012
Lecture Medical Alternatives Press, Novi, MI June 16, 2012
Lecture A4M Fellowship Program, Las Vegas, NV. September 7, 2012
Lecture IAOMT. September 21, 2012
Lecture Biotics Research. Virginia Beach, VA. September 29. 2012
Lecture A4M Fellowship. Tampa, FL. October 12, 2012
Lecture Age Management. Las Vegas, NV. November 2, 2012
Radio Interview Power Hour. November 30, 2012
Guest On Your Health TV Show, Dallas, TX. February 21, 2013
Lecture American Academy of Antiaging Medicine. Las Vegas, NV. March 1, 2013
Webinar. Biotics Research. March 12, 2013
Lecture International Academy of Oral Medical Toxicology. March 15, 2013
Lecture Westin A. Price Foundation. Romulus, MI March 24, 2013
Lecture Biotics Research. Orlando, FL. April 13, 2013
Lecture Biotics Research. Chicago, IL. May 11, 2013
Host of Thyroid Summit. June, 2013
Lecture Viotron Intl. Nashville, TN. September 28, 2013
Lecture Viotron Intl. Novi, MI. October 26, 2013
Lecture American Academy of Restorative Medicine, San Diego, CA. Oct.3-6, 2013
Lecture Westin A Price International Meeting. Atlanta, GA. November 10, 2013

Lecture PCCA. Las Vegas, NV. Feb. 21, 2014
Lecture Total Health. Toronto, Ontario. April 4-5, 2014
Lecture Holistic Dental Assoc. Chicago, IL. April 11, 2014
Lecture Restore Health. Indianapolis, IN May 3, 2014
Lecture Biotics Research. Harrisburg, PA. May 17, 2014
Documentary Interview – Cure for Cancer. Aug. 29, 2014
Lecture IAOMT. Las Vegas, NV. Sept. 12, 2014
Lecture ICIM, Dearborn, MI. Sept. 26, 2014
Lecture Biotics Research. San Antonio, TX. Nov. 8, 2014
Lecture Biotics Research, New York, NY Nov. 15, 2015
Lecture Biotics Research. Charlotte, NC March 7, 2015
Lecture Biotics Research. Bethesda, MD March 21, 2015
Radio Interview Sal DiBella Radio Show, April 17, 2015
Lecture Orthomolecular Society. Toronto, Ontario April 24, 2015
Lecture AARM. Blaine, WA. Oct 1, 2015
Lecture Chicago Dental Society. Chicago, IL. Oct. 9, 2015
Lecture A4M Fellowship Program. Chicago, IL. Oct. 10, 2015
Lecture Biotics Research. Cleveland, OH. Nov. 14, 2015
Lecture: ICIM. Grand Rapid, MI. October 5, 2017, Workshop on Intravenous IV Therapy.
Lecture: ICIM. Minneapolis, MN October 27, 2018
Lecture: Holistic Medicine for the 21st Century. Livonia, MI. February 2, 2019

EMPLOYMENT EXPERIENCE:

Medical Director, The Center for Holistic Medicine May, 1999-present
Staff Physician - Detroit Medical Center, November 1993 – April, 1999
Staff Physician - Specialists in Family Practice, Novi, Mi. July 1992- October, 1993
Emergency Room - Providence Hospital, Novi, Mi. 1991- 1994

Exhibit 1-D

October 20, 2019

To: National Academies of Sciences, Engineering, and Medicine (NASEM)
Ad Hoc committee to assess the clinical utility of treating patient with compounded
"bio-identical hormone replacement therapy" (BHRT) drug products

From: Angela DeRosa, DO, MBA, CPE

Re: Importance of compounded hormones

Dear Committee Members,

As a female physician and menopausal woman, I felt it important to express the grave concern I have regarding the attempts to limit patient's rights and physician's ability to not only prescribe hormone therapies, particularly compounded bio-identical hormone replacement therapy (BHRT), but in a manner that individualizes their medical care.

In today's medical environment, we are becoming more and more restricted in the name of "protecting patients"; but the only way to truly do so is to not allow patients any exposures to any medicines, compounds etc. Every day, physicians are faced with the challenges of choosing the right treatment plans for each of our patients, but now sadly insurance companies, regulatory bodies and those with financial interests are directing care decisions and taking the provider and patient out of the equation. This time-honored relationship demands the ability to have informed choice, individualization and an unencumbered decision-making process that isn't influenced by untoward outside parties who have conflicts of interest. This relationship is being threatened on many levels and we must take a stand to protect it.

I have been a practicing internal medicine physician with over 20 years of specialty training and expertise in women's health. I have dedicated my career to the understanding and knowledge surrounding women's unique medical needs, particularly focused on the role that hormones played in them. (See attached curriculum vitae for full professional history and practice descriptions)

My career interests did not happen by accident. They were driven by my own personal struggles as a patient who went through premature menopause at the age of 35; experiencing the signs and symptoms all the while I was in medical school and residency training.

At the young age of 30, I found myself on multiple FDA approved medication to treat the symptoms of premature menopause (sleeping pills, antidepressants, beta blockers) and had thousands of dollars of medical work ups; all which could have been prevented if the medical profession had a better understanding of hormones and the vital role of hormone replacement. Once I found customized compounded hormones, my life changed for the better and the "band-aid" medications were stopped.

It was through this personal experience, that fueled my fire to understand how I could change the paradigm of women's health and the fears that were created by much misinformation and skewed media exposures to datasets that even the most novice statisticians could poke holes through.

I saw first-hand, while working as the west coast senior medical director at Procter & Gamble (P&G) pharmaceuticals, the inner workings of drug development, product marketing, and the FDA drug approval processes. I also saw the gender biases that were at play in female hormonal health. (I was responsible for their female hormonal health/sexual health and bone health product lines.) P&G spent years and millions of dollars in an attempt to bring to market the first female FDA approved testosterone product (Intrinsa matrix delivery patch) only to be shut down by the FDA due to unfounded fears about cardiovascular risk and breast health even when all the data to the contrary was evident. To make matters worse, there have been many forces at play that have not allowed female patients the same health choices as men and this is very apparent in the area of hormonal health.

Even, the majority of “key opinion” consensus statement/recommendations/guidelines from organizations are heavily funded by the pharmaceutical industry making them both financially and intellectually biased. This obvious conflict of interest propagates the bias against compounding hormones even when there is much research to support its utilization and the benefits of personalized medicine.

The sad truth is that this failure to approve was over two decades ago and we still do not have any FDA approved testosterone products for women. This failure shouldn't not only be alarming but embarrassing to the medical profession as a whole in our inability to provide equal access to essential hormones that have been made available for men, but not to women. The good news, is that as in nature, when there is a void, something will attempt to fill it.

In the hormonal space, compounding pharmacies created BHRT products to fill the gap of not only the lack of availability of testosterone for women, but the ability to customize a dose or hormone combinations that cannot be accomplished with standard FDA approved products.

Although I agree with measures to ensure that patients receive quality compounded bioidentical hormones, we should not limit what doctors can prescribe or what patients need, when there is no medical data to suggest that harm is being done from these products, specifically when dosed correctly for each individual patient. Historically, negative hormonal outcomes usually occur due to first pass liver effect clotting from oral medications or from synthetic derivatives that the body doesn't quite know how to process as in progestins.

It's not to suggest we shouldn't use FDA approved products when appropriate; but we need more “tools in the toolbox”. The current FDA approved product tool boxes have many broken tools, ones that don't work properly or most notably are missing some tools to do the job. Compounds can fill that void. (exhibit A)

I can personally attest to the fact that the compounded BHRT space saved my life and the lives of the thousands of patients I have had the privilege to treat over the last twenty years.

Through my exploration, learnings and trials experience over these twenty plus years, I have tried the multitude of FDA approved products, over the counter products, and then finally compounded hormones (creams, troches, pellets) in my practice. I have seen first-hand how patients are able to gain back their lives and health with many coming off multitudes of medications, losing weight and improving their metabolic risk factors, enjoying satisfying intimacy with their partners and building health, wellness and joy back into their family units.

My career has been very rewarding watching these life changing events versus having to continue to prescribe medication after medication to put band aids on symptoms which could all be resolved while getting to the root cause of many underlying chronic illness...hormone imbalances or deficiencies.

As patient advocates, it is important to remember the unique needs of our patients and we must fight protect our abilities to treat as such. This is reminiscent of Gaileo's fight against orthodoxy, to make the sun the center of the solar system, the heliocentric view, rather than an immobile earth.

I welcome your questions and opportunity to speak in person with the committee if desired. Thank you for your consideration.

Best Regards,



Angela DeRosa, DO, MBA, CPE

480-316-5220

drderosa@drhotflash.com

Exhibit A

Most common conditions I treated with compounded drugs

1. Menopause/Peri-Menopause
 2. Premature ovarian failure
 3. Andropause
 4. Hormone deficiencies
 5. Pelvic Pain Syndromes
 6. Fibromyalgia
 7. Vaginismus
 8. Yeast Infection
 9. Vaginosis
 10. Dermatitis
 11. Mood disorders
 12. Muscle wasting syndromes
 13. Deconditioning
 14. Spinal cord injuries
 15. Fibroids
 16. Fibrocystic breast disease
 17. Interstitial cystitis
 18. PCOS
 19. Ovarian Cysts
 20. Vitamin deficiencies
 21. Sexual health
 22. PMS
 23. Hypothyroidism
 24. Androgen resistance
 25. Thyroid resistance
 26. Sub-clinical hypothyroidism
 27. Adrenal dysfunction
 28. Autoimmune disorders
 29. Bone health
 30. Cognitive decline
 31. Cardiometabolic disease
 32. Insulin resistance/diabetes
 33. Incontinence
 34. Neurodegenerative diseases
 35. Obesity
 36. Vulvodynia/Vestibulodynia
 37. Vulvar vestibulitis
 38. Lichen sclerosis
 39. Dyspareunia
 40. Atrophic vaginitis
-

Angela DeRosa DO, MBA, CPE

Email: angeladerosa@cox.net

Phone: 480-316-5220

Scottsdale, Arizona

www.linkedin.com/in/angeladerosa

EXECUTIVE SUMMARY

Highly accomplished Visionary, Entrepreneur, Senior Executive, C-Suite Officer, Consultant, Educator, Public Speaker and Board Member with extensive experience and successes in medicine, pharmaceuticals, hospital, clinic and long-term care medicine, managed care and government sectors. Leveraging extensive experience in leadership, operations and branding; valuable asset for similar sector companies looking for acumen in mergers and acquisitions, (M&A) due diligence and integrations, drug/productive development and launch, medical affairs and R&D. Broad expertise includes strategic planning, corporate development and growth, operations management, brand position and management, relationship building and management, physician sales and marketing strategy, regulatory affairs, policy and legislation, clinical practice and trials, internal medicine, women's health care and public speaking.

PROFFESIONAL COMPETENICES

- | | | |
|--|--------------------------------------|-----------------------------------|
| *CEO/Business and Operations Leaders | *Board Communications/Collaboration | *Sale and Marketing |
| *Strategic Planning/Business Development | *Revenue Growth/Profit Delivery | *Internal Medicine/Women's Health |
| *M&A/Due Diligence/Integrations | *Brand Equity and Marketing Strategy | *Relationship Building/Management |
| *Innovation/Complex Problem-Solving | *Media Relations/Public Speaking | *Drug/Product Development/R&D |

SELECTED ACCOMPLISHMENTS

- Created business plan and strategy, competitive/SWOT analysis and marketing/brand equity vision for DeRosa Medical, PC startup business in 3 months. Executed, operationalized and lead the business plan strategy for a total women's healthcare clinic, creating a culture of women caring for women with 3 locations across the Phoenix metropolitan area with 50 + employees over a 7-year period.
- Developed and executed strategy to convert DeRosa Medical, PC into a \$7M platform company for partner acquisition to further leverage business legacy and met target in 9/2017 with acquisition by Nobilis HealthCare.
- Created business plan and strategy, competitive/SWOT analysis and marketing/brand equity vision for MiraVita, LLC a supplement and wellness program start up business in 2014. Operationalized and lead deployment of products into market (brick and mortar and on-line sales) with over \$200K in sales in 3 years.
- Wrote and published "How Your Doctor is Slowly Killing You: A Women's Health Survival Guide" with full marketing and sales plan and launch in March 2014 with over 25K in sales/royalties.
- Won the 2016 Phoenix Business Journal "Healthcare Hero's Innovator of the Year" award for an innovative approach to delivering comprehensive women's' health care and approach to training and mentorship of women in the medical workforce in Arizona.
- Won the 2013 Arizona Osteopathic Medical Association, "Mentor of the Year" award for excellence in teaching osteopathic medical students.
- Created, developed and implemented the 1st On-line Second Year Medical School Women's Health and Human Development curriculum in 2007 for ATSU, College of Osteopathic Medicine. This coursework has become the platform for their on-going training of medical students remotely throughout the United States.
- Responsible for the development, expansion and coordination of the United States 19th women's health fast track curriculum and program of the department of Internal Medicine at Lutheran Medical Hospital/Advocate Medical Group in 1998 with subsequent development and leadership of the hospitals multi-disciplinary comprehensive women's health clinic.

EXPERIENCE

Founder and President: Hormonal Health Institute

08/2018-Present

Created and Launch a hormonal health consultancy, for physicians seeking medical and practice development training on bio-identical hormone replacement therapy, with an emphasis on pellet therapy.

- *Strategic Development includes a variety of training formats and programs including live concierge level one-on-one training in physician's office, live and recorded webinars, self-paced digital classes, and peer support.*
- *Launched a digital education platform www.drhotflash.com, with two channels; one for physicans and one for consumers seeing easy to understand and comprehensive hormonal health content.*

Founder, President and Chief Medical Officer, DRM, Integrative, LLC

04/2019- Present

Created business plan and strategy, competitive/SWOT analysis and marketing/brand equity vision for DRM Integrative, LLC. Executed, operationalized and lead the business plan strategy for a multi-location concierge hormonal health clinic.

President: Women's Health Division, Nobilis Health Corporation

10/2017-Present

Reporting to Chief Strategy Officer responsible for leading strategic marketing and innovative growth/revenue plans for DeRosa Medical and Women's Health Service lines within Nobilis Health Medical Practices in Arizona and Texas.

- *Strategic Development and Growth of Primary Care Acquisitions and Interplay within companies brands as well as total women's care and hormonal health service line expansions within acquired organizations*

Founder, President and Chief Medical Officer, DeRosa Medical, PC

1/10-9/2017

Created business plan and strategy, competitive/SWOT analysis and marketing/brand equity vision for DeRosa Medical, PC startup business in 3 months. Executed, operationalized and lead the business plan strategy for a total women's healthcare clinic, creating a culture of women caring for women with 3 locations across the Phoenix metropolitan area with 50 + employees over a 7-year period.

- *Developed and executed strategy to convert DeRosa Medical, PC into a \$7M platform company for partner acquisition to further leverage business legacy and met target in 9/2017 with acquisition by Nobilis HealthCare.*

Board Certified Internist, Women's Health Specialist

8/98-Present

Special Training and Focus on Menopausal and Hormonal Medicine

- *Licensed in Arizona, California, Tennessee, Illinois, Ohio, New Mexico,*
- *Certified Physician Executive*
 - *Board certification in medical management given to physicians who have completed the American College of Physicians Executives degree course work& demonstrate they have reached a level of excellence within the medical management profession, to effectively lead an organization.*

Clinical Assistant Professor

8/01-Present

Midwestern University, Chicago College of Osteopathic Medicine

- *Internal Medicine Preceptor and Research Elective Rotations*

Vice President of Medical Affairs & Chief Compliance Officer

02/08-2011

Matrix Medical Network/Community Care Health Network, Inc.

Reporting to Chief Operations Officer and Chief Medical Officer provided national management, budgeting/financial objectives and oversight to physician groups and managed care provider practice s and medical affairs department.

- *Responsible for Development and Initiation of quality improvement, research/grants, coding and compliance programs*
- *Lead operational strategic and tactical resource allocation& utilization for Health Risk Assessment Programs nationally*

Medical Director, Sub Acute Care Division:

10/06-12/07

American Physician Inc.

Reporting to the Chief Medical Officer responsible for leading/managing business development and strategies a team of 15-20 Sub Acute Care Physicians within 50+ facilities in the Phoenix Metro area.

Senior Medical Director:

8/00-10/06

Procter and Gamble Pharmaceuticals

Reported to Global Medical Director. Responsible for the oversight and development of regional, national and international key opinion leaders, oversight of technical and scientific teams for curriculum & training needs of scientific and sales force nationally.

- *Medical and Technical Liaison between regional teams and Medical& Technical Affairs including scientific data evaluation, Non- Company Sponsored Trials & Grants, scientific strategic planning & life cycle management & Phase IIIB and IV studies.*
- *Managed a \$250,000 regional budget for R&D development based on investor scientific merit*
- *Lead Scientific & Business Development Strategies for all brands including osteoporosis, IBD and Female Sexual Health.*
- *Assist in the execution of phase IIIB and IV Company sponsored trials. Attend investigator meetings, monitoring issues, provision of follow-up and execution of timelines.*

Director of Women's Health Services and Education

6/98-6/99

Lutheran General Hospital, Advocate Medical Group

Reporting to Internal Medicine Department Chief lead the development of a multi-disciplinary, comprehensive women's health clinic.

- *Physician liaison between large multispecialty group and hospital administrator in implementing joint efforts in women's health programs and coordination of educational programs between the Department of Ob/Gyn and Internal Medicine.*

EDUCATION

University of Massachusetts, Amherst, The Isenberg School of Management
MBA in Medical Management

Lutheran General Hospital/Advocate Medical Group
Internship and Residence in Internal Medicine/Women's Health

Chicago College of Osteopathic Medicine
Doctor of Osteopathic Medicine

Wayne State University
Bachelor of Arts with Honors in Biological Sciences

PROFESSIONAL ACTIVITIES

Board of Directors: Arizona Osteopathic Medical Association 1/12- present

- *Current President 2018-2019*
- *Board of Delegates District 5*
- *Chair: Public Relations Committee*
- *AOA/AOMA speaker's bureau*

Board of Directors: American Osteopathic Foundation 7/03-5/09

- *AOF is the premier philanthropic organization within the osteopathic organization. The Mission is to support education, research and the promotion of the osteopathic profession.*
- *Development Committee Chair: Responsible for initiating, developing and creating fundraising events for the Foundation*
- *Secretary of Board of Directors 2006-2007.*

PROFESSIONAL ASSOCIATIONS

- American Osteopathic Association
- Arizona Osteopathic Medical Association and PAC
- American Academy of Anti-Aging Medicine
- International Society for the Study of Women's Sexual Health
- European Menopause and Andropause Society
- International Menopause Society
- American College of Physician Executives

PUBLICATIONS/POSTERS

Women's Health Curriculum and Syllabus-Department of Medicine, Lutheran General Hospital.

Oral Presentation: "Are Physicians Treating Osteoporosis after Hip Fracture? Susan Broy, Angela Bohren-DeRosa, Tim Harrington, Angelo Licatta, Shewman ASBMR Toronto Sept.2000

Poster and Media Presentation: "Are Physicians Treating Osteoporosis after Hip Fracture? Susan Broy, Angela Bohren, Tim Harrington, Angelo Licatta, Shewman, ACR, October 2000.

MRS. AMERICA PAGEANT, Guest Lecturer to the Delegates on Osteoporosis and Health and Fitness Judge, September 2001

Poster Presentation: "Sustained Effects of Risedronate on Vertebral and Non-Vertebral Fractures over 5 years", American Osteopathic Association Annual meeting, Las Vegas, NV. Oct. 2002

Original Article: Arthritis and Rheumatism "Hip Fracture Patients Are Not Treated for Osteoporosis: A Call to Action" Harrington, Broy, DeRosa, Licata, Shewmon. Vol. 47, No. 6. Dec 15, 2002 pp 651-654

"To BMD or not to BMD" Journal of Osteopathic Association: Women and Wellness. Volume 1, number 2, Sept 2004 Page16.

"Taking a New Twist in Practice Guidelines" AOA Health Watch. Volume 3 Number 2, June 2008

"Hypothyroidism causes false positive: The BT test. AOA National Convention, October 2012

Gray, DeRosa Subcutaneous Pellets Testosterone Replacement Therapy: The "First Steps" in treating men with spinal cord injuries" JAOA, December 2013 Volume113, 921-925

DeRosa A, Adams S, Fee EK. Progressively worsening cyclic rash: diagnosis and approach to care. J Am Osteopath Assoc. 2015; 115(12):738-744. doi:10.7556/jaoa.2015.150.

"How Your Doctor is Slowing Killing You: A Women Health Survival Guide" Dr. Angela DeRosa

References Available upon Request

Exhibit 1-E

Statement From Bruce Dorr, MD, FPMRS

Qualifications

My name is Dr. Bruce Dorr, MD, FPMRS. My professional background is as follows. I received my Bachelor of Arts, *Cum Laude*, in chemistry and biology, with minors in German and psychology, from Hope College in 1986. I received the Presidential Scholar Scholarship and the Vienna Summer School Scholarship while I attended Hope College. I received my Medical Doctorate from Wayne State University School of Medicine in 1990, where I received honors for Ob/Gyn, Gyn Oncology, Medicine, Pediatric ICU and ENT with recommendations for Surgery, Pediatrics, and Family Medicine. I completed my internship and residency at the University of Colorado Health Sciences Center in obstetrics and gynecology in 1994, where I also received the Golden Apple Teaching Award for Outstanding Teaching Resident in 1990. I completed a clerkship at Sloan-Kettering Memorial Hospital in New York, New York in 1993, where I was part of the Galloway Fellowship in Gynecologic Oncology. I also completed a clerkship in urogynecology at the Evanston Continence Center in Evanston Illinois in 1996, where I studied urodynamics and urogynecology with Peter Sand, MD, who is affiliated with the Northwestern School of Medicine.

My work experience is as follows. I was a Loum Tenens Physician at Jackson & Coker, CompHealth from 1994 to 1995, where I performed local physician work in Arizona, Oregon, Michigan, New York, and Virginia. I was an Assistant Clinical Professor at the Denver Health Medical Center from 1995 to 1997, where I was the principle instructor of UroGynecology. I was a physician reviewer for the Colorado State medical Board from 2000 to 2010. I have been a Proctor at Intuitive Surgical since 2010, where I proctor and train new physicians for robotic surgery on XI and SI platforms I have been the Chairman of the Centura Littleton Robotics Division since 2013, where I have developed and consulted for hospital advancements in robotics surgery. I have been a Medical Missionary for Centura Global Health Initiatives since 2018, where I am the Chief Gyn Surgeon for Peru and Nepal missions. I previously served as the Chairman of the Department of Women's Services at Littleton Adventist Hospital, a position I held since 2014, where I reviewed credentials, peer reviewed cases, and served on the Medical Executive Committee.

Additionally, I am currently a physician in urogynecology, general gynecology, and minimally invasive surgery at Littleton Gyn and Wellness/Right Balance Hormone Health, a single specialty practice. I am specialty board certified in female pelvic medicine. I have an active patient base of approximately 5,000 patients, and approximately 10,000 patients in EMR. I treat these patients for, among other things, thyroid optimization, surgery, pelvic support surgery, and hormone issues in male and female patients.

Experience in Prescribing and Treating with Compounded BHRT

Approximately 30-40% of my patients are being treated with some form of compounded BHRT. My practice treats over 400 patients with compounded BHRT pellets per month.

Medical Conditions and Patient Populations Treated with Compounded BHRT

I treat a variety of medical conditions in my male and female patients of all ages with compounded BHRT. Specifically, I treat the following symptoms and conditions with compounded BHRT:

- Hormone replacement therapy for women during menopause
- Hormone deficiencies experienced by women prior to menopause
- Hormone depletion in men and women ages 20-29
- Endometriosis
- Breast cancer
- Depression
- Sleep issues
- Collagen or vascular disorders
- Rheumatologic disorders
- Autoimmune disorders

Why is Compounded BHRT Preferred Over Commercially Available BHRT?

In my professional medical judgment, I prefer to treat my patients with compounded BHRT instead of the commercially available BHRT because hormone therapy requires individualized treatment and a constant reassessment and adjustment of the hormone dose and the medication—it is effectively impossible to treat patients with a one-size-fits-all hormone therapy treatment.

I prefer to treat my female patients with compounded BHRT because there is no commercially available testosterone approved for treatment in women. In my professional experience, I have witnessed many female patients that require testosterone treatment and, as a result, are relegated to self-treating with their husbands' testosterone, which is dosed at male ranges and is unsafe for self-treatment by women. I am able to successfully treat these female patients with compounded bio-identical testosterone in pellet form to resolve low libido, sexual side effects of testosterone deficiency, sleep issues, and bone mass deficiencies. I prefer to treat with the hormone pellets instead of transdermal creams or oral troches because then the hormone is delivered the way the ovaries are used to delivering hormones. Further, patient compliance with the pellet therapy is, in my professional experience, much higher than when my patients are treated with patches, creams, or pills.

Compounded bio-identical testosterone is also a necessary option for women because women are contraindicated to treatment with estrogen and testosterone is often the only option. Without treatment with compounded bio-identical testosterone, women are at an increased risk for

David J. Watson,
Bruce R. Dorr,
Jeannie Key,
Katherine Tiedt,

heart disease, dementia, and bone health deficiencies, among many others. For so many of my patients, compounded bio-identical testosterone is lifesaving. When my female patients are treated appropriately (i.e., with the right dosage strength and the right dosage form for what the patient can tolerate), their bone density will normalize within a year, they will lose weight appropriately, they will gain back energy, and many patients find that they no longer need sleeping aids or antidepressants.

I prefer to treat my male patients with compounded bio-identical testosterone in pellet form because every other dosage form of testosterone (e.g., shots, gels, creams, or the commercially available Testopel) delivers inconsistent levels of the hormone. That is, when bio-identical testosterone is prescribed in other dosage forms besides pellet therapy, the patient will experience peaks and troughs of the effects, or the patient might not absorb it at a consistent rate, or the patient may not absorb it at all. The bio-identical testosterone pellet delivers the hormone the way the body is meant to receive it, but commercially available bio-identical testosterone cannot do this.

Finally, I prefer to treat my patients who have a history of blood clotting with compounded subcutaneous pellet therapy. Pellet therapy is the only hormone therapy available for patients with a history of clotting, such as deep vein thrombosis or pulmonary embolus. There is no commercially available hormone replacement therapy that can treat these patients.

Sincerely,

s/ Bruce Dorr, MD, FPAIRS



Bruce Dorr

MD, FPMRS

7750 S. Broadway, Suite 200, Littleton, Colorado 80122 | 303-730-6000 | bdorr@kcoya.net

Education

High School 1979 - 1982
Redford Union High School

General studies during High School 1982 - 1982
Oakland Community College

Bachelor of Arts 1982 - 1986
Hope College
Majors: Chemistry, Biology
Minors: German, Psychology

Directed European Studies 1984 - 1984
Center for European Studies, Vienna, Austria
Directed Studies in Art History and European economics

Medical Doctorate 1986 - 1990
Wayne State University School of Medicine

Internship and Residency 1990 - 1994
University of Colorado Health Sciences Center
Obstetrics and Gynecology

Clerkship July 1993 - August 1993
Sloan-Kettering Memorial Hospital, New York, New York
Galloway Fellowship in Gynecologic Oncology

Clerkship in Urogynecology January 1996 - February 1996
Evanston Continence Center, Evanston, Illinois
Course of study in Urodynamics and Urogynecology with Peter Sand, MD--affiliated with the Northwestern School of Medicine

Work experience

Chairman, Department of Women's Services 2014 - present
Littleton Adventist Hospital
Reviewed credentials, peer review of cases, service on Medical executive committee

Skills

Honors/Awards

2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024

Undergraduate

Cum Laude Graduate,
Presidential Scholar Scholarship
Vienna Summer School Scholarship
Mortar Board Honor Society President

Medical School

Honors for Ob/Gyn, Gyn Oncology,
Medicine, Pediatric ICU and ENT with
recommendations for Surgery,
Pediatrics and Family Medicine

Residency

Golden Apple Teaching Award for
Outstanding teaching resident 1990
Galloway Fellowship in Gyn Oncology

Littleton Gyn and Wellness/Right Balance Hormone Health
Physician in Urogynecology, general gynecology, minimally invasive surgery

Medical Missionary 2018 - current
Centura Global Health Initiatives
Chief Gyn Surgeon for Peru and Nepal missions

Chairman 2013 - present
Centura Littleton Robotics Division
Develop and consult for hospital advancements in robotics surgery

Platinum Trainer and Mentor 2013 - present
BioTE Medical
train practitioners in bio-identical hormone replacement and optimization therapy

Physician Reviewer 2000 - 2010
Colorado State Medical Board
Reviewer for State Medical board for requested cases

Proctor 2010 - present
Intuitive Surgical
Proctor/train new physicians for robotic surgery on Xi and Si platforms

Assistant Clinical Professor 1995 - 1997
Denver Health Medical Center
Principle instructor of UroGynecology

Admissions Committee Representative 1995 - 1997
University of Colorado Health Sciences Center
Committee representative for medical student admissions

Locum Tenens Physician 1994 - 1995
Jackson & Coker, CompHealth
Local physician work in Arizona, Oregon, Michigan, New York and Virginia

Skills

Research

~~REDACTED~~

Medical School

Dorr, B., V. Maivya, G. Deppe, et al,

"Does Limited Lymphadenectomy Based on Frozen Section of Uterus Decrease Survival in Patients with Endometrial Cancer."

Dorr, B., J. Abbott, and W. Schlaff, "Vaginal Bleeding in the Emergency Room"

Exhibit 1-F



**BIO-IDENTICAL
WELLNESS**

CHRISTINE FARRELL MSN, FNP-C

Statement From Christine Farrell M.S.N., F.N.P.-C

Qualifications

My name is Christine Farrell M.S.N., F.N.P.-C. My professional background is as follows. I received my Bachelor of Science, *cum laude*, from the University of California, Los Angeles in 1989. I received my Family Nurse Practitioner/Masters in Nursing from California State University, Long Beach in 1997, where I focused in FNP training and acute/emergent care. My up to date CV is enclosed for reference.

I worked as a Registered Nurse in the Medical ICU at Huntington Memorial Hospital, in Pasadena, California from 1989 to 1990. I was responsible for the care of medically ill patients in critical condition and included treatment of respiratory, neurological, infectious disease, and gastrointestinal issues. I worked as a critical care flight nurse from 1992 to 1994, where I was independently responsible for the care of critically ill patients during flight transport nationally and internationally. It included Swan-Ganz monitoring, intubated patients, and ACLS institution as needed. I worked as a Registered Nurse at Northridge Hospital in Northridge, California from 1990 to 1992, where my responsibilities included care of critically ill patients, including open-heart, Swan-Ganz monitoring, vasopressors, ventilators, and code blue response team. I also worked as a Registered Nurse at the Northridge Hospital Trauma Center in Northridge, California from 1991 to 1994. My responsibilities included care of emergency room/trauma patients, which included orthopedic, OBGYN, pediatric, urgent care, cardiac, trauma, near-drowning, burn, and general medicine care. I was also the clinical care coordinator and charge for the unit. I assisted part-time in the hyperbaric chamber/center in emergency and wound care of patients.

After working in various roles at Northridge Hospital, I worked as a transplant nurse coordinator at the University of California San Diego Medical Center. My responsibilities included patient education, work-up, follow-up, physical assessment, in-patient assessment, and nursing education. I gained specialized knowledge of immunosuppression, pharmacology, cardiac/pulmonary pathophysiology, laboratory values, and crisis intervention. I worked as a Registered Nurse in the emergency room of Columbia West Hills Medical Center from 1996 to 1997.

I worked as a Family Nurse Practitioner at Affiliates in Medical Specialties Medical Group from 1997 to 2005. My responsibilities included primary care, internal medicine, and urgent care. I managed all levels of care, both chronic and acute, including women's health, diabetes, obesity, hypertension, orthopedics, and pediatrics, among others. I was a Wellness Program Director and

Aesthetic Clinical Specialist at Aesthetic Surgical Partners from 2005 to 2006, where I provided bio-identical hormone consultation and treatment, nutritional/weight loss counseling, pre- and post-op evaluations, laser treatments (e.g., Titan, Genesis, hair removal, vascular, and IPL), and injectable cosmetic enhancements (e.g., Botox, Restylane, Sculptra, Radiesse, and Jevederm). I worked as a Family Nurse Practitioner at AFP Associates from 2008 to 2010. My responsibilities included primary care and family practice, specifically managing all levels of care, both chronic and acute, including women's health and hormone therapy, orthopedics, hypertension, and diabetes.

I have been an Associate Clinical Professor at the University of California, Los Angeles since 2001. I am a clinical instructor/preceptor for the Nurse Practitioner program. I have also been a legal nurse consultant for PJ West and Associates since 2004, where I have provided expert testimony and case review of billing and medical records.

I belong to the North American Menopause Society, the International Menopause Society, and the International Hormone Society. I am certified in Vitapel hormone implant therapy.

Experience With Treatment Of Compounded Bio-Identical Hormone Therapy

I currently work as a nurse practitioner, owner, and president of Christine Farrell MSN, FNP-C, Inc./Bio-Identical Wellness. I specialize in the treatment of hormonal imbalances in men and women of all ages. I provide women's health care and general health care. I have been in the practice of treating hormone imbalances for over 17 years.

I treat all of my patients with hormone therapy. Approximately 90-95% of my patients are treated with compounded Bio-Identical Hormone Replacement Therapy ("BHRT"). Approximately 75% of my patients treated with compounded BHRT are female, and approximately 25% are male. In my professional medical experience, I have witnessed a near 100% effectiveness rate when patients are appropriately treated with compounded forms of BHRT.

Medical Conditions and Patient Populations Treated with Compounded BHRT

I treat a variety of medical conditions in my male and female patients with compounded BHRT. The table below represents some of the medical conditions and symptoms with which my patients present and that are effectively treated by compounded BHRT:

Male Patients

- Andropause
- Depression
- Hyperlipidemia
- Hypothyroidism
- Insulin Resistance
- Joint Pain
- Libido
- Loss Of Muscle Mass
- Memory Issues
- Sleep Issues

Female Patients

- Dysmenorrhea
- Hot flashes
- Hyperlipidemia
- Hypothyroidism
- Insulin resistance
- Irregular menstrual cycles
- Joint pain
- Libido
- Memory issues
- Menopause

- Weight Management
- Mood issues (anxiety and depression)
- Perimenopausal symptoms
- Polycystic ovarian issues
- Sleep issues
- Vaginal atrophy
- Weight management

Why is Compounded BHRT Preferred Over Commercially Available BHRT?

In my professional medical judgment, I prefer to treat my patients with compounded BHRT instead of the commercially available BHRT because hormone therapy requires individualized treatment and a constant reassessment and adjustment of the hormone dose and the medication—it is effectively impossible to treat patients with a one-size-fits-all hormone therapy treatment. I monitor my patients’ hormone levels by drawing blood every 2-3 months in the beginning, and then at a minimum every six months thereafter. Compounding allows me to make slight adjustments based off what my patients’ blood results indicate.

In my professional medical opinion, FDA-approved BHRT is not suitable to treat the entire patient population that requires hormone therapy. For example, Prometrium is an FDA-approved bio-identical progesterone oral capsule that is dosed in 100 mg and 200 mg dosages. If I treat five different women each with a 100 mg capsule of Prometrium, each woman’s blood test results will indicate different hormone levels. Additionally, Estrogel is an FDA-approved bio-identical Estradiol topical gel that is typically prescribed to female patients in doses of one pump (1 gram) per day, however, most female patients require more than one pump to effectively treat their symptoms. Not only is two pumps significantly more expensive for patients, but most patients cannot absorb two pumps (2 grams) of Estrogel in a consistent manner because of the amount of surface area on the body that the topical cream needs to cover. In these instances, I prescribe compounded bio-identical Estradiol in a more concentrated dose. With double the strength in one pump, patients get a better treatment that is tailored to what they actually need and their compliance with the prescribed dose is higher than if patients had to use two pumps of Estrogel each day.

Just because an FDA-approved, standardized dose exists does not mean that that dose is right for all patients. Frequently, FDA-approved dosages are either not adequate for what a patient needs or is not approved in a dosage form that is consistently and easily absorbed by the patient. Individualized hormone care is safer and more effective for patients requiring hormone therapy.

Sincerely,

/s/ Christine Farrell M.S.N., F.N.P.-C

343 s. Moorpark Rd, Thousand Oaks, CA 91361

818-865-8500

Christine Farrell M.S.N., F.N.P.-C

438 Havenside Ave.
Newbury Park, CA 91320
805-208-4439 cell
818-865-8500 work
818-865-8022 fax

P r o f e s s i o n a l e x p e r i e n c e

Sept 2006- *Christine Farrell MSN, FNP-C, Inc./ Bio-identical Wellness*

Present *Private practice- owner / president*

Responsibilities: *Specializing in the treatment of hormonal imbalances in men and women of all ages. Providing women's health care and general health care.*

Jan 2008- *AFP Associates*

Dec 2010 *Family Nurse Practitioner*

Responsibilities: *Primary Care / Family Practice – manages all levels of care, both chronic and acute, including: women's health/hormone therapy, orthopedics, hypertension, diabetes, etc.*

July 2005- *Aesthetic Surgical Partners*

Sept 2006 *Wellness Program Director / Aesthetic Clinical Specialist*

Responsibilities: *Bio-identical hormone consultation and treatment, Nutritional/Weight loss Counseling, Pre/Post-op evaluations, laser treatments (Titan, Genesis, hair removal, vascular, IPL), injectable cosmetic enhancements (Botox, Restylane, Sculptra, Radiesse, Juvederm)*

May 2004- *PJ West and Associates*

Present *Legal Nurse Consultant.*

Responsibilities: *Expert testimony. Case review (billing and medical record).*

Apr 2001- *Associate Clinical Professor, University of California Los Angeles*

Present *Clinical instructor/preceptor for Nurse Practitioner program.*

June 1997- *Affiliates in Medical Specialties Medical Group.*

Sept 2005 *Family Nurse Practitioner*

Responsibilities: *Primary care / Internal Medicine / Urgent Care- manages all levels of care, both chronic and acute, including: women's health, diabetes, obesity, hypertension, orthopedics, pediatrics, etc.*

Jun 1996- *Columbia West Hills Medical Center*

Jun 1997 *Registered Nurse, Emergency Room*

Responsibilities: *Care of emergent and acute patients of all age groups.*

Christine Farrell M.S.N., F.N.P.-C, L.N.C.

Oct 1995- University of California, San Diego Medical Center

Jun 1996 Transplant Nurse Coordinator

Heart/Lung Transplant Division- Adult / Pediatric

Responsibilities: Patient education, work-up, follow-up, physical assessment, in-patient assessment and nursing education. Includes specialized knowledge of immunosuppression, pharmacology, cardiac/pulmonary pathophysiology, laboratory values, and crisis intervention. Assistant editor of "transplant talk", organ procurement runs, community marketing and education

MARCH 1990-AUG 1994 Northridge Hospital Medical Center

Aug 1991- Northridge Hospital Trauma Center, Northridge, CA.

Aug 1994 Registered Nurse, Emergency Room

Clinical Care Coordinator

Responsibilities: Care of emergency room/trauma patients, including: orthopedic, OBGYN, pediatrics, urgent care, cardiac, trauma, near-drowning, burns, general medicine. Clinical care coordinator/charge for unit. Part-time assistance in the hyperbaric chamber/center in emergency and wound care of patients.

Mar 1990- Northridge Hospital, Northridge, CA.

Mar 1992 Registered Nurse, CCU, ICU, Trauma ICU

Responsibilities: Care of critically ill patients including: open-heart, Swan-Ganz monitoring, vasopressors, ventilators, code blue response team

Jul 1992 - Air Ambulance Incorporated, Van Nuys, CA.

Aug 1994 Critical Care Flight Nurse, on call (while still full time at NHMC)

Responsibilities: Independent care of critically ill patients during flight transport nationally and internationally. Included: Swan-Ganz monitoring, intubated patients, ACLS institution as needed.

Jun 1989 - Huntington Memorial Hospital, Pasadena, CA.

Mar 1990 Registered Nurse, Medical ICU

Responsibilities: Care of medically ill patients in critical condition. Included: respiratory, neuro, infectious disease, GI.

Christine Farrell M.S.N., F.N.P.-C, L.N.C.

E d u c a t i o n

California State University, Long Beach

Family Nurse Practitioner/Masters in Nursing

FNP training acute/emergent care focused

May 1997

University of California, Los Angeles

Bachelors in Science

Graduated June 1989, **cum laude**

P r o f e s s i o n a l m e m b e r s h i p / C e r t i f i c a t i o n s -

DEA# MF0544646

NPI# 1215197033

National Board Certification Family Nurse Practitioner (FNP-C)

Associate Clinical Professor, **UCLA**

Member International Menopause Society

Member American Academy of Nurse Practitioners

Member North American Menopause Society

Member American College for the Advancement of Medicine

Member American Academy of Anti-Aging Medicine

Member of California Coalition of Nurse Practitioners

Member of Association Legal Nurse Consultants (local and national)

Member, North American Transplant Coordinators Organization

Anti-Aging/Aesthetic/Bio-Identical Hormone Training Course/Certification 2005

Restylane Training/Certification 2005

Sculptra Training/Certification 2005

Cutera Laser Training/Certification 2005

Bio-IdenticalHormoneTraining/Preceptorship 2004

Botox Training/Certification 2003

Trauma Nursing Care Course (TNCC) 1994

Certified Critical Care Nurse (CCRN) 1991

Advanced Cardiac Life Support 1994

Pediatric Advanced Life Support 1997

Trauma Management Course 1991

A c c r e d i t a t i o n s

Who's Who of Professional Women 2004

Pi Lambda Theta Honor Society, member

Mobile Intensive Care Nurse of the Year, 1993

Outstanding College Students of America, member

Golden Key National Honor Society, member

References available upon request

Exhibit 1-G



Women's Wellness Center
www.womenswellnessnow.com

Statement From Laura Grant, MD

Qualifications

My name is Dr. Laura Grant. My professional background is as follows. I received my Bachelor of Science in biology, *magna cum laude*, from Southwest Texas State University in 1986. I received my Medical Degree from the University of Texas Health Science Center, San Antonio in 1990. I completed my residency in obstetrics and gynecology at the University of Texas Health Science Center, San Antonio in 1994. I am board-certified by the American Board of Obstetrics and Gynecology, continuously since 1996. I have been a Certified Menopause Practitioner by the North American Menopause Society (“NAMS”) since 2009.

I have been practicing obstetrics and gynecology since 1994 in Columbia, Missouri. I now focus exclusively on gynecology and women’s health. Recognizing the value of a multidisciplinary approach to women’s healthcare, I founded Women’s Wellness Center in 2007. I now specialize in perimenopausal health, and as stated above, I earned and continue to maintain the credential of NAMS Certified Menopause Practitioner, awarded by NAMS, the preeminent scientific organization focused on menopausal health. Those who hold this certification have demonstrated and maintain special competency in the field of menopause.

Another focus of my practice is on non-invasive office-based treatment of pelvic floor dysfunction, which is the root cause of bladder and bowel control problems such as urinary incontinence, overactive bladder, urinary urgency/frequency, and fecal incontinence. Pelvic floor dysfunction is also the cause of many chronic pelvic pain conditions, such as chronic sexual or genital pain, chronic pelvic pain, and chronic bladder pain or interstitial cystitis.

Experience Treating with Compounded BHRT

Starting in 1994, for the first 13 years of practice I provided full OB/GYN services in private practice, including treating menopausal symptoms. For the past 12 years of private practice, I have specialized in menopausal hormone therapy, and focused on that as a major part of my practice. When I use the term “bioidentical hormone” it refers to a hormone formulation where the hormone molecule is identical to what the body produces. There are commercially available bioidentical hormones, and there are compounded bioidentical hormones. It is my professional medical opinion, based on my research of published data and my experience, that bioidentical hormones are the best hormone treatment option for patients, because they replace the same compounds the human body lacks after menopause. Synthetic products (such as Premarin, Provera) were the only options when hormone therapy first came into use, but since biochemical advances have made it possible to isolate and produce the identical match of the body’s hormones, it is my professional medical opinion that that is the best and safest approach, and we should abandon hormone substitutes. For example, published studies have linked synthetic progestins, not bioidentical progesterone, to breast and cardiac risk.

I have treated thousands of patients in my career, and I would estimate that at least half of my patients are relying on compounded BHRT as their “life saving” therapy. (I put that in quotes because they would *live* without hormone replacement, but by their own descriptions, their quality of life would be so poor that it would not be worth living.) The fact is, there are many patients that absolutely cannot get relief of symptoms with commercially available products, therefore, other choices are needed in our armamentarium.

Hormone therapy does not offer a one-size-fits-all solution. Typically when I start a patient on hormone therapy, initially I prescribe commercially available bioidentical products as my first line therapy, such as the estradiol patch and oral micronized progesterone. However, for reasons discussed below, sometimes a commercial regimen is not sufficient for the needs of certain patients. Then, we try different options until the patient is satisfied and symptoms are controlled. This often leads me into the compounded products, and I am so glad to have these options for my patients.

Medical Conditions and Patient Populations Treated with Compounded BHRT

My goal is to treat my patients with the most effective, safest, and most convenient solution. The method chosen will vary significantly from patient to patient. Accordingly, I often prescribe the following compounded BHRT instead of the commercially available for the following reasons.

- **Estradiol.** I prescribe estradiol to treat symptoms of estrogen depletion, such as hot flashes, night sweats, brain fog, mood instability, decreased libido, vaginal atrophy (dryness and painful intercourse), sleep disturbance, and cyclic headaches (estrogen withdrawal headaches that occur when endogenous estradiol levels are low).

Bioidentical estradiol is available commercially in patch, gel, or spray formulations, but these products are sometimes not absorbed or tolerated well by patients. Sometimes with the patch they develop a skin rash, or the patch will not adhere well to the skin, making it ineffective. Sometimes the patch or gels are not effective in controlling symptoms. Based on my professional medical knowledge and experience, in these cases I prescribe compounded estradiol in a cream.

Although bioidentical estrogen is commercially available in oral tablets, I prefer not to prescribe oral estrogen to midlife women due to their increased risk for thrombosis. This and other first-pass metabolism effects of oral estrogen can be avoided if the hormone is compounded into a transdermal estradiol cream. If skin absorption is not effective, or the cream is not tolerated by the patient, I prescribe compounded estradiol troches, which, like transdermal, avoids the first-pass effect when used properly.

- **Progesterone.** I prescribe progesterone for premenopausal patients to regulate and/or reduce volume of menstrual flow, to treat PMS, mood disturbance, anxiety, or sleep disturbance. For postmenopausal women who have not had hysterectomy, I prescribe oral progesterone to accompany estradiol and thereby protect the endometrium, as unopposed estrogen would increase risk of endometrial cancer.

There are several indications for compounded progesterone, as opposed to commercially available products. Micronized progesterone is commercially available only in 100 mg and 200 mg oral dosage. In cases where lower potency is needed, I can order progesterone as a compounded capsule of lower dose. Further, I can order a topical progesterone cream for even lower potency, and this is very effective for treating women in the menopause transition, or those who have anxiety, PMS, night sweats, or sleep disturbance. Oral micronized progesterone in doses potent enough to protect the uterine endometrium, can give many patients CNS side effects, such as dizziness and fatigue. For these women, I often prescribe a progesterone vaginal suppository, which avoids the first-pass liver effect that is responsible for the sleepiness and other CNS side effects. And finally, those with a peanut allergy cannot take the commercially available micronized progesterone because it contains

peanut oil. Compounded oral progesterone products typically contain olive oil or a progesterone powder, and are well tolerated.

- **Testosterone.** I prescribe compounded testosterone topical cream or troches for women with low libido, or postmenopausal mood disturbance. Currently, there are no bioidentical testosterone products available for women commercially. Therefore, custom compounded testosterone products are the only option available.

In my professional medical experience, testosterone is often needed for optimal well-being and quality of life in female patients. According to their testimonies, compounded testosterone has saved so many of my patients and their intimate relationships. There really is no substitute for compounded testosterone.

- **Vaginal Hormone Creams/Suppositories (Estradiol, Testosterone, DHEA).** I prescribe vaginal hormone creams or suppositories to treat vaginal atrophy after menopause, which is a cause of painful intercourse and loss of intimacy. The other important use of vaginal hormones in my practice is to improve the health of bladder and vaginal mucosa for those undergoing pelvic floor therapy.

As mentioned above, a major part of my practice is providing office-based pelvic floor therapy for conditions related to pelvic floor dysfunction. Efficacy of this treatment necessitates a healthy vaginal mucosa, which is lacking in a hormonally depleted woman. Without the availability of compounded bioidentical hormone products, there are many patients who would not be able to receive vaginal tissue rejuvenation that allows them to receive pelvic floor therapy. One reason for this is that sometimes the commercially available products are simply not effective for some patients. Another issue is that the commercially available products sometimes cause skin or vaginal irritation, and in those cases we can prescribe a compounded vaginal gel or cream in a hypoallergenic base. Further, there are some patients who do not wish to use estrogen, or in whom estrogen is contraindicated. For these, I prescribe vaginal DHEA or testosterone, which are equally effective as estrogen in restoring vaginal health. There is no vaginal testosterone (or any bioidentical testosterone for females) available commercially. And finally, all of the commercially available FDA approved vaginal hormone products are often prohibitively expensive.

Healing vaginal atrophy and pelvic floor dysfunction represents a major proportion of my practice, and truly it would be tragic to deny women access to tolerable and affordable vaginal hormonal creams and suppositories. In some cases, it literally can make or break a woman's success in pelvic floor therapy outcome, not to mention the ability to have comfortable and pleasurable intimacy with their partner. Again, choices are needed, it's not one size fits all.

Why is Compounded BHRT Sometimes Preferred Over Commercially Available BHRT?

Based on my professional medical judgment and clinical experience, there are many instances in which it is necessary to have the option of compounded BHRT to prescribe for our patients. As a specialist in menopausal hormone therapy, my medical practice exposes me to multitudes of women who have already been to their general ob/gyn or primary care physician looking for a solution to their symptoms related to the menopausal transition. Their doctor or doctors typically have prescribed one or more of the commercially available options, and the patient has found it to be insufficient.

As detailed above, reasons for insufficiency are many: ineffectiveness, non toleration of side effects, insufficient dosage options to relieve symptoms, lack of variety in dosage and routes of administration, and complete non-availability of testosterone.

My medical practice will be significantly hindered without the compounded hormone option, and female patients will be very poorly served to see this option removed. When the patient example above returns

to her ob/gyn or PCP for a better solution than commercial product given, the doctor responds, "That's your only choice, take it or leave it." I believe that we, as professionals entrusted with the care of midlife women experiencing life altering menopausal symptoms, can do a better job, and we must not be hobbled in trying to do so.

Sincerely,

Laura Grant, MD

Exhibit 1-H



Statement From Arlene Jean Jacobs, M.D.

Qualifications

My name is Dr. Arlene Jean Jacobs. My professional background is as follows. I received my Bachelor of Science from Tulane University, Newcomb College in 1981. I received my Doctor of Medicine, *summa cum laude*, from Tulane University School of Medicine in 1985, where I graduated second in my class. I completed an OB/GYN internship from 1985 to 1986 at Southwestern University, Parkland Memorial Hospital. I completed an OB/GYN residency from 1986 to 1989 at Southwestern University, Parkland Memorial Hospital. I have been licensed to practice medicine in Texas since 1985. I have been board-certified in obstetrics and gynecology since 1992. I have been working as an OB/GYN in private practice at Plano Women's Healthcare, P.A. since 1989. My private practice focuses on women's health, obstetrics, gynecology, surgery, preventive health care, hormone therapy, bladder health, brain health, bone health, and mental health.

I have been honored as D Magazine's Best Doctor in 2003, 2004, 2014, 2015, 2016, 2017, 2018, and 2019. I was Plano Star Courier's Best Women's Healthcare Doctor in 1999, 2003, 2009, 2016, and 2017. I have been awarded Texas Monthly's Best Doctor numerous times since 2003 and have been awarded as a Texas Super Doctor in 2006 and 2007. I have been honored as one of America's Top Obstetricians & Gynecologists in 2015, 2016, and 2017. For a complete list of my honors and awards, please see my enclosed CV.

I have also served numerous roles within the Medical Center of Plano. I have served as Chief of OB/GYN and Chief of Medical Staff, and I have served various roles on the Board of Trustees. For a complete list of my additional committee participations, please see my enclosed CV. I am a member of the following professional societies: the American Medical Association, the Texas Medical Association, the Dallas County Medical Association, the American College of Obstetrics and Gynecology, and the Society of Laparoendoscopic Surgeons.

Experience With Treatment Of Compounded Bio-Identical Hormone Therapy

My entire private practice treats our patients with compounded BHRT. In my professional medical opinion, there is no effective commercially available BHRT. Compounding allows for optimization to change dosage forms and dosage strengths throughout patient treatment.

I treat over 300 patients per month with BHRT, of which approximately 200 of those are in the form of compounded pellet therapy. I have been treating patients successfully with compounded BHRT for approximately seven years. Based on my professional medical experience and judgment, I have chosen not to treat patients with synthetic and/or conjugated hormones for at least the past eight to nine years because of their associated negative side effects and general ineffectiveness, and the lack of ability to optimize dosage forms and strengths to meet patient needs.

Medical Conditions and Patient Populations Treated with Compounded BHRT

Based on my professional medical judgment, I have set out below the compounded BHRT that I prescribe to treat certain medical conditions and symptoms in my patients.



- **Compounded Progesterone.** I treat patients with compounded progesterone in transdermal creams, oral capsules, vaginal suppositories, and troches to treat the following conditions and symptoms:
 - Premenstrual syndrome
 - Dysfunctional bleeding
 - Heavy menses
 - Menopausal symptoms
 - Postmenopausal symptoms
 - Sleep and hormonal imbalance in hysterectomy patients

The FDA-approved progesterone currently available on the market is a generic version of Prometrium, which is currently approved in 100 mg and 200 mg oral capsules. These capsules are not as well absorbed by patients and often cause negative side effects, such as abnormal bleeding and inadequate improvement of symptoms. Instead, many of my patients absorb the compounded progesterone better when taken vaginally or orally. Further, the generic version of Prometrium contains peanut oil, which is contraindicated in patients with peanut allergies. Compounding allows for the medication to be made without such an allergen.

- **Compounded Estradiol.** I treat patients with compounded estradiol to treat the following medical conditions and symptoms in my patients:
 - Menstrual migraines
 - Perimenopausal bleeding
 - Menopausal symptoms, such as hot flashes, night sweats, sleeping issues, vaginal dryness, pain with intercourse, and mood instability
 - Bone loss, such as osteopenia and osteoporosis
 - Patients with family histories of dementia and Alzheimer's
 - Cardiovascular issues
 - Cholesterol issues

Regarding bone loss specifically, there is no commercially approved hormone therapy that combines bioidentical testosterone and bioidentical estradiol. The combination of these two bioidentical hormones helps rebuild bones naturally, which I validate through bone density testing routinely conducted with my patients to monitor their responsiveness to the hormone therapies.

I prefer to treat my female patients with compounded bioidentical estradiol because the commercially available versions, i.e., Vagifem and Femring, do not resolve symptoms and are not



absorbed in my patients as well as the compound. Specifically, Vagifem is a local medication only—it does not have any systemic benefits, it does not absorb as well through the vagina, and it does not help longevity in my patients. Vagifem is only available in a few dosage strengths, so tailoring the hormone to the needs of my individual patient is difficult, if not sometimes impossible. Additionally, commercially available Femring is absorbed within the body systemically, but patient compliance with this treatment regimen is an issue as patients often cannot tolerate the side effects, such as discomfort and irritation, and it is difficult to place in the vagina. And, like Vagifem, Femring is not as effective due to absorption issues in the vagina. Therefore, I prefer to treat my patients with compounded bioidentical estradiol in dosage forms that my patients can successfully absorb and in strengths tailored to what my patient needs.

- **Compounded Testosterone.** I treat patients with compounded testosterone to treat the following medical conditions and symptoms in my patients:
 - Hormone imbalances in breast cancer survivors
 - Premenopausal symptoms
 - Perimenopausal symptoms, such as low energy, low stamina, impatience, low sex drive, low sex desire, cognition issues, and sleep issues
 - Migraine prevention
 - Bone loss
 - Cardiovascular issues
 - Cholesterol issues
 - Alzheimer's
 - Dementia

Compounded bioidentical testosterone must be made available for female patients because there is no commercially available testosterone approved to treat female patients. Further, as stated above, regarding bone loss, there is no commercially approved hormone therapy that combines bioidentical testosterone and bioidentical estradiol. The combination of these two hormones helps rebuild bones naturally, which I validate through bone density tests routinely conducted with my patients to monitor their responsiveness to the hormone therapies.

Additionally, compounded bioidentical testosterone is successful in treating male patients for androgen deficiencies, low sex drive, weight management, cholesterol issues, cognitive issues, bone loss, and to treat patients with family histories of Alzheimer's and dementia. I prefer to treat my male patients with compounded bioidentical testosterone because commercially available testosterone approved for treatment in men is too structured in dosing and does not allow the flexibility in treatment that is required in hormone therapy. In my professional medical opinion, in order to best treat my patients, I need to be able to adjust their hormone therapy based on the patient's lifestyle changes, illnesses, activity level, etc., and the commercially available



testosterone dosage strengths do not allow me this flexibility like the compounded bioidentical testosterone does.

Why is Compounded BHRT Preferred Over Commercially Available BHRT?

In my professional medical judgment, I prefer to treat my patients with compounded BHRT instead of the commercially available BHRT because of the way the compounded BHRT is processed by the body. Synthetic hormones are processed through the liver, whereas compounded bioidentical hormones bypass the liver. This is critical for patients who have suffered a stroke or some form of blood clot and therefore require hormone therapies to bypass the liver.

Further, I prefer to treat my patients with compounded BHRT because they feel better on compounded BHRT. It is a safer treatment as there is no risk of clotting and compounded BHRT carries far less side effects. There are not enough dosage forms and strengths of commercially available BHRT to treat the idiosyncratic nature of hormones. With compounded BHRT, I have the ability to adjust and optimize the patient's medication dosages rather than relegating my patients to cookie cutter, commercially available medication that does not work for them. With compounds, I am able to perform blood tests on my patients every 5-6 weeks to evaluate and re-evaluate how the patients is responding to the hormone therapy.

Finally, having the ability to treat patients with pellet therapy allows the hormone treatment to go straight into the bloodstream in a consistent manner. I prefer this dosage form so as to avoid the peaks and troughs of absorption caused by treatment in transdermal creams and troches.

Sincerely,

Arlene Jean Jacobs, M.D.

Curriculum Vitae
Arlene Jean Jacobs, M.D.
Plano Women's Healthcare, P.A.
1600 Coit Road, Suite 202 Plano, TX 75075

Licensure: Texas, 1985
Board Certified, 1992, Obstetrics/Gynecology

Education: Tulane University, Newcomb College, B.S. 1979-1981
Tulane University School of Medicine, 1981-1985

Postgraduate Education:
Southwestern University, Parkland Memorial Hospital
Internship: 1985-1986 (OB/GYN)
Southwestern University, Parkland Memorial Hospital
Residency: 1986-1989 (OB/GYN)

Work History: Private Practice, 1989 to present, Plano Women's Healthcare, P.A.

Awards and Honors:

Summa Cum Laude, 1985
Phi Beta Kappa
Omicron Delta Kappa
Tulane Scholar
Alpha Omega Alpha
Graduated 2nd in medical school class
D Magazine Best Doctor 2003, 2004, 2014, 2015, 2016, 2017, 2018
Plano Star Courier Best Women's Healthcare Doctor 1999, 2003, 2009, 2016, 2017
Texas Monthly Best Doctor 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010
Texas Super Doctors 2006, 2007
Top Ob/GYN 2006, 2007, 2008, 2009, 2010, 2016
Patients Choice Award – 2010
America's Top Obstetricians & Gynecologists – 2015, 2016, 2017

Medical Center Of Plano:

Board of Trustees, 2004-2008, 2010-2014, 2016-2020
Board of Trustees Vice-Chair, 2018
Board of Trustees, Chairman of the Board, 2019
Past Chief, Medical Staff, 2003
Chief, Medical Staff, 2002
Vice Chief, Medical Staff, 2001
Chief, OB/GYN, 1996-1997

Committees:

Executive Committee, 1996-1997, 2002-2003
Operating Room Committee, 1996-1997
Peer Review Committee, 1995-1996
Credential Committee 1993-1995
Infection Control Committee, 1990-1993
Sweet Success – Maternity Diabetes Program Director, 2004
Diabetes Committee, 2005-2015

IT Committee, 2005
Day Surgery of Plano – Governing Board Committee 2004-Present
Crimson Tide Project 2010, 2011
TMCP Advisory Board 2009-present
Graduate Medical Education Committee, 2011-present
Continuing Medical Education Committee, 2012-present
Robotics Committee, 2012-Present

Professional Societies:

American Medical Association
Texas Medical Association
Dallas County Medical Society
American College of Obstetrics and Gynecology
Society of Laparoendoscopic Surgeons
Past Speaker; Cord Blood Banking

Personal & Professional References: Furnished upon request

Exhibit 1-I

Steven A. Komadina, M.D.
4801 McMahon Blvd. NW #101
Albuquerque, New Mexico 87114
(505) 893-2840

November 1, 2019

Statement From Steven A. Komadina, M.D.

Qualifications

My name is Dr. Steven A. Komadina. My professional background is as follows. I went to but did not receive an undergraduate degree from the University of New Mexico, because of early admission to medical school after just 3 years of undergraduate study. I received my Doctor of Medicine, with honors, from the University of New Mexico School of Medicine in 1970. I completed a rotating internship at the Naval Medical Center in San Diego, California from 1970-1971, where I was chosen as the Outstanding Surgical Intern. I also completed an OB-GYN residency at the Naval Regional Medical Center in San Diego, California from 1971-1974. I became fully board certified by the American Board of Obstetrics and Gynecology in 1976. In 1977 I became a Fellow of the American College of Obstetrics and Gynecology.

In 1969-70, I served as a missionary doctor in Katmandu, Nepal. After eight years of active duty in the U.S. Navy, I returned to Albuquerque to practice as a full-time private practice OB-GYN from 1977-2001. Since 2001, I have practiced gynecology and preventive medicine, doing lifestyle medicine and office gynecology. I treat male and female patients with a specific focus on hypothyroidism, male and female hormone balance, cardiac function, infertility, healthy lifestyle, and nutrition counseling. Also, since 2001, I have become an internationally recognized lecturer on weight loss, health, and nutrition, and more specifically on preventative medicine and dietary prevention of disease. I have lectured to the public and to physicians on five continents. I am licensed to practice medicine in New Mexico.

I have served as Hospital Chief of Staff, President of the Greater Albuquerque Medical Association, and a Councilor of the New Mexico State Medical Society and President of the New Mexico Medical Society. I have served as a member of the clinical faculty in the Department of Ob-Gyn at the University of New Mexico School of Medicine, UCLA, UC San Diego and UC Irvine.

From 2008-2019, I have served on the New Mexico Board of Medicine, which licenses all doctors and physician assistants in New Mexico. Most recently I served as Secretary, until completing my term a few months ago.

I have professional memberships with the American Medical Association, American Fertility Society, New Mexico Medical Society (where I served as President from 2000-2001), Greater Albuquerque Medical Association, Southwest Ob-Gyn Society, and the International Society of Clinical Densitometry.

In addition to the practice of medicine, I also served 8 years from 2001-2008 as a New Mexico State Senator. For a full list of my public elected offices, please see my enclosed CV.

Experience With Treatment Using Compounded Bio-Identical Hormone Therapy

I have been prescribing hormone therapy to my patients since 1970. In my medical experience and judgment, where it is best for the patient, I prefer to treat them today with compounded Bio-Identical Hormone Therapy ("BHRT"). In the last twenty years, I have treated over 40,000 patients with compounded BHRT. In the last 7 years, I have used compounded sterile hormone pellets, compounded hormone troches and compounded vaginal creams almost exclusively. My patients treated with compounded BHRT routinely thank me for saving their lives, as the compounded BHRT treatment allows these patients to stop taking cholesterol medication and SSRIs and benzodiazepines for mood disorders, among others. My patients treated with compounded BHRT report to me that they feel hormonally balanced and feel like they have gotten their lives back.

Medical Conditions and Patient Populations Treated with Compounded BHRT

I use compounded BHRT to treat patients of all ages depending on their individual symptoms and laboratory tests. Specifically, I use compounded capsules of progesterone to successfully treat heavy vaginal bleeding in female patients of all ages and inadequate luteal phase in infertility patients. Depending upon the age and symptoms of the patient, it may be more appropriate and/or effective to treat with non-pellet therapy, such as prescribing compounded BHRT troches to treat menopause, andropause, perimenopause, and polycystic ovarian disease. Compounded hormone cream is also used for lichen sclerosis et atophica and senile vaginitis in elderly patients.

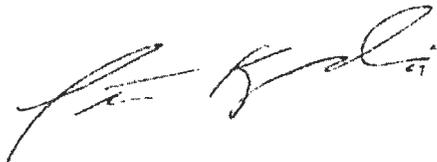
Based on my medical judgment, and when best for the patient, I choose to prescribe subcutaneous pellet therapy in both men and women with low hormone symptoms and to prevent diseases caused by low hormones, such as osteoporosis. I also successfully treat a large number of male and female patients with compounded BHRT for anxiety and depression. As a result, I am often able to get these patients off of their psychiatric medications they have been prescribed.

Why is Compounded BHRT Preferred Over Commercially Available BHRT ?

In my professional medical judgment, I choose to treat my patients with compounded BHRT instead of commercially available BHRT, because I can customize the dosage based on age, weight, symptoms and lab results in order to best treat my patients, I need to be able to customize the dose and the dosage form of the medication throughout treatment and only compounded BHRT allows me to do that. I have observed that my patients demonstrate a significantly better results and tolerance to compounded BHRT therapy than when these patients were treated with commercially available BHRT. My patients also experience more consistent results from treatment with compounded BHRT than when treated with commercially available BHRT.

Prior to becoming familiar with treating patients with compounded BHRT, I used to treat patients with commercially available hormone therapy such as Premarin and Provera. When I switched to treating patients with compounded BHRT, the health of these patients significantly and quickly improved at rates that I was not seeing when treating patients with commercially available hormone therapies. If I had to return to treating my patients with only commercially available BHRT, I know that I would witness a decline in my patients' health and wellbeing.

Respectfully,

A handwritten signature in black ink, appearing to read 'Steven Komadina', with a stylized flourish at the end.

Steven Komadina, M.D.



**NEW MEXICO STATE SENATOR
STEVEN A. KOMADINA, M.D.
CURRICULUM VITAE**

PUBLIC ELECTED OFFICE:

2001-2008 New Mexico State Senator, District 9
Senate Judiciary Committee 2001-2004
Senate Public Affairs Committee 2001-present
Senate Rules Committee 2005- present
Legislative Health and Human Services
Committee
Revenue Stabilization and Tax Policy Committee
Tobacco Settlement Revenue Oversight
Committee
Information Technology Oversight Committee
Water and Natural Resources Committee

**2003-2005 National Conference of State Legislatures
Health Committee**

**2003-2004 Council of State Governments
National/Associates Advisory Council**

**2004-2008 ALEC Health and Human Services
Committee**

WHO'S WHO LISTINGS:

**Marquis Who's Who.....
In American Colleges and Universities
In America
In the West
In American Politics
In Science and Engineering
In Medicine and Healthcare
In Professionals and Executives
In Finance and Industry
America's Top Ob-GYNs 2004-2018**

EDUCATION:

Undergraduate: 1963-1966 University of New Mexico

**Medicine: 1966-1970 University of New Mexico School of
Medicine, M.D.**

**1970-1971 Rotating -O- Intern
Naval Regional Medical Center, San Diego, Ca.**

**1971-1974 OB-GYN Residency,
Naval Regional Medical Center, San Diego, Ca.**

Honors:

**President of Freshman, Sophomore, Junior and Senior
Men's Scholastic Honorary University of New Mexico
Three years in University of New Mexico Student
Senate
G.E. College Bowl
Early admission to Medical School (age 19)
President of Medical School Class four years
Graduation from Medical School with honors
President of Intern Class
Chosen Outstanding Surgical Intern**

**NM Medical Society Community Service Award 2000
Outstanding Freshman Senator Designee 2001**

LICENSURE / CERTIFICATION:

**Medical License: New Mexico
California (not current)**

**Certification: Diplomat American Board of
Obstetrics and Gynecology 1976**

**Member American College of Physician
Executives 1989**

Certified Clinical Densitometrist 1999

Professional Memberships:

**American College of Physician Executives.
American Medical Association 1970-2010
American College of Obstetrics and Gynecology
1974-2013
American Fertility Society
New Mexico Medical Society
Greater Albuquerque Medical Association.
Southwest Ob-Gyn Society
International Society of Clinical Densitometry**

Professional Activities:

**September 1969-May 1970 Physician District
Clinics United Mission to Nepal, Kathmandu
July 1974-June 1977 Deep selected as
Commander and Captain in the US Navy
Medical Corps, Long Beach Naval Regional
Medical Center.
January 1976-June 1977 Chairman OB-GYN
Dept. Long Beach Naval Regional Medical
Center
July 1977-December 1988 Private Practice OB-
GYN Albuquerque, NM
January 1989-December 1989 Vice President
St. Joseph Healthcare System, Albq., N.M.
January 1987-September 1987 CEO Foundation
Health Plan**

January 1982-December 1986 Member of Congressional Issue Advisory Board for Congressman Manual Lujan, Jr.

January 1989-December 1989 Part time Gynecology practice

January 1995-2005 Associate Clinical Professor UNM School of Medicine, Department of OB-GYN

January 1996-97 President of The Greater Albuquerque Medical Association.

April 1997- Medical Director “Global Hilton” around the world balloon flight attempt

May 1998- Medical Director “Spirit of Peace” around the world balloon flight attempt

January 1990-2001 Full-time Private Practice OB-GYN, Albq, NM

March 2000-2001 President New Mexico State Medical Society

October 2001-present: Private practice of Lifestyle Medicine and Office Gynecology. Treating both men and women. Special focus on hypothyroidism, male and female hormone balance, cardiac function, infertility, healthy lifestyle and nutrition counseling.

2001-present: Internationally recognized lecturer on weight loss and health and nutrition. Frequently seen on television and lectures monthly around the world. Lectures on preventative medicine and health and nutrition with an emphasis on weight loss and dietary prevention of disease. He has lectured to the public and physicians on 5 continents.

2003 – 2010: Clinical associate with Dr. David Heber at UCLA Center for Human Nutrition

2003—2010: Educator on Nitric Oxide working under Nobel Prize Laureate for Medicine 1998, Dr. Louis Ignarro

2004-Present International Teacher of Neonatal Resuscitation to medical school faculty and public health workers worldwide

2009-2019 New Mexico Medical Board member. Elected Secretary of the Board 2018-2019.

HONORS:

Community: Selected by the Albuquerque Tribune as the "Rising Star" in Health for New Mexico, 1989.

Elected by State Medical Society to the Wyeth-Ayerst Award for outstanding community service outside of medicine 1999

AUTHOR:

Born to be Healthy and Thin: South Carolina:
BookSurge (2005)

CAREER GOALS: To teach my patients that health lies not in the treatment of disease, but in the proper nourishment of our bodies, lifestyle choices and prevention of disease.

To help patients understand that illness is based chiefly on lack of nutrition, malnutrition, and unhealthy lifestyles.

To empower patients to wisely make informed health care decisions.

Exhibit 1-J



MELVILLE MEDICINE

THE CHIEF FOR YOUR PRESENT & FUTURE WELLNESS

Statement From Dr. Daniel Elias Melville, M.D.

Qualifications

My name is Dr. Daniel Elias Melville, M.D. My professional background is as follows. I received my Bachelor of Science in biology and general engineering, with distinction, from the United States Air Force Academy, in Colorado in 1999. I received my Doctor of Medicine from the Louisiana State University College of Medicine in 2004. I completed a family medicine internship and family medicine residency at the Louisiana State University Health Sciences Center from 2004 to 2007. I was the Chief Resident of the Louisiana Department of Family Medicine – Rural Tract at the Louisiana State University Health Sciences Center from 2006 to 2007.

I was an independent physician contractor in emergency medicine at North Caddo Medical Center in Vivian, Louisiana from 2006 to 2007. I then worked as a physician contractor in emergency medicine at Bourbon Community Hospital in Paris, Kentucky from 2008 to 2010. During this time, I also worked as a staff family medicine physician at Paris Primary Care in Paris, Kentucky from 2007 to 2009. I also worked as an Assistant Professor and Medical Director of Inpatient and Outpatient Service Lines at the University of Kentucky Department of Family & Community Medicine in Lexington, Kentucky from 2009-2012. From 2012 to 2014, I worked as the Medical and Laboratory Director of Doctors Express in Southlake, Texas. Subsequently, from 2014 to 2018, I worked as the Medical Director and Lead Physician of Destination Health in Southlake, Texas. Currently, I am an emergency room physician at Texas Health Harris and I am the Owner and Medical Director of Melville Medicine, which is a comprehensive and integrated concierge family medicine practice striving to find the best and safest balances of increasing life expectancy with improving quality of life.

I have current clinical privileges at Texas Health Resources Southlake. I am a Diplomat of the American Board of Family Medicine. I am a member of the National Speaker Bureau for Bale Doneen Cardiovascular Prevention Method. I am certified with Reversing Cognitive Decline (ReCODE) Program through the Institutes of Functional Medicine. I am a member of the American Academy of Family Physicians, the Texas Medical Society, the North Tarrant County Medical Society, and the Beta Beta Beta National Biological Honor Society.

I am an author of numerous publications on borderline personality disorder as well as literature regarding abdominal trauma and meeting the health challenges of seniors. For a complete list of my publications as well as additional information as to my professional background, please see my enclosed CV.

Experience With Treatment Of Compounded Bio-Identical Hormone Therapy

I have been prescribing compounded bio-identical hormone replacement therapy (“BHRT”) for nearly 15 years in various forms. At the present time, I treat approximately 75 patients total and approximately 35 of my patients are being actively treated with compounded BHRT. I have witnessed great success with resolution of my patients’ symptoms and improvement in medical conditions with the appropriate treatment of compounded BHRT.

Medical Conditions and Patient Populations Treated with Compounded BHRT

I prescribe compounded BHRT as a component of a prevention strategy for heart attack, stroke, and dementia. With the prevalence of heart attacks/strokes/dementia increasing in postmenopausal women, I try to focus on the current statistics in balance with health risks, such as breast cancer. Regarding the cardiovascular system alone, hormone



MELVILLE MEDICINE

THE CHOICE FOR YOUR PRESENT & FUTURE WELLNESS

optimization increases HDL, decreases LDL, smooths and dilates blood vessels so perfusion improves, and decreases free radicals, which ultimately can damage arteries and other healthy tissue (which is the primary cause of Alzheimer's dementia). Before prescribing a targeted therapy, the patients and I review benefits/risks, ensure that the patients are updated on all preventive screens, and educate the patients on the ever-evolving hormone and medical treatment strategies.

In my medical opinion, compounded BHRT is highly effective at treating hormone imbalance in general in male and female patients. That is, I prescribe compounded BHRT to treat low libido, fatigue, cognitive decline, andropause and menopause symptoms, insomnia, and metabolic syndrome (which is a triad of high cholesterol, glucose metabolic deficiencies, and hypertension). I also prescribe compounded BHRT to prevent the inflammatory cascades that increase risks of breast cancer, prostate cancer, heart attack, and stroke.

Why is Compounded BHRT Preferred Over Commercially Available BHRT?

In my professional medical judgment, I choose to treat my patients with compounded BHRT instead of commercially available BHRT because the commercially available hormone therapies do not yield the same results in my patients. Compounding allows me to tailor important hormone therapy to the individual needs of my patients. Because of the critical nature of hormone therapy, I check in with my patients on compounded BHRT at frequent intervals—I then meticulously adjust the patient's hormone therapy based on the patient's inflammatory markers, clinical responses to the hormone therapy, and changes in cholesterol profile, among others. I am not able to make these important adjustments with the same accuracy with commercially available BHRT, but I am able to do so with compounded BHRT.

- **Progesterone.**

I prescribe compounded, micronized bioidentical progesterone in an oral pill instead of the commercially available progesterone because although the commercially available version may be labeled as "micronized," it is often not fragmented as finely as the compounded, micronized bioidentical progesterone. The fragmentation/particle size is critical for the medication to cross the absorption barrier, and it is my professional medical opinion that symptoms in my patients are improved with better absorption of the compounded medication.

I also prefer to treat my patients with lower doses of compounded bioidentical progesterone than is offered by commercially available bioidentical progesterone. Compounding allows me to adjust the amount of progesterone in very small increments, which further allows me to better treat and tailor the medication to the individual needs of my patient.

- **Estrogens**

I typically prescribe compounded estrogens in transdermal form and in pellets because the ratio of estradiol to estrone in commercially available oral estrogen is, in my professional medical opinion, unfavorable to patients. Estradiol and estrone must be carefully balanced, as estradiol carries many of the therapeutic effects while estrone, in the wrong ratio, can carry more toxic effects (although our bodies do need some of it). Compounding allows me to better control the ratio of estradiol to estrone in the therapy I prescribe my patients, whereas commercially available estrogens tend to cause estrone levels in patients to spike to dangerously high levels.



MELVILLE MEDICINE

THE CHOICE FOR YOUR PRESENT & FUTURE WELLNESS

I have anecdotally observed that compounded estrogens in pellet forms help resolve inflammatory markers in my patients, which are the body's internal metrics as to whether the body is responding well to certain treatments. The proper balancing of hormones lowers inflammation within the body, and I am able to control this outcome with compounded bioidentical estrogens in a way that I cannot do with commercially available bioidentical estrogens.

- **Testosterone**

I prescribe compounded bioidentical testosterone, typically in pellet form, for my female patients because there is no commercially available bioidentical testosterone approved for treatment in women. I prescribe compounded bioidentical testosterone, typically in pellet form, to treat my male patients because it produces consistent serum levels in the bloodstream as opposed to the inflammatory spikes that are caused by the commercially available gels and creams. Creams and gels, such as commercially available Androgel, are inflaming and do not absorb into the body as well as pellet therapy. Additionally, creams and gels also carry the risk of being transmitted to other parties aside from the patient, such as partners, children, or pets. Because of this, patient compliance with the commercially available options are low, whereas patient compliance on pellet therapy increases tenfold.

Bioidentical testosterone is also commercially available as an injectable for treatment in men. However, injectables that must be administered weekly or biweekly cause more inflammation than subcutaneous pellets that are administered every 5-7 months in male patients.

In conclusion, in my medical experience, I have seen more patients benefit from the balanced and judicious use of hormone therapies afforded by compounded BHRT. Individualization of hormone therapies is where I have found the most success, and compounded BHRT allows the most precision with this individualization.

Through these experiences, among many other anecdotal observations, I have adopted an approach to hormones that some presence of hormones is better than none, but that too little is just as detrimental as too high (cumulatively speaking). Therefore, individualized and precise hormone therapy treatment (via compounding) is the best way to optimize hormone levels in patients and resolve hormone deficiencies.

I sincerely hope that physicians and clinicians may maintain a certain degree of autonomy when prescribing therapies for our respective patients.

Sincerely,

Daniel Elias Melville, M.D.

Daniel Elias Melville, M.D.

1545 E Southlake Blvd, Ste 110 • Southlake, TX 76092

Doctor@MelvilleMedicine.com • (817) 676-2010

EDUCATION

July 2006-June 2007	Louisiana State University Health Sciences Center , Vivian and Shreveport, LA Department of Family Medicine – Rural Tract Chief Resident
July 2005- June 2007	Louisiana State University Health Sciences Center , Vivian and Shreveport, LA Department of Family Medicine – Rural Tract Family Medicine Residency
July 2004-June 2005	Louisiana State University Health Sciences Center , Shreveport, LA Department of Family Medicine Family Medicine Internship
August 2000- June 2004	Louisiana State University College of Medicine , Shreveport, LA Doctor of Medicine
July 1995- May 1999	United States Air Force Academy , USAFA, CO Bachelor of Science, Biology and General Engineering Distinguished Graduate

LICENSURE AND CERTIFICATIONS

- Texas Medical Board License #P4352 (active)
- Kentucky Medical Board License #41035 (inactive)
- Louisiana Medical Board License #MD.200658 (inactive)
- Diplomate of American Board of Family Medicine
- Member of National Speaker Bureau for Bale Doneen Cardiovascular Prevention Method
- Certified with Reversing Cognitive Decline (ReCODE) Program through IFM
- Certified Provider of BioTE Hormone Replacement Therapy
- Current Clinical Privileges at Texas Health Resources Southlake

EMPLOYMENT

June 2019-Present	Melville Medicine , Southlake TX Owner and Medical Director
April 2014-Present	Texas Health Harris Southlake , TX Emergency Room Physician

March 2014-June 2018 **Destination Health**, Southlake TX
Medical Director and Lead Physician

September 2012-March 2014 **Doctors Express**, Southlake TX
Medical and Laboratory Director

October 2009-September 2012 **University of Kentucky Dpt of Family & Community Medicine**, Lexington, KY
Assistant Professor, Medical Director of Inpatient and Outpatient Service Lines

August 2007-July 2009 **Paris Primary Care**, Paris, KY
Staff Family Medicine Physician

July 2008-April 2010 **Bourbon Community Hospital**, Paris, KY
Physician Contractor-Team Health, Emergency Medicine Coverage

July 2006-June 2007 **North Caddo Medical Center**, Vivian, LA
Independent Physician Contractor-Correct Care, Emergency Medicine Coverage

July 2001-June 2004 **Intelligent Fitness**, Shreveport, LA
Personal Fitness Instructor and Nutritionist Counselor

PROFESSIONAL MEMBERSHIPS

- American Academy of Family Physicians
- Texas Medical Society
- North Tarrant County Medical Society
- Beta Beta Beta National Biological Honor Society

PUBLICATIONS

Melville DE, Elder W. "Borderline Personality Disorder." 5 Minute Clinical Consult. Lippincott Williams & Wilkins. 2015.

Melville DE, Elder W. "Borderline Personality Disorder." 5 Minute Clinical Consult. Lippincott Williams & Wilkins. 2014.

Melville DE, Elder W. "Borderline Personality Disorder." 5 Minute Clinical Consult. Lippincott Williams & Wilkins. 2013.

Melville DE, Elder W. "Borderline Personality Disorder." 5 Minute Clinical Consult. Lippincott Williams & Wilkins. 2012.

Melville DE, Melville SC. "Abdominal Trauma." Current Diagnosis and Treatments in Emergency Medicine, Seventh Edition. McGraw-Hill. 2011. Chapter 25.

Melville DE, Melville SC. "Central Venous Catheter Placement." The Essential Guide to Primary Care Procedures. Lippincott Williams & Wilkins. 2009. Ch 6: pgs. 33-42.

Melville DE. Meeting the health challenges of seniors. Healthpoint. 2009 May: 2.

Exhibit 1-K



Statement from Dr. John Joseph Peet, MD, FACOG

Qualifications

My name is Dr. John Joseph Peet, M.D., FACOG. My professional background is as follows. I received my Bachelor of Arts in zoology from the University of Texas at Austin in 1992, and I received my Doctor of Medicine from Texas A&M University Health Science Center in 1996. I completed both internship and residency in obstetrics and gynecology at the Scott & White Memorial Hospital from 1996 to 2000. I received the Special Service Award from the Scott & White Abstinence Based Sex Education Program in 2000. I also received the Patricia J. Sulak Award for Excellence in Resident Research for best paper in 1999, the Organon, Inc. Resident Research Award for Outstanding Research in Women's Health in 1999, and the Texas A&M University Academic Excellence Award in 1993, 1994, and 1995. In addition to professional awards, I have also received numerous academic awards, which are further detailed in my enclosed CV.

After completing my residency, I practiced at the Sadler Clinic Health Center for Women in The Woodlands, Texas from 2000 to 2010. I then joined St. Luke's – Texas OBGYN Specialists, which is part of the Woodlands Doctor Group, in The Woodlands, Texas from 2010 to 2012. Presently, I am an owner of and practitioner at the Woodlands Medical Aesthetics Institute and owner of and practitioner at the Woodlands Gynecology & Aesthetics, PLLC. I have held these ownership positions since 2013. I have been licensed to practice medicine in Texas since 1997. I have been certified by the American Board of Obstetrics & Gynecology since 2002.

I have held practice affiliations as active staff physician with the Memorial Hermann Hospital The Woodlands and the Conroe Regional Medical Center. I was an active teacher in family medicine at the Lone Star Family Health Center. I am currently affiliated with St. Luke's Community Medical Center The Woodlands in The Woodlands, Texas and Memorial Hermann Conroe Surgery Center in Conroe, Texas as an active physician. I was also the Vice Chair OB/PEDI of Section 2002 at Conroe Regional Medical Center. I am a member of the Texas Medical Association, the Montgomery County Medical Society, the Texas Association of Obstetricians and Gynecologists, and the American Association of Anti-Aging Medicine, and I am a fellow of the American College of Obstetricians and Gynecologists.

For a full recitation of my prior and ongoing research activities and my professional activities, please see my enclosed CV.

Experience With Treatment Of Compounded Bio-Identical Hormone Therapy

I have over 20 years of experiencing prescribing hormone therapy, and I have been prescribing compounded Bio-Identical Hormone Therapy ("BHRT") specifically for ten years. I have over 5,000 patients currently being effectively treated with compounded BHRT.



Approximately 90-95% of my male and female patients treated with some form or combination of compounded BHRT have their symptoms completely resolved. Over 90% of these patients are still complying with their compounded BHRT plan years later, and the side effect profile is only 5-10% (and they are all easily managed, modifiable and not dangerous).

Medical Conditions and Patient Populations Treated with Compounded BHRT

I prescribe compounded BHRT to treat male and female patients of all ages depending on their individual symptoms. Specifically, I prescribe compounded BHRT in the following forms and combinations to treat the following medical conditions in **female patients**:

- **Compounded estradiol in transdermal creams, sublingual troches, subcutaneous pellets, and transvaginal creams:** Compounded estradiol treats menopausal symptoms, such as hot flashes, genitourinary syndrome, cognitive decline, skin changes, hair changes, insomnia, depression, and urinary incontinence. Systemically, estradiol helps to prevent bone loss, heart disease, colon cancer and Alzheimer's dementia.
- **Compounded testosterone in transdermal creams, sublingual troches, subcutaneous pellets, and transvaginal creams:** Compounded testosterone treats female androgen deficiency in pre- and post-menopausal female patients. Androgen deficiency symptoms include fatigue, muscle loss, insomnia, anxiety, depression, decreased libido, poor sexual response, concentration problems, and lack of motivation/drive. Testosterone helps to prevent bone loss, Alzheimer's dementia and likely also breast cancer.
- **Compounded progesterone in oral capsules and sublingual troches:** Compounded progesterone treats chronic insomnia and mood problems. It is also required to treat female patients with an intact uterus who are receiving estradiol to prevent uterine cancer. It also treats menstrual disorders in pre-menopausal women, such as heavy or irregular bleeding. I prescribe compounded BHRT in the following forms to treat the following medical conditions in **male patients**:
- **Compounded testosterone in subcutaneous pellets:** Compounded testosterone in the form of subcutaneous pellets treats androgen deficiency from all causes (i.e., regardless of whether the androgen deficiency is caused by, for example, testicular issues, cancer and radiation issues, or brain issues). Symptoms associated with androgen deficiency that are treated by compounded testosterone subcutaneous pellets are fatigue, muscle loss, insomnia, anxiety, depression, decreased libido, joint pains, concentration problems, motivation problems, and erectile dysfunction. Testosterone also prevents bone loss, Alzheimer's dementia, and likely prostate cancer.



Why is Compounded BHRT Preferred Over Commercially Available BHRT?

In my professional medical judgment, I choose to treat my patients with compounded BHRT instead of commercially available HRT because the commercially available hormone therapy cannot treat my patients as well as the compounded hormone therapy. Specifically, the commercially available HRT carries too many side effects for patients and does not effectively treat their symptoms, which causes patients to forego their prescribed treatment plans and end up with worse health than when the patient first required hormone treatment. It is known that 50% of patients prescribed Premarin will quit in less than one year. Commercially available forms of HRT also contain allergens that cannot be prescribed to certain patient populations (peanut oil in progesterone). And, compounding the hormone therapies allow me to get better hormone serum levels which is simply not an option with commercially available bioidentical hormone therapies. We have very specific goals for serum levels and dose testosterone pellets with a computer algorithm that includes age, weight, starting hormone levels and renal function on labs. All patients are lab tested 4-6 weeks post treatment to insure adequate and balanced levels.

Below, I set out my reasoning, based on my medical experience and judgment, as to why I prefer to treat my patients with compounded estradiol, progesterone, and testosterone as opposed to the commercially available bioidentical hormones.

- **Estradiol**

Estradiol is commercially available as an oral pill. Oral estradiol increases the risk of blood clotting disorders such as deep vein thrombosis as well as risk of pulmonary embolism because they are metabolized by the liver prior to systemic delivery. Because of the increased clotting, they may not be protective against heart attack and stroke as desired. They also can cause liver and gallbladder problems because of first pass liver metabolism.

Compounded transdermal estradiol and compounded estradiol in subcutaneous pellets do not increase the risk of blood clotting disorders such as deep vein thrombosis and do not increase the risk of pulmonary embolism. Compounded transdermal estradiol and compounded estradiol in subcutaneous pellets actually *reduce* the risk of heart attack and stroke and they cause no issues with the liver or gallbladder. They bypass first pass liver metabolism and are absorbed directly into the bloodstream.

I do use synthetic transdermal commercially available estradiol some, but the doses are too low and rarely return the estradiol levels to the premenopausal range. They are better for symptom control than for disease prevention.

- **Progesterone**



Only approximately half of the patients treated with commercially available progestins can tolerate the hormone because the side effects are so severe that they cause patients to discontinue the treatment. The side effects of commercially available progestins include mood changes,

headaches, nausea, bloating, menstrual cramps, fluid retention, and irritability. Progestins, such as Provera have been shown to increase the risk of blood clots and breast cancer. This medicine should have been taken off of the market years ago in my opinion.

Prometrium is a commercially available bioidentical progesterone medication available as an oral capsule. I do use this medication often, but it has its problems. The capsule contains heat sensitive oils that can denature the progesterone during shipping and delivery of the medication. Additionally, the capsules contain peanut oil, so those patients with a peanut allergy cannot be treated with it. Finally, only approximately 80% of the patient population treated with Prometrium can tolerate the medication because of the progestin-type side effects. If left to only Prometrium, approximately 20% of patients needing progesterone treatment would be left untreated.

On the other hand, compounded progesterone sublingual troches and oral capsules that I treat my patients with are tolerated by 99% of my patients with absolutely no side effects.

- **Testosterone**

The only commercially available testosterone for women is Estrotest for the treatment of androgen deficiencies, which is a *synthetic* testosterone (not bioidentical) combined with an oral estrogen. Even if patients can tolerate the side effects of oral estrogen, Estratest rarely effectively treats the patient's androgen deficiency symptoms, and it does not treat the deficiencies to the extent that compounded bioidentical testosterone does. And as stated earlier, I do not use oral estrogens because of the risks. So, this leaves women (millions of them) with no commercial alternative to treat female androgen deficiency syndrome. There are no options except for bioidentical testosterone that is compounded.

I prescribe compounded testosterone for women in creams, sublingual troches, and subcutaneous pellets. I prefer to prescribe compounded testosterone as a subcutaneous pellet because pellets deliver more consistent serum levels with less peaks and troughs compared to the creams and troches. The more peaks in serum levels cause more side effects (acne, abnormal hair growth, oily skin, fluid retention); the more troughs in serum levels means the treatment is less effective. Approximately 90-95% of my female patients being treated with compounded testosterone pellets for androgen deficiency have all androgen deficiency symptoms resolve without any side effects. Any side effects that are caused by the compounded testosterone pellets are minor, temporary, and easy to treat and timely resolve. There are no dangerous or permanent side effects.



Androgel, the commercially available testosterone cream for men, does not reliably absorb well in male patients—rather, the serum levels spike too high and cause side effects or drop too low and the result is poor efficacy. The serum level spikes and troughs both occur within 24 hours of application of the cream. Similar risks are associated with commercially available injectable testosterone for men—the serum level spikes (day 2) are too high and cause acne, hair loss, fluid retention, elevated estradiol levels and elevated red blood cell count. And the serum level troughs (days 5-7) are too low and result in less efficacy of the treatment.

I prescribe bioidentical compounded testosterone for men in creams and subcutaneous pellets. I prefer to prescribe compounded testosterone as a subcutaneous pellet to my male patients because pellets deliver more constant serum levels with less peaks and troughs compared to the commercially available creams and injections. The efficacy is far superior to the commercial creams and the side effects are much more rare. Any side effects that are caused by the compounded testosterone pellets in men are minor, temporary, and easy to treat. There are no dangerous or permanent side effects.

I sincerely appreciate you allowing me to share my experience and thoughts. Thank you for taking the time to fully evaluate compounded bioidentical hormones. Thousands of my patients and millions more would suffer if their availability were to disappear.

Sincerely,

A handwritten signature in black ink, appearing to read "J. Peet MD". The signature is fluid and cursive, with the letters "J" and "P" being particularly prominent.

John Joseph Peet, M.D., FACOG

JOHN JOSEPH PEET, M.D.
Curriculum Vitae

PRACTICE EXPERIENCE

- Jan 1, 2013 to present Owner, Woodlands Gynecology & Aesthetics, PLLC
17350 St. Luke's Way
Medical Arts Center 2, Suite 390
The Woodlands, TX 77384
- Oct 2013 to Present Owner, Woodlands Medical Aesthetics Institute
17350 St. Luke's Way
Medical Arts Center 2, Suite 380
The Woodlands, TX 77384
- June 6, 2010 to Dec 31, 2012 St. Luke's - Texas OBGYN Specialists
Woodlands Doctor Group
17198 St. Luke's Way, Medical Arts Center 1, Suite 440
The Woodlands, TX 77384
- July 1, 2000 to June 5, 2010 Sadler Clinic Health Center for Women
17191 St. Luke's Way
The Woodlands, TX 77384
Sadler Clinic Board of Directors 2/02 - 12/09

PRACTICE AFFILIATIONS

- July 1, 2000 to 2018 Memorial Hermann Hospital the Woodlands
9250 Pinecroft Dr
The Woodlands, TX 77380
Active Staff Physician
- July 27, 2000 to 2017 Conroe Regional Medical Center
504 Medical Center Blvd
Conroe, TX 77304
Active Staff Physician
Vice Chair OB/PEDI Section 2002
- September 11, 2003 to present St. Luke's Community Medical Center the Woodlands
17200 St. Luke's Way
The Woodlands, TX 77384
Active Staff Physician

August 11, 2000 to present Memorial Hermann Conroe Surgery Center
1501 River Pointe Dr
Conroe, TX 77304
Active Staff Surgeon - Owner
Board of Managers 3/03 - 4/06
Block Time Committee 3/03 - 4/06

Nov 1, 2004 to Sept 30,2009 Lone Star Family Health Center
Conroe Family Medicine Residency
704 Old Montgomery Road
Conroe, TX 77301
American Academy of Family Physicians
Active Teacher in Family Medicine

UNDERGRADUATE EDUCATION

June, 1988 to June 1992 Bachelor of Arts in Zoology
University of Texas at Austin
Office of the Registrar
Austin, TX 78712

MEDICAL SCHOOL

July, 1992 to June, 1996 Doctor of Medicine
Texas A & M University Health Science Center
159 Reynolds Medical Building
College Station, TX 77843-1114

INTERNSHIP

July, 1996 to June, 1997 Obstetrics/Gynecology
Scott & White Memorial Hospital
2401 S. 31st Street
Temple, TX 76508
254-724-2111

RESIDENCY

July, 1996 to June, 2000 Obstetrics/Gynecology
Scott & White Memorial Hospital
2401 S. 31st Street
Temple, TX 76508
254-724-2111

HONORS AND AWARDS - PROFESSIONAL

Special Service Award - Scott & White Abstinence Based Sex Education Program, 2000
Patricia J. Sulak Award for Excellence in Resident Research - Best Paper - 12th Annual Resident Research Day, 1999
Organon, Inc. Resident Research Award for Outstanding Research in Women's Health, 1999
Texas A&M University Academic Excellence Award, 1993, 1994, 1995
BioTE Practitioner of the Year 2017

HONORS AND AWARDS

Order of Omega, 1991
Alpha Epsilon Delta, 1990
The University of Texas Athletic Director's Academic Honor Roll, 1989
Texas Banc Savings Academic and Citizenship Scholarship, 1988

PROFESSIONAL ACTIVITIES

Treasurer - Friends of Senator Brandon Creighton - Texas State Senate, District 4, 2002 to Present

Cellular Medicine Association(CMA)-
Faculty Trainer, 4/16 to present

First Financial Bank (FFIN) - Board of Directors, 12/2015 to present

Sciton Laser-Clinical Investigator/Physician Educator/Luminary, 5/15 to present

BTL Aesthetics-Luminary, 10/17 to present

Age Management Medical Group (AMMG)-Faculty Speaker, 6/17 to present

BioTE Medical - Practice Mentor/Consultant, 6/15 to present
Coordinator-Clinical Advisory Team, 1/18 to present
Coordinator-Mentor Program, 2/18 to present

Vice President, Texas A&M College of Medicine Class of 1996,
1992 – 1996

Volunteer, First Co-Chairman of the Board of Directors, Chairman of Supply Committee and Member of Founding Group of Texas A&M Medical Students for Martha's Health Clinic, a student-managed health care clinic for the homeless

LICENSURE/CERTIFICATION

Medical License – Texas, 1997 to Present
American Board of Obstetrics & Gynecology – 2002 to Present

RESEARCH

Johnny J Peet MD. The Safety and Tolerability of Ablative Fractional Er:YAG Laser Treatment for Vaginal Rejuvenation. 2015.

JJ Peet, KP Huddleston, MD Custer. "Isolated Fetal Cystic Lymphangioma of the Anterior Abdominal Wall and Groin: A Case Report with Sonographic Findings." Presented at Bunkley Research Day, Texas A&M-Scott & White, 1998.

JJ Peet, KM Maedo, KW Coates, TJ Kuehl. "Bacteriuria in an Ambulatory Urogynecologic Referral Population." Presented at Bunkley Research Day, Texas A&M-Scott & White, 1999.

ONGOING RESEARCH

Safety and Efficacy of Hybrid Fractional Laser (diVa) Treatment for Symptoms of Genitourinary Syndrome of Menopause

Safety and Efficacy of Hybrid Fractional Laser (diVa) Treatment for Treatment of Symptoms of Urinary Incontinence

PROFESSIONAL SOCIETIES

Texas Medical Association (TMA)
Montgomery County Medical Society (MCMS)
Fellow - American College of Obstetricians and Gynecologists (ACOG)
Texas Association of Obstetricians and Gynecologists (TAOG)
American Association of Anti-Aging Medicine (A4M)

INTERESTS AND ACTIVITIES

Family, Baseball Coach
Church Sunday School Teacher
Fishing, Hunting, Golf, Exercise, Travel

Exhibit 1-L



JOHN J. PIERCE, DO
MEDICAL DIRECTOR
www.AgelessForever.net

6020 S RAINBOW SUITE C
LAS VEGAS, NV 89118

PH. 702-838-1994
FAX 702-870-0068

To whom it may concern,

I am writing this letter in support of compounded bio identical hormone therapy (BHRT). I have been practicing medicine for over 16 years and have been using compounded BHRT for over 13 years. In my clinical experience I have found that compounded products are very safe, reliable and reproducible results on labs and patient outcomes. I have found the ability to tailor an individual's needs based off of their symptoms and labs is a much better approach to care than the "one size fits all" approach offered by commercial hormone products.

Compounded products allow me to offer my patients options for delivery that fit their personal needs better than commercial products. BHRT pellets are a prime example of this. Hormone therapy is most effective when there are steady state levels and this is best provided in a pellet delivery. This minimizes forgotten doses, untimely refill requests and other patient errors that can allow for side effects associated with vacillations in hormone levels.

I have read the report submitted by Catalent Applied Drug Delivery Institute, titled "Comments Supporting Nominations of Certain Reproductive Hormone Drug Products For Inclusion on the Demonstrably Difficult to Compound List" I have a few comments on this paper that should be brought to the attention of the readers so that they are not mislead by the writing. The author(s) are apparently trying to do deceive the reader using medical myth and dogma to support their position. The problem is some of this fear mongering has been proven to be false in the medical literature.

Example 1. "estradiol has been linked to increased risk of breast and endometrial cancer". This statement is false. While estradiol has been implicated in breast cancer, there is not a medical study to date that shows that receiving estradiol therapy increases the risk of breast cancer. In fact, the Women's Health Initiative showed the opposite. A nice summary of the many studies that show this to be true is found in an article by Allan Lieberman, MD titled 'In Defense of Progesterone: A Review of the Literature'. The endometrial cancer aspect of unopposed estrogen is true. This is prevented with progesterone and the above article will help sort out the differences between progesterone and progestins. Once one understands the differences and the harm of progestin use, one would be left to wonder why these carcinogenic patented synthetic hormones are still available.

Example 2. "Risks for overdosing of testosterone therapy can include exacerbation of BPH or prostate cancer and increased risk of blood clots." The most recent medical literature proves that testosterone replacement therapy (TRT) has no negative impact on prostate cancer. In fact, there are cases of prostate cancer patients being treated with testosterone to eliminate the disease. (Teply, Benjamin A, et al. "Extreme Response to High-Dose Testosterone in BRCA2- and ATM-Mutated Prostate Cancer." *European Urology*)

To say testosterone exacerbates BPH shows yet more ignorance to the medical literature as illustrated in the article by Rasrelli et al titled 'Testosterone and Benign Prostatic Hyperplasia', which concluded "Testosterone is not detrimental for the prostate, and treating hypogonadism could even produce relief from LUTS and limit prostatic inflammation, which generates and maintains the process leading to BPH."

There are many studies that have tried to make the link to TRT and venous thromboembolism due to the secondary erythrocytosis caused by TRT. To date there has not been a single study that makes this link. The most that can be said is the link is inconclusive. ("Erythrocytosis and Polycythemia Secondary to Testosterone Replacement Therapy in the Aging Male." *Sexual Medicine Reviews*, Elsevier, 16 Dec. 2015)

Example 3 "However, recent evidence shows increases in endometrial cancers resulting from the use of compounded estradiol and progesterone." The author of this paper must not respect the intelligence of the reader as the article she cites does not make this statement at all. The author actually concluded, "This survey indicates substantial use of C-HT across the country and the possibility of higher rates of endometrial side effects with such products." Possibility is the key word. In science we all understand that correlation does not equal causation.

These three examples of how the author of the paper tries to use nonsense to scare the reader, in my humble opinion, invalidates any other point the author is feebly trying to make. I have found in my years of experience working with compounded hormones and the commercially available products there is relatively no difference in quality and consistency. I have found compounded products offer me many more options to fit the needs of individual patients. I can treat PMS issues with low dose progesterone orally. These doses do not exist in the commercial "one size fits all" world. Patients that have sensitivities to the fillers in commercial products are able to find treatment options in compounded products.

In my opinion, the push to try to remove hormones from the hands of competent compounding pharmacists is based not on patient safety concerns, as I have not seen any peer reviewed literature to suggest safety issues based off of evidence, but more on financial concerns of revenue lost to the bigger pharmaceutical companies to more personalized compounded pharmaceutical products. If safety was the concern, as it should be, the offenders should be under the scrutiny and jurisdiction of their state pharmacy boards. This should not be an FDA issue, but a state issue, in my opinion.

I thank you for your time and consideration in reading my position and I hope I have shed some light on the subject of how important and safe the use of compounded hormones are in medical practice.

Sincerely,



Dr. John J. Pierce, DO

Exhibit 1-M



MODERN MEDICINE

PERSONALIZED, PROGRESSIVE CARE

Statement From Cory Stephen Rice, D.O.

Qualifications

My name is Dr. Cory Rice. My professional background is as follows. I received my Bachelor of Science in forensic science and biochemistry from Baylor University in Waco, Texas in 2000. I completed my Doctor of Osteopathic Medicine at the Arizona College of Osteopathic Medicine Midwestern University in Glendale, Arizona in 2006. I completed my residency and chief residency in internal medicine at Methodist Dallas Medical Center in Dallas, Texas from 2006 to 2009. I became ABIM board certified in internal medicine in 2009.

After I completed my residency, I worked as a staff physician, hospitalist, and intensivist at Lake Pointe Medical Center in Rowlett, Texas in 2009. From 2011 to the present, I have been the owner and operator of Modern Medicine, PLLC in Addison, Texas and Forney, Texas. My practice treats patient with an emphasis in functional and lifestyle medicine. We employ nutritionists to help patients through chronic disease and disease burden. We also specialize in thyroid and hormone management.

I am a published author in the subject of thyroid disease. For a complete list of my publications and research endeavors, please see my enclosed CV.

Experience Treating with Compounded BHRT

Approximately 60% of my patients are female and approximately 40% are male. Approximately 85% of my total patient based is currently being treated with compounded BHRT. Of this percentage, approximately 65% of these patients are female and approximately 35% are male.

Medical Conditions and Patient Populations Treated with Compounded BHRT

I treat the following medical conditions and symptoms with compounded BHRT in my male and female patients:

- Cardiometabolic disease
- Diabetes



MODERN MEDICINE

PERSONALIZED, PROGRESSIVE CARE

- Autoimmune diseases, such as thyroid disease and arthropathies
- Neurodegenerative diseases, such as Alzheimer's and Parkinson's
- Obesity
- Bone health
- Mood disorders, such as anxiety, depression, and sleeping issues
- Sexual health, such as erectile dysfunction, vaginal health, stress issues, and incontinence

Why is Compounded BHRT Preferred Over Commercially Available BHRT?

Based on my professional medical judgment and clinical experience, I prefer to treat my patients with compounded BHRT instead of commercially available BHRT or synthetic hormone therapies because compounded BHRT allows me to treat patients as individuals. I was trained on synthetic hormone replacement therapy. When patients were treated with synthetic hormones, they suffered severe side effects such as weight gain, cognitive issues, and acne, which often led to patient noncompliance with the hormone therapy. Specifically, patients would return often having never refilled their prescription after the first prescription fill.

This experience with patient noncompliance caused me to research compounded BHRT, specifically in the forms of transdermal creams and subcutaneous pellets. When I treated patients with compounded subcutaneous pellets, I found that patient retention and compliance with the hormone therapy increased. I also saw fewer side effects than with the commercially available BHRT.

Moreover, my patients treated with compounded BHRT have been able to stop taking their other prescription medications for conditions such as depression and anxiety. Treatment with compounded BHRT has reduced the disease burden for my patients, as I have witnessed fewer heart attacks and stroke compared with patients treated with commercially available BHRT. In light of the above, it is my professional opinion that it would be medical negligence to withhold compounded BHRT from patients.

Sincerely,

Cory Stephen Rice, D.O.

Cory Stephen Rice, DO
992 E US Highway 80, Suite C
Forney, TX 75126
Office: (972) 552-2920

EDUCATION AND TRAINING

August 2009 ABIM Board Certification in Internal Medicine

2006 – 2009 Chief Resident 2008-2009
Internal Medicine Residency Program
Methodist Dallas Medical Center
Dallas, Texas

2002 - 2006 Doctor of Osteopathic Medicine
Arizona College of Osteopathic Medicine
Midwestern University
Glendale, Arizona

1996- 2000 Bachelor of Science in Forensic Science/Biochemistry
Baylor University
Waco, Texas

PROFESSIONAL EXPERIENCE

2011- Present Owner/Operator
Modern Medicine, PLLC
(Locations in Addison, TX, Forney, TX)

2009 Staff Physician/Hospitalist/Intensivist
Lake Pointe Medical Center
Rowlett, TX

2000 – 2002 Instructor and Lab Director
Department of Anthropology, Sociology and Forensic Science
Baylor University
Waco, Texas

PROFESSIONAL SOCIETIES

American Board of Internal Medicine (Diplomate)
American College of Physicians
American Medical Association
Institute for Functional Medicine

PUBLICATIONS

Thyroid Disease- A White Paper Monograph, July 2018
Gary S. Donovitz M.D., Cory Rice D.O., Mandy Cotten D.N.P.

Linder, Jeffrey D., **Rice, Cory S.**, Brown, De'Andre A., King, Philip W., Tarnasky, Paul R., "Is Deep Sedation with Propofol Safe During ERCP?", Digestive Disease Week, May 2007.

RESEARCH

Principal Investigator- IRB approved Clinical Case Observational Study involving Resolvins/Specialized Pro-Resolving Mediators (Fall 2015)

Principal Investigator- IRB approved Clinical Case Observational Study involving a medical food for digestive health (Spring 2016)

Exhibit 1-N



Statement From Ann Elizabeth Stanger, MD

Qualifications

My name is Dr. Ann Stanger. My professional background is as follows. I attended the Indiana University School of Medicine from 1985 to 1989. While there, I received the Faculty Women's Club Scholarship, the Dr. Margaret Hatfield Award, and the John B. Hemenway Scholarship. I completed my residency in obstetrics and gynecology from the University of Wisconsin Hospitals and Clinics from 1989 to 1990. I completed advanced practice modules in hormone, cardiometabolic, detoxification, immune, energy, and GI at the Institute for Functional Medicine between 2011 and 2016. I completed a professional course at the National Center for Homeopathy in 1990, and I completed a course in applying functional medicine in clinical medicine at the Institute for Functional Medicine in 2003. In 2008, I completed courses in clinical thermography and physician thermology from the American College of Clinical Thermography.

I worked as a physician volunteer at the Madison Community Health Center in 1993. I worked as a core physician at the VRG international Research Group from 1993 to 1994. While there, I worked as an associate physician at Walk-In Medical of Madison from 1991 to 1996. After that, I worked as an associate physician and a primary care physician at Midwest Health Systems, Inc. from 1996 to 2001. From 2001 to 2008, I worked in general outpatient medicine as the owner of Innovative Health Clinic.

I have been a certified thermology reader with the Electronic Medical Interpretation Group since 2010. I have been the medical director of Amanda Reed Medical Spa since 2013, and I have been the owner of Meridian Health Center since 2017. I have been the owner of Ann Stanger, MD, LLC, a practice in functional medicine, since 2008.

I am a member of the State Medical Society of Wisconsin, the Institute for Functional Medicine, and the American College of Clinical Thermography. Further details are set out in my enclosed CV.

Experience Treating with Compounded BHRT

My current practice focuses on functional medicine, which means we treat male and female patients with compounded BHRT. I have 20 years of experience treating patients with compounded BHRT.

I treat approximately 1,000 patients per year. Approximately half of these patients are successfully treated with compounded BHRT. Of this 50%, approximately 80% are female patients and approximately 20% are male patients. Compounded BHRT is an effective treatment in all of my patients who are treated appropriately with it.



Medical Conditions and Patient Populations Treated with Compounded BHRT

I treat the following medical conditions and symptoms with compounded BHRT in my male and female patient.

- I prescribe **compounded bioidentical estradiol with bioidentical estriol and bioidentical testosterone**, if indicated, in various dosage strengths based on laboratory testing of the patient in a cream or a gel dosage form, with a separate progesterone oral capsule, at a lower dose than is commercially available, to be taken at bedtime. I prescribe this formulation to menopause symptoms, including hot flashes, night sweats, vaginal dryness, and mood issues (e.g., anxiety and depression). I also prescribe this formulation to treat postmenopausal symptoms and bone density issues.
- I prescribe **compounded bioidentical estriol** in a cream or gel to treat vaginal dryness. Bioidentical estriol is not commercially available, but in my professional medical experience it is much more effective at treating vaginal dryness and has a lower risk of endometrial thickening compared to commercially available bioidentical estradiol (i.e., the commercially available form of estrogen approved to treat vaginal dryness). I also prescribe this formulation to treat postmenopausal symptoms and bone density issues.
- I prescribed **compounded bioidentical progesterone** in topical creams or oral capsules to treat PMS and PMDD because I am able to prescribe higher doses of the bioidentical progesterone than is available in FDA-approved bioidentical progesterones.
- I prescribe **compounded bioidentical estriol** to treat interstitial cystitis. Sometimes, I prescribe compounded bioidentical estriol with progesterone if the patient's individual lab results indicate the appropriate need.
- I prescribe **compounded bioidentical testosterone with estriol** to treat low libido and sexual dysfunction in women, and **compounded bioidentical testosterone with progesterone** to treat low libido and sexual dysfunction in men.
- I prescribe **compounded thyroid hormones (levothyroxine or liothyronine) or adrenal hormones (DHEA or hydrocortisone) and bioidentical testosterone** to treat fatigue in my male and female patients.

Why is Compounded BHRT Preferred Over Commercially Available BHRT?

Based on my professional medical judgment and clinical experience, I prefer to treat my patients with compounded BHRT because the one-size-fits-all nature of FDA-approved BHRT does not come in enough dosage strength variety and in enough different dosage forms to treat all of my patients. The commercially available BHRT are only available in certain dosing—physicians and patients need more flexibility in dosage strengths and forms. Not all patients can



tolerate a patch or a thick, transdermal cream. Alternatively, many patients are sensitive to the fillers in commercially available oral capsules.

Further, compounding allows for greater ease in dosing the individual patient. With compounding, I am able to prescribe combinations of multiple bioidentical hormones in one transdermal cream or capsule, which makes the use of hormone therapy more tolerable for patients. The more tolerable the medication, the greater the patient compliance with the treatment regimen. I know which hormones and combinations thereof my patients require because I evaluate blood tests on my patients every three months to once a year. These blood test results allow me to consistently monitor hormone levels of my patients and adjust hormone treatment dosages accordingly. For example, many menopausal women cannot tolerate the side effects (e.g., dizziness, fatigue, and depression) of 100 mg of micronized progesterone, which is the lowest commercially available dose. Many women better tolerate lower doses of micronized progesterone, and progesterone is necessary treatment if these women are on an estrogen therapy and have a uterus. Thus, being able to compound lower doses of micronized progesterone is critical for these patients to avoid the side effects of the commercially available option. And, compounded bioidentical testosterone is very important for women, as there is currently no bioidentical testosterone FDA-approved for treatment in women.

Additionally, there is no treatment as successful at treating bone density issues as hormone therapy. I receive multiple referrals from the University of Wisconsin Bone Density specialists and endocrinologists for patients who are unable to tolerate the commercially available hormone therapy. I am able to prescribe compounded combinations of bioidentical hormones to successfully treat these patients.

Being appropriately treated with the right dosage and right form of compounded BHRT is often lifesaving for my patients. Many of my female patients initially present to me nearly suicidal because of menopause or premenstrual symptoms and feeling that they cannot function in day-to-day tasks. If these patients' hormone needs are not met, they cannot be functioning members of society. These patients cannot be effectively treated by the FDA-approved BHRT—they need individualized dosages and combinations that is an option only available through compounded BHRT.

Sincerely,

/s/ Ann Elizabeth Stanger, MD

ANN ELIZABETH STANGER, MD

2984 TRIVERTON PIKE DRIVE

FITCHBURG, WI 53711

Voice: 608-233-2378, Fax: 608-233-2375

drann@meridianhealthcenter.com

MEDICAL EXPERIENCE

Meridian Health Center Owner	May 2017-present
Ann Stanger, MD, LLC Functional Medicine	May 2008 to the present
Amanda Reed Medical Spa Medical Director	April 2013 to the present
Innovative Health Clinic, owner General outpatient medicine	June 2001-May 2008
Electronic Medical Interpretation Group Certified Thermology reader	April 2010-present
Midwest Health Systems, Inc Primary care physician-Lake Edge Clinic Associate physician-Dane County Jail	November 1996-June 2001
Walk-In Medical of Madison Associate physician	December 1991-November 1996
VRG International-Research Group Core physician	February 1993-September 1994
Madison Community Health Center Physician Volunteer	March 1993-October 1993

MEDICAL EDUCATION

American College of Clinical Thermography Clinical Thermography course Physician Thermologist course	April 2008
Institute for Functional Medicine Applying Functional Medicine in Clinical Medicine	March 2003

National Center for Homeopathy
Professional course

June 1990

Institute for Functional Medicine
Advanced Practice Modules

Hormone
Cardiometabolic
Detoxification
Immune
Energy
GI

July 2011
March 2015
July 2015
February 2016
July 2016
October 2016

University of Wisconsin Hospitals and Clinics
Obstetrics/Gynecology residency

July 1989-December 1990

Indiana University School of Medicine
Honors: Faculty Women's Club Scholarship
Dr. Margaret Hatfield Award,
John B. Hemenway Scholarship

August 1985-May 1989

PROFESSIONAL ORGANIZATIONS

State Medical Society of Wisconsin
Institute for Functional Medicine
American College of Clinical Thermography

Exhibit 1-0

G. DeAn Strobel, MD, PA

Hormonal Balance & Wellness

G. DeAn Strobel, MD
230 East Evergreen Street, Sherman, TX 75090
(903) 957-0275 Fax (903) 957-0279

Statement From Gennell DeAn Strobel, MD

Qualifications

My name is Dr. Gennell DeAn Strobel. My professional background is as follows. I received my Bachelor of Science in Mathematics and Spanish from the University of Louisiana in Monroe, Louisiana, in 1989. For a short time, I attended graduate school in engineering at Louisiana Tech University before deciding to pursue medicine as a career. I later received my Doctor of Medicine from Louisiana State University Medical Center in Shreveport, Louisiana, in 1995. I completed my residency in obstetrics and gynecology at Baylor University Medical Center in Dallas, Texas from 1995 to 1999. I am currently Board Certified and have completed annual recertifications since 2005. I completed my written board examination in 1999 and my American Board of Obstetrics and Gynecology Oral Board Exam in 2002.

I earned several awards throughout my undergraduate, graduate, and doctoral degrees. While at the Louisiana State University Medical Center, I received the Bernstein Memorial Scholarship, the Reginald and Ruby Slaughter Scholarship, the L.P. Whitehead Scholarship for Christians, the Louisiana Presbyterian Scholarship Foundation Award, and the Lewis Gottlieb Scholar Award, which goes to a "student that clearly demonstrates scholarship and devotion." During my residency at Baylor University Medical Center, I received the Five-Star Spirit Award, which is nominated by patients. I also received the Teaching Award, which is nominated by fellow residents.

Throughout my life and career, I have enjoyed teaching. While an undergraduate, I tutored students in mathematics and chemistry on behalf of the university as well as private tutoring. While completing my studies in biological sciences and chemistry prior to attending medical school, I worked as an instructor in the Department of Foreign Languages and taught introductory and intermediate level Spanish classes. I also worked as graduate student teacher in the Department of Chemistry. During my residency in Obstetrics & Gynecology, I presented countless lectures during grand rounds and resident learning periods as well as presenting a series on Fetal Heart Rate Monitoring in the Perinatology Conference Annual Meeting in Dallas, Texas, in 1998.

Following completion of my residency training, I continued my teaching while in private practice by participating as guest faculty with the family medicine residency program in Texoma Medical Center for lectures as well as an optional site rotation. I have given lectures and presented across the country and in Mexico on various topics including osteoporosis, laser technologies, and hormone replacement therapy. I am also certified through the International Society for Clinical Densitometry (ISCD) and have worked to teach many physicians and their offices in proper interpretation and techniques for DEXA scans.

My employment experience is as follows. I was an employed physician in obstetrics and gynecology at Hillcrest Healthcare Association, Inc. from 1999 to 2002. I have been the Medical Director and Owner of Allure Laser & Medical Spa since 2004, and I also own a private practice, G. DeAn Strobel, MD, PA, where I have practiced since 2002.

I have had several hospital appointments and committee participations. I was active staff at the Wilson N. Jones Medical Center in Sherman, Texas from 1999 to 2012. I served on the Surgical/Invasive Committee and the Medical Executive Committee, both in Sherman, Texas, from 2004 to 2006. I was the Department Chair of Obstetrics and Gynecology at the Wilson N. Jones Medical Center from 2004 to 2006. I have worked at the Texoma Medical Center Hospital, Heritage Park Surgical Hospital, and Baylor Scott & White Hospital in Sherman, Texas, from 2010 to the present. For a full list of my hospital appointments and committee participations, please see the enclosed CV.

I have also had many leadership and committee roles. I served on the Baylor Outpatient Clinic Continuity Committee and the Medical Education Committee while completing my residency at Baylor University Medical Center. While at the Wilson N. Jones Medical Center from 2001 to 2006, I served on the Women's & Children's Strategic Planning Committee, the Information Technology Committee, the Utilization Review Committee, the Surgical Invasive Committee, the Medical Executive Committee, and I was the Department Head of Obstetrics and Gynecology. I was on the Medical Executive Committee of Heritage Park Surgical Hospital from 2014 to 2017. For a complete list of my leadership roles, please see my enclosed CV.

I am currently part of the Grayson County Medical Society, the Texas Association of Obstetrics and Gynecology, the Texas Medical Association, the American College of Obstetrics and Gynecology, and the American Medical Association. I was part of the Dallas County Medical Society from 1995 to 1999, and the American Association of Gynecologic Laparoscopists from 1999 to 2001.

Experience With Treatment Of Compounded Bio-Identical Hormone Therapy

I am an actively practicing, board-certified obstetrician gynecologist, and I treat many of my patients with compounded Bio-Identical Hormone Replacement Therapy (“BHRT”). My practice is in north Texas in an area of the country with a large geriatric patient population. The average household income in my city is approximately \$32,000 per year. My practice is a traditional payor mix (commercial insurance, Medicare, and uninsured) with patients of all races, ages, and ethnicities. My practice treats approximately 60-80 patients per day. Once I stopped practicing obstetrics and started doing gynecology only in private practice, my menopausal patient population soared. As mentioned in the opening section, I am ISCD-certified. Because of the region of the country where I practice and live, I have a huge patient population with osteopenia and osteoporosis as well as many other medical comorbidities such as cancer, heart disease, and more.

I began studying options for BHRT after I quickly learned that commercially-available pharmaceutical products did not relieve most of my patients' symptoms. I came to understand that a “one size fits all” strategy using traditional HRT did not work to relieve many symptoms. Of course, HRT can often help with hot flashes or even vaginal dryness, but there were many other things of which my patients complained for which I had no answer or remedy. Some of these complaints

were things such as memory disturbances, night sweats, anxiety or depression, sleep disruption, fatigue, weight gain (or difficulty losing weight despite exercise and diet), joint pain, low libido, and orgasmic disorders. I, like many, was determined to implement the standard of care for many of these issues and firmly believed that other prescription medications and psychological evaluation (which is what we are taught to offer for anxiety, depression and sexual dysfunction) would help with many of these issues.

I tried to prescribe or recommend various antidepressants, sleep medications, etc. to try to alleviate some of those symptoms. Unfortunately, my attempts to use the standard therapies were proven unsuccessful when patient after patient did not see improvement but rather experienced side effects to some of the therapies. It was around this time that many of my patients started telling me that they went to other doctors to get “bioidentical” hormone replacement via either compounded creams or pellets and had fantastic results. Patient after patient begged me to learn more. I resisted as I had seen a position statement from ACOG regarding bioidentical hormones, but I didn’t really understand what “bioidentical hormone replacement therapy” or BHRT meant. I decided to read and learn about BHRT and, specifically, about testosterone use in women.

I began to call some of the compounding pharmacies since there are no available testosterone products for women. I had many conversations with the pharmacists to confirm the exact method of compounding to assure the safety for my patients and began cautiously using compounded testosterone creams (of various strengths) for my female patients with or without the addition of a commercially-available product for estrogen (I have used them all – pills, patch, gels, & depot injections). I followed serum lab values as well as clinical response and side-effects. I learned that creams were variably absorbed by patients (but so were patches and gels) but that vaginal dosing was absorbed much better than topical. Slowly, my patients started telling me they were seeing improvements.

Gradually, I felt more comfortable with prescribing compounded testosterone cream and was able to learn better how to tailor dosing to each patient. But the issue I still found was that the half-life of many creams and gels required twice daily (BID) dosing in order to achieve satisfactory results. Patient compliance was an issue. Some patients also did not get any results, and other patients complained of a “mess” or vaginal irritation, so I had to consider learning about other options as well. I had heard about the use of subcutaneous implants or pellets by many of my patients. Several of my patients traveled to Dallas to get these implants. I had no idea how to dose them nor how to have a pharmacy safely manufacture them, so I decided not to pursue that avenue at that time.

A few years later, in 2009, became trained in dosing and in the use of pellets and began using pellets in my practice immediately. To date, I have performed over 18,000 insertions. Once I began to learn how to truly optimize patients’ hormones, I began to receive countless letters and calls thanking me and my practice for “giving them their life back” or “saving their marriage”. Never had I received such incredible satisfaction!

My experience treating thousands of menopausal and perimenopausal patients over the last several years is that very few women have complete resolution of their menopausal and perimenopausal symptoms with traditional HRT, but this data is drastically different with compounded BHRT. Compounded BHRT resolves over 80% of those symptoms—if sterile subcutaneous implants are used, over 90% of their symptoms are improved.

I strongly believe that hormone therapy must be individualized with respect to the type of hormone (s), the dose, and the delivery system according to the patient's symptoms, medical history and laboratory evaluation. Prescriptions of traditional HRT do not take into account any of these factors, and, in fact, most OB/GYNs across the country are taught that doing lab evaluation of hormones is "not necessary". I cannot disagree more.

Medical Conditions and Patient Populations Treated with Compounded BHRT

I prescribe many forms of compounded BHRT in my practice to treat a variety of patient conditions and symptoms. Many of my patients have complex medical conditions and are referred to me by other physicians (including oncologists, cardiologists, neurologists, psychiatrists, and more) for hormone evaluation and treatment. Only compounded BHRT allows customization of therapy in so many ways and for so many patients and reasons.

Patients present to my office at all ages and with a myriad of complaints. I perform a complete medical and family history as well as physical examination and laboratory evaluation and have them return for discussion and formulation of a treatment plan. A healthy, young woman has many more options than an older woman or a woman with a complex medical history such as breast CA, stroke, heart attack, and hypercoagulability. Each treatment plan must consider these individuals and their needs.

While there are many forms of estrogen available on the market, estrogen is not the hormone that resolves most complaints from patients. Testosterone was initially used in the 1930s to relieve the symptoms of menopause in castrate women and was found to have good results, but when conjugated estrogens were isolated in the late 1930s and marketed widely in the 1940s, testosterone was "forgotten" by many as the pharmaceutical company era began.

The chief complaints from my female patients are that traditional hormone replacement therapy (i.e., FDA-approved hormone replacement therapy or synthetic hormones) do not adequately address their symptoms, which include night sweats, hot flashes, orgasmic dysfunction, fatigue, weight gain, low libido, and more. These conditions have improved and/or been resolved by treatment with compounded testosterone, which is a hormone treatment that is not currently considered standard therapy for women.

In my experience, I have found that testosterone use, in most of my female patients, has led to significant improvement and/or resolution of the following conditions or complaints: night sweats, sleep disruption, irritability, brain fog, difficulty concentrating, fatigue, weight gain (difficulty losing weight), joint pain, low libido, orgasmic dysfunction, vaginal dryness, and even osteoporosis. Prior to using testosterone in women, I would never have believed that improvement or even resolution and normalization of bone mineral density in women would be possible! I spent many years traveling as a lecturer for Eli Lilly on the drugs Evista (raloxifen) and Forteo (teriparatide). I also have spent considerable time using almost all of the currently-available osteoporosis drugs, but none seem to compare to the use of testosterone in improvement of bone

mineral density. Plus, the side “benefits” of testosterone use in these women are extraordinary as opposed to the many side-effects and long-term risks of bisphosphonates.

Lichen sclerosus is a chronic, debilitating skin condition which affects the genital and anal areas and is most commonly seen in prepubescent and postmenopausal women. It causes a patchy, white area which is usually widespread and bilateral and symptoms of severe pruritus and burning. Often it leads to genital deformities as well. The traditional therapy for this condition is topical steroids and topical testosterone. In my prior experience, this was one of the most frustrating conditions because most women saw only control of symptoms (if they were lucky) but no resolution. With the use of testosterone pellets, I have seen huge improvements and, in many cases, resolution of this condition as well. One patient told me that she had not been able to have intercourse or even wear panties or slacks for over 9 years and was able to resume these activities happily after 6 months of therapy!

Additionally, some of my other female patients with complex medical histories include women who are or would have been suffering needlessly without hormone therapy. These patients include patients with a history of hypercoagulable state, history of breast cancer, history of stroke and/or heart attack, and many more.

Commercially-available oral estrogen replacement therapies (such as Prempro, Premarin, Estrace, generic oral estradiol) as well as progestins (PremPro, Provera) are contraindicated in patients with history of hypercoagulable states, stroke, and heart attack. While non-oral options are now known NOT to increase risk of hypercoagulability, most clinicians are unaware of this fact and continue to tell patients with these conditions that they “can never use hormones”. These patients could use one of the non-oral forms of estrogen, but oral micronized progesterone (which is absolutely critical to use in patients on estrogen with an intact uterus) until recently was only available in one product, Prometrium. Prometrium and its generic equivalent contain peanut oil and many patients with severe peanut allergy are unable to take this product. This makes the need for compounded micronized progesterone vital.

In addition to patients with hypercoagulable states, many other patients (and relationships with their partner/spouse) have suffered needlessly for too long. One of the best examples is the breast cancer survivor. Breast cancer survivors traditionally have been told that they CANNOT be treated with any type of hormone. After their diagnosis and treatment, they not only have to endure mutilation and fear of death, but they also suffer from quality of life issues and changes in their intimate relationship that they did not expect. Quality of life issues that these patients endure are poor sleep, chronic fatigue, temperature dysregulation, night sweats and hot flashes, severe joint pain, “brain fog”, vaginal dryness, and dyspareunia. Many times, the dyspareunia is so severe that they are no longer able to have intercourse at all! There have been many studies over the last several decades using testosterone replacement in breast cancer survivors, but these studies are not widely known. Once I became more comfortable with the data regarding hormone replacement in these patients, I began to treat them and quickly realized the impact of this treatment when women (and their spouses) literally cried tears of joy when they “felt like a woman again” because they were able to enjoy intimacy again. Women also would tell me that their sleep, energy, hot flashes, moods and many other aspects of life were improved as well.

Another group of patients in which compounded testosterone is vital is the male patients. As a gynecologist, I previously only saw male patients for infertility consultations or treatment for sexually-transmitted infections when they were in a relationship with one of my female patients, but this drastically changed about 10 years ago when patient after patient literally begged me to see their husband, boyfriend, son, or relative. The patients knew that proper optimization of their hormones had made such an impact that they wanted the same thorough evaluation and individualized approach to help their male relatives. I began seeing males and have noted the same trend in improvement in their quality of life. The impact of testosterone replacement in men with testosterone deficiency is vital. Many studies show that patients with testosterone replacement have worsening dyslipidemia, weight gain, increased insulin resistance, increased incidence of heart disease, poor cognition, bone loss, and more. Over time, most of these patients have IMPROVEMENTS in these conditions. The patients will begin to lose weight, and they are often able to come off of many of the prescription medications such as anti-hypertensives, statins, NSAIDs for pain, and diabetes medications.

Why is Compounded BHRT Preferred Over Commercially Available BHRT?

I have witnessed many patients who are now seeking compounded BHRT because the therapy can be monitored and tailored to the patient. Hormone replacement therapy simply does *not* work with a one-size-fits-all approach. Regardless of the therapy, each patient is an individual with a unique medical history genomic structure which is vital for metabolizing hormones and other medications — all of which must be taken into consideration when evaluating a patient.

In my professional medical judgment, I prefer to treat my patients with compounded BHRT instead of the commercially available BHRT because hormone therapy requires a constant reassessment and adjustment of the hormone dose and the medication. It is impossible to treat patients with a one-size-fits-all hormone therapy treatment. The commercially available options are limited in the dosages available.

As stated above, many of my patients are medically complex. For women, there are three separate components to BHRT: Estradiol, Testosterone, and Progesterone. For the postmenopausal patient who needs Estradiol, there are several options if the patient is under 60 years old and healthy—that is, these patients can be treated with oral pills, transdermal patches or gels, and vaginal rings, all of which are commercially available. There are many dosages available in oral form, but the oral forms are not advised in patients with gallbladder dysfunction, dyslipidemia, history of stroke or heart attack, or in patients with family history of hypercoagulable states. The oral form is contraindicated also in patients with personal history of deep venous thrombosis or pulmonary embolism. There are commercially available brand-name and generic estradiol options as well, but the dosages are much more limited (the patches come in several dosages, but the highest dose is not often adequate for many; the gels come in only 1 strength). In addition, only approximately *half* of patients are able to absorb the transdermal formulations which means that the available strengths often are not sufficient. If the patient desires to continue transdermal administration, often a compounded, stronger version of the BHRT is required in order to treat the patient in the way the patient needs. Transvaginal absorption will yield improved results in many, but the commercially available products are gel which is alcohol-based so cannot be applied or inserted to the vaginal area. Also, compounded subcutaneous pellets offer better absorption, improved results, and better patient satisfaction, but these are not at all commercially available.

The next component that often is needed in female patients is Progesterone. Until the last year, all commercially-available HRT combination products (one product with an estrogen AND a progesterone-like product) contained progestins. Because of the risks and side-effect profile of progestin therapy, I stopped prescribing these products and implemented the use of micronized oral progesterone instead of progestin therapy several years ago. Bioidentical or micronized oral progesterone is commercially available but only in two dosages – 100 and 200 mg. Also, as mentioned earlier, the commercially available products contain peanut oil and cause severe somnolence and dizziness in some women. I have many patients that require much smaller or much higher dosages than the 100 mg and 200 mg capsules that are commercially available.

The last component of female bioidentical hormone replacement – and the most critical and vital, in my opinion – is Testosterone. Why testosterone replacement is not commercially-available nor widely used is a mystery to me. I have spent countless hours over the last many years studying and implementing testosterone replacement in females, and strongly believe that inability to prescribe compounded testosterone would be disastrous to women across the country. I think fear and misinformation are the leading factors with this. Also, in the past, there has been no established “normal” levels for testosterone that are widely used. I believe that there are 2 vital papers related to testosterone use in women that summarize its use and safety well. One of the papers is a review paper written by Dr. Rebecca Glaser and Dr. Constantine Dimitrakakis entitled “Testosterone therapy in women: Myths and misconceptions”. It was published in *Maturitas* in 2013. The other is the recently published “Testosterone Insufficiency and Treatment in Women: International Expert Consensus” by Dr. Gary Donovitz, et al.

Although there are various commercially-available testosterone products for males, many male patients cannot get adequate serum levels nor results from traditional formulations or strengths and require compounded testosterone. Current options include testosterone injections, patch, gels/creams, intranasal spray, sublingual rapidly-dissolving tablets, and pellets. Injectables are notorious for being dosed incorrectly at only 1 or 2 injections per month (half-life is 4-8 days). Transdermal application of these products in men has the same concerns over absorption with only ~half of men absorbing the products (achieving adequate serum levels to resolve symptoms).

Testopel is currently the only commercially-available testosterone pellet option, and it is only approved for use in males. The dosages are restricted to 75 mg pellets only, and a maximum of 6 pellets can be used for men. Many men do not achieve adequate serum levels nor results with this dose (this is mostly seen in men over 180 pounds since testosterone dosing is weight-dependent). The other compounded options (such as pellets) or higher strengths (in compounded creams) allow the patient to have adequate serum levels as well as improved results from the therapy.

I hope you find the information provided in my statement to be insightful and helpful. I appreciate your time in reading this letter.

Sincerely,



G. DeAn Strobel, MD, FACOG

Gennell DeAn Strobel, MD
230 East Evergreen, Sherman, TX 75090
Office: (903) 957-0275 Fax: (903) 957-0279
Email: gdstrobelmd@gmail.com

Personal Information

Marital Status	Happily married with twin sons
Board certification status	Board certified Written board examination, June 1999 American Board of Obstetrics & Gynecology Oral Board Exam, January 2002 Annual recertification, 2005 thru present
Birthdate	January 17, 1968
Birthplace	Vicksburg, Mississippi
Citizenship	United States of America
Medical licensure	Texas K3004 National Board of Medical Examiners, 1996
UPIN number	G95979

Education

Postgraduate	Residency, Obstetrics & Gynecology Baylor University Medical Center Dallas, Texas, July 1995- June 1999
Graduate	Doctor of Medicine Louisiana State University Medical Center Shreveport, Louisiana, June 1995 Studies in biological sciences, chemistry Northeast Louisiana University Monroe, Louisiana, 1989-91 Studies in engineering Louisiana Tech University Ruston, Louisiana, 1989
Undergraduate	Bachelor of Science, Mathematics and Spanish Northeast Louisiana University (now University of Louisiana – Monroe) Monroe, Louisiana, May 1989

Hospital Appointments & Committees

Heritage Park Surgical Hospital Sherman, TX	2010 to present
Texoma Medical Center Hospital Sherman, TX	2010 to present

Department Chair, Obstetrics/Gynecology	Wilson N. Jones Medical Center July 2004 to July 2006
Medical Executive Committee Sherman, TX	July 2004 to 2006
Surgical/Invasive Committee Sherman, TX	July 2004 to 2006, 2008
Wilson N. Jones Medical Center Sherman, Texas	Active staff, August 1999-2012
Utilization Review Committee Sherman, TX	July 2000 to 2006
Utilization Review Committee Chairperson	August 2005 to 2006
Community Medical Center	Courtesy staff, 1999-2001 (hospital bought out)
Center for Ambulatory Surgery	2003 to present
Heritage Park Surgery Center	2008 to present
WNJ Foundation board member	October 2005 to 2008

Committees and Leadership Roles

BioTE Medical	Director of Clinical Education, April 2018 to present Medical Advisory Board, 2013 to present Mentor, 2013 to present Teaching Faculty, 2017 to present	
Heritage Park Surgical Hospital	Medical Executive Committee, 2014 – 2017	
Wilson N. Jones Medical Center	Department Head, Obstetrics & Gynecology, 2004 – 2006 Medical Executive Committee, 2004 – 2006 Surgical Invasive Committee, 2004 – 2006 Utilization Review committee, 2000 – 2006 Information Technology committee, 2000 – 2006 Women's & Children's Strategic Planning committee, 2001 – 2005	
Baylor University Medical Center	Baylor Outpatient Clinic continuity committee, 1995- Medical Education committee, 1998	1999
Louisiana State University Medical Center	Class president, 1991 – 1995 Freshman, Sophomore, Junior and Senior years Honor Council, 1992	

Subcommittee for university self-evaluation, 1992-93
 Medical Student Research Forum, 1994
 Northeast Louisiana University
 Group leader for Women and Minorities in Science, 1987

Professional Organizations

American Medical Association, 1991-present
 American College of Obstetrics and Gynecology, 1995-present
 Texas Medical Association, 1995-present
 Texas Association of Obstetrics and Gynecology, 1995-present
 American Association of Gynecologic Laparoscopists, 1999-2001
 Dallas County Medical Society, 1995-1999
 Grayson County Medical Society, 2000-present

Research Experience

Syneron
 FDA trial for VelaSmooth , 2004 – 2005
 Research led to FDA-approval for cellulite reduction
 FDA trial for VelaSmooth, 2005 to 2007
 Research in device's effects on stretch marks
 Baylor University Medical Center
 "Mitochondrial Defects in Fat Oxidation", 1999 - 2000
 Louisiana State University Medical Center
 "Clinical and Echocardiographic Findings in Heart Failure"
 Abstract published in *Journal of the Louisiana State Medical Society*, July 1994
 Louisiana Tech University
 Research assistant, civil and mechanical engineering, 1989
 Applied Research Associates, Inc.
 Vicksburg, Mississippi
 Engineering research assistant, Summer 1988
 Research in conjunction with United States Department of Defense

Employment Experience

G. DeAn Strobel, MD, PA
 Physician, Self-Employed
 Private Practice, October 2002 to present
 Allure Laser & Medical Spa
 Medical Director, Owner
 May 2004 to present
 Hillcrest Healthcare Association, Inc.
 Physician, Obstetrics & Gynecology, 1999-2002
 Northeast Louisiana University
 Instructor, Spanish
 Beginning and intermediate levels, 1989-91

Graduate Assistant
Spanish and chemistry, 1989

Tutor
Mathematics, 1986-89

Louisiana Tech University

Graduate Assistant
Engineering, 1989

Tutor
Physics and mathematics, 1989

Honors and Awards

Baylor University Medical Center

Teaching Award
Awarded by fellow residents, 1997

Five-Star Spirit Award
Nominated by patients, 1997

Louisiana State University Medical Center

Lewis Gottlieb Scholar Award
Award to "student that clearly demonstrates scholarship
and devotion", 1995

Louisiana Presbyterian Scholarship Foundation
1991-92, 1993-94

L. P. Whitehead Scholarship for Christians, 1992-93

Reginald and Ruby Slaughter Scholarship, 1992-93

Bernstein Memorial Scholarship, 1991-92

Northeast Louisiana University

Alpha Epsilon Delta, 1990
Pre-Med Honor Society
Valedictorian, May 1989 Largest graduating class

Outstanding Senior Mathematics Award, 1989

Outstanding Graduating Senior Award, 1989
Alpha Lambda Delta

One of NLU's Outstanding Juniors and Seniors, 1988

Sigma Delta Pi, 1988
National Spanish Honor Society

Gabriela Mistral Award, 1988

Phi Kappa Phi, 1988
National Honor Society

Outstanding Initiate Award
Phi Kappa Phi

Omicron Delta Kappa, 1988
National Honor Society

Alpha Lambda Delta, 1985
Freshman Honor Society

Rho Lambda, 1988
 Honor Society for Panhellenic women
 Vice-president

Outstanding Freshman Mathematics Award, 1985

Presentations and Lectures

Texoma Medical Center Family Medicine Residency program	Guest faculty and clinical training site, 2015 – 2018
Medical Advisory Board	BioTE Medical, 2013 to present Clinical trainer
Guest Speaker	Age-Management Medicine Group, November 2017 “Estrogen” and “Abnormal Bleeding in the Peri- and Menopause Patient” Age-Management Medicine Group, November 2015 “Hormone Hold-Ups”
Speakers’ Bureau	Syneron, 2003 to 2008 Educate medical staff on non-ablative laser technology
Speakers’ Bureau	Eli Lilly Co., June 2004 to 2012 Osteoporosis (Evista & Forteo)
Preceptorship Program	Boston Scientific, October 2005 to 2007 Instructor for HTA (Hydrothermal Ablation)
Sherman, Texas	“Urinary Incontinence” Patient education seminar, 2002
Sherman, Texas	“HRT in the 21 st Century – What You Need to Know” Educational meeting for family practitioners, 2001
Austin College Sherman, Texas	“HRT in the 21 st Century” Community Educational series, 2001 “Women’s Health in 2004” Breast Cancer Awareness month, October 2004 “Today’s Woman: Her Health & Beauty Needs” Staff Development Day, January 2005
Wilson N. Jones Medical Center Sherman, Texas	“Pregnancy and Preexisting Diabetes” Women’s & Children’s Grand Rounds, 2000 “Fetal Hydronephrosis” Women’s & Children’s Grand Rounds, 2000
Texas Medical Association Dallas, Texas	“Fetal Heart Rate Monitoring” Annual Meeting, 1999
Texas Association of Obstetricians & Gynecologists Dallas, Texas	“First Reported Case: Prenatal Diagnosis of Carnitine-Acylcarnitine Translocase Deficiency” Annual Meeting, 1999
Baylor University Medical Center	“Fetal Heart Rate Monitoring”

Dallas, Texas

Perinatology Conference, 1998

“Mitochondrial Fatty Acid Oxidation Defects”
Dallas Doctors’ Club, 1998

“Fetal Heart Rate Monitoring”
Grand Rounds, OB/GYN, Sherman, TX, 1998

“Carnitine-acylcarnitine Translocase Deficiency”
Grand Rounds, Neonatology, 1998

“Carnitine-acylcarnitine Translocase Deficiency”
Perinatology Conference, 1998

“Antibiotic Therapy in Gynecologic Infections”
Continuing Medical Education, 1998

“Hemorrhage in Pregnancy”
Continuing Medical Education for nurses, 1996-98

“Hypertensive Disorders of Pregnancy”
Continuing Medical Education for nurses, 1998

“Thrombosis and Vascular Complications of Surgery”
Gynecology Morbidity and Mortality Conference, 1998

Northeast Louisiana University

Guest speaker for Women and Minorities in Science, 1990

Abstracts

1. “Clinical and echocardiographic findings in heart failure”. GD Strobel, T Ratts
2. “First Prenatal Diagnosis of Carnitine-Acylcarnitine Translocase Deficiency using Tandem Mass Spectrometry”. GD Strobel, D Roe, JM Graham, C Roe, M Brivet
3. “Identification of a novel mutation in patient with carnitine-acylcarnitine translocase (CACT) deficiency”. JH Ding, BZ Yand, JM Mallory, DS Roe, GD Strobel, M Brivet, CR Roe

Special Skills

Bilingual
Martial arts
Medical mission work

Spanish and English
Taekwondo, 1st degree black belt
San Luis Potosi, Mexico, 1994

Interests

Family activities
Health & wellness
Foreign and domestic travel
Languages

Exhibit 1-P

ALLAN WARSHOWSKY MD, FACOG, ABIHM

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Statement From Allan B. Warshowsky M.D. FACOG, ABIHM

Qualifications

My name is Dr. Allan B. Warshowsky FACOG, ABIHM. My professional background is as follows. I received my Bachelor of Arts, *magna cum laude*, from Queens College of CUNY in Queens, New York in 1969. I received my Doctor of Medicine from Downstate Medical Center of SUNY in Brooklyn, New York in 1973. I completed my rotating internship, OB/GYN residency, and OB/GYN Chief Residency at Long Island Jewish Medical Center in Queens, New York from 1973 to 1977.

I am a board-certified OB-GYN. I am a founding Diplomat and Director Emeritus of the American Board of Integrative Holistic Medicine, a past member of the American Holistic Medical Association, a member of the American Board of Obstetrics and Gynecology, and a respected member of the Board of Xymogen Advisors. I was a founding physician and director of the Women's Program at Beth Israel's Continuum Center for Health and Healing in New York City from 2000 to 2003. I am the author of multiple articles on topics that include natural cures to fibroids and health risks to women. For a complete list of my publications, please see my enclosed CV.

I am at the forefront of integrative, holistic medicine. Despite being conventionally trained, I am a leader in the field of integrative, holistic medicine treating men and women of all ages. I have been in practice for over 35 years, and my practice combines the best of conventional medicine with the latest in integrative, holistic modalities.

Experience With Treatment Of Compounded Bio-Identical Hormone Therapy

My practice covers many areas of medicine and healing, which specifically includes compounded bio-identical hormone replacement therapy (“BHRT”) for men and women. Approximately half of my patients are currently being successfully treated with compounded BHRT.

Medical Conditions and Patient Populations Treated with Compounded BHRT

I prescribe compounded BHRT in my practice to treat a variety of patient conditions and symptoms. Specifically, I treat the following conditions with some form of compounded BHRT:

- Aging optimally in women and men
- Autoimmune diseases – Hashimoto’s, SLE (lupus)
- Bladder problems
- Breast disorders, including menopausal care after breast cancer
- Cancer risk reduction through an integrative holistic approach in women and men
- Cervical dysplasia and abnormal pap smears
- Chronic fatigue, fibromyalgia and chemical sensitivity in women and men
- Chronic pelvic pain
- Chronic yeast disorders
- Contraceptive counseling and management
- Detoxification disorders in women and men
- Endometriosis
- Fertility Problems –through an integrative, holistic approach
- Fibroid tumors of the uterus
- High cholesterol
- Hormone imbalance in women and men
- Heavy metal toxicity in women and men
- Intestinal problems including irritable bowel syndrome, constipation and IgG4
- Food allergies
- Migraine headaches
- Menstrual irregularities of all kinds
- Metabolic Syndrome
- Nutritional and wellness counseling
- Obstetrical counseling – to achieve an optimally healthy pregnancy
- Optimal aging and disease prevention
- Osteoporosis and bone health
- Ovarian Cysts
- Perimenopausal and Menopausal care
- Premenstrual Syndrome
- Preventive health care
- Polycystic ovary syndrome
- Sleep Disorders
- Thyroid and other endocrine disorders
- Uterine problems
- Vulvar pain syndromes

More specifically, I use the follow compounded bioidentical hormones or combinations thereof to treat the follow medical conditions and symptoms.

- **Compounded Progesterone.** I prescribe compounded progesterone in oral capsules to treat any patient that exhibits an estrogen dominance. Specifically, compounded progesterone treats my patients with the following medical conditions and symptoms:
 - Premenstrual Syndrome, especially in women who are already taking birth control and are not making enough progesterone on their own
 - Polycystic ovary syndrome
 - Perimenopausal and Menopausal care
 - Hormone imbalance in women and men
 - Endometriosis
 - Early pregnancy losses in young women who have frequent miscarriages when their bodies are not making enough progesterone
 - Preventive health care, specifically when treating menopausal symptoms to lower risk of cognitive decline, heart problems, and colon cancer
 - Cognitive decline in men and women

- **Compounded Estradiol + Estriol.** I prescribe compounded Estradiol and Estriol to treat symptoms of menopause, specifically hot flashes, night sweats, mood issues (depression, sadness, and anxiety, among others), and osteoporosis, and to treat patients with a family history of colon cancer, dementia, and/or Alzheimer's. Estriol is very weak and tends to be a balancing form of estrogen that reduces any negative effects of the stronger hormone, Estradiol.
- **Compounded Pregnenolone + Dehydroepiandrosterone ("DHEA").** I prescribe compounded Pregnenolone and DHEA in transdermal creams to treat adrenal fatigue in men, women, and children or in patients who are under severe stress. For male patients with low testosterone, compounded DHEA will convert into testosterone in the body and treats adrenal fatigue, exhaustion, poor stress management, weight management, sleep management, body temperature regulation, and frequent infections, among others.
- **Compounded Testosterone.** I prescribe compounded testosterone in a transdermal cream to treat fatigue, muscle weakness, loss of commitment and focus, and low libido in my male and female patients. I also prescribe it to treat the following medical conditions in men specifically:
 - Unhealthy aging
 - Decrease in muscle tone
 - Sarcopenia
 - Erectile Dysfunction
 - Lack of interest in sex
 - Muscle strength loss

Why is Compounded BHRT Preferred Over Commercially Available BHRT?

In my professional medical judgment, I prefer to treat my patients with compounded BHRT instead of the commercially available BHRT because compounded BHRT allows me to dose medication to the individual patient. Hormone therapy is inherently idiosyncratic and therefore the hormones or combinations thereof, dosage strengths, and dosage forms need to be tailored to the individual patient. Bioidentical hormone therapy is not a one-size-fits-all therapy.

Commercially available synthetic estrogens do not effectively treat female patients for the conditions and symptoms they experience as a result of hormone imbalances or deficiencies. Instead, women often end up taking too much of the commercially available synthetic estrogens without the balancing effects of Estriol. Being able to compound combinations of bioidentical hormones allows me to treat patients better with less risk and fewer side effects experienced by the patient.

Similarly, Premarin is an FDA-approved conjugated equine estrogen, which carries a dose of estrogen that is far too strong for most women. The primary hormone in Premarin is Estrone, which is an inflammatory estrogen that carries negative side effects for women. These may include weight gain, breast tenderness, abdominal bloating and irregular uterine bleeding.

Additionally, Prometrium is the only natural FDA-approved progesterone therapy. Prometrium is a commercially available combination medication available as an oral capsule and

contains heat sensitive oils that can denature the progesterone during shipping and delivery of the medication. The capsule also contains peanut oil, so those patients with a peanut allergy cannot be treated with it. Without compounded BHRT, there is no way for these patients with allergies to get appropriately treated with progesterone.

Further, if men are inflamed, their bodies turn testosterone into estrone, which causes male breasts and/or abdominal bloating. These men often need to be treated with a combination of therapies to reduce inflammation and conversion of testosterone to estrone.

In my professional medical experience, many of my female patients initially come to me already being treated with commercially available BHRT and it is not working for them—that is, they are not being fully treated, they are not able to tolerate the side effects, and they do not feel like they are getting better. When I switch these patients to individually tailored, compounded BHRT, their health improves, their symptoms resolve, and there are far less side effects.

Sincerely,

/s/ Allan B. Warshowsky M.D. FACOG, ABIHM

Allan B. Warshowsky M.D. FACOG , ABHM

(Diplomate of the American Board of Holistic Medicine)

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Preferred e-mail – Abw88pe@aol.com

CELL 914 400 7380

EDUCATION

*Queens College of CUNY, Queens, New York, BA 1969, Phi Beta Kappa,
Magna Cum Laude*

Downstate Medical Center, of SUNY, Brooklyn, NY, M.D. 1973

Long Island Jewish Medical Center, Queens, NY

Internship (Rotating) -1973-1974

Residency (OB/GYN) -1974-1976

Chief Residency (OB/GYN) -1976-1977

WORK EXPERIENCE

*Private practice in Obstetrics and Gynecology (Conventional and Holistic
OB/GYN) on Long Island, NY 1977-March ,2000*

*Associate attending at Long Island Jewish Medical Center, Long Island
campus for Albert Einstein Medical Center*

Director of the Women's Program, Beth Israel's Continuum Center for Health and Healing, New York, NY April '00 –October '03

Private practice in Integrative Holistic Women's Health October '03 – 8/06 in NYC

Private practice in Integrative holistic women's healthcare in Bethesda, MD 8/06 – 6/08

Private practice in integrative holistic health care in Rye, NY 6/08 - present

PROFESSIONAL ORGANIZATIONS/ACHIEVEMENTS

Director Emeritus, American Board of Holistic Medicine (ABIHM) 1998-present

Created 1st board certification exam in Holistic Medicine –given Dec. 2000, and then 2x/year since then

Board of Directors, American Holistic Medical Association (AHMA) 1997-2000

member American Board of Obstetrics and Gynecology

Fellow American College of Obstetrics and Gynecology

Board of Advisors, Xymogen Professional Formulas 4/10 - present

Board of advisors, Sharpe Again Naturally - (Alzheimer's education group)

Author

"Healing Fibroids- a Doctors Guide to a Natural Cure"- published by Simon and Schuster

"Women at Risk"– coauthored with Dr. Gregory Henderson, published by Penguin abnormal pap smears, HPV, Holistic approach

Textbook of Integrative Medicine, University of Wisconsin Integrative Medicine

Dr. Allan Warshowsky is a board certified Ob-Gyn who had been in private practice from 1977 –present in the New York City area. He spent the last ten years developing a practice of integrative holistic women's healthcare. He has expanded his practice to include men and teens located in Rye, NY.

His practice therapies range from the conventional to the purely holistic. Some of these holistic modalities include: nutritional therapy, vitamin and herbal treatments, lifestyle changes, visualization and imagery, and other stress modification therapies.

He has had great results treating the discomforts and problems of menopause using natural, bio-identical hormones and other integrative, holistic approaches.

Dr. Warshowsky has been very successful as a facilitator of optimal health to those in need. His book "Healing Fibroids - A Doctors Guide to a Natural Cure", published by Simon and Schuster, describes Dr. Warshowsky's holistic program for fibroid tumors of the uterus.

Dr Warshowsky was a founding physician and director of the Women's Program at Beth Israel's Continuum Center for Health and Healing from 2000 -2003

Dr Warshowsky is a Founding Diplomat of and Director Emeritus of the American Board of Integrative Holistic Medicine

Exhibit 1-Q

Statement From David Watson, M.D., FACOG

Qualifications

My name is Dr. David Watson, MD, FACOG. My professional background is as follows. I earned my undergraduate degree in zoology from the University of Arkansas and earned my Doctor of Medicine from the University of Arkansas School of Medical Sciences. I graduated from medical school in 1988, having received the Elvin Shuffield Award in Excellence. I completed my internship and residency at St. Joseph Hospital in Denver, Colorado in 1992.

I began practicing medicine, specifically obstetrics and gynecology, at Littleton Gynecology & Wellness in 1992. I am credentialed by the American Board of Obstetrics and Gynecology. I am skilled in traditional pelvic surgery as well as DaVinci robotic surgery, and I am co-chairman of the Robotics Committee at Littleton Adventist Hospital. I became a certified BioTE medical practitioner in 2014.

Experience With Treatment Of Compounded Bio-Identical Hormone Therapy

I have over 20 years of experience in hormone management for my patients, and it is my professional medical judgment that compounded Bio-Identical Hormone Therapy (“BHRT”) is a better course of treatment than commercially available hormone replacement therapy. Since 2014, I have provided hormone pellet therapy to both of my male and female patients, and I currently treat virtually all of my patients with individualized forms of compounded BHRT.

When I first began practicing medicine, I treated my patients with conventional, commercially available hormone therapies. Unfortunately, I did not see the health of these patients improve, and often these patients returned with health decline, exhibiting conditions and symptoms such as Type II Diabetes, bone loss, general decline in wellbeing, and cardiovascular issues, among others. I made the decision, based on my medical judgment, to switch to treating patients with compounded BHRT, and I saw a near immediate improvement in these patients’ overall health, which is further discussed below. It simply made sense to me —put the missing bioidentical hormones back into the body and tailor them to the individual and mimic how the body managed the hormones. I now effectively treat over 400 patients per month with compounded BHRT.

Medical Conditions and Patient Populations Treated with Compounded BHRT

I treat a variety of medical conditions in my male and female patients with compounded BHRT. In men specifically, I prescribe compounded BHRT to treat erectile dysfunction. In women, I prescribe compounded BHRT to treat all menopausal symptoms. In both men and women, I prescribe compounded BHRT to treat the following medical conditions:

- Anxiety
- Cardiovascular issues and function
- Depression
- General health decline
- Diabetes
- Erectile dysfunction in men
- Fatigue
- Mild Alzheimer’s disease

- Joint pain
- Libido and sexual health issues in women
- Mental illness
- Osteopenia
- Osteoporosis
- Symptoms of menopause
- Vaginal dryness

Why is Compounded BHRT Preferred Over Commercially Available BHRT?

Using my professional medical judgment, I prefer to treat my patients with compounded BHRT instead of the commercially available hormone replacement therapy. I treat my patients according to the "Five Rights of Medicine" – that is, the Right patient, the Right drug, the Right dose, the Right route, and the Right time – a practice that is only possible with the individualized treatment available from a personalized, compounded medication rather than the one-size-fits-all, commercially available treatment.

Based on my professional medical experience, it seems the conventional medical industry has made the false assumption that all estrogens, all progestins, and all androgens behave the same in all human bodies. This is akin to assuming that all alcohols behave the same within the body, whereas consumption of ethanol versus consumption of a standard cocktail cause vastly different reactions in the human body.

When the Five Rights of Medicine are applied to hormone replacement therapy, it is clear that compounding the hormone medication (i.e., tailoring the dosage strength and form of administration to the individual patient) is the only appropriate way to treat hormone imbalance within patients. For example, when certain testosterone is converted into methyl-testosterone and absorbed in the gastrointestinal tract, it is converted by the liver into estrogens that have been proven to contribute to risks of breast cancer. However, when treating a patient with bioidentical testosterone in the dosage form of pellet therapy, the hormone is absorbed into the bloodstream and bypasses the liver – this has resulted in a 70% reduction in breast cancer risk in patients where pellet therapy was the right dosage form for him or her.

All patients are different, and therefore each patient has different sensitivities, tolerances, and reactions to hormone therapy that must be monitored throughout treatment so that the dosages and/or combinations of hormones can be adjusted appropriately. The commercially available BHRT does not, in my experience and medical judgment, allow me to effectively treat my patients the same way and to the same degree to that of compounded BHRT. There are no commercially available BHRT options that can adhere to the Five Rights of Medicine like pellet therapy. Especially now, when physicians have access to compounding facilities that adhere to very strict compounding standards, there is no reason physicians would not want this treatment option available for their patients.

It is critical that hormone levels be monitored in patients and tailored to an individual. For instance, a patient with an estrogen receptor positive breast tumor should not receive systemic

estrogen, or a patient with a history of endometriosis might require lower doses of estrogen to avoid re-igniting the disease. Further, if a patient's skin type does not allow proper absorption of hormone cream, pellet therapy would be a better option in order to receive the full benefit of the hormone therapy. Or, a patient may require a smaller dose of hormone in the pellet as time goes on. Being able to make these BHRT adjustments for patients is only possible with compounded BHRT—the commercially available BHRT cannot be tailored in this way, and therefore cannot treat patients to the same degree of effectiveness and success that the compounded version can. Individualization of therapy is tantamount to good outcomes, and these outcomes are difficult, at best, to achieve with current commercially available BHRT products.

I routinely witness severe osteopenia and osteoporosis completely reversed in patients after appropriate treatment with compounded BHRT. This is quite logical as it is when sex hormones are depleted which can be iatrogenic with the use of GNRH analogs or surgical removal of gonads or spontaneous as in menopause that we see the greatest degree of bone loss. It requires synergy between testosterone which promotes osteoblastic activity and estrogen which modulates osteoclastic activity in bone that we see the greatest results. No drug on the market can make that claim.

I commonly see my patients require less medication after being treated with compounded BHRT—for example, these patients are no longer relying on mood stabilizers, erectile dysfunction medication, pain medication, and sleep aids. Specifically, one of my patients was being treated with numerous medications and prednisone for eight years to treat joint pain, but this medication regimen was ineffective. Since this patient began treatment with compounded BHRT in pellet form, this patient's joint pain has been completely resolved and the patient is no longer taking prednisone. When the pellet treatment wears off, the joint pain returns but quickly dissipates when the pellets are reinserted. Further, compounded BHRT has proven invaluable for aiding in opioid addiction. And, as testosterone is an excellent insulin receptor sensitizer, I have witnessed better diabetic control in patients than before they were treated with compounded BHRT. Compounded BHRT is real, it is effective, and it should be here to stay.

Sincerely,

s/ David Watson, M.D.

Exhibit 2



200 Boylston Street, A309 | Chestnut Hill, MA 02467 | p. 617-277-5000 | f. 617-277-5444 | www.menshealthboston.com

October 31, 2019

Statement regarding compounded testosterone pellets from Abraham Morgentaler, MD

To whom it may concern,

I have extensive experience using testosterone pellets for the treatment of male hypogonadism over more than ten years. In that time I have had the occasion to use the FDA-approved pellet (Testopel) as well as compounded pellets from several sources. Whereas early in my experience it was my impression that challenges in the production of pellets were likely to make compounded pellets less reliable, this is no longer the case. In my current practice we routinely use compounded pellets. They are consistent in appearance, firmness, and resistance to breakage, and our clinical experience with them is excellent, based on follow-up testosterone levels and duration of response.

Compounded pellets are a critical part of the treatment armamentarium for men suffering from hypogonadism. I make this assessment based on: my own clinical experience; serving as President of the Androgen Society, an international, multidisciplinary organization dedicated to excellence in research, education, and clinical practice regarding testosterone deficiency and its treatment, where I interact with experts from around the world; serving as co-author on three sets of international society clinical recommendations for the management of testosterone deficiency, including lead author on one, and peer-reviewer for the Guidelines published by the American Urological Association in 2018. It would be damaging to the health and well-being of many men across the United States if new restrictions were placed on the use and availability of compounded testosterone pellets.

Sincerely,

Abraham Morgentaler, MD

Exhibit 3

Kimzey LM, Gumowski J, Merriam GR, Grimes GJ Jr, Nelson LM. (1991). Absorption of micronized progesterone from a nonliquefying vaginal cream. *Fertility and Sterility*, 56(5), 995-996.

Population: 8 healthy women with regular menses

Intervention: During the follicular phase of their menstrual cycle, five women inserted 3.3 grams of compounded micronized progesterone in Unibase at a concentration of 100 mg per 1.1 gram and five women took 3 compounded micronized progesterone in oil suspension in gelatin capsules at 100 mg per capsule (2 women received both interventions during different cycles).

Comparison: Serum progesterone levels at 1, 2, 4, 6, 8, 12, 16, 20, and 24 hours after administration.

Outcome: See figure below for serum progesterone levels. Vaginal progesterone and oral progesterone were absorbed at differing rates, but both showed absorption into serum at appreciable levels.

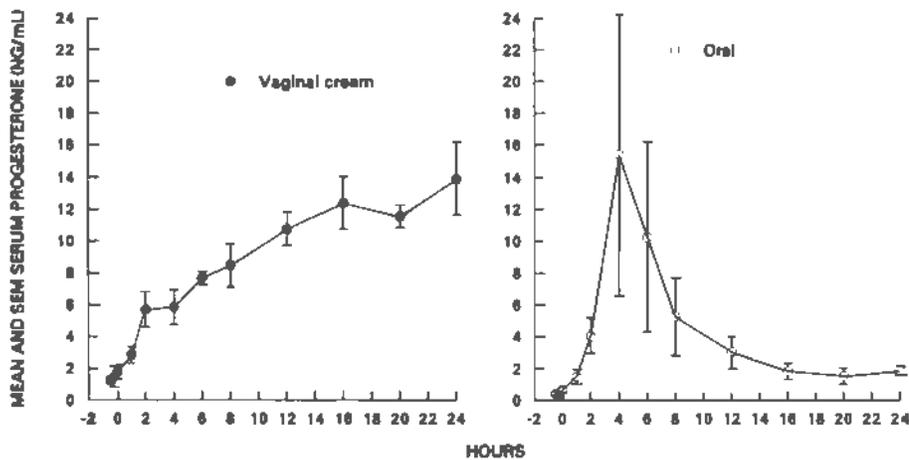


Figure 1 Serum P concentrations after vaginal applicator administration of 300 mg of micronized P in a nonliquefying cream and after oral administration of gelatin capsules containing 300 mg of micronized P in oil.

Maxson WS, Hargrove JT. (1985). Bioavailability of oral micronized progesterone. *Fertility and Sterility*, 44(5), 622-626.

Population: Nine health postmenopausal women and one male. Five women were receiving estrogen supplementation, one woman had previously received a progestogen, but all subjects had not taken any progestin within 3 week of onset of study.

Intervention: After fasting, all subjects were given 2 capsules of 100 mg of compounded micronized progesterone in a gelatin capsule

Comparison: Blood was drawn at 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, and 24.0 hours after administration.

Outcome: Various serum concentrations were measured and compared. Progesterone reached maximum absorption approximately 4 hours after administration.

Table 2. Serum Concentrations of Steroids, Enzymes, and Lipids in Female Subjects (n = 9) Receiving Oral Micronized P 200 mg at Time 0

Test	Units ^a	Time				
		0	2	4	6	24
P	ng/ml	0.2 ± 0.1 ^b	7.5 ± 3.1 ^c	9.1 ± 2.2 ^d	3.2 ± 4.1 ^d	0.6 ± 0.1
E ₂	pg/ml	72 ± 24	57 ± 16	60 ± 18	62 ± 19	56 ± 14
DHEA-S	ng/ml	1603 ± 614	1488 ± 578	1646 ± 611	1713 ± 590	1860 ± 688
FSH	mIU/ml	70 ± 11	63 ± 13	65 ± 11	73 ± 12	73 ± 12
LH	mIU/ml	68 ± 13	69 ± 12	69 ± 12	73 ± 10	74 ± 13
Cortisol	µg/dl	12 ± 3				11 ± 2
Aldosterone	ng/dl	18 ± 4				18 ± 2
Cholesterol ^e	mg/dl	284 ± 19				279 ± 20
HDL ^e	mg/dl	43 ± 4				43 ± 4
Triglycerides ^e	mg/dl	190 ± 23				188 ± 19
Alkaline phosphatase ^e	Bodansky U/dl	4.3 ± 0.8				4.3 ± 0.5
SGPT ^e	IU/l	11 ± 0.2				11 ± 1
Bilirubin ^e	mg/dl	0.2 ± 0.1				0.2 ± 0.1

^aAll values are recorded as mean ± SEM.

^bStatistical comparison of baseline values to subsequent measurements by Student's *t*-test. All comparisons not significant (*P* > 0.05), except as noted.

^c*P* < 0.05.

^d*P* < 0.001.

^eValues include one male subject (n = 10).

Tzingounis VA, Aksu MF, Greenblatt RB. (1978). Estriol in the Management of Menopause. *JAMA*, 236(16), 1638-1641

Population: Fifty-two postmenopausal women split into 4 different dosage groups.

Intervention: Oral estriol at dosages of 2 mg per day, 4 mg per day, 6 mg per day, and 8 mg per day for 6 months.

Comparison: Improvement in menopausal symptoms using the menopausal index of Kupperman, as well as comparison of various hormone serum levels over time.

Outcome: Improvement in menopausal symptoms for all dosages (see figure below).

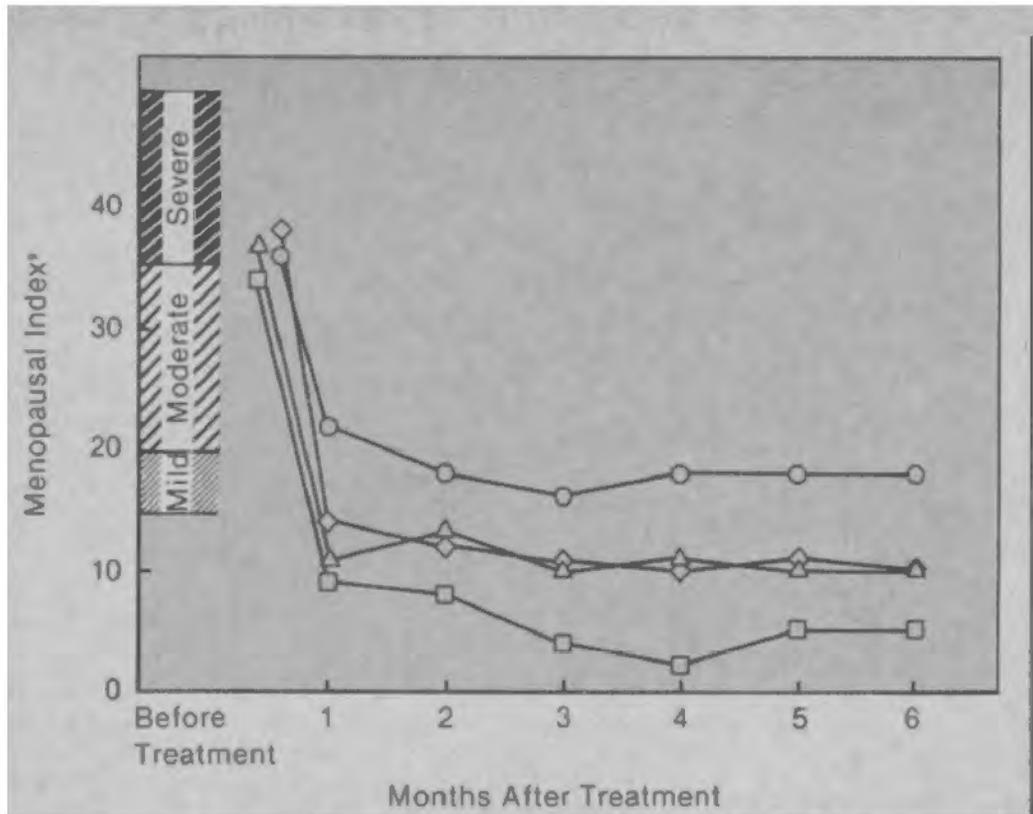


Fig 1.—Menopausal index by Kupperman et al⁸ before and after treatment. Circles indicate group A (20 women; 2 mg estriol); diamonds, group B (16 women; 4 mg); triangles, group C (8 women; 6 mg); and squares, group D (8 women; 8 mg).

Devogelaer JP, Lecart C, Dupret P, De Nayer P, Nagant De Deuxchaisnes C. (1998). Long-term effects of percutaneous estriol on bone loss and bone metabolism in postmenopausal hysterectomized women. *Maturitas*, 28, 243-249.

Population: Forty-three postmenopausal women who have had hysterectomies and may or may not have had oophorectomies.

Intervention: Compounded estriol gel at a dose of 1.5 mg daily cyclically with a placebo tablet versus placebo gel with a 2 mg estriol tablet daily cyclically.

Comparison: Bone mineral density via DXA measurement every 3 months

Outcome: Bone mineral density increased in the lumbar spine in the estriol gel group as compared to a decrease in density in the estriol tablet group. Bone mineral density also decreased in the proximal femur in the estriol tablet group, where there was no significant loss or gain in the estriol gel group.

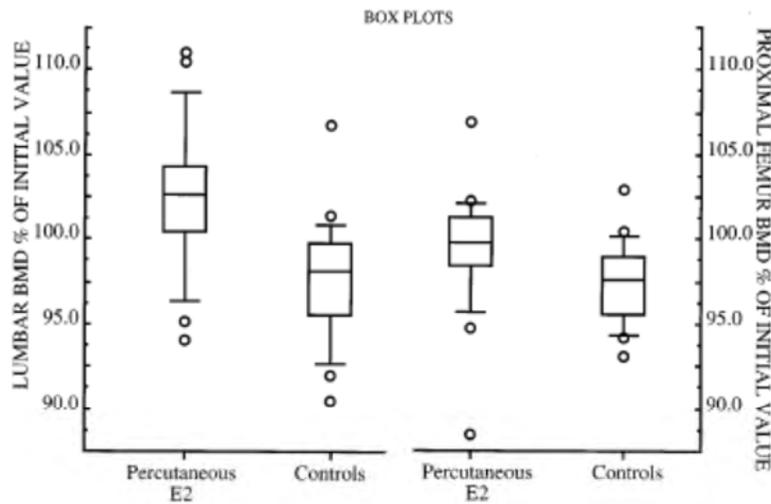


Fig. 2. Box plots: percentage changes at 24 months as compared to the initial value of BMD of lumbar spine and proximal femur in the percutaneous E₂ group and in the control-E₃ group. The midline of the box corresponds to the median of BMD changes. The upper extremity of the box corresponds to percentile 75, and the lower extremity to percentile 25. The upper whiskers correspond to percentile 90, while the lower ones correspond to percentile 10.

Hargrove JT, Maxson WS, Wentz AC, Burnett LS. (1989). Menopausal hormone replacement therapy with continuous daily oral micronized estradiol and progesterone. *Obstetrics & Gynecology*, 73(4), 606-612.

Population: Ten menopausal women

Intervention: Five women were given 0.625 mg of oral conjugated (manufactured) estrogens with 10 mg of oral medroxyprogesterone acetate (manufactured) daily for first 10 days of each calendar month for 12 months. The other 5 women were given a compound of 0.35 mg of micronized estradiol combined with 100 mg of micronized progesterone in an oil base in gelatin capsules, 1 capsule in the morning and 1 or 2 capsules in the evening daily for 12 months.

Comparison: Patients were seen at 0, 1, 3, 6, and 12 months, where symptoms were assessed and labs were drawn. Mammograms were obtained at 0 and 12 months.

Outcomes: Symptoms improved significantly in the compounded group versus the manufactured group (see figure below).

Table 1. Estrogen Replacement Therapy: Effect on Symptoms

Symptom	E2 and progesterone (N = 10)		Conjugated estrogens and medroxyprogesterone (N = 5)	
	Baseline	12 mo	Baseline	12 mo
Hot flashes	9	0	5	3
Night sweats	6	0	4	3
Insomnia	4	1	3	1
Decreased libido	6	0	2	0
Dyspareunia or vaginal dryness	5	0	3	2
Anxiety	6	3	3	1
Depression	1	1	3	0

E2 = estradiol.

Data are presented as number of patients with symptom. Symptom severity is scored as none, mild, moderate, or severe. Only moderate and severe symptoms were considered positive.

Wright DW, Kellermann AL, Hertzberg VS, Clark PL, Frankel M, et al. (2007). ProTECT: A randomized clinical trial of progesterone for acute traumatic brain injury. *Annals of Emergency Medicine*, 49(4), 391-402.

Population: One hundred adult traumatic brain injury patients who arrive to the ER within 11 hours of injury

Intervention: Seventy-seven patients received compounded IV progesterone with a loading dose of 0.71 mg/kg for 1 hour, the continuous infusion at 0.5 mg/kg for next 11 hours, then 5 additional 12-hour maintenance infusions for a total of 3 days of treatment was compared to 23 patients who received a placebo infusion.

Comparison: Measurements such as duration of time to awakening from coma, duration of posttraumatic amnesia, and mortality within 30 days of injury.

Outcome: Patients in the progesterone group had lower 30-day mortality rate than control. Additionally moderate traumatic brain injury survivors had better outcomes if they received progesterone compared to placebo.

Miller BE, De Souza MJ, Slade K, Luciano AA. (2000). Sublingual administration of micronized estradiol and progesterone, with and without micronized testosterone: effect on biochemical markers of bone metabolism and bone mineral density. *Menopause*, 7(5), 318-326.

Population: Fifty seven postmenopausal, healthy women who either had hysterectomies or had an intact uterus.

Intervention: The women who had hysterectomies were randomized into 1 of 2 groups: compounded sublingual micronized estradiol 0.5 mg or compounded sublingual micronized estradiol 0.5 mg + micronized testosterone 1.25 mg. The women with intact uteri were randomized into 1 of 2 groups: compounded micronized sublingual estradiol 0.5 mg + micronized progesterone 100 mg or compounded sublingual micronized estradiol 0.5 mg + micronized progesterone 100 mg + micronized testosterone 1.25 mg. The women took 1 compounded tablet twice a day

Comparison: Blood was drawn at baseline, 2 months, 6 months, and 12 months. Bone mineral density was measured using DXA at baseline and 12 months.

Outcome: Bone mineral density in the lumbar spine increased over the 12 months in both groups, and total hip bone mineral density increased in the non-testosterone group, while it was only maintained in the testosterone group.

Stephenson K, Neuenschwander PE, Kurdowska AK, Pinson B, Price C. (2008). Transdermal progesterone: Effects on menopausal symptoms and on thrombotic, anticoagulant, and inflammatory factors in postmenopausal women. *International Journal of Pharmaceutical Compounding*, 12(4), 295-304.

Population: Thirty healthy postmenopausal women

Intervention: The women were split into 2 groups, one group received a compounded progesterone 20 mg per day cream to apply transdermally daily for 4 weeks, followed by a 4 week washout period where no cream was applied, then a 4 week period where a placebo cream was applied. The other group received a placebo cream to apply transdermally for 4 weeks, followed by a 4 week washout period where no cream was applied, then a 4 week period where a compounded progesterone 20 mg per day cream was applied transdermally daily for 4 weeks.

Comparison: Blood was drawn at baseline, after 4 weeks, and at the end of the study, as well as menopausal symptoms using the Greene Climacteric Scale.

Outcome: Neither group had a significant increase in blood levels that would effect clotting or inflammation after use of the progesterone. Administration of the progesterone also improved menopausal symptoms in both groups.

EXHIBIT 2

July 24, 2020

Via Online Access Portal

Food and Drug Administration
Division of Freedom of Information
Office of the Executive Secretariat, OC
5630 Fishers Lane, Room 1035
Rockville, MD 20857

RE: Freedom of Information Act Request

To Whom It May Concern:

We are submitting the following Freedom of Information Act (“FOIA”) request to the U.S. Food & Drug Administration (“FDA”).

A. Requestor's name, address, and telephone number.

Rachael Pontikes
10 South Wacker Drive
40th Floor
Chicago, IL 60606
(312) 207-2857

B. A description of the records being sought. The records should be identified as specifically as possible. A request for specific records that are releasable to the public can be processed much more quickly than a request for "all information" on a particular subject. Also fees for a more specific and limited request will generally be less.

I request the following records:

- All communications* between FDA (including, but not limited to, FDA’s Center for Drug Evaluation and Research (“CDER”)) and the National Academies of Sciences, Engineering, and Medicine (including, but not limited to, Leigh Jackson), from January 1, 2016, to the present regarding the following subjects:

* For purposes of this FOIA request, the term “communications” includes, but is not limited to, e-mail messages, letters, memoranda, and calendar invitations and notations.

- Bioidentical hormones;
 - Compounded bioidentical hormone therapy (otherwise known as “cBHT” or “cBHRT”);
 - Difficult to compound;
 - Clinical utility ;
 - Pharmacy Compounding Advisory Committee (otherwise known as “PCAC”);
 - Jane Axelrad; or
 - Axelrad Solutions LLC.
- All communications between FDA (including, but not limited to, FDA’s CDER) and Jane Axelrad from May 1, 2016, to the present regarding the following subjects:
 - National Academies of Sciences, Engineering, and Medicine (otherwise known as “NASEM”);
 - Bioidentical hormones;
 - Compounded bioidentical hormone therapy (otherwise known as “cBHT” or “cBHRT”);
 - Difficult to compound;
 - Clinical utility; or
 - Pharmacy Compounding Advisory Committee (otherwise known as “PCAC”).
- All communications between FDA (including, but not limited to, FDA’s CDER) and Axelrad Solutions LLC from December 6, 2016, to the present regarding the following subjects:
 - National Academies of Sciences, Engineering, and Medicine (otherwise known as “NASEM”);
 - Bioidentical hormones;
 - Compounded bioidentical hormone therapy (otherwise known as “cBHT” or “cBHRT”);
 - Difficult to compound;
 - Clinical utility; or
 - Pharmacy Compounding Advisory Committee (otherwise known as “PCAC”).
- All communications between FDA (including, but not limited to, FDA’s CDER) and the Pharmacy Compounding Advisory Committee, from November 27, 2013, to the present regarding the following subjects:
 - Bioidentical hormones;
 - Compounded bioidentical hormone therapy (otherwise known as “cBHT” or “cBHRT”);
 - Difficult to compound;
 - Clinical utility;
 - National Academies of Sciences, Engineering, and Medicine (otherwise known as “NASEM”);
 - Jane Axelrad; or
 - Axelrad Solutions LLC.

Food and Drug Administration
July 24, 2020
Page 3

ReedSmith

C. A statement concerning willingness to pay fees, including any limitations.

I will pay all fees associated with this request. If the agency estimates that those fees will exceed \$1,000.00, please contact me before proceeding further.

Very truly yours,

Rachael G. Pontikes

Rachael G. Pontikes
For Reed Smith LLP

RGP:rl

EXHIBIT 3

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA**

REED SMITH LLP
225 Fifth Avenue
Pittsburgh, PA 15222,

Plaintiff,

v.

Civil Action No. 20-2786

FOOD AND DRUG ADMINISTRATION
10903 New Hampshire Avenue
Silver Spring, MD 20993,

Defendant.

COMPLAINT FOR INJUNCTIVE RELIEF

Plaintiff Reed Smith LLP brings this action seeking disclosure of wrongfully withheld agency records pursuant to the Freedom of Information Act (“FOIA”), 5 U.S.C. § 552, and alleges as follows:

JURISDICTION AND VENUE

1. This Court has jurisdiction over this action pursuant to 5 U.S.C. § 552(a)(4)(B) and 28 U.S.C. § 1331.
2. Venue lies in this district under 5 U.S.C. § 552(a)(4)(B).

PARTIES

3. Plaintiff Reed Smith LLP (“Reed Smith”), which submitted the FOIA request at issue here, is a limited liability partnership organized under the laws of the State of Delaware. Reed Smith’s principal business address is 225 Fifth Avenue, Pittsburgh, Pennsylvania 15222.
4. Defendant Food and Drug Administration (“FDA”), which received the FOIA request at issue here, is an agency within the Department of Health and Human Services. FDA is an

“agency” within the meaning of 5 U.S.C. §§ 551(1) and 701(b)(1). FDA’s principal business address is 10903 New Hampshire Avenue, Silver Spring, Maryland 20993.

STATEMENT OF FACTS

5. On July 1, 2020, the National Academies of Sciences, Engineering, and Medicine (“NASEM”) published a report entitled *The Clinical Utility of Compounded Bioidentical Hormone Therapy: A Review of Safety, Effectiveness, and Use* (the “Report”). The Report was the result of a study, commissioned by FDA, to examine the clinical utility of treating patients with compounded bioidentical hormone replacement therapy (“cBHRT”).

6. On July 31, 2020, Reed Smith submitted a FOIA request to FDA requesting agency records related to NASEM’s study and the Report. Specifically, the FOIA request sought communications between FDA (including, but not limited to, FDA’s Center for Drug Evaluation and Research) and relevant individuals and entities, within a specified timeframe, regarding the following subjects: (1) NASEM, (2) bioidentical hormones, (3) cBHRT, (4) difficult to compound, (5) clinical utility, (6) the Pharmacy Compounding Advisory Committee, (7) Jane Axelrad, and (8) Axelrad Solutions, LLC. A true and correct copy of the FOIA request is attached as Exhibit A. Although the letter containing the FOIA request is dated July 24, 2020, as reflected by FDA’s FOIA Request Confirmation attached as Exhibit B, the FOIA request was submitted to FDA via the agency’s online access portal on July 31, 2020.

7. FDA confirmed receipt of the FOIA request via e-mail on July 31, 2020. A true and correct copy of FDA’s July 31 e-mail is attached as Exhibit C.

8. On August 4, 2020, FDA advised Reed Smith via e-mail that FDA had assigned the FOIA request a control number but indicated that “[d]ue to an increase in the number of incoming requests, we may be unable to comply with the twenty-working-day time limit in this case, as well as the ten additional days provided by the FOIA.” FDA provided no date upon which it intended

to respond to the FOIA request, nor did FDA seek any information from Reed Smith in order to assist FDA with responding to the request in the time required by statute. A true and correct copy of FDA's August 4 e-mail is attached as Exhibit D.

9. FOIA provides that an agency must "determine within 20 days (excepting Saturdays, Sundays, and legal public holidays) after the receipt of [a FOIA] request whether to comply with such request and shall immediately notify the person making such request of . . . such determination and the reasons therefor." 5 U.S.C. § 552(a)(6)(A)(i). The 20-day period "shall commence on the date on which the request is first received by the appropriate component of the agency, but in any event not later than ten days after the request is first received by any component of the agency that is designated in the agency's regulations . . . to receive" FOIA requests. *Id.* § 552(a)(6)(A). "In unusual circumstances . . . the time limits . . . may be extended by written notice to the person making such request setting forth the unusual circumstances for such extension and the date on which a determination is expected to be dispatched." *Id.* § 552(a)(6)(B)(i). "No such notice shall specify a date that would result in an extension for more than ten working days" except in certain circumstances not relevant here. *Id.*

10. FDA received the FOIA request on July 31, 2020. Even allowing for an additional ten days in order for the request to be provided to the appropriate FDA component, the time limit for FDA to determine whether to comply with the FOIA request expired on September 11, 2020. At no time did FDA provide any information supporting an extension of that time limit due to unusual circumstances, seek to modify or narrow the FOIA request, or provide a date certain on which a determination is expected to be dispatched.

11. To date, Reed Smith has not received a determination from FDA as to whether FDA will comply with the FOIA request.

CAUSE OF ACTION

Violation of the Freedom of Information Act for Improper Withholding of Agency Records

12. Reed Smith repeats and realleges paragraphs 1-11.
13. The documents requested by the FOIA request constitute “agency records” subject to mandatory disclosure under FOIA.
14. FDA has improperly withheld the requested agency records in violation of 5 U.S.C. § 552(a)(3)(A).
15. Reed Smith has constructively exhausted its administrative remedies pursuant to 5 U.S.C. § 552(a)(6)(C)(i).

REQUEST FOR RELIEF

WHEREFORE, Reed Smith requests that the Court:

- A. Order FDA to produce all agency records responsive to the FOIA request by a date certain;
- B. Award Reed Smith its costs and reasonable attorney’s fees incurred in this action pursuant to 5 U.S.C. § 552(a)(4)(E); and
- C. Grant such other relief as the Court deems just and proper.

Dated: October 1, 2020

Respectfully submitted,

REED SMITH LLP

By: /s/ James F. Segroves
James F. Segroves (D.C. Bar No. 480630)
1301 K Street, NW
Suite 1000 – East Tower
Washington, DC 20005
202.414.9200
202.414.9299 (fax)
jsegroves@reedsmith.com

Counsel for Plaintiff

**EXHIBIT A:
FOIA Request**

**Complaint for Injunctive Relief,
Reed Smith LLP v. Food & Drug Administration,
Civil Action No. 20-2786**



Driving progress
through partnership

Rachael G. Pontikes

Direct Phone: +1 312 207 2857

Email: rpontikes@reedsmith.com

Reed Smith LLP
10 South Wacker Drive
Chicago, IL 60606-7507
+1 312 207 1000
Fax +1 312 207 6400
reedsmith.com

July 24, 2020

Via Online Access Portal

Food and Drug Administration
Division of Freedom of Information
Office of the Executive Secretariat, OC
5630 Fishers Lane, Room 1035
Rockville, MD 20857

RE: Freedom of Information Act Request

To Whom It May Concern:

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Rachael Pontikes
10 South Wacker Drive
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Food and Drug Administration
July 24, 2020
Page 2

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 - Clinical utility ;
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 - Jane Axelrad; or
 - Axelrad Solutions LLC.
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Food and Drug Administration
July 24, 2020
Page 3

ReedSmith

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Very truly yours,

Rachael G. Pontikes

Rachael G. Pontikes
For Reed Smith LLP

RGP:rl

EXHIBIT B:
FOIA Request Confirmation

Complaint for Injunctive Relief,
Reed Smith LLP v. Food & Drug Administration,
Civil Action No. 20-2786



FOIA Request Confirmation

Confirmation Number: FDA2067155

Requester:

General

Description of Requester:	Commercial user
Max Amount Willing to Pay:	\$1,000

Organization

Organization Name:	Rachael Pontikes		
Primary Phone:	312-207-2857	Other Phone:	312-207-2876
Email:	rpontikes@reedsmith.com		

Mailing Address

Address 1:	10 South Wacker Drive
Address 2:	40th Floor
City:	Chicago
State:	IL
Zip Code:	60606

Billing Address

Address 1:	10 South Wacker Drive
Address 2:	40th Floor
City:	Chicago
State:	IL
Zip Code:	60606

Details

Requester Name:	Rachael Pontikes		
Requester File #:		Request Letter:	FDA FOIA Request.pdf
Requested Date From:		Requested Date To:	
Subject of Request:	• All communications between FDA (including, but not limited to, FDA's Center for Drug Evaluation and Research ("CDER")) and the National Academies of		

Waiver of Fees

Justification:	
----------------	--

Expedited Processing

Reason:	
Justification:	

[Print](#) [Create Another Request](#) [Close](#)

Within 10 business days of the submission of your online request, you will receive by electronic mail an FOIA Control Number. If you need to communicate with FDA regarding your request, please refer to this Control Number. Requests received after 4:00 P.M. E.S.T. will be considered to have been received on the following business day.

If your informational needs change, and you need to cancel your request, please contact the Division of Freedom of Information by telephone, mail, or fax. Please include your control number in the correspondence. For contact information, please see [FDA's FOIA page](#).

**EXHIBIT C:
July 31, 2020 E-mail**

**Complaint for Injunctive Relief,
Reed Smith LLP v. Food & Drug Administration,
Civil Action No. 20-2786**

Hussey, Emily L.

From: noreply@fda.gov
Sent: Friday, July 31, 2020 10:03 AM
To: Pontikes, Rachael G.
Subject: FOI Request Received

EXTERNAL E-MAIL - From noreply@fda.gov

*** This is an automated message. Please do not reply to this email. ***

Reference: FDA2067155

Dear Requester,

This is to confirm that you submitted a request for record(s) from the Food and Drug Administration pursuant to the Freedom of Information Act.

FOIA staff will review your request to determine whether it has sufficient information to be processed; if so, you will receive another email as a formal acknowledgement of your request, with a control number for your request.

If your request is not sufficiently described, or if there are any other deficiencies with your submission, FOIA staff will contact you via telephone or email.

EXHIBIT D:
August 4, 2020 E-mail

Complaint for Injunctive Relief,
Reed Smith LLP v. Food & Drug Administration,
Civil Action No. 20-2786

Hussey, Emily L.

From: FDA_FOI@fda.gov
Sent: Tuesday, August 4, 2020 7:23 AM
To: Pontikes, Rachael G.
Subject: FDA Receipt of FOI Request

EXTERNAL E-MAIL - From FDA_FOI@fda.gov

Rachael Pontikes Rachael Pontikes

Re: Confirmation # FDA2067155
Requester Ctrl #:
In Reply refer to: 2020-5664

The Food and Drug Administration (FDA) has received your Freedom of Information Act (FOIA) request for records regarding:

? All communications between FDA (including, but not limited to, FDA?s Center for Drug Evaluation and Research (?CDER?)) and the National Academies of Sciences, Engineering, and Medicine (including, but not limited to, Leigh Jackson), from January 1, 2016, to the present regarding the following subjects: o Bioidentical hormones; o Compounded bioidentical hormone therapy (otherwise known as ?cBHT? or ?cBHRT?); ETC

We will respond as soon as possible and may charge you a fee for processing your request. If your informational needs change, and you no longer need the requested records, please contact us to cancel your request, as charges may be incurred once processing of your request has begun. For more information on processing fees, please see <http://www.fda.gov/RegulatoryInformation/FOI/FOIAFees/default.htm>.

Due to an increase in the number of incoming requests, we may be unable to comply with the twenty-working-day time limit in this case, as well as the ten additional days provided by the FOIA. The actual processing time will depend on the complexity of your request and whether sensitive records, voluminous records, extensive search, and/or consultation with other HHS components or other executive branch agencies are involved. Please note that requests for medical device approval records (e.g. 510K, PMA, DEN) may take up to 18 to 24 months to process.

If you have any questions about your request, please call Rochelle A. Coleman, Information Technician at 301-796-8982 or write to us at:

Division of Freedom of Information,
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1050
Rockville, MD 20857
Fax: 301-827-9267

You also have the right to seek dispute resolution services from:

FDA FOIA Public Liaison
Office of the Executive Secretariat
5630 Fishers Lane, Room 1050

Rockville, MD 20857
E-Mail: FDAFOIA@fda.hhs.gov

and/or:

Office of Government
Information Services
National Archives and Administration
8601 Adelphi Road - OGIS
College Park, MD 20740-6001
Telephone: 202-741-5770
Toll-Free: 1-877-684-6448
E-Mail: ogis@nara.gov
Fax: 202-741-5769

Note: Do NOT reply directly to this E-mail

<input type="radio"/> G. Habeas Corpus/ 2255 <input type="checkbox"/> 530 Habeas Corpus – General <input type="checkbox"/> 510 Motion/Vacate Sentence <input type="checkbox"/> 463 Habeas Corpus – Alien Detainee	<input type="radio"/> H. Employment Discrimination <input type="checkbox"/> 442 Civil Rights – Employment (criteria: race, gender/sex, national origin, discrimination, disability, age, religion, retaliation) *(If pro se, select this deck)*	<input checked="" type="radio"/> I. FOIA/Privacy Act <input checked="" type="checkbox"/> 895 Freedom of Information Act <input type="checkbox"/> 890 Other Statutory Actions (if Privacy Act) *(If pro se, select this deck)*	<input type="radio"/> J. Student Loan <input type="checkbox"/> 152 Recovery of Defaulted Student Loan (excluding veterans)
<input type="radio"/> K. Labor/ERISA (non-employment) <input type="checkbox"/> 710 Fair Labor Standards Act <input type="checkbox"/> 720 Labor/Mgmt. Relations <input type="checkbox"/> 740 Labor Railway Act <input type="checkbox"/> 751 Family and Medical Leave Act <input type="checkbox"/> 790 Other Labor Litigation <input type="checkbox"/> 791 Empl. Ret. Inc. Security Act	<input type="radio"/> L. Other Civil Rights (non-employment) <input type="checkbox"/> 441 Voting (if not Voting Rights Act) <input type="checkbox"/> 443 Housing/Accommodations <input type="checkbox"/> 440 Other Civil Rights <input type="checkbox"/> 445 Americans w/Disabilities – Employment <input type="checkbox"/> 446 Americans w/Disabilities – Other <input type="checkbox"/> 448 Education	<input type="radio"/> M. Contract <input type="checkbox"/> 110 Insurance <input type="checkbox"/> 120 Marine <input type="checkbox"/> 130 Miller Act <input type="checkbox"/> 140 Negotiable Instrument <input type="checkbox"/> 150 Recovery of Overpayment & Enforcement of Judgment <input type="checkbox"/> 153 Recovery of Overpayment of Veteran’s Benefits <input type="checkbox"/> 160 Stockholder’s Suits <input type="checkbox"/> 190 Other Contracts <input type="checkbox"/> 195 Contract Product Liability <input type="checkbox"/> 196 Franchise	<input type="radio"/> N. Three-Judge Court <input type="checkbox"/> 441 Civil Rights – Voting (if Voting Rights Act)

V. ORIGIN
 1 Original Proceeding
 2 Removed from State Court
 3 Remanded from Appellate Court
 4 Reinstated or Reopened
 5 Transferred from another district (specify)
 6 Multi-district Litigation
 7 Appeal to District Judge from Mag. Judge
 8 Multi-district Litigation – Direct File

VI. CAUSE OF ACTION (CITE THE U.S. CIVIL STATUTE UNDER WHICH YOU ARE FILING AND WRITE A BRIEF STATEMENT OF CAUSE.)
 Action seeking disclosure of agency records under the Freedom of Information Act, 5 U.S.C. § 552.

VII. REQUESTED IN COMPLAINT	<input type="checkbox"/> CHECK IF THIS IS A CLASS ACTION UNDER F.R.C.P. 23	DEMAND \$ JURY DEMAND:	Check YES only if demanded in complaint YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>
------------------------------------	--	---	--

VIII. RELATED CASE(S) IF ANY	(See instruction)	YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>	If yes, please complete related case form
-------------------------------------	-------------------	---	---

DATE: <u>October 1, 2020</u>	SIGNATURE OF ATTORNEY OF RECORD <u>/s/ James F. Segroves</u>
------------------------------	--

INSTRUCTIONS FOR COMPLETING CIVIL COVER SHEET JS-44
 Authority for Civil Cover Sheet

The JS-44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and services of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently, a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. Listed below are tips for completing the civil cover sheet. These tips coincide with the Roman Numerals on the cover sheet.

- I.** COUNTY OF RESIDENCE OF FIRST LISTED PLAINTIFF/DEFENDANT (b) County of residence: Use 11001 to indicate plaintiff if resident of Washington, DC, 88888 if plaintiff is resident of United States but not Washington, DC, and 99999 if plaintiff is outside the United States.
- III.** CITIZENSHIP OF PRINCIPAL PARTIES: This section is completed only if diversity of citizenship was selected as the Basis of Jurisdiction under Section II.
- IV.** CASE ASSIGNMENT AND NATURE OF SUIT: The assignment of a judge to your case will depend on the category you select that best represents the primary cause of action found in your complaint. You may select only one category. You must also select one corresponding nature of suit found under the category of the case.
- VI.** CAUSE OF ACTION: Cite the U.S. Civil Statute under which you are filing and write a brief statement of the primary cause.
- VIII.** RELATED CASE(S), IF ANY: If you indicated that there is a related case, you must complete a related case form, which may be obtained from the Clerk’s Office.

Because of the need for accurate and complete information, you should ensure the accuracy of the information provided prior to signing the form.

**UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA**

REED SMITH LLP

Plaintiff

v.

FOOD AND DRUG ADMINISTRATION

Defendant

)
)
)
)
)
)
)
)
)
)

Civil Action No. 20-2786

SUMMONS IN A CIVIL ACTION

To: *(Defendant's name and address)*

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

A lawsuit has been filed against you.

Within 30 days after service of this summons on you (not counting the day you received it) you must serve on the plaintiff an answer to the attached complaint or a motion under Rule 12 of the Federal Rules of Civil Procedure. The answer or motion must be served on the plaintiff or plaintiff's attorney, whose name and address are:

James F. Segroves
Reed Smith LLP
1301 K Street, NW
Suite 1000 – East Tower
Washington, DC 20005
202.414.9294
jsegroves@reedsmith.com

If you fail to respond, judgment by default may be entered against you for the relief demanded in the complaint. You also must file your answer or motion with the court.

ANGELA D. CAESAR, CLERK OF COURT

Date: _____

Signature of Clerk or Deputy Clerk

Civil Action No. 20-2786

PROOF OF SERVICE

(This section should not be filed with the court unless required by Fed. R. Civ. P. 4 (l))

This summons for *(name of individual and title, if any)* _____
was received by me on *(date)* _____.

I personally served the summons on the individual at *(place)* _____
_____ on *(date)* _____ ; or

I left the summons at the individual's residence or usual place of abode with *(name)* _____
_____, a person of suitable age and discretion who resides there,
on *(date)* _____, and mailed a copy to the individual's last known address; or

I served the summons on *(name of individual)* _____, who is
designated by law to accept service of process on behalf of *(name of organization)* _____
_____ on *(date)* _____ ; or

I returned the summons unexecuted because _____ ; or

Other *(specify):* _____

My fees are \$ _____ for travel and \$ _____ for services, for a total of \$ _____ 0.00 _____.

I declare under penalty of perjury that this information is true.

Date: _____

Server's signature

Printed name and title

Server's address

Additional information regarding attempted service, etc:

**UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA**

REED SMITH LLP

Plaintiff

v.

FOOD AND DRUG ADMINISTRATION

Defendant

)
)
)
)
)
)
)
)

Civil Action No. 20-2786

SUMMONS IN A CIVIL ACTION

To: *(Defendant's name and address)*

William P. Barr
Attorney General of the United States
United States Department of Justice
950 Pennsylvania Avenue, NW
Washington, DC 20530

A lawsuit has been filed against you.

Within 30 days after service of this summons on you (not counting the day you received it) you must serve on the plaintiff an answer to the attached complaint or a motion under Rule 12 of the Federal Rules of Civil Procedure. The answer or motion must be served on the plaintiff or plaintiff's attorney, whose name and address are:

James F. Segroves
Reed Smith LLP
1301 K Street, NW
Suite 1000 – East Tower
Washington, DC 20005
202.414.9294
jsegroves@reedsmith.com

If you fail to respond, judgment by default may be entered against you for the relief demanded in the complaint. You also must file your answer or motion with the court.

ANGELA D. CAESAR, CLERK OF COURT

Date: _____

Signature of Clerk or Deputy Clerk

Civil Action No. 20-2786

PROOF OF SERVICE

(This section should not be filed with the court unless required by Fed. R. Civ. P. 4 (l))

This summons for *(name of individual and title, if any)* _____
was received by me on *(date)* _____.

I personally served the summons on the individual at *(place)* _____
_____ on *(date)* _____; or

I left the summons at the individual's residence or usual place of abode with *(name)* _____
_____, a person of suitable age and discretion who resides there,
on *(date)* _____, and mailed a copy to the individual's last known address; or

I served the summons on *(name of individual)* _____, who is
designated by law to accept service of process on behalf of *(name of organization)* _____
_____ on *(date)* _____; or

I returned the summons unexecuted because _____; or

Other *(specify)*: _____

My fees are \$ _____ for travel and \$ _____ for services, for a total of \$ _____ 0.00 _____.

I declare under penalty of perjury that this information is true.

Date: _____

Server's signature

Printed name and title

Server's address

Additional information regarding attempted service, etc:

Civil Action No. 20-2786

PROOF OF SERVICE

(This section should not be filed with the court unless required by Fed. R. Civ. P. 4 (l))

This summons for *(name of individual and title, if any)* _____
was received by me on *(date)* _____.

I personally served the summons on the individual at *(place)* _____
_____ on *(date)* _____ ; or

I left the summons at the individual's residence or usual place of abode with *(name)* _____
_____, a person of suitable age and discretion who resides there,
on *(date)* _____, and mailed a copy to the individual's last known address; or

I served the summons on *(name of individual)* _____, who is
designated by law to accept service of process on behalf of *(name of organization)* _____
_____ on *(date)* _____ ; or

I returned the summons unexecuted because _____ ; or

Other *(specify)*: _____

My fees are \$ _____ for travel and \$ _____ for services, for a total of \$ _____ 0.00 _____.

I declare under penalty of perjury that this information is true.

Date: _____

Server's signature

Printed name and title

Server's address

Additional information regarding attempted service, etc:

EXHIBIT 4

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

REED SMITH LLP,)	
)	
Plaintiff,)	
)	
v.)	Civ. A. No. 20-2786 (RC)
)	
FOOD AND DRUG ADMINISTRATION,)	
)	
Defendant.)	
)	

JOINT STATUS REPORT

Defendant, the United States Food and Drug Administration (“FDA”), jointly with Plaintiff, Reed Smith LLP (“Plaintiff”), by and through undersigned counsel, hereby respectfully file this joint status report:

1. At issue in this Freedom of Information Act (“FOIA”) lawsuit is a FOIA request submitted to FDA on July 31, 2020.
2. Plaintiff initiated this action on October 1, 2020 (ECF No. 1), and FDA filed an answer on November 12, 2020 (ECF No. 5.) That same day, the Court ordered the parties to meet and confer and submit a proposed briefing schedule by November 30, 2020.
3. One office within FDA has been identified by FDA as having records potentially responsive to Plaintiff’s FOIA request: the Center for Drug Evaluation and Research (“CDER”).
4. On October 23, 2020, the parties met and conferred to discuss Plaintiff’s FOIA request. FDA explained that CDER has a substantial backlog of FOIA requests and was not yet able to estimate the volume of potentially responsive records or how many productions might be required to respond to Plaintiff’s FOIA request. The parties discussed ways to prioritize or focus

the FOIA request to enable CDER to identify potentially responsive records and begin productions sooner.

5. In October and November 2020, FDA conducted a preliminary analysis of sources of potentially responsive records in CDER's possession. FDA identified several individuals, including Ms. Gabrielle Cosel and Ms. Elizabeth Hankla, with potentially responsive records.

6. On November 23, 2020, the parties agreed that, by January 8, 2021, FDA would produce to Plaintiff all responsive, non-exempt contracts; all responsive, non-exempt records in Ms. Cosel's files; and all responsive, non-exempt records in Ms. Hankla's files. The parties acknowledged that some responsive, non-exempt records in Ms. Hankla's files might be inaccessible until Ms. Hankla returns from leave. To the extent any such records exist, FDA will release those records within six weeks of Ms. Hankla's return from leave (anticipated to occur in mid to late January 2021).

7. Once Plaintiff has a reasonable opportunity to review FDA's production, the parties will meet and confer in good faith to discuss whether Plaintiff believes that additional searches for documents responsive to Plaintiff's FOIA request or additional productions may be necessary.

8. In light of the parties' agreement, FDA does not intend to request an *Open America* stay. The parties believe that production of a *Vaughn* Index, or draft *Vaughn* Index, is premature until productions are complete. The parties also believe it is premature to set a briefing schedule for dispositive motions at this time.

9. In light of the current posture of the proceedings, the parties propose submitting a further status report on March 31, 2021.

Respectfully Submitted,

By: /s/ James F. Segroves

JAMES F. SEGROVES (D.C. Bar No. 480630)
REED SMITH LLP
1301 K Street, NW
Suite 1000 – East Tower
Washington, DC 20005
202.414.9200
202.414.9299 (fax)
jsegroves@reedsmith.com
Counsel for Plaintiff

MICHAEL SHERWIN
Acting United States Attorney

DANIEL F. VAN HORN, DC Bar #924092
Chief, Civil Division

By: /s

BENTON G. PETERSON, BAR # 1029849
Assistant United States Attorney
555 4th Street, N.W. – Civil Division
Washington, D.C. 20530
(202) 252-2534

EXHIBIT 5

From: Pontikes, Rachael G. <RPontikes@reedsmith.com>
Sent: Tuesday, February 9, 2021 4:31 PM
To: Heller, Seth <Seth.Heller@fda.hhs.gov>
Cc: Peterson, Benton (USADC) <Benton.Peterson@usdoj.gov>; Segroves, James F. <JSegroves@reedsmith.com>
Subject: RE: Reed Smith LLP v. FDA, No. 1:20-cv-02786-RC (D.D.C.)

Hi Seth,

In response to your email below, in preparation for our meet and confer, we have now reviewed the documents FDA produced. As set out in Paragraph 5 of Document 6, the Joint Status Report (reattached here for reference), "FDA identified several individuals . . . with potentially responsive records." Initially, FDA identified Ms. Gabrielle Cosel and Ms. Elizabeth Hankla as initial sources of potentially responsive records to the FOIA at issue. As set forth in Paragraph 7 of the Joint Status Report, our initial review has indicated that additional searches from additional individuals are necessary to complete FDA's response to our FOIA request. Based on the frequency with which they appear in key correspondence, we have identified the following additional key individuals:

- (1) Gail Bormel;
- (2) Sara Rothman;
- (3) Amy Akparewa; and
- (4) Lesley-Anne Furlong.

Please let us know if you would like to set up a call to discuss, or in the alternative, the date by which FDA will be producing the documents from the individuals as outlined above. We appreciate your reaching out to us regarding the completion of FDA's production and look forward to working with you to bring this matter to a resolution.

Best,
Rachael

Rachael G. Pontikes (She/Her/Hers)
+1 312 207 2857
rpontikes@reedsmith.com

Reed Smith LLP
10 South Wacker Drive
Chicago, IL 60606-7507
+1 312 207 1000
Fax +1 312 207 6400

EXHIBIT 6

Department of Health and Human Services Acquisition Plan (AP)

Acquisition Title:	Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy"
Agency:	FDA
Acquisition Year:	2018
Author:	Amy Akparewa

FAR 7.105 (a) Acquisition Background and Objectives

FAR 7.105 (a)(1) Statement of Need

Statement of Need

Hormone Therapy

FDA has approved many drug products for hormone therapy in men and women, including derivatives of estrogen, progesterone, and testosterone. These drug products are indicated to, among other things, increase the levels of hormones in the body or otherwise address hormonal imbalances associated with menopause, aging, or other causes. However, approved hormone therapies are associated with safety risks. For example, drug products containing estrogen are labeled with a "black box" warning of cancer and, in some cases, cardiovascular disorders and dementia. Similarly, in 2015, FDA required manufacturers to add to the labeling of their testosterone drug products information about increased risk of heart attacks and strokes. Progesterone is associated with, among other things, risks of abnormal blood clotting and breast cancer.

Certain healthcare practitioners and patients have sought to use compounded drug products instead of FDA-approved drug products for hormone replacement therapy. Examples of hormones and hormone derivatives commonly used in compounded drug products are estriol, estradiol, estradiol cypionate, progesterone, testosterone, and testosterone propionate.

These compounded drug products are often marketed as "bioidentical" or "natural" because the hormones and hormone derivatives may be produced from plants or animals rather than by chemical synthesis. Treatment with these compounded hormone products is often referred to as "bioidentical hormone replacement therapy" (BHRT). Marketers of BHRT have stated that compounded bioidentical hormone products have certain advantages over FDA-approved products, such as they are safer or better for patients than FDA-approved products. However, in contrast to FDA-approved products, these "bioidentical" compounded products have not undergone a scientifically rigorous assessment of quality, bioavailability, safety, or effectiveness.

FDA recently became aware of many adverse events associated with compounded implantable hormone pellets. For example, during an inspection FDA discovered that one marketer collected more than 4,000 reports of adverse events associated with these products over approximately four years. These adverse events concerned endometrial cancer, prostate cancer, stroke, heart attack, deep vein thrombosis, breast cancer, cellulitis, and pellet extrusions. FDA is currently reviewing these cases.

Compounding

Compounding is generally regarded as a practice in which a licensed pharmacist, a licensed physician, or, in the case of an outsourcing facility, a person under the supervision of a licensed pharmacist, combines, mixes, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient. If certain conditions are met, drug products compounded by those entities are exempt from certain requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act), including requirements for FDA approval of drugs and labeling with adequate directions for use.

Compounded drugs are not approved and do not, therefore, undergo premarket FDA review for safety, effectiveness, and quality before they are marketed. Compounded drugs are typically not labeled with warnings, and compounders generally do not report to FDA adverse events associated with their drug products. Because compounded drugs are subject to a lower regulatory standard than FDA-approved drugs, FDA advises patients and healthcare practitioners that patients should not receive a compounded drug unless their medical needs cannot be met by an approved drug.

Technical and Contractual History

--

Acquisition Alternatives

The original plan for the study was to use to BAA announcement, however, after further review, it was discovered that NASEM has qualified for single eligibility in the past.

FAR 7.105(a)(2) Applicable Conditions

Compatibility

No compatibility requirements exist

Constraints

The money being used to fund this contract is S&E funds and will expire by September 30, 2018.

FAR 7.105(a)(3) Cost

Cost

Provide a completed IGCE utilizing the HHS IGCE Template Package. Will this procurement with all options have a value equal or greater than \$20,000,000?

- Yes
- No

If Yes, see [HHSAR Part 334](#).

Include a completed IGCE utilizing the HHS IGCE Template Package.

FAR 7.105 (a)(4) Capability or Performance

Compatibility or Performance

Due to the nature of the requirement, it is in the public interest to receive the independent advice of unparalleled objectivity of the highest quality that provides an inherent degree of acceptability. Considering the volunteer nature of committee members as well as the independence, objectivity, quality and acceptance of Academy recommendations, the Academy represents a cost effective means for examining the critical issues of this project.

FAR 7.105 (a)(5) Delivery or Performance-Period Requirements

Delivery or Performance-Period Requirements

The total performance period for this contract is 18 months.

FAR 7.105(a)(6) Trade-offs

Trade-offs

By using the Academy to conduct the study and hold the committee meetings, the Academy represents a cost effective means for examining the critical issues of this project

FAR 7.105 (a)(7) Risks

Technical, Cost, and Schedule Risks

There are no schedule risks that are apparent at this time.

Organizational Conflict of Interest

There are no potential conflicts of interest associated with the vendor or the requirement.

FAR 7.105 (a)(8) Acquisition Streamlining

Acquisition Streamlining

N/A

FAR 7.105 (b) Develop Plan of Action

FAR 7.105 (b)(1) Sources

Sources

The National Academies of Science, Engineering, and Medicine

Small Business

A small business was not considered for this study.

Market Research

Market research was conducted to the extent of which organization can perform the the needed tasks. Due to the nature of the requirement and the work involved, it was determined that NASEM would be the best contractor.

FAR 7.105(b)(2) Competition also see FAR, Subpart 7.102, (2)

Competition

It is anticipated that this requirement will be awarded via a sole source contract using the authority of Section 301 of the Public Health Service Act (42 U.S.C. § 241)

Include the Justification and Approval for other than Full and Open/Limited Source Justification/Exception to Fair Opportunity, if applicable.

Major Components or Subsystems Competition

N/A

Spares and Repair Parts Competition

N/A

Subcontract Competition

N/A

FAR 7.105(b)(3) Contract Type Selection

Contract Type Selection

This contract is expected to be Firm-Fixed Price.

FAR 7.105(b)(4) Source-Selection Procedures

Source Selection Procedures

The source's proposal will be deemed technical acceptable or not technically acceptable.

FAR 7.105(b)(5) Acquisition Considerations

Special Contracting Methods

Sealed bidding will not be used because the requirement is intended to be awarded non-competitively. The award will be fully funded and has an intended period of performance of 18 months.

Unique Solicitation Clauses or Provisions

N/A - There are no intended or expected deviations from the FAR associated with this requirement. There are also no intended special solicitation provisions, or any special clauses expected to be added as a result of the requirement.

Lease or Purchase

No equipment will be leased or purchased.

Performance-Based Acquisition

The deliverable will be in the form of a final report.

Information Technology Acquisition

N/A - This is not an IT acquisition

FAR 7.105 (b)(6) Budgeting and Funding**Budgeting**

The IGCE was created after in-depth discussion of the SOW with the subject matter experts and acquisition liaisons.

IGCE Date of Completion: 06/20/2018

Funding

This requirement will be fully funded at the time of award. The funds being used is one year funds.

Funds Certifying Official's Certification:

- I hereby certify that (a) this requirement represents a bona fide need of the fiscal year or years for which the appropriation was made and complies with the Anti-deficiency Act; and (b) funds are committed for the entire performance period of this acquisition.
- I hereby certify that (a) this requirement represents a bona fide need of the fiscal year or years for which the appropriation was made and complies with the Anti-deficiency Act; and (b) funds are committed for the base period or first increment of performance of this acquisition.
- This acquisition will use the multi-year contracting procedures authorized in [FAR Part 17.1](#) and [HHSAR Part 317.1](#). I hereby certify that:
 - (a) this requirement represents a bona fide need in the fiscal year or years for which the appropriation was made and complies with the Anti-Deficiency Act; and
 - (b) funds are committed for the first year of performance plus the estimated amount of the full cancellation ceiling. Funds are not currently committed for this acquisition.
- Funds are not currently committed for this acquisition

FAR 7.105 (b)(7) Product or Service Descriptions

Product or Service Descriptions

See attached SOW

FAR 7.105(b)(8) Priorities, Allocations, and Allotments

Priorities, Allocations and Allotments

N/A – This requirement is not related to national defense, emergency preparedness, or energy programs.

FAR 7.105 (b)(9) Contractor versus Government Performance

Contractor versus Government Performance Consideration

The government will be using a federally chartered non-profit institution for this requirement.

FAR 7.105 (b)(10) Inherently Governmental Functions

Inherently Governmental Functions

The government will be using a federally chartered non-profit institution for this requirement.

Services Certification:

- This acquisition is for supplies only, it does not cover the procurement of services (this will not require an acquisition plan.)
- This acquisition plan is for the acquisition of services. I hereby certify that this service requirement:
 - Is for an inherently governmental function:

- Yes (If yes, please do not proceed with this acquisition plan.) Conduct assessment to determine if a government employee is required)
- No

Is closely associated with an inherently governmental function:

- Yes
- No

(Please indicate your rationale for selecting either "yes" or "no.")

The requirement does not meet the roles identified in Subpart 7.5.

Is for a critical governmental function:

- Yes
- No

(Please indicate your rationale for selecting either "yes" or "no.")

The study will address scientific considerations and implications for compounded drugs.

FAR 7.105(b)(11) Management Information Requirements

Contractor Monitoring Management System

The contractor will be monitored by a Level III COR and also monitored day to day by the government technical lead (GTL). The COR will be responsible for contract oversight and compliance and the GTL will be responsible for technical acceptability of deliverables.

Section 508

This contract does not anticipate requiring section 508 compliance. Section 508 applies when the contractor creates stimuli that include videos, print promotion, and websites. This task is not included in the requirement however, the contractor shall be familiar with Section 508 of the Rehabilitation Act, 29 U.S.C. 794d.

FAR 7.105 (b)(12) Make or Buy

Make or Buy Program Considerations

Make or buy programs do not apply to this requirement.

FAR 7.105 (b)(13) Test and Evaluation

Test and Evaluation

This is not a major system acquisition, test program is not required.

FAR 7.105 (b)(14) Logistics Considerations

Contractor or Agency Maintenance Support

N/A - Maintenance will not be required post receipt of deliverables.

Reliability, Maintainability, and Quality Assurance Requirements

This contract does not require a quality assurance requirement. The deliverable will be in the form of a written document/presentation, no equipment will be provided.

Contractor Data Requirements

N/A - This requirement doesn't involve data to be collected outside of the data provided by the government. The contractor will not need/have any rights to government provided data.

Standardization Concepts

This section does not apply because this is a contract for services and not the development or purchase of software/equipment.

FAR 7.105 (b)(15) Government-Furnished Property

Government-Furnished Property

No GFE is required

FAR 7.105 (b)(16) Government-Furnished Information

Government Furnished Information

No GFI

FAR 7.105 (b)(17) Environmental and Energy Conservation Objectives

Environmental and Energy Conservation Objectives

The work required is expected to be completed primarily at the vendor site and not any government owned or leased facility.

FAR 7.105 (b)(18) Security Consideration

Classified Matters Security Considerations

N/A - There will be no classified information for this contract

Information Technology Security Considerations

Should it be determined that the contractors are required to have access to networks, all contractors will undergo the badging process and be in compliance with HSPD-12.

Contractor Facility Access and Identity Verification Security Considerations

Should it be determined that the contractors are required to have access to facilities and systems, all contractors will undergo a background investigation to be in compliance with HSPD-12.

FAR 7.105(b)(19) Contract Administration

Contract Administration

The contractor will be monitored by a Level III COR and also monitored day to day by the government technical lead (GTL). The COR will be responsible for contract oversight, inspection of deliverables, and compliance of contract and the GTL will be responsible for technical acceptability of deliverables.

FAR 7.105(b)(20) Other Considerations

Other Considerations

N/A - There are no other considerations.

FAR 7.105(b)(21) Milestones For the Acquisition Cycle

Acquisition Milestone

Acquisition Milestone	Target Date	Revised Date	Completion Date

FAR 7.105(b)(22) Identification of Participants in Acquisition Plan Preparation

Amy Akparewa, COR
 240-402-0360
 Amy.Akparewa@fda.hhs.gov

Reviews and Approvals of Acquisition Plan

Official	N/A	Name and Title	Signature	Date
Funds Certifying Official / FDA Budget Officer	<input type="checkbox"/>	Hope Butler, Management Analyst, OEP		
Requiring Activity Representative / FDA Program/Center Requisitioner or COR	<input type="checkbox"/>	Amy Akparewa, COR, OEP		
Requiring Activity Representative's Immediate Supervisor / FDA Program/Center Requisitioner's (COR's) Immediate Supervisor	<input type="checkbox"/>	Stephanie Donovan, Acting PMT Director, (
Program Manager / FDA Program/Center/AS P/PM	<input type="checkbox"/>	Hope Butler, Management Analyst, OEP		
Head of the Sponsoring Program Office / FDA Program/Center P/PM's Immediate Supervisor	<input type="checkbox"/>			
Contracting Officer / FDA Cognizant OAGS Contracting Officer	<input type="checkbox"/>			
Chief of the Contracting Office / FDA Cognizant OAGS Division Director	<input type="checkbox"/>			
Office of the General Council (Legal)	<input type="checkbox"/>			
Head of the Contracting Activity / FDA HCA / Director, OAGS	<input type="checkbox"/>			
Competition Advocate	<input type="checkbox"/>			
HHS Senior Procurement Executive	<input type="checkbox"/>			

FDA Specific Reviews and Approvals of Acquisition Plan

Note: Please fill in with N/A for Reviews and Approvals that are not required due to the value of the Acquisition.

FDA Program/Center Acquisition Liaison	<input type="checkbox"/>			
IT - FDA Program/Center IT IRB	<input type="checkbox"/>			
IT - FDA OC Super Office POC or SMO	<input type="checkbox"/>			
IT - FDA ADCIO (or Equivalent)	<input type="checkbox"/>			

IT - FDA CIO	<input type="checkbox"/>			
	<input type="checkbox"/>			

PROJECT TITLE: Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy"
Detailed Price Summary

Note: This template can be modified based on the contract type (i.e. Firm Fixed Price, Time and Materials, and Cost Reimbursement)

Contract Line Item Description	Base Period			Option Year Two				Option Year Three				Option Year Four		
	Quantity	Unit	Unit Price	Total Price	Quantity	Unit	Unit Price	Total Price	Quantity	Unit	Unit Price	Total Price	Quantity	Unit
Committee Meetings				(b) (4)										
Direct Labor														
Line Item Subtotal														
Fringe Benefits														
Subtotal Line Item & Fringe														
Overhead														
Subtotal Line Items, Fringe and Overhead														
ODC's														
Travel														
Subcontracts														
Consultants														
Materials														
Technology and Communications														
Other ODCs														
Subtotal ODCs														
Subtotal - All Costs														
G&A														
Total Cost														
Fee/Profit														
Total Estimated Yearly Values														
TOTAL ESTIMATED VALUE OF CONTRACT														
				\$				1,345,719.00						

Assumptions:	Percent
Inflation Rate Per Year	(b) (4)
Fringe Benefits Rate	

**Food and Drug Administration
Center for Drug Evaluation and Research
Office of the Center Director
Report on the Clinical Utility of Treating Patients with Compounded “Bioidentical
Hormone Replacement Therapy”**

STATEMENT OF WORK

1. BACKGROUND

Hormone Therapy

FDA has approved many drug products for hormone therapy in men and women, including derivatives of estrogen, progesterone, and testosterone. These drug products are indicated to, among other things, increase the levels of hormones in the body or otherwise address hormonal imbalances associated with menopause, aging, or other causes. However, approved hormone therapies are associated with safety risks. For example, drug products containing estrogen are labeled with a “black box” warning of cancer and, in some cases, cardiovascular disorders and dementia. Similarly, in 2015, FDA required manufacturers to add to the labeling of their testosterone drug products information about increased risk of heart attacks and strokes. Progesterone is associated with, among other things, risks of abnormal blood clotting and breast cancer.

Certain healthcare practitioners and patients have sought to use compounded drug products instead of FDA-approved drug products for hormone replacement therapy. Examples of hormones and hormone derivatives commonly used in compounded drug products are estriol, estradiol, estradiol cypionate, progesterone, testosterone, and testosterone propionate. These compounded drug products are often marketed as “bioidentical” or “natural” because the hormones and hormone derivatives may be produced from plants or animals rather than by chemical synthesis. Treatment with these compounded hormone products is often referred to as “bioidentical hormone replacement therapy” (BHRT). Marketers of BHRT have stated that compounded bioidentical hormone products have certain advantages over FDA-approved products, such as they are safer or better for patients than FDA-approved products. However, in contrast to FDA-approved products, these “bioidentical” compounded products have not undergone a scientifically rigorous assessment of quality, bioavailability, safety, or effectiveness.

FDA recently became aware of many adverse events associated with compounded implantable hormone pellets. For example, during an inspection FDA discovered that one marketer collected more than 4,000 reports of adverse events associated with these products over approximately four years. These adverse events concerned endometrial cancer, prostate cancer, stroke, heart attack, deep vein thrombosis, breast cancer, cellulitis, and pellet extrusions. FDA is currently reviewing these cases.

Compounding

Compounding is generally regarded as a practice in which a licensed pharmacist, a licensed physician, or, in the case of an outsourcing facility, a person under the supervision of a licensed pharmacist, combines, mixes, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient. If certain conditions are met, drug products compounded by those entities are exempt from certain requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act), including requirements for FDA approval of drugs and labeling with adequate directions for use.

Compounded drugs are not approved and do not, therefore, undergo premarket FDA review for safety, effectiveness, and quality before they are marketed. Compounded drugs are typically not labeled with warnings, and compounders generally do not report to FDA adverse events associated with their drug products. Because compounded drugs are subject to a lower regulatory standard than FDA-approved drugs, FDA advises patients and healthcare practitioners that patients should not receive a compounded drug unless their medical needs cannot be met by an approved drug.

2. SCOPE OF WORK

An ad hoc committee of the National Academies of Sciences, Engineering, and Medicine (NASEM) will conduct a study to assess the clinical utility of treating patients with compounded BHRT drug products. The committee will:

- Review the current and historic use of compounded BHRT drug products to treat patients, including information about the medical condition(s) that these compounded drug products have been used to treat;
- Evaluate the physical and chemical characteristics of compounded BHRT drug products (e.g., active ingredient, inactive ingredient(s), dosage forms, routes of administration, strengths);
- Review and assess the available evidence (or lack of evidence) regarding the safety and effectiveness of BHRT drug products;
- Based on the available evidence, summarize findings and make recommendations with respect to
 - the clinical utility of compounded BHRT drug products;
 - the circumstances under which these products may or may not be safe and effective for treatment of patients; and
 - the circumstances under which these products may or may not be used as an alternative to FDA-approved drug products.

Specifically, the report may address the following items, with respect to compounded BHRT drug products and their uses:

1. Review the current and historic use of BHRT drug products to treat patients

- a. Review the current and historic use of BHRT drug products to treat patients, including information about the medical condition(s) that different types of compounded BHRT drug products have been used to treat.
 - b. Describe reasons why healthcare providers and patients may seek to use compounded BHRT drug products for hormone replacement therapy as an alternative to FDA-approved drugs.
2. Evaluate the physical and chemical characteristics of compounded BHRT drug products
 - a. Describe the pertinent physical and chemical characteristics of compounded BHRT drug products (e.g., active ingredient, inactive ingredient(s), dosage forms, routes of administration, strengths).
3. Review and assess the available evidence (or lack of evidence) regarding the safety of BHRT drug products
 - a. Based on the available evidence, describe the safety issues/risks, if any, associated with the use of compounded BHRT drug products, including whether safety issues depend on the characteristics of the compounded drug product (e.g., strength, route of administration, dosage form). Safety issues/risks may be identified by conducting a literature review to assess:
 - i. Pharmacology, toxicology, and pharmacokinetics, including general pharmacology of the compounded BHRT drug product, pharmacokinetic and toxicokinetic data, toxicity, genotoxicity, developmental and reproductive toxicity, and carcinogenicity;
 - ii. Human safety, including adverse reactions, clinical trials assessing safety, published case reports, pharmacokinetics, and availability of alternative FDA-approved products.
 - b. Evaluate available scientific evidence on the safety of compounded BHRT drug products as compared to FDA-approved drug products, and assess the strength of that evidence.
 - c. Determine whether available data indicate that compounded BHRT drug products are associated with risks different from, or in addition to, those described in the labeling of comparable FDA-approved drug products.
4. Review and assess the available evidence (or lack of evidence) regarding the effectiveness of BHRT drug products
 - a. Based on the available evidence, describe the effectiveness, or lack of effectiveness, of compounded BHRT drug products for their intended use, including whether clinical outcomes depend on the characteristics of the compounded drug product (e.g., strength, route of administration, dosage form). Effectiveness data may be identified by a literature review to assess:
 - i. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, for the compounded BHRT drug product;
 - ii. Whether the compounded BHRT drug product is intended to be used in a serious or life-threatening disease; and

- iii. Whether there are FDA-approved therapies that may be as effective or more effective for the intended use.
- b. Evaluate available scientific evidence regarding compounded BHRT drug product effectiveness profiles as compared to FDA-approved drug products, and assess the weight of that evidence (e.g., whether results from studies appear to be credible).
 - i. Given that there is no FDA-approved drug product that contains estriol, evaluate the available evidence regarding the effectiveness of derivatives of estrogen, such as estradiol, for patients who would be prescribed compounded BHRT drug products containing estriol.

3. DELIVERABLES

A committee of approximately 12-15 members will be appointed in accordance with National Academies' nomination policies to respond to the statement of work. Over the course of 18 months, the committee will hold five meetings, including one public workshop. At least two of the committee meetings will allocate time for public comment to be received. The committee will also identify other avenues for receiving input from interested stakeholders.

Anticipated Study Timeline

- Foundational Work; Committee Nomination & Approval; Background Research – Month 1-2
- Committee Meeting #1 – Month 3-4
- Committee Meeting #2 and Public Workshop – Month 5-6
- Committee Meeting #3 and Open Session – Month 7-8
- Committee Meeting #4 and Open Session – Month 9-10
- Committee Meeting #5 – Month 11-12
- External Review – Month 13-14
- Deliver Report (Uncorrected Proofs) to Sponsor – Month 15-16
- Final Books to Sponsor – Month 18

<u>Description</u>	<u>Delivery in Months</u>
Kick-off meeting between FDA and NASEM/HMD staff	Within one week of award or as expeditiously as possible schedules permitting
Committee Meeting #1-5 with Sponsor	Within 12 months of award or as expeditiously as possible schedules permitting
Delivery of Report (Uncorrected Proofs) to Sponsor	Within 16 months of award
Final Books to Sponsor	Within 18 months of award

EXHIBIT 7

The National Academies of Sciences, Engineering, and Medicine

Health and Medicine Division

Board on Health Sciences Policy

**Clinical Utility of Treating Patients with Compounded
“Bioidentical Hormone Replacement Therapy”**

JUNE 2018

Quad Chart

White Paper

Addendum

Research and Development Justification

QUAD CHART

Clinical Utility of Treating Patients with Compounded “Bioidentical Hormone Replacement Therapy”

Research Area: 9. Strengthening the Global Product Safety Net
Andrew M. Pope, National Academies of Sciences, Engineering, and Medicine

<p>Objective: To assess the clinical utility of treating patients with compounded “Bioidentical Hormone Replacement Therapy” (BHRT) drug products.</p> <p>Description of effort: A National Academies ad hoc committee will:</p> <ul style="list-style-type: none">• Review current and historic use of compounded BHRT drug products to treat patients;• Describe the physical and chemical characteristics of compounded BHRT drug products;• Review and assess the available evidence (or lack of evidence) regarding the safety and effectiveness of compounded BHRT drug products.	
<p>Benefits of Proposed Technology: N/A</p> <p>Challenges: Compounded drugs are not approved by FDA and do not undergo premarket FDA review for safety, effectiveness, and quality before they are marketed.</p> <p>Research and Development Justification: Healthcare practitioners and patients have sought to use compounded drug products instead of FDA-approved drug products for hormone replacement therapy. The proposed study would inform FDA’s compounding work, including its evaluation of which active ingredients may be used in compounding by outsourcing facilities; healthcare providers’ prescribing decisions; and patients’ choices about hormone therapy.</p>	<p>Milestones (Year 1):</p> <ul style="list-style-type: none">• Kick-off meeting between FDA and National Academies staff• Committee meeting #1 with sponsor• Quarterly progress reports <p>Milestones (Year 2):</p> <ul style="list-style-type: none">• Delivery of prepublication report• Delivery of final printed books <p>Proposed Funding: \$1,345,718</p> <p>Period of Performance: August 1, 2018 – January 31, 2020</p> <p>Contact Information Andrew M. Pope, Ph.D., Director, Board on Health Sciences Policy, Health and Medicine Division The National Academies of Sciences, Engineering, and Medicine Email: apope@nas.edu Phone: 202-334-1739</p>

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

**Clinical Utility of Treating Patients with Compounded
“Bioidentical Hormone Replacement Therapy”**

WHITE PAPER

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A. DESCRIPTION OF PROPOSED PROJECT

This proposal is for funding from the Food and Drug Administration (FDA) to sponsor National Academies of Sciences, Engineering, and Medicine (National Academies) consensus study to assess the clinical utility of treating patients with compounded “bioidentical hormone replacement therapy” (BHRT) drug products. This project will be undertaken by the National Academies for 18 months from August 1, 2018 through January 31, 2020 in the amount of \$1,345,718. The document includes an overview of the project background, plan of action, and deliverables. It continues with a description of the qualifications and supportive aspects of the National Academies.

Statement of work

An ad hoc committee of the National Academies of Sciences, Engineering, and Medicine (National Academies) will conduct a study to assess the clinical utility of treating patients with compounded BHRT drug products. The committee will:

- Review the current and historic use of compounded BHRT drug products to treat patients, including information about the medical condition(s) that these compounded drug products have been used to treat;
- Describe the physical and chemical characteristics of compounded BHRT drug products (e.g., active ingredient, inactive ingredient(s), dosage forms, routes of administration, strengths);
- Review and assess the available evidence (or lack of evidence) regarding the safety and effectiveness of compounded BHRT drug products;
- Based on the available evidence, summarize findings and make recommendations with respect to
 - the clinical utility of compounded BHRT drug products;
 - whether the available evidence of safety and effectiveness supports use of compounded BHRT drug products to treat patients; and
 - the patient populations that might need a compounded BHRT drug product in lieu of an FDA-approved drug product.

Specifically, the report may address the following items, with respect to compounded BHRT drug products and their uses:

1. Review the current and historic use of BHRT drug products to treat patients
 - a. Include information about the medical condition(s) that different types of compounded BHRT drug products have been used to treat.
 - b. Describe reasons why healthcare providers and patients may seek to use compounded BHRT drug products for hormone replacement therapy as an alternative to FDA-approved drugs.
 - c. Describe the physical and chemical characteristics of compounded BHRT drug products (e.g., active ingredient, inactive ingredient(s), dosage forms, routes of administration, strengths).

2. Review and assess the available evidence (or lack of evidence) regarding the safety of compounded BHRT drug products
 - a. Based on the available evidence, describe the safety issues/risks, if any, associated with the use of compounded BHRT drug products, including whether safety issues depend on the characteristics of the compounded drug product (e.g., strength, route of administration, dosage form). Safety issues/risks may be identified by conducting a literature review to assess:
 - i. Pharmacology, toxicology, and pharmacokinetics, including general pharmacology of the compounded BHRT drug product, pharmacokinetic and toxicokinetic data, toxicity, genotoxicity, developmental and reproductive toxicity, and carcinogenicity;
 - ii. Human safety, including adverse reactions, clinical trials assessing safety, published case reports, pharmacokinetics, and availability of alternative FDA-approved products.
 - b. Evaluate available scientific evidence on the safety of compounded BHRT drug products as compared to FDA-approved drug products, and assess the strength of that evidence.
 - c. Determine whether available data indicate that compounded BHRT drug products are associated with risks different from, or in addition to, those described in the labeling of comparable FDA-approved drug products.

3. Review and assess the available evidence (or lack of evidence) regarding the effectiveness of BHRT drug products
 - a. Based on the available evidence, describe the effectiveness, or lack of effectiveness, of compounded BHRT drug products for their intended use, including whether clinical outcomes depend on the characteristics of the compounded drug product (e.g., strength, route of administration, dosage form). Effectiveness data may be identified by a literature review to assess:
 - i. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, for the compounded BHRT drug product;
 - ii. Whether the compounded BHRT drug product is intended to be used in a serious or life-threatening disease; and
 - iii. Whether there are FDA-approved therapies that may be as effective or more effective for the intended use.
 - b. Evaluate available scientific evidence regarding compounded BHRT drug product effectiveness profiles as compared to FDA-approved drug products, and assess the weight of that evidence (e.g., whether results from studies appear to be credible).
 - i. Given that there is no FDA-approved drug product that contains estriol, evaluate the available evidence regarding the effectiveness of derivatives of estrogen, such as estradiol, for patients who would be prescribed compounded BHRT drug products containing estriol.

Workplan

The National Academies' Health and Medicine Division will convene an expert committee of approximately 12–15 members in accordance with National Academies' nomination policies. Over the course of 18 months, the committee will hold five meetings, including one public workshop. At least two of the committee meetings will allocate time for public comment to be received. The committee will also identify other avenues for receiving input from interested stakeholders. An approximate timeline is shown below.

A committee of approximately 12-15 members will be appointed in accordance with National Academies' nomination policies to respond to the statement of task. Over the course of 18 months, the committee will hold five meetings, including one public workshop. At least two of the committee meetings will allocate time for public comment to be received. The committee will also identify other avenues for receiving input from interested stakeholders.

The first committee meeting will be organizational and will include the required composition, balance and conflict of interest discussion; a public session for the sponsor to deliver the charge to the committee, including an in-depth discussion with the sponsor about the task; discussion of available sources of information; and planning of a public workshop to be held in conjunction with a forthcoming meeting. During the public session the sponsor will be asked to provide background and context for the study in order to enable the committee to identify data sources and examine specific issues related to the statement of task.

It is anticipated that the second meeting may be held in conjunction with open public sessions in workshop format, including an open public comment period, and will also include time for the committee to discuss the outcomes, deliberate in closed session, and organize the writing of the report. The third meeting may include an open session for additional public comment, if deemed necessary by the committee. This meeting will be used to begin the committee's deliberations on the findings and recommendations. The fourth and fifth meetings will be held entirely in closed session for the committee to draft and finalize recommendations and the report text.

The report will then go through the National Academies' report review process and be subject to appropriate institutional review procedures prior to release in prepublication form (uncorrected proofs). Final books formatted and published by the National Academies Press will be sent to the sponsors before the end of the period of performance.

B. DEVELOPMENT PLAN FOR LICENSURE

N/A

C. GANTT CHART

Item	Task/Deliverable	Timeline (Months from Contract Start Date)	Price
1	Kick-off meeting between FDA and National Academies staff	Within one week of aware or as expeditiously as possible schedules permitting	
2	Foundational work: Seek committee nominations and assemble committee; begin background research; contact stakeholders; discussions with sponsors	1-2	
3	First committee meeting: Conduct balance and conflict of interest discussion; discuss charge to the committee and context for the study with the sponsor; identify information needs; develop plans for obtaining stakeholder input	3-4	
4	Second committee meeting with public workshop: Develop report outline and workplan; hold working group conference calls; seek and receive input from stakeholders	5-6	
5	Third committee meeting: Draft and revise the report; hold working group conference calls; seek and receive input from stakeholders	7-8	
6	Fourth committee meeting: Draft and revise the report; draft recommendations	9-10	
7	Fifth committee meeting: Finalize report text, findings, and recommendations	11-12	
8	Report review: Send report out for external review; prepare response to review; finalize report	13-14	
9	Deliver prepublication (uncorrected proof) to the sponsor: public release of the report; post report online	15-16	

10	Deliver published books to the sponsor: Prepare report for publication and send to publishers	18	
11	Total		\$1,345,718

D. DESCRIPTION OF OFFERER’S INTELLECTUAL PROPERTY OWNERSHIP

The Academy may assert copyright in any data first produced in the performance of this contract. When asserting copyright, the Academy shall affix the applicable copyright notice of 17 U.S.C. 401 or 402, and an acknowledgment of Government sponsorship (including contract number), to the data when such data are delivered to the Government, as well as when the data are published or deposited for registration as a published work in the U.S. Copyright Office. For data other than computer software, the Academy grants to the Government, and others acting on its behalf, a paid-up, nonexclusive, irrevocable, worldwide license for all such data to reproduce, prepare derivative works, distribute copies to the public, and perform publicly and display publicly, by or on behalf of the Government. For computer software, the Academy grants to the Government and others acting on its behalf, a paid-up, nonexclusive, irrevocable, worldwide license for all such computer software to reproduce, prepare derivative works, and perform publicly and display publicly (but not to distribute copies to the public), by or on behalf of the Government.

Federal Advisory Committee Act (FACA)

The Academy has developed policies and procedures to implement Section 15 of the Federal Advisory Committee Act, 5 U.S.C. App., Section 15. Section 15 includes certain requirements Regarding public access and conflicts of interest that are applicable to agreements under which the Academy, using a committee, provides advice or recommendations to a Federal agency. In accordance with its Congressional Charter and the requirements of Section 15, the Academy must provide independent, unbiased advice without actual or perceived interference or management of the outcome (findings and recommendations). Therefore, the Academy requires the right to publish all unclassified materials without any restriction over content and release, including any restriction that may require prior approval from the sponsoring agency. In accordance with Section 15 of FACA, the Academy shall submit to the government sponsor(s) following delivery of each applicable report a certification that the policies and procedures of the Academy that implement Section 15 of FACA have been substantially complied with in the performance of the contract/grant/cooperative agreement with respect to the applicable report.

Public Information About the Project

In order to afford the public greater knowledge of Academy activities and an opportunity to provide comments on those activities, the Academy may post on its website (<http://www.nationalacademies.org>) the following information as appropriate under its

procedures: (1) notices of meetings open to the public; (2) brief descriptions of projects; (3) committee appointments, if any (including biographies of committee members); (4) report information; and (5) any other pertinent information.

E. OVERVIEW OF OFFERER’S CAPABILITIES AND EXPERIENCE:

National Academy of Sciences

The National Academy of Sciences (NAS) was established by an Act of Congress and signed by President Lincoln in March 1863 to “investigate, examine, experiment, and report upon any subject of science or art...whenever called upon by any department of the Government.” The National Research Council was established by executive order under President Wilson in 1916, expanding the operational capacity of the National Academy of Sciences. The National Academy of Sciences, National Academy of Engineering, and National Academy of Medicine work together as the National Academies of Sciences, Engineering, and Medicine to provide independent, objective analysis and advice to the nation and conduct other activities to solve complex problems and inform public policy decisions. The National Academies also encourage education and research, recognize outstanding contributions to knowledge, and increase public understanding in matters of science, engineering, and medicine.

One central purpose of the National Academies is to advise the government on issues of science, medicine, and technology. The National Academies and its affiliated organizations are private, independent, nonprofit institutions that jointly possess a unique status as congressionally chartered advisers to the government. Every year many studies are requested of the National Academies. In addition to federal sources, requests for studies are also received from foundations and other private sector organizations. A small number of studies receive internal support.

The Health and Medicine Division, formerly known as the program unit of the Institute of Medicine, is a division of the National Academies. The Health and Medicine Division’s aim is to help those in government and the private sector make informed health decisions by providing evidence upon which they can rely. Each year, more than 3,000 individuals volunteer their time, knowledge, and expertise to advance the nation’s health through the work of the division.

The National Academies have a long tradition of providing policy advice from a national perspective. This tradition rests on the ability of the institution to convene committees of experts who are charged to deliberate important issues of health and health care policy in an objective and independent environment that assures rigorous analysis. It can serve an important function by bringing representatives from diverse groups together to achieve consensus on complex issues.

Facilities and Equipment

The meeting facilities of the National Academies are available to the constituent organizations of the National Academies complex. These include the National Academy of Sciences Main Building, 2101 Constitution Avenue, N.W., Washington, D.C.; 500 Fifth

Street, N.W. Washington, D.C.; The Arnold and Mabel Beckman Center in Irvine, California; and the J. Erik Jonsson Woods Hole Center in Woods Hole, Massachusetts. These facilities are used to conduct hundreds of committee meetings each year. Thus, the National Academies will provide facilities and equipment required for the proposed project, for both committee members and staff.

Examples of Previous Projects

Return of Individual-Specific Research Results Generated in Research Laboratories (Consensus Study)

1. Name of Contracting Organization: National Institutes of Health
2. Contract Number: HHSN263201200074I/HHSN26300117
3. Contract Type: Cost-reimbursement
4. Total Contract Value: \$1,149,986
5. Description of Requirement:

The Health and Medicine Division of the National Academies (NASEM) will undertake a study that will review and evaluate the return of individual-specific research results from research laboratories, which are required to be returned in accordance with the Clinical Laboratory Improvement Amendments of 1988 (CLIA). Currently, any research laboratory that returns individual-specific research results is regulated by CLIA. Research laboratories that do not report patient specific results are excepted from the CLIA regulations. The purpose of the study is to consider whether the current regulatory environment (including CLIA and any other applicable laws and regulations) governing the return of individual-specific research results ensures or fails to ensure minimization of risks and maximization of the benefits that accrue to individuals and society, and if so, whether alternative policies or regulatory requirements might better address the appropriate return of individual-specific research results.

The committee will not undertake any examination of or deliberation on specific research results to be returned. The committee will also not make recommendations on the return of non-individual specific results (e.g., results in aggregate form). The committee will also not provide any legal interpretation or analysis regarding the scope or applicability of CLIA.

6. Contracting Officer's Name and Telephone Number: Robert Day, 202-334-3873
7. Program Manager's Name and Telephone Number: Michelle Mancher, 202-334-2464
8. North American Industry Classification System (NAICS) Code: 541690

Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse (Consensus Study)

1. Name of Contracting Organization: U.S. Food and Drug Administration
2. Contract Number: HHSF223201610015C
3. Contract Type: cost-reimbursement
4. Total Contract Value: \$1,271,380
5. Description of Requirement:

The Health and Medicine Division in the National Academies of Sciences, Engineering, and Medicine will convene an ad hoc committee to develop a report that will inform FDA as to the state of the science regarding prescription opioid abuse and misuse, including prevention, management, and intervention, and to provide an update from the 2011 Institute of Medicine report Relieving Pain in America, which includes a further characterization of the evolving role that opioid analgesics play in pain management. The report will additionally make recommendations on the options available to FDA to address the prescription opioid overdose epidemic, from both the individual and public health perspectives, and to otherwise further advance the field.

6. Contracting Officer's Name and Telephone Number: Robert Day, 202-334-3873
7. Program Manager's Name and Telephone Number: Andrew Pope, 202-334-1739
8. North American Industry Classification System (NAICS) Code: 541690

Ethical and Social Policy Considerations of Novel Techniques for Prevention of Maternal Transmission of Mitochondrial DNA Diseases (Consensus Study)

1. Name of Contracting Organization: U.S. Food and Drug Administration
2. Contract Number: HHSP23320140020B/HHSP2337010
3. Contract Type: cost-reimbursement
4. Total Contract Value: \$1,165,245
5. Description of Requirement:

An ad hoc committee of the Institute of Medicine will conduct a study to develop a report that will inform FDA in consideration of review of applications in the area of genetic modification of eggs and zygotes for the prevention of mitochondrial disease. The development of novel techniques in this area raises complex ethical and social policy issues.

Taking into consideration these ethical and social policy issues, the committee's report will address the conduct of clinical trials investigating these novel techniques, including the foundational question of whether safeguards such as specific measures and public oversight could adequately address the social and ethical concerns, or whether those concerns preclude clinical trials.

6. Contracting Officer's Name and Telephone Number: Robert Day, 202-334-3873

7. Program Manager's Name and Telephone Number: Andrew Pope, 202-334-1739

8. North American Industry Classification System (NAICS) Code: 541690

F. ESTIMATE OF COSTS:

The estimated total cost of the project is \$1,345,718 for 18 months from August 1, 2018 through January 31, 2020. Please see the cumulative summary estimate of costs below.

Cumulative Summary Estimate of Costs				
8/1/18 to 01/31/20				
	Year 1	Year 2	Project Total	
Direct Labor	(b) (4)			
Overhead				
Overhead Cost of Money				
Travel				
Reports				
Technology/Communication				
Meeting Expense				
Other Direct Costs				
Subtotal:	(b) (4)			
General and Administrative Costs	(b) (4)			
G&A Cost of Money				
Total:	(b) (4)		\$1,345,718	

ADDENDUM

Overview of Key Personnel

The project will be conducted under the oversight of Andrew Pope, Ph.D., director of the Health and Medicine Division's Board on Health Sciences Policy. Dr. Pope has a Ph.D. in physiology and biochemistry from the University of Maryland and has been a member of The National Academies of Sciences, Engineering, and Medicine staff since 1982 and of the Health and Medicine Division staff since 1989. His primary interests are science policy, biomedical ethics, and environmental and occupational influences on human health. During his tenure at the Academies, Dr. Pope has directed numerous studies on topics that range from injury control, disability prevention, and biologic markers to the protection of human subjects of research, National Institutes of Health priority-setting processes, organ procurement and transplantation policy, and the role of science and technology in countering terrorism. Since 1998, Dr. Pope has served as Director of the Board on Health Sciences Policy, which oversees and guides a program of activities that is intended to encourage and sustain the continuous vigor of the basic biomedical and clinical research enterprises needed to ensure and improve the health and resilience of the public. Ongoing activities include Forums on Neuroscience, Genomics, Drug Discovery and Development, and Medical and Public Health Preparedness for Catastrophic Events. Dr. Pope is the recipient of the Health and Medicine Division's Cecil Award and the National Academy of Sciences President's Special Achievement Award.

Project staff will also include a senior program officer, who will serve as the project director, including overseeing staff, implementing National Academies procedures, communicating regularly with committee members, handling correspondence, managing the project timeline, guiding logistic and other meeting arrangements, overseeing drafting of the report, serving as the liaison with National Academies leadership and external parties, directing and monitoring expenditures, and overseeing the dissemination process.

In addition to the Board Director and Senior Program Officer, the project will have a Research Associate and Senior Program Assistant to provide support to the project, including working on meeting logistics arrangements, research, and report production. The Board on Health Sciences Policy's Program Coordinator will also provide some administrative support, and the Financial Associate will monitor the finances and provide regular updates and guidance on financial aspects. The communications staff, including an Editorial Projects Manager, will provide word processing, editing, and related support, and oversee communications efforts related to the disseminating the report.

Carolyn Shore, Ph.D., is a Senior Program Officer with the Board on Health Sciences Policy of the National Academies of Sciences, Engineering, and Medicine. She is staff director of the Forum on Drug Discovery, Development, and Translation. Before joining the National Academies, Dr. Shore was an officer on Pew's antibiotic resistance project, leading work on research and policies to spur the discovery and development of urgently needed antibacterial therapies. She previously served as a foreign affairs officer at the U.S. Department of State, where she led an initiative on open data and innovation-based solutions to global challenges. She also served as the State Department's representative

ADDENDUM

to intergovernmental organizations focusing on food safety, plant and animal health, biosecurity, and agricultural trade policy. Previously, Dr. Shore was an American Society for Microbiology congressional fellow, working on science-based policy related to antibiotic stewardship and other public health issues. She holds a doctoral degree in Microbiology and Molecular Genetics from Harvard University. As a graduate student, she studied anti-malarial drug resistance in Senegal and worked jointly between the Medicines for Malaria Venture, Genzyme Corporation, and the Broad Institute of Harvard and MIT to discover new anti-malarial compounds. Dr. Shore was awarded a Fulbright Fellowship for work at the University of Queensland in Brisbane, Australia, and a National Institutes of Health Training Grant for postdoctoral work at the University of Iowa.

Justification for Research and Development

FDA has approved many drug products for hormone therapy in men and women, including derivatives of estrogen, progesterone, and testosterone. These drug products are indicated to, among other things, increase the levels of hormones in the body or otherwise address hormonal imbalances associated with menopause, aging, or other causes. However, approved hormone therapies are associated with safety risks. For example, drug products containing estrogen are labeled with a “black box” warning of cancer and, in some cases, cardiovascular disorders and dementia. Similarly, in 2015, FDA required manufacturers to add to the labeling of their testosterone drug products information about increased risk of heart attacks and strokes. Progesterone is associated with, among other things, risks of abnormal blood clotting and breast cancer.

Certain healthcare practitioners and patients have sought to use compounded drug products instead of FDA-approved drug products for hormone replacement therapy. Examples of hormones and hormone derivatives commonly used in compounded drug products are estriol, estradiol, estradiol cypionate, progesterone, testosterone, and testosterone propionate.

These compounded drug products are often marketed as “bioidentical” or “natural” because the hormones and hormone derivatives may be produced from plants or animals rather than by chemical synthesis. Treatment with these compounded hormone products is often referred to as “bioidentical hormone replacement therapy” (BHRT). Marketers of BHRT have stated that compounded bioidentical hormone products have certain advantages over FDA-approved products, such as they are safer or better for patients than FDA-approved products. However, in contrast to FDA-approved products, these “bioidentical” compounded products have not undergone a scientifically rigorous assessment of quality, bioavailability, safety, or effectiveness.

FDA recently became aware of many adverse events associated with compounded implantable hormone pellets. For example, during an inspection FDA discovered that one marketer collected more than 4,000 reports of adverse events associated with these products over approximately four years. These adverse events concerned endometrial cancer, prostate cancer, stroke, heart attack, deep vein thrombosis, breast cancer, cellulitis, and pellet extrusions. FDA is currently reviewing these cases.

The proposed study would inform FDA’s compounding work, including its evaluation of which active ingredients may be used in compounding by outsourcing facilities; healthcare providers’ prescribing decisions; and patients’ choices about hormone therapy.

EXHIBIT 8

From: [Cosel, Gabrielle](#)
To: [Jackson, Leigh Miles](#); [Dohm, Julie](#)
Cc: [Ju, Ruey](#); [Shore, Carolyn](#); [Pope, Andrew](#)
Subject: RE: The National Academies- Seeking committee member nominations for compounded drug studies
Date: Friday, November 09, 2018 6:49:00 PM
Attachments: [NASEM Committee Suggestions 110918.docx](#)
[image001.png](#)

Dear Leigh,

Thank you for the opportunity to provide recommendations for NASEM's Committees.

Attached please find our suggestions. Please let us know if you have any questions, or if you would like us to try to identify any additional experts.

Best,

Gabey

Gabrielle Cosel

Office of Unapproved Drugs and Labeling Compliance

CDER Office of Compliance

Food and Drug Administration

301-796-4179

gabrielle.cosel@fda.hhs.gov

From: Jackson, Leigh Miles <LMJackson@nas.edu>

Sent: Thursday, November 01, 2018 10:08 AM

To: Dohm, Julie <Julie.Dohm@fda.hhs.gov>

Cc: Cosel, Gabrielle <Gabrielle.Cosel@fda.hhs.gov>; Ju, Ruey <Ruey.Ju@fda.hhs.gov>; Shore, Carolyn <CShore@nas.edu>; Pope, Andrew <APope@nas.edu>

Subject: The National Academies- Seeking committee member nominations for compounded drug studies

Hello Everyone,

It's nice to virtually meet you. My name is Leigh Jackson and I will be the study director for the two recently launched studies: the *Committee on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy"* and the *Committee on the Assessment of the Available Scientific Data Regarding the Safety and Effectiveness of Ingredients Used in Compounded Topical Pain Creams*.

At this time, we are collecting nominations for potential committee members. As our sponsoring agency, you may have a few particularly helpful suggestions.

If you or your colleagues would like to submit a nomination, please access our online forms by **Friday, November 9, 2018**.

- Committee suggestions for the topical pain cream study -

<https://www.surveygizmo.com/s3/4648789/>

- Committee suggestions for the bioidentical hormone replacement therapy study -

<https://www.surveygizmo.com/s3/4648857/>

Note: The National Academies is committed to increasing the participation of under-represented minorities in all phases of its work. Your assistance in identifying potential committee members from under-represented minority groups is greatly appreciated.

Thank you for your continued support of our work.

I look forward to meeting everyone at our kick-off meeting.

All the best,

Leigh

Leigh Miles Jackson, PhD

Senior Program Officer

The National Academies of Sciences, Engineering, and Medicine

500 Fifth Street, NW

Washington, DC 20001

Office: 202-334-2047

Email: lmjackson@nas.edu



November 9, 2018

FDA recommendations for NASEM Committees

Thank you for the opportunity to provide recommendations for the following NASEM Committees:

Committee on the Assessment of the Available Scientific Data Regarding the Safety and Effectiveness of Ingredients Used in Compounded Topical Pain Creams.

Committee on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy"

Some experts we have identified currently serve as special government employees (SGEs) and are associated with various FDA advisory committees. Some SGEs have standing appointments to advisory committees. Others, called consultants, are called on to attend an advisory committee meeting as a temporary member when their specific expertise is needed.

Recommendations for the Committee on the Assessment of the Available Scientific Data Regarding the Safety and Effectiveness of Ingredients Used in Compounded Topical Pain Creams.

Pain Management

Robert Kerns, PhD. Professor of Psychiatry, of Neurology and of Psychology, Yale School of Medicine. One of three directors of the Yale-based NIH-DoD-VA Pain Management Collaboratory Coordinating Center.

https://medicine.yale.edu/psychiatry/people/robert_kerns.profile

John T. Farrar, M.D., Ph.D. Associate Professor of Epidemiology, Perlman School of Medicine, University of Pennsylvania. Currently he is the principal investigator of the Center of Excellence for Pain Education. His current research is focused on the evaluation of new methodologies for understanding how patients report their pain, studies in a large population of patients with pelvic pain, and functional brain imaging in people with pain.

<https://www.cceb.med.upenn.edu/bio/john-t-farrar-md-phd>

John D. Markman, M.D. Professor Departments of Neurology and Neurosurgery, University of Rochester School of Medicine and Dentistry. Dr. Markman leads the Department of Neurosurgery's Neuromedicine Pain Management Center, a multi-specialty pain practice with a focus on patients with chronic pain associated with nerve injury. Dr. Markman is Chairman-elect of the Pain and Palliative Care Section of the American Academy of Neurology, the guest editor of the recent Continuum Edition of Neuropathic Pain, a member of the editorial board of the Journal of Pain and an examiner for the American Board of Psychiatry and Neurology.

<https://www.urmc.rochester.edu/people/21192807-john-douglas-markman>

Gregory W. Terman, MD, PhD. Anesthesiologist and director of the Acute Pain Service at University of Washington Medical Center. He is also a UW professor of Anesthesiology and Pain Medicine.

Note: Dr. Terman is or has recently been a consultant to FDA's Anesthetic and Analgesic Drug Products Advisory Committee and is an active Special Government Employee.

<https://www.uwmedicine.org/bios/gregory-terman>

Daniel Alford, MD, MPH. Professor of Medicine, Boston University School of Medicine. Director, Safe and Competent Opioid Prescribing Education (SCOPE of Pain) Program.

<https://www.bumc.bu.edu/care/faculty/daniel-alford/>

Gary A. Walco, PhD. Director, Pain Medicine, Seattle Children's. Professor, Department of Anesthesiology; Adjunct Professor, Department of Pediatrics at the University of Washington School of Medicine.

Note: Dr. Walco is or has recently been an expert consultant to FDA's Anesthetic and Analgesic Drug Products Advisory Committee and is an active Special Government Employee.

<https://www.seattlechildrens.org/directory/gary-a-walco/>

Roger Chou, M.D. Professor in the Departments of Medicine, and Medical Informatics & Clinical Epidemiology at Oregon Health & Science University (OHSU) School of Medicine, and Staff Physician in the Internal Medicine Clinic at OHSU. He has conducted systematic reviews in a number of areas, including chronic pain and musculoskeletal conditions, screening and prevention, diagnostic testing, and prognosis. He has served as Director of the American Pain Society clinical guidelines program, and co-chair of the National Quality Forum Musculoskeletal Standing Committee, among others.

<https://www.ohsu.edu/xd/education/schools/school-of-medicine/departments/clinical-departments/medicine/divisions/general-internal-medicine/faculty/roger-chou-md.cfm>

Sean Mackey, M.D., Ph.D. Chief of the Division of Pain Medicine and Redlich Professor of Anesthesiology, Perioperative and Pain Medicine, Neurosciences and Neurology at Stanford University. He is the Immediate Past President of the American Academy of Pain Medicine. Under Dr. Mackey's leadership, the Stanford Pain Management Center has been designated a Center of Excellence by the American Pain Society, one of only two centers to receive this honor twice. In 2011 he was a member of the Institutes of Medicine committee that issued the report on Relieving Pain in America. He is currently Co-Chair of the Oversight Committee for the NIH/Health and Human Services National Pain Strategy, an effort to establish a national health strategy for pain care, education and research.

<https://profiles.stanford.edu/sean-mackey>

Michael C. Rowbotham, MD. Scientific Director, California Pacific Medical Center Research Institute, Professor, Anesthesia, University of California San Francisco.

<https://profiles.ucsf.edu/michael.rowbotham>

Edward Michna, MD. Director, Pain Trials Center, Brigham and Women's Hospital; Instructor, Harvard Medical School, Anesthesia and Pain Management. Clinical interests in back pain, cancer pain, fibromyalgia, neurologic pain, pelvic pain.

Note: Dr. Michna is or has recently been a consultant to FDA's Anesthetic and Analgesic Drug Products Advisory Committee and is an active Special Government Employee.

<https://physiciandirectory.brighamandwomens.org/details/1113/edward-michna-anesthesia-and-pain-management-chestnut-hill>

Friedhelm Sandbrink, MD. Acting National Program Director for Pain Management in the Department of Veterans Affairs. Leads the comprehensive interdisciplinary Pain Management Program at the Washington VA Medical Center. Clinical Associate Professor in Neurology at the Uniformed Services University of the Health Sciences in Bethesda, MD and also has academic appointments at Georgetown University and George Washington University. Federal member of new HHS Pain Management Best Practices Inter-Agency Task Force.

<http://www.gwumc.edu/smhs/facultydirectory/profile.cfm?empName=Friedhelm%20Sandbrink&FacID=2050942433>

<http://clevelandpainconference.com/speakers/friedhelm-sandbrink-md/>

Clinical Pharmacology

Adel H. Karara, PhD, FCP. Professor of Pharmaceutical Sciences, University of Maryland, Eastern Shore.

Note: Dr. Karara is or has recently been a consultant to FDA's Advisory Committee for Pharmaceutical Science and Clinical Pharmacology and may be an active Special Government Employee (term date may have ended).

<https://www.umes.edu/Pharmacy/Content/Faculty-and-Staff-Bios/Adel-Karara/>

Pharmaceutical Science / Drug Formulation

Tonglei Li, PhD. Allen Chao Chair and Professor of Industrial and Physical Pharmacy, Purdue University. Specialization: Solid-state organic chemistry, computational chemistry, formulation, and drug delivery

Note: Dr. Li is a member of FDA's Advisory Committee for Pharmaceutical Science and Clinical Pharmacology.

Phone: 765-494-1451; E-mail: tonglei@purdue.edu

<https://www.ipph.purdue.edu/faculty/tonglei>

James E. Polli. Professor and Ralph F. Shangraw/Noxell Endowed Professor in Industrial Pharmacy and Pharmaceutics at the University of Maryland School of Pharmacy. Co-director of the University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), an FDA-funded collaborative agreement with the Agency.

Note: Dr. Polli is currently a PI on a collaborative agreement with FDA to research the current and historical use of certain bulk drug substances used in compounding.

Phone: 410-706-8292; Email: jpolli@rx.umaryland.edu

<https://faculty.rx.umaryland.edu/jpolli/>

Pharmacokinetics / Skin Absorption

Conor L. Evans, PhD. Assistant Professor at the Harvard Medical School, an Affiliated Faculty member of the Harvard University Biophysics Program, a Faculty member of the Laser Biomedical Research Center, and leads his lab at the Wellman Center for Photomedicine at Massachusetts General Hospital.

Note: While his biography describes a focus on biomedicine and optics, Dr. Evans' work has been dedicated to the dermal absorption of drugs and its quantification.

<http://wellman.massgeneral.org/faculty-evans-pi.htm>

Howard Maibach, MD. UCSF. Expert in contact and occupational dermatitis. His specialty is dermatotoxicology, or skin exposure toxicity; allergies and skin disorders; and dermatopharmacology or the study of medications for skin disorders.

<https://www.ucsfhealth.org/howard.maibach>

Grazia Stagni, MS, PhD. Professor of Pharmaceutics at the Arnold & Marie Schwartz College of Pharmacy, Long Island University

Note: Dr. Stagni has experience in microdialysis in the skin and a variety of methods in enhancing dermal absorption

<http://www.liu.edu/Pharmacy/Academics2/Faculty/Faculty/S/Grazia-Stagni?rn=Faculty&ru=/Pharmacy/Academic-Programs/Faculty>

Audra L Stinchcomb, PhD. Faculty at University of Maryland, Baltimore. Pharmaceutical Sciences. Expertise in pharmaceutical development, pharmaceutics, bioavailability, drug formulations.

<http://umaryland.academia.edu/AudraStinchcomb>

Hartmut Derendorf, PhD. Emeritus professor of pharmaceutics at the University of Florida College of Pharmacy in Gainesville. Editor or Associate Editor of the Journal of Clinical Pharmacology, International Journal of Clinical Pharmacology & Therapeutics. Served as President of ACCP (American College of Clinical Pharmacology) in 2006/08 and President of ISAP (International Society of Antiinfective Pharmacology) in 2004/06.

<https://pharmacy.ufl.edu/faculty/hartmut-derendorf/>

S. Narasimha Murthy, PhD. Professor of Pharmaceutics, University of Mississippi. Expertise in transdermal drug delivery and dermatokinetics, among other topics.

<https://pharmacy.olemiss.edu/pharmaceutics/team/dr-s-narasimha-murthy/>

Vinod Shah, PhD. Expert Consultant, NDA Partners. Former Senior Research Scientist in the Office of Pharmaceutical Sciences and Biopharmaceutics Expert Committee member of U.S. Pharmacopeial Convention

<https://www.ndapartners.com/consultants/index.php?page=shah>

Toxicology

Barbara Insley Crouch, PharmD, MSPH. Professor (Clinical) and Vice-Chair, Department of Pharmacotherapy, University of Utah. Director, Utah Poison Control Center.

<https://pharmacy.utah.edu/pharmacotherapy/faculty/crouch.php>

David E. Malarkey, DVM, PhD, MS, DACVP. Head, National Toxicology Program, Pathology Group, National Institute of Environmental Health Sciences, NIH. Adjunct Assistant Professor, Population Health and Pathobiology, College of Veterinary Medicine, North Carolina State University.

Phone: 919-541-1745; Email: malarkey@niehs.nih.gov

https://www.niehs.nih.gov/businesscards/docs/malarkey_david_508.pdf

Paul M. Foster, Ph.D. Discipline Leader for Reproduction and Development Chief, Toxicology Branch, National Toxicology Program, National Institute of Environmental Health Sciences, NIH. Phone: 984-287-3131; Email: foster2@niehs.nih.gov

Jeanmarie Perrone, MD. Professor of Emergency Medicine at the Hospital of the University of Pennsylvania, Director, Division of Medical Toxicology, Department of Emergency Medicine, University of Pennsylvania.

Note: Dr. Perrone is or has recently been a consultant to FDA's Drug Safety and Risk Management Advisory Committee.

<https://www.med.upenn.edu/apps/faculty/index.php/g321/p1870>

Lewis S. Nelson, MD. Professor of Emergency Medicine, Chair, Dept. of Emergency Medicine, Rutgers New Jersey Medical School, Chief of Service, Emergency Department, University Hospital.

Note: Dr. Nelson is or has recently been a consultant to FDA's Drug Safety and Risk Management Advisory Committee

http://njms.rutgers.edu/departments/emergency_medicine/fac_adult.cfm

Anne-Michelle Ruha, M.D., FACMT. Vice Chief, Department of Medical Toxicology, and Section Chief, Addiction Medicine, Banner – University Medical Center, Phoenix. Faculty Physician, Division of Medical Toxicology and Precision Medicine, Department of Medicine, University of Arizona College of Medicine

Note: Dr. Ruha is currently a member of FDA's Drug Safety and Risk Management Advisory Committee

Phone: 602-839-6690; Email: michelle.ruha@bannerhealth.com

<https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM528865.pdf>

Regulatory Matters

Jane A. Axelrad, JD. Principal, Axelrad Solutions LLC

Note: Ms. Axelrad was formerly the associate director for Policy, Center for Drug Evaluation and Research, Food and Drug Administration for 25 years. Following the fungal meningitis outbreak, Axelrad was the agency lead on drug compounding. We are recommending Ms. Axelrad for the Committee on compounded topical pain medications, as she has indicated she may have a current business conflict with regard to hormone therapy

Phone: (301) 704-8657, Email: jane.axelrad@gmail.com

Recommendations for the Committee on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy"

Reproductive Endocrinology / Hormone Therapy

Margery Gass, MD. Former executive director of The North American Menopause Society (NAMS). Former clinical faculty at Cleveland Clinic Lerner College of Medicine at Case Western Reserve University, and University of Cincinnati, Department of Obstetrics and Gynecology.

<https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM616373.pdf>

Nanette Santoro, MD. Professor and E. Stewart Taylor Chair Department of Obstetrics & Gynecology, University of Colorado Denver.

Note: Dr. Santoro is an academic reproductive endocrinologist (clinician and researcher)

<https://som.ucdenver.edu/FIMS/Content/faculty/1292/Santoro%20CV%20January%202015.pdf>

James H. Liu, MD. Chair and Professor Department of Reproductive Biology School of Medicine, Professor Division of General Medical Sciences School of Medicine, Case Western University.

Note: Dr. Liu is or has recently been a consultant to FDA's Bone, Reproductive and Urologic Drugs Advisory Committee

<https://case.edu/medicine/reproductive-biology/faculty-residents-fellows/academic-faculty/james-h-liu>

Clinical Pharmacology, Pharmaceutical Science / Drug Formulation, and Toxicology

Experts in these subjects that FDA recommended for the pain study Committee could also be considered for the BHRT study Committee. Please see recommendations above.

Leadership of the following organizations may also be of interest as subject-matter experts. These entities have all expressed strong interest in this topic to FDA, in particular NAMS and ACOG. Most have public positions on "bioidentical" hormone therapy.

- The North American Menopause Society (NAMS)
 - JoAnn V. Pinkerton, MD, NCMP, Executive Director
 - James H. Liu, MD, NCMP, President-Elect
- American College of Obstetricians and Gynecologists (ACOG)
 - Sandra A. Carson, MD, Vice President, Education
 - Barbara S. Levy, MD, Vice President, Health Policy
- Endocrine Society
 - Kathy Martin, MD, Senior Deputy Editor, Endocrinology and Metabolism, Up-to-Date
 - Ms. Stephanie Kutler, Director of Advocacy and Policy
- American College of Physicians
 - Kristine E. Ensrud, MD, MPH, Master's Member (MACP), American College of Physicians
- National Association of Nurse Practitioners in Women's Health (NPWH)
 - Ms. Gay Johnson, Chief Executive Officer
 - Ms. Sue Kendig, Director of Policy
- HealthyWomen
 - Beth Battaglione, RN, Chief Executive Officer
 - Ms. Phyllis Greenberger, Senior Vice President for Policy and Advocacy
- National Women's Health Network
 - Sarah Christopherson, Program Director. (202) 682-2640. SChristopherson@nwhn.org.

EXHIBIT 9

From: [Jane Axelrad](#)
To: [Cosel, Gabrielle](#)
Subject: Re: Recommendation for NASEM committee
Date: Friday, November 09, 2018 10:00:58 AM

Hi Gabey,

I don't think I can do it as I have a client interested in bioidentical hormones. I nominated 5 people for that, 4 outside doc experts and one I would think that would be a conflict. Maybe I could do pain creams? You will have to decide as I'm about to board a plane to come home from CA. Talk soon.

Jane

Jane A. Axelrad, Principal
Axelrad Solutions LLC
(301) 704-8657

On Nov 9, 2018, at 6:35 AM, Cosel, Gabrielle <Gabrielle.Cosel@fda.hhs.gov> wrote:

Hi Jane – how are you? It has been awhile!

As you may have seen, we're launching two studies with the National Academies of Sciences, Engineering and Medicine – one on compounded topical pain medications and another on compounded "bioidentical" hormone therapy.

NASEM have asked us to recommend people for their consideration for their expert committees for the projects. Among other experts, they are looking for people with knowledge of regulatory matters.

If you are open to it, we'd like to include your name in our recommendations to them.

Let me know what you think! Unfortunately they have asked us to send them names today – apologies for the quick request.

If they did decide to reach out to you, you would still have the option to decline.

Hope you are well. (b) (6) Time flies.

Gabey

Gabrielle Cosel
CDER/OC/OU DLC
301-796-4179

EXHIBIT 10



Justification for Other than Full and Open Competition

1. Identification of the agency and contracting activity:

a. Federal agency and contracting activity.

Food and Drug Administration (FDA), Office of Acquisitions and Grant Services (OAGS)

b. Sponsoring organization.

Center for Drug Evaluation and Research (CDER)

c. Contracting Officer's Representative (COR)/Requiring Activity Point of Contact (POC) information.

- i. Name: Amy Akparewa
- ii. Mailing address: 10903 New Hampshire Ave, Silver Spring, MD 20993
- iii. E-mail address: Amy.Akparewa@fda.hhs.gov
- iv. Telephone number: 240-402-0360

2. Nature and/or description of the action being approved.

This is a cost type, no fee contract to be issued to the National Academy of Sciences (Academy). The Academy will convene an ad hoc committee for Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy

a. Acquisition purpose and objectives.

The National Academies of Sciences, Engineering, and Medicine will convene ad hoc committees to develop a report that assesses the clinical utility of treating patients with compounded BHRT drug products.

b. Project background.

See attached Statement of Work for background. This is a new requirement anticipated for the National Academies of Science, Engineering, and Medicine. The period of performance for this study is eighteen (18) months from the date of award. The total amount is \$1,345,719.00.

3. Description of the supplies or services required to meet the agency's needs (including the estimated value).

The National Academies of Sciences, Engineering, and Medicine will convene ad hoc committees to develop a report that assesses the clinical utility of treating patients with compounded BHRT drug products.

a. Project title.

Report on the Clinical Utility of Treating Patients with Compounded “Bioidentical Hormone Replacement Therapy

b. Project Description.

Please see attached Statement of Work (SOW).

Requirement type.

- Research & Development (R&D)
- R&D support services
- Support services (non-R&D)
- Supplies/equipment
- Information Technology (IT)
- Construction
- Architect-Engineer (A&E) services
- Design-build
- Other:

Type of action.

- New requirement
- Follow-on
- Other:

Proposed contract/order type.

- Firm-fixed-price
- Other fixed-price:
- Cost-plus-fixed-fee
- Other cost reimbursement: Cost Reimbursement, No Fee.
- Time and materials
- Indefinite delivery:
- Other:
- Completion Form
- Term Form

Acquisition identification number: CDER-18-C-0635

Report on the Clinical Utility of Treating Patients with Compounded “Bioidentical Hormone Replacement Therapy.

c. Total estimated dollar value and performance/delivery period.

\$1,345,719.00

Period of Performance: Eighteen (18) months from date of Award

4. Identification of the statutory authority permitting other than full and open competition. Check the applicable block below based on the acquisition circumstance.

Federal Acquisition Regulation (FAR):

- [6.302-1](#) Only one responsible source and no other supplies or services will satisfy agency requirements. This acquisition is conducted under the authority of United States Code (U.S.C.) [10 U.S.C. 2304\(c\)\(1\)](#) or [41 U.S.C. 3304\(a\)\(1\)](#).
- [6.302-2](#) Unusual and compelling urgency. This acquisition is conducted under the authority of United States Code (U.S.C.) [10 U.S.C. 2304\(c\)\(2\)](#) or [41 U.S.C. 3304\(a\)\(2\)](#).
- [6.302-3](#) Industrial mobilization; engineering, developmental, or research capability; or expert services. This acquisition is conducted under the authority of United States Code (U.S.C.) [10 U.S.C. 2304\(c\)\(3\)](#) or [41 U.S.C. 3304\(a\)\(3\)](#).
- [6.302-4](#) International agreement. This acquisition is conducted under the authority of United States Code (U.S.C.) [10 U.S.C. 2304\(c\)\(4\)](#) or [41 U.S.C. 3304\(a\)\(4\)](#).
- [6.302-5](#) Authorized or required by statute. This acquisition is conducted under the authority of United States Code (U.S.C.) [10 U.S.C. 2304\(c\)\(5\)](#) or [41 U.S.C. 3304\(a\)\(5\)](#).
- [6.302-6](#) National security. This acquisition is conducted under the authority of United States Code (U.S.C.) [10 U.S.C. 2304\(c\)\(6\)](#) or [41 U.S.C. 3304\(a\)\(6\)](#).
- [6.302-7](#) Public interest. This acquisition is conducted under the authority of United States Code (U.S.C.) [10 U.S.C. 2304\(c\)\(7\)](#) or [41 U.S.C. 3304\(a\)\(7\)](#).
- [13.501\(a\)\(1\)\(ii\)](#) Sole source, including brand name, under Simplified Procedures for Certain Commercial Items. This acquisition is using this justification format, modified to reflect that the procedures in [FAR subpart 13.5](#) were used in accordance with [41 U.S.C. 1901](#) or the authority of [41 U.S.C. 1903](#).

5. Demonstration that the proposed contractor(s) unique qualifications or the nature of the acquisition requires use of the authority cited.

a. Name and address of the proposed contractor:

The National Academies of Science, Engineering, and Medicine
500 Fifth Street, NW
Washington, DC 20001

b. Nature of the acquisition and proposed unique qualifications of the contractor(s).

Only One Responsible Source and no other type of services will satisfy the needs of the agency. Created by a Congressional Charter signed by President Lincoln in 1863, the Academy is a federally chartered non-profit institution dedicated to the furtherance of science and its use for the general welfare. The Congressional Charter is codified at 36 U.S.C.A. 150301-150305. Although the Academy is a private non-profit corporation, it is called upon by the terms of its Congressional Charter to act as an official, yet independent, advisor to the federal government in matters of science and technology.

The capacity of the Academy to play a unique role in advising the Federal government stems from the net impact of three interrelated attributes:

To a degree unmatched elsewhere, the Academy can elicit the participation of virtually any expert whom it invites to serve. As a consequence, there are at any one time some 800 committees, addressing an enormous diversity of problems, peopled by about 8,000 unpaid volunteers.

The credibility of Academy Reports is maximized by the recognized impartiality of the institution, which manufactures no product, possesses no funds to disperse, has no power of decision over the scientific establishment, and enjoys no executive or regulatory authority. Thus, there is no vested interest in the outcome of deliberations and the independent advice is of unparalleled objectivity.

Finally, for those studies that involve sharply divergent and well-fixed points of view, the Academy has repeatedly been able to bring together about its conference tables assemblages of persons who have been conspicuously reluctant to address mutual issues, in an atmosphere of comparative calm.

Committees are composed of the nation's top scientists, doctors, engineers and other experts, all of whom volunteer their time to study specific concerns. Nominees for membership in committees at the Committee are subjected to rigorous procedures for appointment. These procedures ensure the selection of the most qualified scientists who represent a broad range of views and who, as a group, represent the spectrum of scientific thought in a subject area.

The Academy's unique status was confirmed by President George Bush in Executive Order 12832 (January 19, 1993), which specifically recognizes the Academy's unique qualifications, and the appropriateness of sole source awards to the Academy:

When a department or agency of the executive branch of the Government determines that the Academy, because of its unique qualifications, is the only source that can provide the measure of expertise, independence, objectivity, and audience acceptance necessary to meet the department's or agency's program requirements, acquisition of services by the Academy may be obtained on a noncompetitive basis if otherwise in accordance with applicable law and regulations.

These unique qualifications were confirmed by the General Accounting Office in Moshman Associates (B-216107), which upheld the Department of Education's sole source justification for an award to the Academy. The Comptroller General agreed with the agency that only the Academy could "provide a combination of the highest caliber of scientific expertise, independence, impartiality, credibility and audience acceptance." The GAO specifically relied on the special independent status of Academy as a nonprofit organization, congressionally chartered for the purpose of conducting studies for the government, and that the Academy historically has enjoyed a high degree of credibility, that its scientific expertise and resources are of the highest caliber, and that it is a "distinguished and respected body."

Most importantly, for this project the Academy will partner with experts, representing various areas of expertise in medical product development, ethics, clinical investigation, clinical care, law, and patient perspectives. There is no other organization of its standing in the United States capable of providing such collaboration and expertise.

No personal remuneration is made for the services of the scientists, engineers and other experts serving on Academy committees and, by law, no fee or profit is paid to the Academy.

Therefore, it is in the public interest to receive the independent advice of unparalleled objectivity of the highest quality that provides an inherent degree of acceptability. Considering the volunteer nature of committee members as well as the independence, objectivity, quality and acceptance of Academy recommendations, the Academy represents a cost effective means for examining the critical issues of this project.

6. Description of efforts made to ensure that offers are solicited from as many potential sources as is practicable, including whether a notice was or will be publicized as required by [subpart 5.2](#) and, if not, which exception under [5.202](#) applies.

A Notice of Intent to Sole Source was published on FedBizOpps from July 25th, 2018 through August 9th, 2018.

7. Determination by the Contracting Officer that the anticipated cost/price to the Government will be fair and reasonable.

Prior to the award of the proposed contract/order, cost or pricing information will be obtained (inclusive of DCAA Audits and Approved Indirect Rate Agreements) from the proposed contractor and price and/or cost analysis will be performed and documented to sufficiently determine that the cost to the Government of the proposed acquisition will be fair and reasonable.

8. Description of the market research conducted (see [FAR Part 10](#)) and the results, or a statement of the reasons market research was not conducted.

Market research, in accordance with FAR Part 10, was conducted by performing internet searches for similar organizations.

9. Any other facts supporting the use of other than full and open competition.

None

10. Listing of sources, if any, that expressed, in writing, an interest in the acquisition.

No other sources have expressed an interest, in writing, in the proposed acquisition.

11. Statement of the actions, if any, the agency may take to remove or overcome any barriers to competition before any subsequent acquisition for the required supplies or services

No other institutions exist which can provide the access to the well known experts on the subjects covered by this contract. There are no subsequent plans to acquire this type of service in the future.

12. Program office certification.

This is to certify that the portions of this justification that have been developed by the undersigned program office personnel, including supporting information and/or data verifying the Government's minimum needs, schedule requirements and other rationale for other than full and open competition, are accurate and complete.

Signature: Amy E. Akparewa -S
Digitally signed by Amy E. Akparewa -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2001865142
cn=Amy E. Akparewa -S
Date: 2018.09.21 12:53:00 -04'00'

Amy Akparewa
COR/Requiring Activity POC
Christopher E. Carlsen

Signature: A
Digitally signed by Christopher E. Carlsen -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, 0.9.2342.19200300.100.1.1=2000531690,
cn=Christopher E. Carlsen -A
Date: 2018.09.21 13:54:32 -04'00'

Chris Carlsen
COR/POC Immediate Supervisor

Signature: Mary Clarke -S
Digitally signed by Mary Clarke -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Mary Clarke -S,
0.9.2342.19200300.100.1.1=2000418300
Date: 2018.09.21 15:31:23 -04'00'

Mary Beth Clarke
Head of the Sponsoring Program Office

13. Contracting Officer Certification.

This is to certify that the justification for the proposed acquisition has been reviewed and that to the best of my knowledge and belief the information and/or data provided to support the rationale and recommendation for approval is accurate and complete.

Signature: _____

Matthew J. Bucher
Contracting Officer

14. Competition Advocate signature.

Signature: _____

Competition Advocate

EXHIBIT 11

From: [Jackson, Leigh Miles](#)
To: [Cosel, Gabrielle](#)
Subject: RE: Checking in
Date: Thursday, February 20, 2020 2:42:02 PM
Attachments: [image001.png](#)

2pm on the 17th works for Andy and me.

I'll send out a calendar hold now.

Thank you,
Leigh

From: Cosel, Gabrielle <Gabrielle.Cosel@fda.hhs.gov>
Sent: Thursday, February 20, 2020 1:53 PM
To: Jackson, Leigh Miles <LMJackson@nas.edu>
Subject: RE: Checking in

Thanks, Leigh. 2pm or 4pm on the 17th would work for us, it looks like. Would either of those times work?

From: Jackson, Leigh Miles <LMJackson@nas.edu>
Sent: Thursday, February 20, 2020 1:50 PM
To: Cosel, Gabrielle <Gabrielle.Cosel@fda.hhs.gov>
Subject: RE: Checking in

Hello Gabey,

I'm circling back to schedule a phone call in mid-March.

Right now, it looks like the afternoon of March 17th and the morning and afternoon of March 19th are open.

Please let me know if you have a preferred date or time for the call.

Thank you,
Leigh

From: Cosel, Gabrielle <Gabrielle.Cosel@fda.hhs.gov>
Sent: Friday, February 7, 2020 10:24 AM
To: Jackson, Leigh Miles <LMJackson@nas.edu>
Subject: RE: Checking in

Many thanks for the update, Leigh. Glad to hear everything is going smoothly. I'm not sure why some of those stakeholders were late in expressing interest, one of the speakers as you may know is a well-known attorney (in our wonky world, haha) who represents compounders so perhaps she had

a hand in organizing the outreach to you.

It would be great to connect over the next month on the upcoming reports. Perhaps sometime mid-March?

(b) (6)

Look forward to speaking soon,
Gabey

From: Jackson, Leigh Miles <LMJackson@nas.edu>
Sent: Thursday, February 06, 2020 10:46 AM
To: Cosel, Gabrielle <Gabrielle.Cosel@fda.hhs.gov>
Subject: RE: Checking in

Hello Gabey,

Welcome back!

(b) (6)

In terms of the compounding studies, they are both moving along smoothly. The topical pain cream report is in the middle of its external review process and we anticipate its release in the next few months.

The cBHRT study is about to enter into external review and we anticipate its release in early summer.

In regard to the January public session, yes, that was definitely a late addition to the study's schedule and is not typical. The cBHRT study, in particular, had a substantial amount of late stakeholder interest and we're not exactly sure as to why. Since the launch of the study, the committee and NASEM staff has worked hard to gather input from providers, patients, and pharmacists, but only in the last few months have these stakeholders expressed interest in providing comments to the committee. Either way, in an effort to ensure that the members of the cBHRT study committee sufficiently considered all available evidence and submitted testimonies, we added one last (virtual) open session meeting to the study's schedule. The committee's response to the meeting was positive and I think they benefited from the added discussion. We do not anticipate any additional public meetings prior to the release of the report.

I'm available for a call if you have additional questions. Also, within the next month or so, it would be helpful to touch base about any anticipated plans for the reports' release.

Thank you for checking in.

Best,
Leigh

Leigh Miles Jackson, PhD
Senior Program Officer

FDACDER_001802

EXHIBIT 12

From: [Jackson, Leigh Miles](#)
To: [Cosel, Gabrielle](#)
Subject: Re: Follow-up
Date: Monday, April 29, 2019 7:35:28 PM
Attachments: [BHRT Open Session Agenda 4-30.pdf](#)

I think that sounds like a good plan.

I spoke with the Chairs for the BHRT study and they were happy with Sara's proposed presentation (a high-level overview on the regulatory oversight of compounding). They were also more than fine with the idea that another FDA representative may have to provide extra context, if needed.

I think we're good to go. A copy of our open session agenda is attached.

Thank you again for your help.

Leigh

From: Cosel, Gabrielle <Gabrielle.Cosel@fda.hhs.gov>

Sent: Monday, April 29, 2019 10:42 AM

To: Jackson, Leigh Miles

Subject: RE: Follow-up

Hi Leigh, following up on our call on Friday.

I'm thinking, especially given short timeline until the 6th, we keep our plan for Sara to present 15 minutes on regulatory oversight of compounding, and I will make sure we have someone from FDA in-audience or on the line who can provide a bit more context on elements of the approved drug review process if needed.

How does that sound?

If on the 6th the experience suggests we should bring in an additional FDA speaker for the 20th, we can discuss.

From: Jackson, Leigh Miles <LMJackson@nas.edu>

Sent: Friday, April 26, 2019 3:42 PM

To: Cosel, Gabrielle <Gabrielle.Cosel@fda.hhs.gov>

Subject: RE: Follow-up

Hi Gabey,

Yes, those times are still correct.

We're hoping to have a presentation or conversation focused on current regulatory policies for cBHRT products, perceived gaps in the evaluation of the safety and efficacy of these products, and the potential impact of the research conclusions that emerge from the current NASEM study.

Within that session there will be an opportunity for the committee to ask follow up questions.

I hope that helps.

Leigh

-----Original Message-----

From: Cosel, Gabrielle <Gabrielle.Cosel@fda.hhs.gov>

Sent: Friday, April 26, 2019 1:45 PM

To: Jackson, Leigh Miles <LMJackson@nas.edu>

Subject: RE: Follow-up

Thanks Leigh. Sorry for delayed response. Just to confirm - I think you had mentioned when we spoke on the phone that you'd want about 15 min from FDA on the topic. Is the 9:30-10:45am timeframe correct?

-----Original Message-----

From: Jackson, Leigh Miles <LMJackson@nas.edu>

Sent: Tuesday, April 23, 2019 3:32 PM

To: Cosel, Gabrielle <Gabrielle.Cosel@fda.hhs.gov>

Subject: RE: Follow-up

Yes, it's in the morning. Based on our current agenda her session is from 9:30-10:45am on the 6th.

I hope that's okay.

Thank you for your help in organizing this session.

Leigh

-----Original Message-----

From: Cosel, Gabrielle <Gabrielle.Cosel@fda.hhs.gov>

Sent: Tuesday, April 23, 2019 11:26 AM

To: Jackson, Leigh Miles <LMJackson@nas.edu>

Subject: RE: Follow-up

I just checked and Sara can also present on May 6 if it is in the morning. Is that the case?

-----Original Message-----

From: Jackson, Leigh Miles <LMJackson@nas.edu>

Sent: Tuesday, April 23, 2019 9:01 AM

To: Cosel, Gabrielle <Gabrielle.Cosel@fda.hhs.gov>

Subject: RE: Follow-up

Hi Gabey,

We're interested in seeing whether Sara Rothman has availability to present at the May 6th BHRT meeting (in addition to the pain cream meeting).

Should I reach out to her directly or is it best to go through internal channels?

Thanks,

Leigh

From: Cosel, Gabrielle [Gabrielle.Cosel@fda.hhs.gov]

Sent: Thursday, April 18, 2019 3:15 PM

To: Jackson, Leigh Miles

Cc: Furlong, Lesley-Anne

Subject: Follow-up

Leigh - attached is the article Dr. Ganley mentioned on our call, and below are the names discussed.

I'm cc-ing Dr. Furlong in case I missed anyone from OWH - I couldn't recall if there was a second name shared for OWH.

Also, here is the link to our website showing inspections of compounders and related 483 forms and warning letters.

<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339771.htm>

Office of Women's Health

Kaveeta P. Vasisht, MD, PharmD

Kaveeta.Vasisht@fda.hhs.gov<<mailto:Kaveeta.Vasisht@fda.hhs.gov>>

FDA's Office of New Drugs, Division of Bone, Reproductive and Urologic Products Dr. Christine P. Nguyen Deputy Director for Safety, DBRUP Christine.Nguyen@fda.hhs.gov<<mailto:Christine.Nguyen@fda.hhs.gov>>

FDA's presenter for the second pain committee meeting.

Sara Rothman, MPH

Senior Policy Advisor, Office of Unapproved Drugs and Labeling Compliance Office of Compliance, CDER

Sara.Rothman@fda.hhs.gov<<mailto:Sara.Rothman@fda.hhs.gov>>

I'm happy to coordinate with Sara on content, what I have is a 15 minute presentation to give an overview of legal framework and regulatory oversight of compounded drugs, including a breakdown of the differences between 503A and 503B. Is there anything else specifically we should be sure to cover?

EXHIBIT 13

From: [Jackson Leigh Miles](#)
To: [Cosel Gabrielle](#)
Cc: [Ganley Charles J](#); [Bormel Frances Gail](#); [Furlong Lesley-Anne](#)
Subject: RE: Adverse event and production volume information - compounded BHT products and topical pain creams
Date: Friday, July 19, 2019 3:47:38 PM

Hi Gabey,

Thank you for these notes.

I will circle back if there are additional questions.

Best,

Leigh

From: Cosel, Gabrielle <Gabrielle.Cosel@fda.hhs.gov>
Sent: Wednesday, July 17, 2019 4:08 PM
To: Jackson, Leigh Miles <LMJackson@nas.edu>
Cc: Ganley, Charles J <Charles.Ganley@fda.hhs.gov>; Bormel, Frances Gail <Frances.Bormel@fda.hhs.gov>; Furlong, Lesley-Anne <LesleyAnne.Furlong@fda.hhs.gov>
Subject: RE: Adverse event and production volume information - compounded BHT products and topical pain creams
Hi Leigh, thank you for sharing the additional questions from the committee. Please find responses in red below. Please let us know if any additional information would be helpful.
Best,
Gabey

From: Jackson, Leigh Miles <LMJackson@nas.edu>
Sent: Monday, July 15, 2019 1:58 PM
To: Cosel, Gabrielle <Gabrielle.Cosel@fda.hhs.gov>
Cc: Ganley, Charles J <Charles.Ganley@fda.hhs.gov>; Bormel, Frances Gail <Frances.Bormel@fda.hhs.gov>; Furlong, Lesley-Anne <LesleyAnne.Furlong@fda.hhs.gov>
Subject: RE: Adverse event and production volume information - compounded BHT products and topical pain creams
Hello Gabey,
Thank for you for sending the three additional resources for the BHRT and Pain Cream committees. I'll make sure that they are appropriately distributed for consideration.
As I mentioned in an earlier email, the BHRT committee had a few additional questions that they've asked me to send your way. Please let me know if you have any thoughts that I can share before their next committee meeting on **August 6-7th**.

- **503B outsourcing facilities production quantities:** Thank you for your work in collecting this information from 2017 and 2018 datasets. The committee would like to know if there are any available datasets from prior to 2017? Maybe from 2015 or 2016? Could this historical data be made available to the committee?
 - FDA does have product reports from before 2017, but these were submitted in various formats (PDF, word, excel) and are not harmonized in their presentation of information. Unfortunately it won't be possible for us to extract and prepare data on production volume from these older reports in an efficient or comparable way.
- **Adverse events:** Thank you for organizing and compiling the excel sheet for the roughly 4000 reported adverse events. The committee wanted to know if it's possible to align the events with the dosage form of the product (e.g., pellet) associated with the incident? I recognize that there may be a heavy lift involved, in terms of redactions, but then again there may be a special search option within your master files. Either way, please let us know your thoughts.
 - It is our understanding that most if not all of the events relate to drugs formulated as pellets, but it is not always possible to clearly determine this in every case based on the information provided regarding the event.
- **FDA-approved BHRT products:** There has been some movement in the area of FDA-approved "bioequivalent" hormone products. The committee would like to confirm that they have the most up-to-date list of FDA-approved "bioequivalent" hormone products. Could you please send us an updated list that covers newly approved products from 2017-2019?
 - Between 2017 and 2019, FDA approved 2 hormone products that we are aware are being marketed as "bio-identical" because the active ingredients are molecularly identical to endogenous human hormones (though this term is not part of approved labeling):
 - Estradiol vaginal insert for dyspareunia from postmenopausal vulvar-vaginal atrophy (VVA)
 - Estradiol+progesterone oral capsules for postmenopausal vasomotor symptoms
 - As a reminder, FDA does not distinguish whether an approved hormone therapy (be it for women or men) is structurally identical to endogenous hormones (in labeling or anywhere else), because we do not have scientific evidence to support that such hormones differ in safety/efficacy than hormones that are not structurally identical to endogenous hormones.
- **Difficult to compound list:** As a follow-up to the difficult to compound list conversations from their open session meeting, the committee was hoping that the FDA would provide an outline of the review process for cBHRT products nominated to the difficult to compound list.
 - FDA's evaluation of products nominated for the difficult to compound list is still in process.
 - On June 18, 2015, and March 9, 2016, FDA presented to the Pharmacy Compounding Advisory Committee (PCAC) the criteria it proposes to use to evaluate whether drug products or categories of products are demonstrably difficult to compound. The briefing materials for the March 9 meeting include the criteria most recently proposed to the PCAC. Please see Tab 7 of the PDF at the following link: <https://www.fda.gov/media/95976/download>
 - Other meeting materials presented at these PCAC meetings are available at <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/default.htm>.
 - After consulting with the PCAC, FDA intends to develop and publish under notice-and-comment rulemaking procedures the drug

products and/or categories of drug products that it proposes be placed on the difficult to compound list. During the notice-and-comment rulemaking process, members of the public will have the opportunity to comment on drug products and/or categories of drug products that FDA proposes to put on the difficult to compound list before it is finalized. FDA will review and consider all comments received before publishing the list as a final rule.

Any thoughts/resources/advice on the above points would be appreciated.

Finally, I want to be sure that you are aware of the committee's recently released stakeholder request for input. This letter was sent out to a diverse group of stakeholders (e.g., consumers, providers, pharmacists) to collect input on the clinical utility of treating patients with compounded hormone replacement therapy. NASEM staff will send you the letter in a separate email.

Thanks again for your support of our work.

Best,
Leigh

From: Cosel, Gabrielle <Gabrielle.Cosel@fda.hhs.gov>

Sent: Friday, July 12, 2019 10:09 AM

To: Jackson, Leigh Miles <LMJackson@nas.edu>

Cc: Bormel, Frances Gail <Frances.Bormel@fda.hhs.gov>; Ganley, Charles J <Charles.Ganley@fda.hhs.gov>; Furlong, Lesley-Anne <LesleyAnne.Furlong@fda.hhs.gov>

Subject: RE: Adverse event and production volume information - compounded BHT products and topical pain creams

Thanks Leigh. We look forward to receiving the additional questions.

In the interim, attached are two more documents that may be of use:

- For the compounded hormone therapy committee – a recent article published on the determination of estrogen and progesterone content in compounded hormone capsules and creams
- For the topical pain committee – we pulled the two court-filed complaint documents related to the False Claims Act case described in the article previously sent, which should have additional information on that case if of interest

From: Jackson, Leigh Miles <LMJackson@nas.edu>

Sent: Monday, July 01, 2019 11:47 PM

To: Cosel, Gabrielle <Gabrielle.Cosel@fda.hhs.gov>

Cc: Ganley, Charles J <Charles.Ganley@fda.hhs.gov>; Bormel, Frances Gail <Frances.Bormel@fda.hhs.gov>; Furlong, Lesley-Anne <LesleyAnne.Furlong@fda.hhs.gov>

Subject: RE: Adverse event and production volume information - compounded BHT products and topical pain creams

Hello Everyone,

Thank you for sending along this article. I'll make sure that the topical pain committee receives it, along with your responses to their submitted questions.

As a heads up, the BHRT committee would like to request a few additional pieces of information. I'll pull their requests into one email and circle back with you soon.

Thank you for your help.

Leigh

From: Cosel, Gabrielle <Gabrielle.Cosel@fda.hhs.gov>

Sent: Saturday, June 29, 2019 1:12 PM

To: Jackson, Leigh Miles <LMJackson@nas.edu>

Cc: Ganley, Charles J <Charles.Ganley@fda.hhs.gov>; Bormel, Frances Gail <Frances.Bormel@fda.hhs.gov>; Furlong, Lesley-Anne <LesleyAnne.Furlong@fda.hhs.gov>

Subject: RE: Adverse event and production volume information - compounded BHT products and topical pain creams

Hi Leigh – thank you for reaching out.

We are continuing to work on the two resources identified below, and hope to share information with you in the coming weeks.

Also, we came across the attached article applicable to topical pain creams and wanted to share in case useful. It describes recent False Claims Act complaints against two compounding pharmacies making compounded topical pain creams.

Here are responses to your additional questions:

1) Is it possible to have a list of the excipients used in the FDA-approved topical creams (broadly—not just for pain creams). The committee asks that you not include GRAS-approved excipients.

FDA maintains a publicly available inactive ingredient database. It is available here: <https://www.fda.gov/media/72482/download>.

The spreadsheet is conveniently sortable by route of administration and dosage form.

We believe you may have interest in the following topically-applied routes/dosage forms identified in the spreadsheet:

- All marked “topical” as route
- Those marked “transdermal” as route, including:
 - Those that have a semisolid dosage form (e.g. “cream”, “gel”, “solution”, “ointment”, etc)
 - If the interest is in the general safety of excipients, then the other dosage forms as well, such as patches, films, etc.

2) Could you please verify the accuracy of the notes below:

Please see proposed edit below. All of the ingredients were identified in examples of compounded topical pain medication formulas. And FDA's interest in potential drug-drug interactions is broadly applicable.

During the launch of this study, the FDA compiled and shared a non-comprehensive list of active pharmaceutical ingredients with the committee. It is the committee's understanding that the listed ingredients had been identified in examples of compounded topical pain medication formulas ~~or~~ showed relevance for drug-drug interaction considerations. The FDA's list was generated through online research efforts, as well as through personal communications with other government agencies (e.g., US Department of Veterans Affairs, US Department of Defense, and Centers for Medicare and Medicaid).

From: Jackson, Leigh Miles <LMJackson@nas.edu>

Sent: Thursday, June 20, 2019 4:17 PM

To: Cosel, Gabrielle <Gabrielle.Cosel@fda.hhs.gov>

Subject: RE: Adverse event and production volume information - compounded BHT products and topical pain creams

Hello Gabey,

Thanks for all of your help with our two studies. At this point, I wanted to check on the status of the remaining FDA resources for the BHRT and Topical Pain Cream committees:

1. *For BHRT* Additional adverse events identified in FAERS related to compounded hormone therapy products.
2. *For Pain Creams* A spreadsheet describing volume output of topical products containing certain ingredients used in pain treatment made by outsourcing facilities.

Based on your timelines, would we be able to receive either of these resources by early July?

In addition to the question above, the Topical Pain Cream committee has two other questions for you.

1) Is it possible to have a list of the excipients used in the FDA-approved topical creams (broadly—not just for pain creams). The committee asks that you not include GRAS-approved excipients.

2) Could you please verify the accuracy of the notes below:

During the launch of this study, the FDA compiled and shared a non-comprehensive list of active pharmaceutical ingredients with the committee. It is the committee's understanding that the listed ingredients had been identified in examples of compounded topical pain medication formulas or showed relevance for drug-drug interaction considerations. The FDA's list was generated through online research efforts, as well as through personal communications with other government agencies (e.g., US Department of Veterans Affairs, US Department of Defense, and Centers for Medicare and Medicaid).

Please let me know if you have any questions about these asks.

Thank you,

Leigh

From: Cosel, Gabrielle <Gabrielle.Cosel@fda.hhs.gov>

Sent: Monday, May 13, 2019 11:59 AM

To: Jackson, Leigh Miles <LMJackson@nas.edu>

Cc: Ju, Ruey <Ruey.Ju@fda.hhs.gov>; Ganley, Charles J <Charles.Ganley@fda.hhs.gov>; Furlong, Lesley-Anne <LesleyAnne.Furlong@fda.hhs.gov>; Bormel, Frances Gail <Frances.Bormel@fda.hhs.gov>

Subject: Adverse event and production volume information - compounded BHT products and topical pain creams

Dear Leigh, attached and described below are documents related to adverse events and production volume for both compounding projects. We have additional items we are still working on for you as well, which I've also noted below. As a reminder, adverse event reports provided here can only be viewed as examples and anecdotal. In addition, information in adverse events reports may not permit a conclusion about causality. If you have any questions I am happy to chat.

Compounded bioidentical hormone therapy products

1. A spreadsheet containing around 4000 adverse events from a single company obtained during an FDA inspection. The adverse events are associated with compounded bioidentical hormone therapy products, mainly pellets. File: **"Adverse event set_Marketer of compounded hormone products"**
 - o We understand these adverse events were collected from 2013 to March 2018.
 - o The first tab of this spreadsheet contains summary counts of when individual reports note certain types of complications (non-exhaustive). Note that the counts are per report, and may not necessarily equate to number of patients. While most reports appear to be for individual patients, we did see a few that were "general" reports made by providers that describe observations in more than one patient.
 - o This spreadsheet originally contained description fields for each adverse event report, some of which contained patient or provider identifying information. At this time we have removed those fields to enable us to provide the document to you. It is possible for us to do a more careful redaction of the document to remove patient and provider information so that you may see the information in those description fields. However because of the length of the document this will take several months. Please advise if this is something you would like us to pursue.
2. *To Come: additional adverse events identified in FAERS related to compounded hormone therapy products. We are still working on this.*
3. A spreadsheet describing aggregated volume output of products containing certain hormone ingredients made by outsourcing facilities in 2017 and 2018. This information is provided to FDA by registered outsourcing facilities in required biannual product reports. File: **"OF volume 2017-2018_hormone product"**
 - o The data for each hormone is aggregated across all outsourcing facilities using the hormones.
 - o The unit for this volume data is the smallest individual saleable package of product prepared for distribution (not a volume or weight-based unit).
 - o Three hormones – Pregnenolone, Estrone, and 7-Keto-DHEA – are not included here because they are made by 2 or fewer outsourcing facilities during one of the annual periods, which could allow for others to infer individual company production volume information. One hormone – Estradiol Cypionate – was not included as no outsourcing facilities made products with this hormone in 2017 or 2018.
 - o As a reminder, outsourcing facility production of compounded products containing these hormones does not represent the total volume of such drugs produced by compounders in the country. Many "503A" compounders (non-outsourcing facilities) also make these products.

Compounded topical pain medications

4. A set of 38 adverse event reports identified in FAERS describing one or more adverse event experiences with a topical compounded pain product in 39 patients. File: **"Compounded topical pain AE_Consolidated_05_07_2019_Redacted"**
5. One case report identified in the literature. File: **"2016 Boonsiri_corneal eye abrasion"**
6. A chart of patient complaints received by a single compounder over a 2-3 year period regarding compounded topical pain medications. File: **"Compounder Complaints Log_Redacted"**.
 - o In addition, a document listing API in each cream product referenced in the complaints chart as identified by "Cream #". File: **"Cream Number API for Complaints Chart"**
7. *To Come: a spreadsheet describing volume output of topical products containing certain ingredients used in pain treatment made by outsourcing facilities. We are still working on this.*

From: [Cosel, Gabrielle](#)
To: [Jackson, Leigh Miles](#)
Cc: [Ganley, Charles J](#); [Furlong, Lesley-Anne](#); [Bormel, Frances Gail](#); [Anderson, Kathleen R](#); [Hankla, Elizabeth](#); [Lawson, Rosilend](#)
Subject: Adverse event cases associated with compounded hormone therapy products
Date: Wednesday, July 31, 2019 3:02:00 PM
Attachments: [rev FAERS cases Redacted.pdf](#)
[Felner Prepubertal Gynecomastia- Indirect Exposure to Estrogen Cream.pdf](#)
[Griffie-Bilateral areolar pigmentation.BHRT.pdf](#)
[Jessel Two cases of endometrial adenocarcinoma in postmenopausal women on bioidentical hormone replacement therapy.pdf](#)
[Khan M.I Precocious Puberty in a two year old.pdf](#)

Dear Leigh,

We are pleased to provide the attached information on examples of adverse events associated with compounded hormone therapy products.

Attached please find a PDF describing 120 FAERS cases and four additional PDFs describing 7 additional literature cases not in FAERS (total of 135 patients).

Please let us know if you have any questions.

Best,
Gabey

EXHIBIT 14

FDA STATEMENT

Statement on improving adverse event reporting of compounded drugs to protect patients

For Immediate Release:

September 09, 2019

Statement From:

Director - Center for Drug Evaluation and Research

Janet Woodcock M.D.

Compounded drugs can serve an important medical need for certain patients, however, they also present risks (<http://wayback.archive-it.org/7993/20170111235218/http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm107836.htm>) [Ⓞ](http://www.fda.gov/about-fda/website-policies/website-disclaimer) (<http://www.fda.gov/about-fda/website-policies/website-disclaimer>) to patients since they are not evaluated by the FDA for safety, effectiveness and quality. The FDA's compounding program aims to help protect patients from poor-quality compounded drugs, while preserving access to lawfully-marketed compounded drugs for patients who have a medical need for them. Along with the development of policy and enforcement of the law, and collaboration with states and industry, our inspections of compounding facilities are vital aspects of this effort. Understanding the nature of the activity these compounders—especially outsourcing facilities— are engaged in helps minimize the risks to patients. While the FDA inspects outsourcing facilities regularly according to our risk-based schedule, we also rely on them to do their part in alerting us to issues that may endanger the health of patients.

As part of this work, several colleagues and I recently called attention to (<https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2749763>) [Ⓞ](http://www.fda.gov/about-fda/website-policies/website-disclaimer) (<http://www.fda.gov/about-fda/website-policies/website-disclaimer>) a particular issue associated with compounded hormones (specifically, in the form of pellets). During an inspection in 2018 of BioTE Medical, our investigators uncovered information about 4,202 adverse events that had never been reported to the agency. The adverse event information our investigators found suggested compounded hormone pellets were possibly associated with endometrial cancer, prostate cancer, strokes, heart attacks, deep vein thrombosis, cellulitis and pellet extrusion. However, because the reports lacked certain critical information, the FDA was able to attribute only a small percentage of the adverse events (61 reports), such as pellet extrusion and cellulitis, to the use of compounded hormone pellets containing testosterone. The company that collected the adverse events did not send them to us during the five years they occurred between 2013 and 2018. However, in light of this discovery, the FDA is continuing to take multiple steps to help protect patients, which we wanted to highlight today in the interest of public health.

Compounded bioidentical hormone replacement therapy (BHRT) products such as progesterone and testosterone, are used at times instead of FDA-approved drugs for hormone replacement therapy. Some compounders market BHRT products as superior to FDA-approved drugs by making assertions that they are more natural, safer or better for patients than FDA-approved drug products. FDA-approved hormone therapy treatments have been reviewed for safety and effectiveness for specific uses, and the FDA has measures in place to ensure quality during manufacturing. However, because, compounded BHRT products are not approved by the agency, there is no assurance of safety and efficacy. Outsourcing facilities, such as those that produced these products, are required to report certain adverse events to the FDA.

The agency uses adverse event reports to monitor safety issues to help protect the public. Adverse event reports can assist the FDA in identifying potential safety problems with a particular product. However, this is more difficult when information is outdated or missing. We maintain a public database ([/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers](#)) to ensure patients and health care professionals can access adverse event data about drugs. Outsourcing facilities are required to report adverse events to the agency and include adverse event reporting information on compounded drug labeling, and we encourage all companies, health care professionals and patients to report adverse events as soon as they know about them. Every year, the FDA receives adverse event reports of patient illnesses and deaths associated with compounded drugs. Information on the safety history of compounded drugs, through the reporting of adverse events is vital to protecting the public health.

Because compounding can serve an important role for patients whose medical needs cannot be met by an FDA-approved drug, we must work to protect patients from the risk of contaminated or otherwise harmful products. As we develop our policy and oversight program, the FDA continually strives to strike a balance between preserving access to compounded drugs for patients who have a medical need for them while protecting patients from the risks associated with compounded drugs that are not made in accordance with applicable quality standards or other requirements.

In this case, outsourcing facilities, Carie Boyd's Prescription Shop and AnazaoHealth Corporation, produced the pellets, but they were marketed by BioTe Medical, which was not registered with the agency as an outsourcing facility. While BioTe had an online portal to collect adverse event data from its customers, it never reported that information to the FDA nor did it provide this information to the outsourcing facilities.

The FDA is still investigating this matter, with respect to Carie Boyd's Prescription Shop, AnazaoHealth Corporation or BioTe and we cannot discuss the status. Outsourcing facilities are subject to regulatory and enforcement action if they do not appropriately label their drugs with adverse event reporting information and to report events to the FDA. The agency intends to take appropriate action if outsourcing facilities do not comply with the adverse event reporting requirements. We remind outsourcing facilities to develop thorough procedures to compile and investigate adverse event reports and share them with the FDA.

We're also using the information we learned from this episode to take steps to improve adverse event reporting and analyses to ensure we're doing the most we can to protect patients. We will continue to work with outsourcing facilities to improve mechanisms for obtaining reports of adverse events associated with their products and for providing adverse event reports to the agency. Furthermore, we continue to work with our state regulatory partners to finalize a standard memorandum of understanding under which states would agree to, among other things, investigate complaints of adverse events associated with certain compounded drugs from pharmacies operating under section 503A and report serious adverse events and serious product quality issues to the agency. States that sign the memorandum of understanding (<https://www.fda.gov/media/91085/download>) with the FDA will agree to investigate and share their findings. Collaboration with states has the potential to help prevent serious and widespread problems by helping to better identify adverse events and product quality issues across the country. For example, if a compounder distributes drugs to multiple states, it can be difficult to gather information about possible adverse events associated with those drugs, connect them to the compounder and undertake coordinated action to address a potentially serious public health problem. Collaboration with our state partners would be crucial in such an instance. While adverse event reports have some limitations, this information is one of the best safety tools we have at our disposal. The FDA is dedicated to increasing public awareness about drug safety issues and we're continuing our efforts to improve reporting for all types of drugs, including compounded medicines. We anticipate finalizing our MOU with the states later this year.

To further enhance our understanding of the safety of compounded hormones, the FDA has contracted with the National Academy of Sciences, Engineering, and Medicine (NASEM) to conduct a study on the risks associated with compounded hormone products. Our collaboration with NASEM will also continue to examine the clinical utility of treating patients with compounded products and the available evidence of the safety and effectiveness of multi-ingredient compounded topical pain creams. The FDA plans to share updates about this study with the public as information is available.

We'll continue to work to ensure patients have appropriate access to compounded medications. However, we must also ensure that all steps are taken to help reduce risks to patients. Patient health and safety is the FDA's highest priority.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

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