Considering the Safety of the Medicine Supply amid Growing Popularity of Unapproved Versions of GLP-1

Panelists:

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I'm going to ask Scott to start us off. Can you describe the important role that compound medicines have in healthcare when they're allowed to be produced and why are they needed?

SCOTT: How much time do you have? Well, we're going to keep it tight. In our healthcare system, FDA-approved drugs are supreme; they are the gold standard. If an FDA-approved drug is available and is judged by a prescriber to be appropriate for a particular patient, the FDA-approved drug should always be what is prescribed and dispensed.

But the fact is, in our healthcare system, FDA-approved drugs are not always available. There are times when, in the judgment of a prescriber, a commercially available drug is not available in a dosage form, dosage strength, or combination to serve a particular patient. In that instance, the Food, Drug, and Cosmetic Act authorizes pharmacies to prepare custom medications made from pure or bulk ingredients based on a prescription for an individual patient.

To be clear, a prescriber in this era of GLP-1 drugs can't write "Lugovoi" on the prescription, and the patient trots down to the pharmacy. The pharmacist won't say, "Oh, I don't have any of that. I'm going to compound it." In our healthcare system and the laws of all 50 states, a prescriber has to write for the compounded drug. They're not going to write "Wegovy"; they

will write "compounded semaglutide injection of a certain dosage strength," and that's what the pharmacy would fill.

In our system, what can be compounded? There is a criterion for what pharmacies can use. It either has to be a component of an FDA-approved drug, as semaglutide turns appetite, or it has to have a USP or National Formulary monograph, or it has to be on this special box list that the FDA maintains.

Compounding is not only authorized in the Food, Drug, and Cosmetic Act but also under the laws of all 50 states. There is a fairly rigorous regulatory framework for compounding, but I want to be clear: it is not the same framework as the one drug makers adhere to. Again, FDA-approved drugs are the gold standard, and they are the gold standard because they go through extensive testing and adhere to current good manufacturing practices, etc.

Compounding is carved out for an instance where a prescriber has a patient and is prescribing a custom medication for that individual patient. So, compounded drugs are not FDA-approved beyond GLP-1s. It's funny; I interact with reporters occasionally who seem to think that compounding has arisen from the GLP-1 frenzy. Compounding has been around for generations—centuries, even.

Some examples of where compounding fills a central need: I have a member on Long Island, Joe Navarra, who was approached by a hospital in Massachusetts a few years ago. The hospital was treating pediatric sickle cell patients. The hydroxyurea formulation commercially available is in a pill that could practically choke a horse. I exaggerate only slightly. A 5-year-old with sickle cell can't swallow that drug. So, Joe now—and for years—has made a hydroxyurea suspension from pure ingredients, not from the FDA-approved drug, because FDA-approved drugs have a variability in potency of 10% either way. If you want real accuracy, you have to use the bulk API. And so, that's an example. Hospitals, if you've ever been in one, use compounded drugs extensively in IV bags. And I'll wrap up by saying this: It's interesting to me that the title of this panel is about unapproved drugs because, technically, compounded drugs are unapproved. But when you're talking about hydroxyurea suspension for pediatric sickle cell patients, nobody's saying, "Hey, those are unapproved drugs." They're compounded drugs that help alleviate suffering and enhance the lives of those children.

Ultimately, that's my view on compounding: not competition for FDA-approved drugs, but to fill gaps that FDA-approved drugs can't fill.

I hope that makes it easier to follow now! Let me know if you'd like any other changes.

Marta, with that set up can you please explain to us how compounded drugs and more conventional FDA approved drugs are regulated differently you've got a great paper on this and I think maybe we'll focus on quality insurance for us or whatever other topics you want to focus on.

MARTA: I think Scott identified the biggest difference. There is an approval process for drugs that are manufactured, whether for branded products or generic products. They have to establish that the drug is either safe or effective. I think a better comparison here is not thinking of the branded products, but the generic products. Generic products have to show that they are the same as the brand, and that's the standard. Compounded drugs do not have to show that they're the same as the brand. If there is a USP monograph for the active ingredient, then they can actually use this.

But what's interesting, and I'll talk about this a little bit later, is that there is no USP monograph for GLP-1s, and I'll come back to this and the implications of this. One thing is that nobody looks at those products before they are on the market. Now, it makes perfect sense when a patient cannot swallow pills and the pharmacist needs to make them a liquid formulation. I mean, can you imagine? This doesn't work right if a patient is allergic to a specific dye and the pharmacist has to make this. There's no way you could have this.

I think what's unusual about the GLP-1s is that they are being used by probably millions of patients, and that's what makes people pause and say, "How is that what was meant by the compounding law?" So, what I wanted to talk about is the evolution of the FDA's oversight.

One thing to mention is that because compounding is a practice of pharmacy, the primary jurisdiction around enforcement and the laws are with the states—specifically state boards of pharmacy—versus the FDA, which really oversees and focuses on manufacturers. Over the years, there has been increased engagement on the FDA's side. Unfortunately, it’s often because bad things happened.

In the late 1990s, I think it was 1997, Congress first passed a law to put in place what are called the 503A pharmacies, which are the more traditional providers. It was on the back end of having a handful of deaths around compounding. The idea behind that law was to try to restrict compounding to what it was really meant to be: individualized prescribing for a patient who really has a need and no alternative.

That law sort of got stalled, and there were a number of provisions. One provision was that you cannot ship more than 5% of what you produce across state lines, for example. That was put in place, and there were also restrictions around the marketing of these products. The provisions for marketing got struck down by the Supreme Court, which put a freeze on the entire law. It wasn't until the New England Compounding Pharmacy debacle—where almost 1,000 patients ended up with meningitis from poorly compounded products—that the FDA and Congress really stepped in. At that time, they said, "You know, we really need to rein in especially sterile compounding and large volume compounding."

What Congress did, though, and I would be curious to hear Connor's perspective, is that instead of saying, "OK, we need to rethink how we're doing this," they created a new category. They left 503A pharmacies alone, took away the problematic marketing provisions, and set up 503B pharmacies that are much more regulated. These pharmacies must register with the FDA, and there is a lot more visibility. They are much more restricted in what they can produce, leaving the 503A pharmacies pretty much untouched. This freed up more because of the marketing component.

Again, there's nothing that goes through FDA approval. The FDA has much more visibility around adverse events from 503B pharmacies, not 503A pharmacies. 503A pharmacies that compound don't even have to register with the FDA—only 503B pharmacies do. The way the FDA conducts inspections is usually based on whether someone is registered and if they have market signals. That's how they decide to inspect somebody. Every 503B pharmacy is registered with the FDA, and they're supposed to be inspected. 503A pharmacies are nowhere to be found on the FDA's website. So even if the FDA wanted to inspect, they might not know where to look.

Again, the responsibility sits with the states, which, from what I understand, are very limited in their capacity to do oversight. But the FDA doesn't have visibility, and they only inspect a 503A pharmacy if there's a problem. So when you go on the FDA's website, you'll see both 503A and 503B pharmacies that have been inspected.

Another challenge is the sheer number of manufacturers. There are many pharmacies, but the number of players involved in compounding makes oversight tremendously challenging. How many pharmacies are there? You guys have 60,000 pharmacies. We don't have nearly as many. So there's a challenge in overseeing it, even if the FDA had the ability, given the resources they'd need.

MODERATOR: Conor, in particular sense there has been a real growth in the use of compounded medicines with the GLP-1s, is Congress taking notice and where is the emphasis? What are you hearing?

CONOR: It's a great question, and I should say before I get into anything substantive, I'm speaking on my own behalf, not on behalf of Senator [NAME], the Senate Finance Committee, or anyone else. I think it's fair to say that with Congress, it is always difficult for any individual topic to get sufficient attention to warrant action. In general, we tend to be a reactive body, especially in the space of healthcare. I think Marta is exactly right to point to the New England Compounding Center catastrophe in 2012; that was really the core impetus for enacting the 2013 legislation. Once that legislation got legs, there was no controversy in Congress. It passed by voice vote in both chambers and was seen as a fairly balanced framework in the early years of implementation.

I think it's fair to say Congress's focus was on overseeing how the FDA was standing up the various prongs of that legislation. The goal was really to ensure that this 2013 legislation prevents another NECC-type case from occurring. Then, can we ensure that the FDA is using the tools we provided in order to balance patient safety? I think in more recent years, part of the challenge is that compounding looks so wildly different in the context of a small business pharmacy, where Congress is not going to want to impose a ton of cumbersome administrative requirements or really costly new reporting, especially because for many of these small pharmacies, it's not as if they have a common line of communication with the FDA. They're not accustomed to that regulatory framework, which is obviously very different from a generic or branded manufacturer, or one of these compounding outsourcing facilities, or a 503B facility.

I think there's been a real reticence on the part of Congress to try to impose additional burdens on 503As while, at the same time, we are constantly nervous about differentiating between good faith actors and bad actors. I think it's fair to say that, along those lines, as Congress looks at this framework that we created, there is no one who doubts that there are good faith actors who are living up to the legislation and the framework we created. The concern is that we have these clear lines in statute, but they're lines that require oversight and enforcement.

So, what happens if you have a pharmacy that is masquerading as a 503A—not that it's interested in skirting the law—but trying to function more like a 503B outsourcing facility? And maybe more to the point, what happens if you have a facility that is nominally a 503B outsourcing facility, but is essentially masquerading as that, trying to function like a generic drug manufacturer, only without the same requirements in terms of an abbreviated new drug application, some of the bioequivalent studies, and testing? Frankly, from a good

manufacturing perspective, you do have to live up to those standards as an outsourcing facility, but there's been a lack of clarity, I would say, even from the FDA on what that looks like in an outsourcing facility versus a generic manufacturer.

So, I think some of these challenges remain, and we are constantly concerned—not about the majority of good faith pharmacists or small businesses—but about bad actors who are trying to go under the radar or skirt their categories. I think one area of concern is just trying to get the energy back around implementation and oversight, which is a core congressional responsibility. Unfortunately, sometimes that does take headline-grabbing issues that are unpleasant.

I think the other issue that's come up in the context of GLP-1s is the advertising and marketing dimension here. Now, I will give a ton of credit to Scott and his trade association for getting out front and trying to be very proactive in terms of the principles of what marketing in this context should look like. There are rules of the road, but I don't think Scott would disagree that there are obviously some actors in this space who have skirted those principles. And again, it's ultimately not on the trade association to regulate the sector—it is on the FDA.

So, I think one congressional area of focus recently has been: can we ensure that the agency holds all sorts of drug makers, including outsourcing facilities, accountable for these advertisements? If I'm Novo Nordisk, or if I'm Eli Lilly, I have to comply with thousands of pages of regulations with respect to any ad that I put on the air. Again, folks may like DTC ads or not; they may be annoyed by them or not, but there's no question we've all seen the text boxes and the dialogue that moves through the various different potential side effects.

I think part of the challenge with the marketing side of this, for Congress, the FDA, and for industry, is that this is a space that is very opaque from the consumer standpoint. If I'm watching TV and I see an advertisement for a drug and it says "side effects may include drowsiness and nausea," I know what that means, I know what that looks like, and I can go to my doctor and have a conversation to decide if this is a product that's right for me. I think the challenge with some of these compounded products, which are essentially carbon copies of traditional drugs that are not meant to be customized, is that you don't see those sorts of warnings or labels on the advertisements.

What I do see is a really low cost, and what I do see, for instance, are ads on my Instagram for oral formulations of GLP-1s. There are companies investing millions of dollars right now on large-scale clinical trials to test and assess the extent to which you can make a safe and effective oral formulation of an effective GLP-1. So, again, when I see ads like that, it does give me pause.

I also think it's fair to say that compounding, in the context of outsourcing facilities, is not supposed to solve a cost or convenience problem; it is supposed to solve a shortage problem. There's no question that we saw massive shortages with respect to tirzepatide and semaglutide, and I think folks can have a good faith debate over how to quantify when something is in shortage, or whether the shortage lists are appropriate. At the same time, I think assertive advertising campaigns marketing compounded GLP-1s as more affordable and equally safe and effective competitors starts to move away from this framework. I just don't think the average patient or consumer knows what pharmacy compounding is or knows what this involves. What they do know is, "Oh, this product looks really attractive to me."

I think we should be looking for any number of different solutions when it comes to combating and preventing drug shortages. I applaud companies that have filled gaps in the past when it comes to those shortage risks. I also think Congress needs to think really carefully about whether this is a tailored solution, or whether we are essentially allowing a market that's not nearly as regulated on the marketing side and may or may not be subject to sufficient oversight on the production side. Are we allowing this to run rampant on our watch? Because I think that's bad for pharmacy compounding as a brand. I think it actually undercuts good faith actors who are. I think about the swine flu—that was a case where compounding was critical for formulations for kids. Are we undercutting them by clouding out the good actors, allowing this to run rampant?

Maybe it's a question of trying to reinvigorate what former commissioner Gottlieb tried to do in 2018, with a clear, transparent plan from the FDA on oversight and enforcement. Or maybe this is a case where Congress needs to revisit this statute and try to strike that appropriate balance again.

So, continuing on that, Joey how does a consumer purchasing an online prescription for GLP one knows the difference between a safe compounded medicine and an unsafe medicine. Do we know how many of these medications are being prescribed? And if there are if there have been any issues and I guess maybe in that answer when you think about oversight, would there be a way for the FDA or others to indicate the difference between a safe compounded or online prescription and maybe one that is dodgier?

JOEY: So, first, let me just address that this isn't necessarily a compounded pharmaceutical issue solely—there’s a bit of correlation, but not necessarily causation. I want to separate that. I do believe, to the first premise of the question, that the consumer has a right to know if the

drug product is exactly what they think it is when they buy it. We've been battling this issue for over 100 years—how do we know you're not selling me some tincture that's been adulterated or messed with? There's a lot of trust involved. When you go into your pharmacy, do you trust the pharmacist? And when the pharmacist buys from a wholesaler, do they trust what the product is? So, what are the checks and balances we have throughout the entire supply chain? Compounders are getting caught up in this, and maybe some of it's their own doing when they aggressively market, but with that said, this is not purely a compounding issue.

I do want to speak on behalf of the compounding pharmacists that I've worked with over the years. They are doing the right thing and are some of the biggest vocal advocates of what's happening in the GLP-1 space. They're saying, "Hey, this isn't us. This isn't what we stand for." So, I think for consumers, the issue is how do we trust what we're getting? We've seen a growing supplement business since the 1990s. If you look at the nutritional supplement sections in your grocery stores and pharmacies, they've exploded in recent years. Similarly, in the weight loss therapeutics space, we see growth everywhere, with more actors coming into the market. Some may be related to compounding, while others are just setting up LLCs and websites to start selling stuff.

So, the real question is: What do we do about it? Is it a federal issue? A state issue? Should we have someone from the FDA involved? Or should it be the licensing boards of pharmacy? I'm licensed to practice pharmacy in three states. I can't call myself a pharmacist in the other 47 states, but I can call myself one in the states where I'm licensed. If I do something in those three states, the board of pharmacy can take action against me. That's a key mechanism. So, we've been battling the question of when should the FDA be involved and when should the states step in?

Now, to your question about how we know how many people are exposed to compounded products—one of the biggest issues is measuring a denominator. Specifically, how do we track how many people are actually getting compounded products? The difficulty arises when patients are paying out-of-pocket, without insurance. For years, we've traditionally used insurance claims to estimate denominators and figure out how many people are getting a drug. When you don't use insurance, though, and pay a cash price, it becomes much harder to track. Many of these compounded products are marketed at a cash price—$200 to $300 a month or on a subscription basis, often mailed directly to you. These are cash transactions, so tracking them is difficult.

We had a similar issue with controlled substances. For many years, drugs like OxyContin, hydrocodone, Lortab, and Vicodin were being diverted in the supply chain. States responded by creating prescription drug monitoring programs (PDMPs), which required all prescriptions to be

monitored. I grew up in Kentucky, where we created one of the first drug monitoring programs, which registered controlled substances from every pharmacy. Maybe this is something we need to explore for compounding—should we talk about prescription drug monitoring programs that include compounded products? That way, we could get a real denominator and track whether products are being purchased with or without insurance. This shouldn't be tied to insurance—it should just be about whether the patient is getting the product or not.

MARTA: One more part of that question—I think that was great. I'd love to chime in and provide an anecdote here. So, you know, does a patient know? A friend of mine told me that she gets semaglutide, and I said, "You know, can you do me a favor and find out where it comes from?" So, she found out which compounding pharmacy was providing it to the medical spa. It's actually a big 503A pharmacy in the state of Utah.

Then I asked her, "Can you get the certificate of analysis for the bulk product?" So, you know, when I was asking her why she was taking this medication, she said, "Well, my doctor who prescribed it to me is taking it, and the nurse at the med spa is taking it. They feel totally comfortable with this."

I said, "OK, can we do a little more homework?" So, she gets me the certificate of analysis, and it comes from a repackager. You can't even see who the manufacturer was on the certificate of analysis—which, by law, is supposed to be listed. That's a red flag right there.

They do have the tests available, and the product says that 15% of the semaglutide—or this sample—is something else that's semaglutide. What is it? I don't know. Then, they do tests for certain bacteria, but the tests they conducted are the ones that the USP would recommend for testing topical products.

This is where I see the issue. So, in a sense, she trusted it because she trusts what her doctor says. Her doctor told her the active ingredient is FDA-approved. She was told by the doctor that the active ingredient is FDA-approved, and then I actually looked at the certificate of analysis for the product. I show it to an analytical chemist, and he says, "Oh my God!"

So, there is this trust issue. You could be following the law, just to talk about what the law says. If you're a bulk manufacturer—and you mentioned this already—you have to follow a USP monograph as a bulk manufacturer, meaning the making of the active ingredient.

To back up, there are two pieces that are really relevant. One is the compounding side: you take the semaglutide powder and mix it in so that it's actually going to be an injectable. That's

what compounding is. But the question is, where does the semaglutide come from, and how is it made? The semaglutide is also not FDA-approved. For semaglutide and all the other GLP-1s, there is no USP monograph.

So, manufacturers that are making it get to decide the recipe for semaglutide. As Scott wants to chime in when she's done, the FDA comes in to inspect and see whether you're following the Good Manufacturing Practices (GMP). You essentially set out your own specifications, and the question is whether you're replicating it right. But there is no external standard for what that specification should be.

There is no USP monograph, no recipe spelled out externally. The manufacturer gets to decide how they're going to make semaglutide, to what extent they'll focus on purity in that context, and what the powdered semaglutide will look like.

SCOTT: Well, then, and to your point, typically with most compounded drugs, there is a USP—that's right. So, there is no doubt about the specifications, the formula, etc. I would argue with semaglutide that, again, I talk with reporters about this all the time. The recipe is on the package insert for the FDA-approved drug; federal law requires that it be on the package insert. So, compounding pharmacies are taking the package insert and utilizing those specs when they create compounded GLP-1s. Again, there is some flexibility there. Do I think that is the best solution? Would I like to see a USP or NF monograph? Absolutely. But there is a recipe; they're not just sort of spitballing.

BACK TO MARTA: So yes, but the recipe looks like this: you know what the chemical compound is. And if you look at small molecules, some are very simple. When you look at something like semaglutide—doctor's appetite—it's a very complex molecule. The FDA decides that a biologic is 40 amino acids or more; appetite is 39. Semaglutide, I think, is 31. I remember working at the FDA, working on the generic drug user fee programs. Manufacturers really struggle coming onto the market when they are making complex molecules because this is where they need a lot of hand-holding with the FDA. Peptides are the example of a complex molecule.

Let me tell you how synthetic manufacturing works because I think it's really important. So, you have the formula, and the way you make semaglutide or some other amino acid like this (it's a chain of 31 amino acids) is you have a resin. You attach one amino acid, then you clear it off. You attach another amino acid, clear it off again, and so on. You end up with a long chain of amino acids. Then, at the very end, you have to detach the resin. There are a lot of reagents and other chemicals that you're introducing in the process. So, yes, you have the formula, but

how well you're going to run the formula and whether you end up with a product with the expected purity profile is a whole different thing.

MODERATOR Scott why don't you give us your last words that I'm going to ask you the next question

SCOTT: Well, and I know that there were several things said that I think require a bit more precision. There are not 60,000 compounding pharmacies in the country, and there are not 15,000 compounding pharmacies in the country.

There may be 5,000 that do some level of compounding, but that might be just two scripts a week where they're putting flavoring in a drug for a child. I would speculate, because numbers are hard to come by, that there are probably 3,000 pharmacies in the country where compounding is 20% or more of their business.

In addition, I know we're about to talk about illicit substances, and I could preach for days about how drug makers are very intentionally conflating the drugs prepared by state-licensed compounding pharmacies with counterfeiting and illicit substances. But let's talk about the fact that we represent legitimate, state-licensed pharmacies.

I think, in some of the conversation here, we are undervaluing the work that state boards of pharmacy do. Connor, I do think it's uneven—some state boards are better at this than others—but tell me another small business, and compounding is a population of small businesses, where you want 3,000 small businesses to report to the federal government.

I just don't think that's workable when the fact is that state boards of pharmacy do inspect regularly, as required by law. It's a condition of licensure, and they generally inspect to FDA guidance. FDA issues guidance for industry documents, and they say these are not enforceable, and FDA does not technically enforce them, but state boards of pharmacy do. So, I would say there's a much more rigorous framework there.

The last thing I want to say, and I'll be brief, is that there's a hierarchy of players here that I think we've all alluded to. There are marketers in this space that are making ridiculous claims. Those aren't pharmacies, those aren't compounders—they're marketers.

There are MedSpas in the space that are making ridiculous claims. Those aren't pharmacies. They may have a contract with the pharmacy, but the pharmacy is not always in control of the marketing claims the MedSpa is making.

I would say the same thing about telehealth platforms. There are telehealth platforms that are model citizens in this space, and there are some that didn't exist a year ago and don't know what the heck they're doing. They are making claims that should raise concerns.

I think that's what we need to get our hands around, and then, all the counterfeiting and illicit activity—that's exactly where we need to focus.

That's exactly the point of this discussion. How do we tell the good actors and bad actors in particular as a patient and what should Congress be doing and asking the FDA to do?
So, Scott, let me give this one to you. You know Senator Banks recently wrote a letter to the acting commissioner of the FDA raising concerns about shipments of the chemicals that make GLP one drugs coming into this country in particular from China and India that aren't getting inspected happened should the FDA be doing to make sure these dangerous drugs aren't coming in the country and being you know distributed to people who may not be aware or maybe possibly the pharmacist isn't even aware I mean talking about how those should be done to keep those substances out of the country.

SCOTT: I think there may be some misunderstanding out there, Mark. You may want to weigh in on this as well, about how the supply chain works. In 99.9% of the cases, state-licensed pharmacies are not ordering API from a drug manufacturer in China or India. They are getting the API from a wholesaler. So, this idea that you've got illicit substances coming in and marked for use in pharmacy compounding, well, I may drive a Corolla and put a sign on it that says it's a Mercedes, but that doesn't make it a Mercedes. Just because they're saying this is for use in pharmacy compounding doesn't mean those drugs are somehow going to state-licensed compounding pharmacies and making their way into drugs that are dispensed to patients. I just don't believe it is happening.

Now, I do believe those substances are coming into the country and they're going to illicit actors. We've got bogus websites, some onshore, some offshore, and for some of them, you don't even need a prescription. Those are a scourge, and we need to work on that. But a state-licensed pharmacy, as Martha has alluded to, they're going to source the API for all their API from a wholesaler. That API is going to come with a certificate of analysis. In many instances, the wholesaler, the middleman, the distributor, will also do additional third-party testing to validate that the drug is what it says it is, at the right potency and purity.

So, that's what comes into the pharmacy. Then, the state-licensed pharmacy, when they are using a new drug that comes from a manufacturer they haven't used before, we urge them (and I know the majority do) to do their own third-party testing of the API to make sure that it is what it says it is, at that potency and purity. Understanding that about the supply chain is important because I think what gets misrepresented here is, you know, you've got the states writing to the FDA saying, "Oh, we're concerned about illicit substances making their way to state-licensed pharmacies." That's not how the system works.

My concern is about how these pharmacies, that are serving their patients with integrity, that are following USP standards to the letter, and that are doing things right, are somehow being swept up in this idea that they may be doing something sketchy or worse, illegal. I don't believe there's a shred of evidence that these substances are making their way to state-licensed pharmacies and then to patients.

MARTA: I just wanted to talk as well. Yeah, so I actually spent some time playing around with the import data that you can see of what's coming into the United States and what kind of semaglutide comes in. One thing you can see is Nova Nordisk shipping semaglutide. That's entirely expected, and they have a major contract manufacturer that makes product for them, Catalent. The vast majority of that is fine. There are some very strange entries, but those are the bad actors. They're small. In my analysis, and I have a paper hopefully forthcoming next week, unless tariffs are going to take up all of my time... um, so what I've been looking at is the set of players that actually are following the rules, meaning they're registered with the FDA and they get an NDC number, and seeing how much shipment there is. My concern there is not that they aren't following the rules. My concern is that the rules are this: "Oh, you inspected? That's right, then you have to." Yes, and a lot of them haven’t been inspected. They have to register with the FDA, meaning you have to tell them that you exist, and you have to have a certificate of analysis on hand. Again, remember, there's no USP monograph for this drug. There is no spelled-out exact recipe and what the purity is supposed to be. You get to decide what the standard is.

So again, it's going to sort of behave like semaglutide, but it's not going to be the same as semaglutide. It might have formaldehyde in it because it's a byproduct of when you remove the product from the resin. That's how formaldehyde ends up in the product. So there isn't this sort of reference. What I see in the data is that some of the players that are registered and presumably have certificates of analysis are shipping tremendous amounts. Again, the FDA often hasn’t inspected them. The data in the imports is self-reported by the importer, so if they

say a certain amount, if I were to actually look at the numbers that they're providing... so just to give you an idea, 1g of semaglutide is 4,000 starting doses. Okay, 4000, 1 gram. I see shipments of 50 kilograms. 1 kilogram is 4 million starting doses, and I see shipments of 50 kilograms. I hope it's wrong, because the numbers are incredibly high, and it is from companies that either got 480 threes that have never been inspected by the FDA. So, you know, they are following the rules, they have COAs, they do have... I think Scott, what I would say is, what you need is to make sure that the bulk is actually the same as the branded product. So that when a compounded pharmacy takes it and makes semaglutide out of this, then you can have full assurance that they got what they should have gotten. The problem is just the way the system is designed, and the oversight that exists doesn't guarantee this. So, even if the compounding pharmacy is following, yes, all of the rules of the road, the problem is there.

CONOR: One thing I think it's worth noting is that whenever we see phenomena that are unusual and that carry concerns or give us pause in the healthcare world, I do think policymakers have a knee-jerk tendency to be reactive. I think that leads to a "whack-a-mole" approach to policymaking. In a lot of these cases, it is useful to look at what the core drivers of these phenomena are. So, I think a perfect example is when Mark Cuban launched his cost-plus model and simultaneously we saw GoodRx gain a lot of traction. Those were symptoms of an insurance problem because patients were facing high out-of-pocket costs under their plans. We were seeing deductibles increase, and we were seeing a shift towards coinsurance. Otherwise, there would have been no appeal for patients to buy outside of their insurance because, again, you're not even getting credit towards your deductible in that case.

So, I think what policymakers should have taken away from that, ideally, is that we need to take a hard look at benefit design and what patients are facing. I think similarly in a case like this, when you look at this substantial surge in GLP-1 from outsourcing facilities, as well as from bad actors and counterfeiters, I think, to me, the big question is: why are consumers going here instead of purchasing the branded drugs through their insurers?

Now, on one hand, it's fair to say there was a substantial shortage. We saw a true uptick in demand, I think, beyond what the manufacturers anticipated. It's actually very rare to have these types of shortages with branded products because they generally are higher-margin products. They generally have this supply and distribution infrastructure, but I think in this case, it's fair to say there was a supply gap that needed to get filled in order to meet the demand.

But now, when you think about the fact that we're continuing to see the marketing of counterfeit products, the marketing of compounded products, and many of their ads are saying,

"Oh my gosh, Novo Nordisk is ripping you off! Eli Lilly is ripping you off with these products," that makes me wonder, why are consumers falling for that? Why aren't they just getting these products through their insurance? The reality is, these are products that have seen significant demand, but they're also products that a number of insurers and public programs don't provide any coverage for, particularly not their indications like obesity. By definition, patients have to operate outside of their health coverage in order to access these products.

Now, we've seen innovation in this space, right? Nova launched the NovoCare pharmacy model and said, "We're going to try to launch a direct-to-consumer model specifically for that cash-pay population." We saw Eli Lilly launch a very similar model around the same time. So, there are private-sector efforts to try to bridge that gap, but the reality is, folks are seeking out avenues to gain access to these products because they know, from the FDA seal of approval and from friends and family, that these products are safe and effective and that they can be game-changing for patients. Yet, through their insurance, they have no access to these products. If you're covered on Wagovi or if you're covered on Semaglutide, you are paying 90% of the time between $0.00 and a $25 copay, but the reality is, a lot of patients lack access.

So, I think for drugs that are still patent-protected, like Semaglutide or like Lugovoy, it's extremely problematic to try to envision policy levers that facilitate patent-breaking competition for those products. That undercuts the entire patent system. If you have products that are still well within their patent lives and we allow massive bulk competition to come to market, whether it's real or counterfeit, we're violating the Hatch-Waxman framework, we're violating PCI, and we are undermining incentives for manufacturers and investors in the future to enter this space.

So, I do think GLP-1s, that's part of the reason they're unique in this context, is like we shouldn't be advocating for or facilitating or making patent-breaking easier outside of a unique shortage situation. But I think the other piece is, with generic products, the question becomes: given how many compounded products are generics... Well, I mean, generics are 90% of prescriptions. They comprise a lot of compounded products. I think we have to ask the question, why would entities want to be a 503B outsourcing facility instead of being a generic manufacturer? What burdens are placed on generic manufacturers that are increasing their costs, such that their margins continue to erode over time? And what incentives can we create for those generic manufacturers to, you know, scale up quality controls? How can we build quality assurances into the system? How can we ensure that we continue to have a steady, strong supply of generic products?

I think if we were able to fix that problem, I actually think you'd see less of a need in many cases, barring shortage situations and rare situations where you need customized,

individualized therapies. You would see less of a need for 503B outsourcing facilities that operate more like generic manufacturers, but without the proper controls. So, I think that's where I want to bifurcate the GLP-1 conversation, where there are really real patent issues and IP issues wrapped up, versus, with respect to the bulk of the products on the market, where I do think it is clearly not sufficiently economically lucrative to bring a generic product to market and supply a low-cost generic drug, especially a sterile injectable, to the market in the first place. That, to me, is the problem that we need to get at, and I think that would actually help to minimize the "whack-a-mole" that we have to do and allow us to target our resources on true bad actors because we wouldn't see as massive of a ground.

MODERATOR: well Joey I would ask you to reply to that and offer your additional commentary on you know what this trend might mean for generic manufacturers and just generally you know this the point of this discussion was the security of the medicine supply so if you could expand on that a little bit

JOEY: Conor really hit on where, but my biggest concern, like, this isn't a compounding-specific thing. This is a history of us, from supply chain. We made a trade-off in the 1960s to allow randomized controlled trials to be the standard to get drugs approved for safety and efficacy. Over the last half century, we've had different steps of regulating these entities and saying what they can say and what they can't say. Some drugs have come to market and have hurt people, and they've gone off the market. I mean, we battle this on a regular basis. But I'll ask you to just follow the money, okay? This is why we can predict what's going to happen over the next five years in this space with no legal intervention. Let's just pretend this is a room of venture capitalists, okay? Maybe something listening on how venture capitalists work. I'm going to give you my Shark Tank, okay? I'm a pharmacist. I'm licensed. I can start a pharmacy and work through the state process to get a pharmacy licensed. I can license that pharmacy and potentially target certain drugs. I have a pharmacoeconomics background. I can actually analyze the top spending drugs. I can see whether we can personalize some of those drugs. If I can acquire those products, the bulk powders, to manufacture or to compound those products in my pharmacy, I could maybe add a vitamin to it, because maybe you're vitamin-deficient as well. I can gain that market share in my pharmacy if I scale it big enough with the right investment. To my VCs in the room, with the right investment, if I scale it, what if I went to Medicare and said, "Hey, Dr. Oz, would you like to lower the spending in Medicare? What if I compounded the top ten drugs that Medicare spent on, and I compounded those for you?"

Why do we even need to negotiate with the drug manufacturers altogether? What if we make them?

So my point is, follow the money. This isn't rocket science. Again, I'm not here to speak on behalf of anyone. Maybe I'll get an investment after this, but I'm not representing any of these groups. I'm just trying to follow the logic of where this is going. This isn't what we intended. Patients are getting caught in the middle. They just want to lose weight, be healthier, and maybe not have to mortgage their house to do so. I've advocated for the drug manufacturers to drop their prices on these specific drugs and maintain market share. The compounders have done a great job testing what the out-of-pocket costs are. There's a lot of data now that says a lot of people will spend $200 to $300 a month. Maybe let's work on that.

So my point is, I appreciate the innovation happening. I think it's pushing us to change, but if we don't do something, this is where I do think government needs to intervene and try to address that. We don't want to follow the money and end up in a space that again—why do we have all this regulation? We started the RCTs in the 60s because children were being born with flipper arms. Thalidomide caused that in the 60s, and we prevented it in the US, thanks to someone at the FDA. Then, again, in 2012, 65 people lost their lives to meningitis. Let's not forget that. I don't want to open my laptop in the morning and read about 5,000 people, or one patient, dying from something we could have prevented. And we won't be able to prevent it all. People will die with an FDA-approved product. It's not necessarily a compounded thing. I just want to stress that this is a broader supply chain issue, but there's a lot of economics involved. Why are we talking about it right now? Well, there's a lot of economics and financing involved. There's a lot of money on the table.

MODERATOR: Thank you so much. Any questions from the audience before we wrap up?

How do we get a different outcome other than some version of regulation that hasn't solved the problems in the past?

JOEY: That's a great question. So, at first, I do think we need to apply the rules that we currently have. Let's also reflect on the spirit of some of these laws. The laws in 2012 were about drug safety—supply chain safety and quality. They weren't meant to create an avenue where, during a shortage, someone could gain market share from a branded drug. That wasn't the spirit of the law. Again, I'm not a lawyer, so how it ends up getting implemented is different. But I think we need to reflect on what the spirit of the law was trying to improve—quality and safety, and prevent harm. I don't know if the DSA would have prevented the New England Compounding Center disaster. Those are things you have to grapple with.

So, how do we do it? If someone is selling drugs in the United States, how do we regulate that? Should it only be the state? States have worked very well. I think state licensing has been effective, but they also rely on budgets. The state budget needs to reflect the individuals who can inspect pharmacies. When I was a pharmacist, I had to be prepared for a board inspection, and if my violations were egregious enough, I could get shut down. You can actually find those instances in your state now. Do we want it to be the FDA? I don't know. It could be, but there are probably arguments for and against, especially when it comes to manufacturers overseas. That's not something we want our states getting involved in, so there's actually a role for the federal government too. We know how to do this; it's whether or not we have the will.

We also have to call out and recognize when there are stakeholders who can gain from loopholes. Part of it is recognizing that there are stakeholders who will take advantage of those loopholes.

CONOR: Oh no, I was just going to say it's also like—see, it's also like we've had successes on this front. To your point, I think about 2012 and that legislation. 2013 too. Since then, we've had FDA inspections. We've had them send letters. They've been involved in well over 100 recalls of products that were implicated by that legislation. The reality is, it's become trendy in certain circles—some circles that have a very vocal voice on FDA policy these days—to treat the FDA as a failed experiment, when in reality, we've seen the FDA facilitate more, especially when joined with private-public partnerships. We've consistently seen safe and effective products come to market that have increased longevity. The reality is, we don't wake up every day to headlines about disastrous cases of widespread fungal meningitis caused by therapy.

I think we should always look to improve these frameworks. What does good implementation look like? I will also say there are tools in the DQSA that could still be used. There was a proposed rule that came out last year to revise and update the "demonstrably difficult to compound" list, which is meant to say, "OK, with respect to certain products, you definitely can't do this if you're a 503A, but maybe you can if you're a 503B." The reality is, whether you love that framework or not, it's a risk-based framework. It strikes me as a responsible tool to leverage in this space.

The last thing I'll say is that federal policy has not had an abysmal track record when it comes to pharmaceutical science and development. Our country has had the best track record in recent decades of any in the world's history. I get that it's convenient for a lot of folks to beat up on the FDA, and I want to be clear, I'm speaking on my own behalf. But it's worth noting that we've put in place a framework. If you were the first generic to successfully file a patent challenge against a branded drug product, you get 180 days of exclusivity on the market. That's a financial economic incentive. Guess what? That legislative framework saw a massive uptick in

generic manufacturers bringing drugs to market. It's not convenient for folks to talk about, but our generic prices are actually lower than other OECD countries, and we have a much higher generic dispensing rate.

So, like, I look at Hatch-Waxman and other compromises that involved economic incentives to try to bring about better policy. I think we need more of that, not less. I don't think we should pretend regulatory policy is always a failure because sometimes it's been successful. Sometimes it's not. And sometimes the sign of success is that mom or grandma didn't get sick from their cancer drug, or that mom, grandma, or dad lived a few years longer than they would have otherwise. It's hard to prove against a counterfactual. We always have these issues in prescription drug debates, but I do want to say that I don't want to throw the FDA or Congress under the bus. The reality is, we could always do better, and we should always try to do better. But I don't think we can definitively say that 2013 legislation has been unhelpful. We can say that the landscape has evolved well.

SCOTT: Speaking for industry, I would say that the 2013 legislation has been extraordinarily helpful. Some of my members might bristle at the very fact that we now have clarity that 503Bs that adhere to current good manufacturing standards can produce compounded drugs in bulk and distribute them to a hospital or a clinic, and recently to a pharmacy. This is helpful. The fact that the FDA has interpreted that to say, if you're a 503A, you can only dispense drugs, you can't distribute drugs, and you need a patient-specific prescription, is important.

I do want to get back to GLP-1 drugs really quickly. Well, we are—this is not a 100-year episode; it's a 1,000-year episode. We've never seen anything like these drugs in our healthcare system before. I think we did see drug makers overhype the drugs on the front end, and that, in part, is what resulted in the shortage. Everybody can hum the Ozempic commercial, right? Then you see prescribers—and we've let them out of this conversation—but nothing happens in a compounding pharmacy until a prescription comes in. We've seen prescribers write for compounded versions of these drugs, providing access to many who otherwise would have had to go without because the drug makers couldn't meet the demand.

Built into this, unfortunately, is the issue of price. It is unusual that the price of this drug is so much less than the FDA-approved drug. Amoxicillin suspension, 20-20-2, had a shortage. Kids were sick and couldn't get the FDA-approved drug. Compound pharmacies stepped in, 503Bs as well, to fill that gap. They held that gap and got that drug for those patients. It was like 100 bucks for one dose for a kid, while the FDA-approved drug was 10 bucks. It's not always that the compounded drug is less, but in this situation, it is.

Given the scale of the shortage, with all these people getting access to this wonder drug at a much cheaper price, we are now in an environment where we're beginning to see price argued as a reason for dispensing a compounded drug in a way that compounded drugs were never intended to be. It positions compounded drugs to look an awful lot like competition for FDA-approved drugs. I would say, if the FDA-approved drug is not available, or the prescriber wants a formulation for a particular patient, that is absolutely within FDA guidance. However, if there are entities—whether legitimate, state-licensed compounding pharmacies, med spas, prescriber compounding, or whatever—that are turning this into a cottage industry for evading the FDA drug approval system, that's a concern. It may adhere to the spirit of the FDA's essentially a copy guidance, or it may adhere to the letter, but I would say it violates the spirit. I don't know that there are a lot of state-licensed pharmacies doing that. They've got formulations coming in from prescribers and they are filling them. But again, price is a concern right now, and it puts us in the odd spot of looking like competition in a way that we don't mean to be.

Thank you so much. END