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COMMENTARY

The Truth About Compounded GLP-1s That Doctors Need to Know

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As a cardiologist specializing in obesity medicine, I often encounter patients who would greatly benefit from the new generation of weight loss drugs that work as glucagon-like peptide 1 (GLP-1) agonists. In the recently published SELECT trial results, for example, semaglutide (marketed by Novo Nordisk as Wegovy for weight loss and Ozempic for type 2 diabetes) demonstrated a 20% risk reduction of heart attacks and strokes in overweight and obese individuals without diabetes and with cardiovascular disease, establishing it as a cardiovascular disease–modifying medication in people without type 2 diabetes.

Unfortunately, the high demand for these new weight loss medications has resulted in a frustrating, long-lasting shortage. The manufacturers of the two FDA-approved drugs, Novo Nordisk and Eli Lilly (tirzepatide, marketed as Zepbound for weight loss and Mounjaro for type 2 diabetes), are struggling to meet the overwhelming need.

To ensure continuation of patient care, federal law allows compounding pharmacies to make "essentially a copy" of the medications that are listed as "currently in shortage" on the US Food and Drug Administration (FDA) drug shortage list. Both semaglutide and tirzepatide are on that list. For Americans who suffer from obesity and other weight-related diseases, these drugs could be a lifeline.

Despite this, the medical community has broadly criticized the utilization of compounded GLP-1 agonists, even those obtained from reputable and legitimate compounding pharmacies.

Yes, high demand has led to the emergence of unregulated companies and scammers producing substandard or counterfeit versions of these medications.

The FDA has found fraudulent products (masquerading as the weight loss drugs) and has issued warning letters to stop the distribution of illegally marketed semaglutide. "These drugs may be counterfeit, which means they could contain the wrong ingredients, contain too little, too much or no active ingredient at all, or contain other harmful ingredients," it cautions. Some products use a similar-sounding semaglutide sodium salt, which has uncertain safety and efficacy, and had generated warnings from the FDA and state boards of pharmacy.

Many of these products are marketed directly to consumers online through websites and social media, with little to no medical oversight. This practice is a significant concern, as it may affect patient safety, and should be discouraged.

However, according to a statement from the Alliance for Pharmacy Compounding (APC), legitimate compounding pharmacies aren't the ones selling these dubious products on the black market, particularly online. This illegal practice has garnered media attention and is sometimes incorrectly associated with legitimate pharmacy compounding.

In contrast, legal and certified versions of GLP-1 agonist medications can be obtained from well-regulated and reputable compounding pharmacies. These pharmacies must adhere to all federal and state regulations and dispense medications only with a valid prescription from a licensed physician.

Meanwhile, the APC statement notes, Novo Nordisk and Eli Lilly have sued compounding companies in several states, questioning, among other things, the purity and potency of some compounded products.

There are different designations for compounding pharmacies: 503A and 503B. 503As are state-licensed pharmacies and physicians, and 503B pharmacies are federally regulated outsourcing facilities that are strictly regulated by the FDA. This regulation, established following a 2012 fungal meningitis outbreak linked to a compounding pharmacy, ensures higher-quality control and oversight, especially for medications intended for intravenous or epidural use. These standards exceed those required for subcutaneous injections like GLP-1 analogs.

In the face of this Wild West climate, where compounded drugs may vary in their source, formulation, potency, and purity, The Obesity Society, the Obesity Medical Association, and the Obesity Action Coalition published a joint statement that advised against the use of compounded GLP-1 agonists, citing safety concerns and lack of regulatory oversight.

This stance, while aimed at ensuring patient safety, inadvertently raises a critical issue.

By completely dismissing compounded medications, experts may unintentionally bolster the black market and overlook the needs of patients who could benefit from these medications, contrary to the intentions of the exemption provided in federal law

for compounding during a drug shortage. In fact, the presence of unreliable suppliers highlights the need to direct the public toward trustworthy sources, rather than imposing a total ban on medically appropriate alternatives.

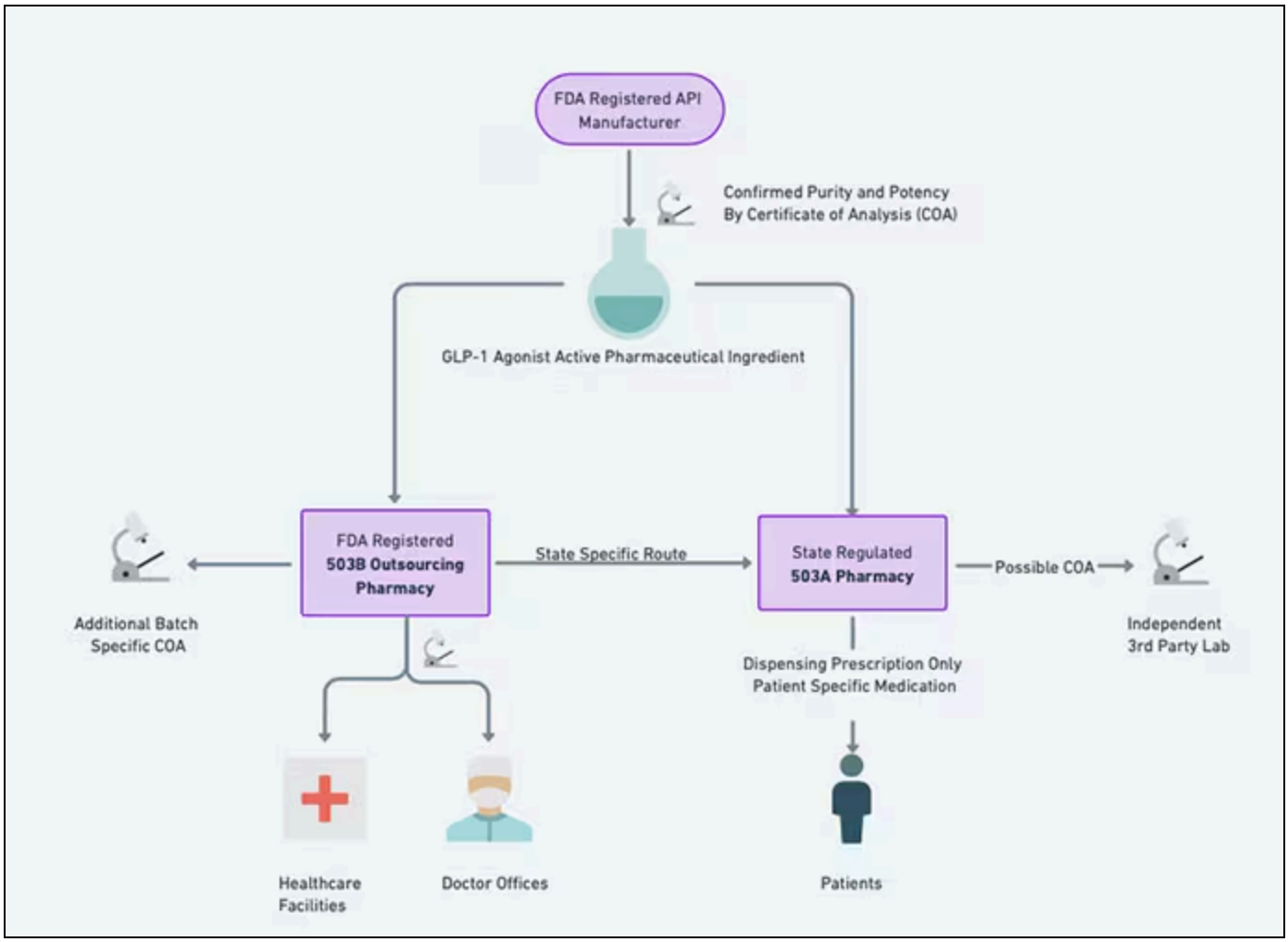
The joint statement calls compounded GLP-1 agonists "counterfeit." This inaccurate overgeneralization probably stems from a misunderstanding of the compounding process and its regulations. Legitimate and regulated pharmacies compound base GLP-1 agonists, which are "essentially a copy" of FDA-approved medications, not counterfeits. Recognizing this is crucial for maintaining trust in both compounding pharmacies and regulatory bodies.

It is correct that "the only FDA-approved manufacturers of these medications are the companies that created the active pharmaceutical ingredients — Novo Nordisk and Eli Lilly," but the joint statement fails to mention the exemptions provided by law that allow compounding copies of the branded medications if they are on the shortage list.

Compounding pharmacies must obtain active pharmaceutical ingredients (APIs) from FDA-registered facilities, which are required to adhere to Current Good Manufacturing Practices (cGMP). This ensures the APIs' quality, potency, and purity, crucial for the safety and efficacy of compounded medications.

Compounded drugs are not FDA-approved, but they aren't inherently unsafe. Compounded medications include critical drugs like resuscitation medications and antibiotics, and are often used in healthcare settings, especially when there's a shortage. This raises the question of why compounded GLP-1 agonists would be treated any differently in such scenarios.

And in the case of alternative drugs for individuals with obesity who have a higher risk for cardiovascular disease, the brand-name FDA-approved alternative may be of more concern than the compounded GLP-1 agonist. The obesity societies advise: "If you cannot find or get access to a GLP-1-based treatment now, there are other treatments available," echoing experts. While the statement doesn't specify the names of the alternatives, experts have advised using alternatives such as Qsymia and Contrave, despite their potential cardiovascular concerns. This recommendation to the public may not represent a responsible risk-benefit analysis.



Rather than outright banning compounded GLP-1 medications, expert associations can contribute to the solution by creating a "seal of approval," recognizing high-quality compounded medications. This would contribute to informed decision-making for clinicians and patients.

Possible Solutions

When prescribing GLP-1 agonists for obesity treatment, doctors should consider all of the following steps to ensure patient safety and effective treatment:

Preference for FDA-approved brands: FDA-approved branded GLP-1 agonist medications should be the primary choice because of their established safety and efficacy.

Risk-benefit analysis for non–FDA-approved products: In cases where FDA-approved options are not available, doctors may consider prescribing a non–FDA-approved copy of the branded medication. Prior to this, conduct a thorough risk-benefit analysis with the patient, ensuring that they are fully informed about the potential risks and benefits of using a non–FDA-approved product.

Choosing semaglutide copies for specific cases: In patients with obesity and cardiovascular disease, the benefits of using a compounded copy of semaglutide, with its cardiovascular disease–modifying properties, may outweigh the risks compared with other FDA-approved antiobesity drugs that might pose cardiovascular risks or compared with no antiobesity treatment at all.

Informed consent and monitoring: When prescribing a non–FDA-approved version of a GLP-1 agonist, obtaining informed consent from the patient is advised. They should be made aware of the differences between the FDA-approved and nonapproved versions.

Choosing between 503A and 503B pharmacies: Prescriptions for non–FDA-approved GLP-1 agonists can be directed to either 503A or 503B compounding pharmacies. However, it's advisable to check whether the product can be compounded by a 503B pharmacy, which is subject to an additional layer of FDA regulation, offering greater quality assurance.

Clear prescription specifications: Ensure that the prescription explicitly states that the compounded GLP-1 agonist should be the base compound without additives.

Requesting a Certificate of Analysis: To further ensure safety, request a Certificate of Analysis from the compounding pharmacy. This provides detailed quality and composition information about the product.

Ongoing monitoring: Continuously monitor the patient's response to the medication and adjust the treatment plan as necessary, maintaining regular follow-ups.

By adhering to these guidelines, doctors can navigate the complexities of prescribing GLP-1 agonists in a way that prioritizes patient well-being, particularly in scenarios where conventional treatment options are limited.

Eldad Einav, MD, is a board-certified cardiologist and a Diplomate of the American Board of Obesity Medicine. He is a fellow of the American College of Cardiology and a member of the Obesity Medicine Association. He serves as the medical director of cardiometabolic health in Guthrie Lourdes in Binghamton, New York, and is the founder of myW8/Cardiometabolic Health located in Beverly Hills, California.

This article solely reflects the personal views of Dr Einav and should not be considered as representing the official stance of Guthrie Lourdes. Dr Einav served as a promotional speaker for Novo Nordisk in 2022. As of now, he has not prescribed any compounded GLP-1 agonist medications in his medical practice.

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