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Frequently asked questions to the 2023 Obesity Medicine Association Position Statement on Compounded Peptides: A call for action

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ABSTRACT

Background: In 2023, the Obesity Medicine Association (OMA) published "Compounded peptides: An Obesity Medicine Association Position Statement." Since this publication, the use of compounded peptides for the treatment of obesity has continued to evolve, leading to additional confusion and questions from obesity medicine clinicians and their patients.
Methods: This frequently asked questions (FAQ) document and "Call for Action" commentary is based upon the existing evidence and practical clinical experiences of the authors.
Results: This FAQ is intended to provide insights beyond the original 2023 OMA Position Statement regarding the use of "compounded peptides" for treating obesity. Three obstacles impair patient access to highly effective peptide anti-obesity medications: insufficient production especially during times of high demand, high costs, and lack of clarity surrounding the role of compounded peptides. Solutions to enhance patient access to these medications lie within the existing legal and regulatory framework and Food and Drug Administration policies. Implementing these solutions necessitates dispelling misinformation and providing clear guidance on the appropriate prescribing and administration of compounded peptides, particularly during times of acknowledged shortage.
Conclusion: Among stakeholders with aligned priorities, challenges can often be overcome by collaboration and communication. Towards the goal of providing patient-centered care, the OMA calls on applicable stakeholders (e.g., pharmaceutical companies, compounding pharmacy organizations, health insurance companies, and the Food and Drug Administration) to work collaboratively to achieve a consensus that improves patient access to safe anti-obesity medications. The purpose of this "Call to Action" is to ask stakeholders to provide clinicians and their patients clarity regarding the role of compounded peptide anti-obesity medications during times of FDA-acknowledged shortages. Finally, this FAQ review provides clinicians with a simple and practical checklist respective to the potential use of compounded peptides.

Introduction

The Obesity Medicine Association (OMA) is the the largest organization of physicians, Nurse Practitioners, Physician Associates/Assistants, and other clinical obesity experts in the United States (i.e., over 5000 members at time of print). The following are frequently asked questions (FAQ) regarding the 2023 OMA publication entitled: "Compounded peptides: An Obesity Medicine Association Position Statement." This follow-up Commentary FAQ concludes with a "Call for Action" such that applicable stakeholders (e.g., clinicians,

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pharmaceutical companies, compounding pharmacists, and the Food and Drug Administration) are unified in ensuring that patients living with the disease of obesity have access to safe and effective anti-obesity medications, even during times of peptide anti-obesity medication shortages.

1. What is the purpose of this compounded peptide FAQ?

In 2023, the OMA published "Compounded peptides: An Obesity Medicine Association Position Statement" [1]. Since this publication, the OMA has received additional questions from OMA members. This FAQ is intended to provide additional insights beyond the original 2023 OMA Position Statement as it pertains to the emerging challenges of "compounded peptides" for treatment of the disease of obesity. The original OMA Position Statement on compounded peptides provides a more detailed background, the fundamentals of compounding, and the history of compounded peptides [1].

2. How do compounded peptides and FDA approved drugs compare regarding FDA oversight?

During the drug approval process, the Food and Drug Administration (FDA) requires rigorous scientific examination of pharmaceuticals to ensure safety and efficacy. This includes oversight of the production of "active pharmaceutical ingredients" (APIs) and regulations on manufacturing to ensure the quality, safety, sterility, and efficacy of FDA-approved medicines. In contrast, compounded peptide anti-obesity medications do not undergo review and approval by the FDA. The FDA has stated that: If your medical needs cannot be met by an FDA-approved drug, a compounded drug might be appropriate. However, compounded drugs pose a higher risk to patients than FDA-approved drugs because compounded drugs do not undergo FDA premarket review for safety, effectiveness, or quality. Compounded drugs should only be used to fulfill the needs of patients whose medical needs cannot be met by an FDA-approved drug" (https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Semaglutide%20Injection&st=c&tab=tabs-1).

3. How accurate are the advertisements from compounded peptide sellers (e.g., medical spas, wellness centers and compounding pharmacies), regarding claims that their anti-obesity drugs are identical to branded or generic anti-obesity medications?

Drug companies invest in the research, development, manufacturing, and attainment of regulatory requirements necessary to attain FDA approval for anti-obesity medications. Applicable patents may include the API composition (i.e., chemical structure), formulation (i.e., crystalline forms, hydrates, complexes), delivery system (i.e., pen), and even therapeutic indications. Prior to potentially becoming generic, the production of patented, branded pharmaceuticals occurs at drug company-affiliated manufacturing facilities. Such manufacturing facilities are expected to comply with rigorous manufacturing standards, may undergo FDA inspections, and are subject to post-FDA audit outcomes such as No Action Indicated (NAI), Voluntary Action Indicated (VAI), or Official Action Indicated (OAI). [U.S. Food and Drug Administration. Overview of Drug Manufacturing Inspections https://www.fda.gov/media/172786/download].

Compounding pharmacies get API from contract manufacturers registered with the FDA. While structurally similar, it is inaccurate (and perhaps unlawful) to refer to a compounded drug by the trade name assigned by the pharmaceutical company owning the patent. It is also inaccurate to claim compounded peptides derived from API represent "generics." Even if a manufacturing facility is approved by the FDA to manufacture generic drugs (https://www.fda.gov/drugs/cder-conversations/generic-drug-approval-process), then at least in the United States, semaglutide and tirzepatide are patented and not yet currently available as generic medications.

4. Are compounded peptides "counterfeit" drugs?

Some have characterized counterfeit semaglutide (Ozempic ®, Wegovy ®) and tirzepatide (Mounjaro ®, Zepbound ®) as a "global-growth industry," with multiple reports of fake semaglutide drug and pens via a complex worldwide network of deception. https://www.vanityfair.com/news/story/counterfeit-ozempic-global-growth-industry#:~:text=%E2%80%9CThey%20wake%20up%20every%20day,enjoyed%20a%20relatively%20serene%20existence.

The National Association of Boards of Pharmacy has concluded that: "Illegal actors are taking advantage of high demand and short supply in

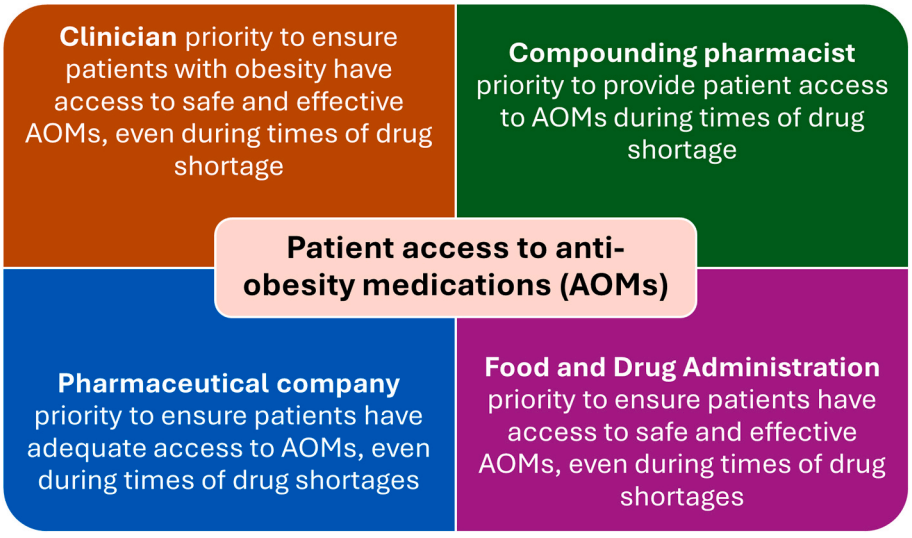

Fig. 1. Universal priority regarding patient access to safe and effective anti-obesity medications. A priority shared by clinicians, compounding pharmacists, pharmaceutical companies, and the Food and Drug Administration should be to ensure that patients have access to safe and effective anti-obesity medications, even during (temporary) times of drug shortage.

Fig. 2. Illustrative stakeholders integral to establishing clear guidelines for use of compounded peptides, such as glucagon-like peptide-1 receptor agonists (GLP-1 RA).

order to sell substandard and falsified versions of these products to patients around the world."

https://nabp.pharmacy/wp-content/uploads/2024/04/RogueRx-Activity-Report-Injectable-Weight-Loss-Drugs-2024.pdf.

The World Health Organization (WHO) has identified specific falsified batches of semaglutide (Brazil in October 2023; the United Kingdom of Great Britain and Northern Ireland in October 2023; and the United States of America in December 2023) [https://www.who.int/news/item/19-06-2024-medical-product-alert-n-2-2024–falsified-ozempic-(semaglutide)]. In response, the WHO has provided guidance to identify falsified products that includes the following.

- Check the Lot Number and Serial Number
- Examine the Pen
- Assess the Label Quality
- Look for Spelling Mistakes

Similarly, according to the FDA, compounded semaglutide and tirzepatide products may be marketed illegally (e.g., primarily through the internet or social media). The FDA has issued an alert regarding reports of overdosing errors associated with compounded injectable semaglutide products, which have resulted in adverse events and hospitalizations (https://www.fda.gov/drugs/human-drug-compounding/fda-alerts-health-care-providers-compounders-and-patients-dosing-errors-associated-compounded). Additionally, the FDA has reported cases where illegally marketed glucagon-like peptide-1 receptor agonists may "contain the wrong ingredients, contain too little, too much or no active ingredient at all, or contain other harmful ingredients" (https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/medications-containing-semaglutide-marketed-type-2-diabetes-or-weight-loss).

In response, the Alliance for Pharmacy Compounding issued a "Statement on rules governing compounding, what FDA guidance says about permissibility of compounding 'essentially a copy' of an FDA-approved drug –and what those have to do with semaglutide." https://a4pc.org/files/APC-Compounding-Semaglutide-Media-Brief-REVISED-October-10-2023.pdf. This statement describes the benefits of compounding, what can be compounded, patent issues, and consumer tips that include.

- Don't buy any substance purported to be semaglutide from an online entity if you do not have a legitimate prescription from a licensed prescriber and/or you cannot verify that the seller is a licensed U.S. pharmacy.
- If you are prescribed compounded semaglutide by a doctor or other healthcare professional and are not choosing the dispensing compounding pharmacy yourself, then ask about the name of the compounding pharmacy, where it's located, and whether it is licensed to dispense or ship to your state. Much of this information can be verified online – via the website of the state board of pharmacy in which the pharmacy is based.
- If you want greater assurance that what you are being dispensed is in fact what the label says it is, you can ask the pharmacist to show you the Certificate of Analysis and any results from an analytical testing lab which can help confirm the identity of the drug dispensed to you.

Additionally, while the WHO and FDA have identified falsified and illegal compounded peptides, the original "Compounded peptides: An Obesity Medicine Association Position Statement" [1] acknowledged the general practice of compounding of pharmacotherapies as an established and accepted practice in the United States:

> " 'Compounding' by a pharmacist or pharmacy is the custom formulation of a medication to fit a unique patient's need, not otherwise met with a commercially available medicinal product. A goal of compounding is to potentially enhance tolerability and/or adherence. Compounding can be defined as 'the preparation, mixing, assembling, altering, packaging, and labeling of a drug, drug-delivery device, or device in accordance with a licensed practitioner's prescription, medication order, or initiative based on the practitioner/patient/pharmacist/compounder relationship in the course of professional practice' "

Thus, while true that FDA-approved drugs and doses should be the first choice in clinical practice, and that falsified and illegal compounded peptides are reported to exist, it is also true that patient-centered solutions may arise where alternative formulations are in the best interest of the patient. These drugs are not considered substitutes, because a compounding pharmacy cannot replace (i.e., "substitute") a prescription written for an FDA-approved drug with a compounded drug.

5. Has the FDA banned compounded peptides?

The FDA has ***NOT*** banned compounded drugs. In fact, the FDA has issued guidance regarding "Drug Compounding and Drug Shortages" (https://www.fda.gov/drugs/human-drug-compounding/drug-compounding-and-drug-shortages):

> "Depending on the circumstances, compounded drugs can be made and distributed with fewer restrictions when the drug appears on FDA's drug shortages list… Compounded drugs must meet a variety of conditions to qualify for exemptions from certain federal requirements that typically apply to drugs. When a drug appears on FDA's drug shortages list, some of these restrictions may be lifted – in particular, restrictions on compounding drugs that are essentially copies of approved drugs. However, other conditions remain, and compounded drugs may not be able to meet these. In some cases, FDA has issued temporary policies for a specific drug in short supply or experiencing increased demand to increase the supply of compounded drugs. For example, in January 2023, with three viral epidemics affecting the United States, FDA issued temporary guidance on compounding ibuprofen oral suspension to bolster the supply of this drug used to treat children's pain and fevers. FDA also issued

temporary guidance on compounding amoxicillin oral suspension in November 2022 in response to high demand for this drug used to treat bacterial respiratory infections in children."

A statement of note in the above is: **"When a drug appears on the FDA's drug shortages list, some of these restrictions may be lifted – in particular, restrictions on compounding drugs that are essentially copies of approved drugs."** Some of the confusion regarding the FDA stance on compounding may be attributable to the definition of a "biologic." As noted in the in the original "Compounded peptides: An Obesity Medicine Association Position Statement" [1]:

"Many anti-obesity medications can be classified as small molecules (e.g., sugars, lipids, amino acids, fatty acids, phenolic compounds, or alkaloids) or biologics (mostly polypeptides). If anti-obesity medication polypeptides are <40 amino acids, then they are no longer considered a "biological product" by the FDA. If pharmacists and pharmacies compound anti-obesity medication polypeptides with <40 amino acids in a way that may be perceived as an attempt to replicate patented therapies, and if the source compound is not legally purchased for compounding, then this may be in violation of standards set by the FDA; … compounding does not include making copies of commercially available drug products, as this is not allowed by law."

Because their chemical structure is < 40 amino acids, semaglutide and tirzepatide are not considered biologics. It may therefore seem that the FDA has taken the position that pharmacies cannot lawfully make copies of these smaller peptides. However, the FDA has explicitly noted circumstances when semaglutide can be compounded (https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/medications-containing-semaglutide-marketed-type-2-diabetes-or-weight-loss):

"When a drug is in shortage, compounders may be able to prepare a compounded version of that drug if they meet certain requirements in the Federal Food, Drug, and Cosmetic (FD&C) Act. As of May 2023, Ozempic and Wegovy are both listed on FDA's Drug Shortages list." (Note: Ozempic and Wegovy are semaglutide).

Thus, once a drug is on the FDA drug shortage list, the FDA may lift restrictions on compounding drugs that are "essentially a copy" of the FDA-approved therapeutic. In such circumstances, the API of semaglutide and tirzepatide may be made available via compounding – albeit often in a different formulation (i.e., vial form) as opposed to prefilled injection device (i.e., pens). That said, tirzepatide is an example of a branded GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist whose prescribing information states that in the U.S., tirzepatide can be administered as a single-dose pen or single-dose vial. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217806s003lbl.pdf. The challenge here is that, even if listed in the Prescribing Information, single dose pens or single-dose vials may not always be available.

6. If compounded peptides are often so easily made by compounding pharmacies, then why don't pharmaceutical companies (whose patented drugs are in acknowledged shortage) simply make more drug?

When the FDA approves a drug, it approves the API as well as the entire formulation, often including the delivery device. If an FDA-approved drug is approved only via a pen, then to get FDA approval for these drugs to be dispensed in vials, the pharmaceutical company would need to undergo additional testing and regulatory processes to demonstrate bioequivalence. For example, the prescribing information of tirzepatide states it is available as a "single-dose pen or single-dose vial." https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217806s003lbl.pdf.

In making the decision to offer a vial formulation, it is possible that the drug supply of the peptide injectable device formulation would be resolved before the vial formulation development program was completed and subsequently approved by the FDA. Conversely, especially when a clinician prescribes a peptide medication to a 503A pharmacist (see section 9 below) during times drugs such as semaglutide pens are in short supply, then the compounding pharmacy may create and sell semaglutide in a vial delivery formulation (https://www.hellokclarity.com/post/compounded-semaglutide/) to meet the timely needs of the patient.

7. According to the FDA, are compounded drugs bioequivalent and/or biosimilar to the branded drug?

Compounded drugs do not undergo evaluation by the FDA. Thus, the FDA does not determine if compounded drugs are bioequivalent. The

Table 1
Clinician checklist for use of compounded peptides. Clinicians who prescribe compounded drugs should have documentation of due diligence in ensuring safety, efficacy, and lawful regulatory practices.

✓ Is the "active pharmaceutical ingredient" (API), dosage, and the specific mode of delivery (e.g., oral, injectable, sublingual), currently on the FDA drug shortage list?
✓ Is the source of the compounded peptide a 503A compounding pharmacy or a 503B outsourcing facility? Knowing the type of pharmacy allows clinicians better insight regarding sourcing, safety, and regulatory compliance. For example, 503A pharmacies require a prescription and produce individually tailored formulations, while 503B outsourcing facilities can produce and distribute drugs with or without a prescription and distribute large batches of drugs that are on the FDA drug shortage list or that appear on the 503B Bulk Drug Substance list.
✓ What is the name and affiliation of the licensed pharmacist who will be compounding the API?
✓ Are both the compounding pharmacist and compounding pharmacy licensed to dispense or ship pharmaceuticals respective to the state of patient residence? *
✓ Is the pharmacy accredited by the Pharmacy Compounding Accreditation Board?
✓ Is the manufacturing facility providing the API to the compounding pharmacy registered with the FDA (with the potential to undergo FDA inspections) and does the facility undergo periodic third-party verification of API safety and purity?
✓ Does the prescribing clinician have a copy of the "Certificate of Analysis"?
✓ Does the compounding pharmacy periodically send a batch of received API for third-party testing, to ensure an independent assessment of sterility, potency, stability and lack of endotoxins and impurities?
✓ Does the prescribing clinician have documentation that the patient underwent an informed consent process, and signed an informed consent document, agreeing to be treated with compounded therapeutics?
✓ If the compounding pharmacy claims that their compounded peptide is a "generic" formulation of a branded pharmaceutical, then did the compounding pharmacist provide the prescribing clinician verification of bioequivalence studies, published in reputable medical journals, and approval by the Food and Drug Administration?
✓ If a clinician or a compounding pharmacist is involved in the prescribing, creation, and administration of a compounded peptide that is not on the FDA drug shortage list, then did the clinician and/or compounding pharmacist notify their respective malpractice carriers to determine the extent claims would be covered, in the event a patient had an adverse health outcome to a non-FDA-approved therapeutic intervention?
✓ Did the clinician and patient consider alternative options for access to anti-obesity peptide medications, such as through pharmaceutical-sponsored programs, employer-sponsored health plans, other private/government health insurance plans, and/or other organizations?

* Not all states require a non-resident pharmacist to be licensed in their state. All states, except Massachusetts, require non-resident licensure of a pharmacy to ship into their state.

FDA does sometimes evaluate the "bioequivalence" of drug products (such as some generic formulations) that have similar drug availability and action (e.g., similar absorption, distribution, metabolism, and excretion). But since compounded semaglutide and tirzepatide are not generic medications, this process does not apply to these compounded peptides. In 2021, the FDA issued a Guidance Document regarding recommendations to applicants planning to include bioequivalence (BE) information in abbreviated new drug applications (ANDAs) and ANDA supplements. [U.S. Food and Drug Administration. Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bioequivalence-studies-pharmacokinetic-endpoints-drugs-submitted-under-abbreviated-new-drug].

It is also sometimes claimed that compounded pharmaceuticals are "biosimilar." However, biosimilar drugs are usually biologics that are large and complex molecules produced from living organisms that are molecularly like a reference product. Biosimilars are evaluated by the FDA to ensure consistent quality, purity, and bioactivity. In contrast to compounded peptides that do not undergo FDA evaluation and testing, FDA-approved biosimilars must meet FDA standards, must be manufactured by FDA-licensed facilities, and must undergo post-marketing surveillance to ensure safety. https://www.fda.gov/media/108905/download.

In short, compounded drugs do not undergo bioequivalence studies overseen by the FDA, nor do they meet the FDA standards required of "biosimilars." However, as part of best practices, compounding pharmacies should receive a "Certificate of Analysis" of the API upon its receipt from the manufacturing facility. The compounding pharmacist may additionally send a portion of the batch API received for periodic, independent, third-party testing, to ensure sterility, potency, and lack of endotoxins and impurities.

8. Are semaglutide and tirzepatide listed on the Food and Drug Administration (FDA) drug shortage list?

The FDA drug shortage list frequently and rapidly evolves. At the time of this writing, certain doses of FDA-approved semaglutide medications (Ozempic ®, Wegovy ®) remain on the FDA drug shortage list (https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm). For example, regarding semaglutide for obesity (Wegovy ®), 0.25, 0.5, and 1 mg doses are listed as limited availability but the 1.7 and 2.4 mg doses are listed as available on the FDA Shortage List. Conversely, all doses of tirzepatide (Zepbound ® and Mounjaro ®) are listed as available (https://supply.lilly.com/zepbound; https://supply.lilly.com/mounjaro). Even though some of these drugs and/or their doses are on the FDA drug shortage list, compounded formulations such as semaglutide salts (i.e, semaglutide sodium or acetate) are not on the FDA drug shortage list, which at least partially explains why many compounding pharmacies no longer compound semaglutide salts.

Over 100 drugs are listed by the FDA as currently undergoing a drug shortage. Historically, compounded drugs have often represented a solution in filling an otherwise unmet need for individual patients. It is the co-occurrence of drug shortage and high demand, as well as other factors such as social media messaging, societal bias, body image stigma, and increasing recognition of obesity as a disease that helps explain why highly effective anti-obesity medications such as semaglutide and tirzepatide have an especially high potential for misuse.

9. What are 503A compounding pharmacies and 503B outsourcing facilities"? [2]

In 2012, a fungal meningitis outbreak was linked to contaminated compounded corticosteroid injections. The supervisory pharmacist who supplied this compounded drug was subsequently convicted of: "racketeering, racketeering conspiracy, mail fraud and introduction of misbranded drugs into interstate commerce with the intent to defraud and mislead" in connection with this fungal meningitis outbreak that led to the death of 64 patients and infection of 793 patients. [*U.S. Food & Drug Administration. January 31, 2018: New England Compounding Center Pharmacist Sentenced for Role in Nationwide Fungal Meningitis Outbreak.* https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/press-releases/january-31-2018-new-england-compounding-center-pharmacist-sentenced-role-nationwide-fungal *].*

Subsequently, two types of compounding pharmacies were designated.

A 503A compounding pharmacy fulfills individual, patient-centered prescriptions. A 503A pharmacy is optimally staffed by a licensed pharmacist who complies with state board regulations, and who utilizes active pharmaceutical ingredients that are manufactured by a FDA - registered facility and accompanied by a Certificate of Analysis. According to an October 10, 2023 letter from the *U.S. Food & Drug Administration* to the National Association of Boards of Pharmacy [

U.S. Food & Drug Administration. Semaglutide National Association of Boards of Pharmacy https://www.fda.gov/media/173456/download?attachment#:~:text=Semaglutide%20salts%20do%20not%20appear,on%20FDA's%20drug%20shortage%20list.&text=Semaglutide%20is%20a%20component%20of,on%20FDA's%20drug%20shortage%20list]:

> "Specifically, under section 503A (which applies to drugs products compounded outside an outsourcing facility registered by FDA, e.g., by licensed pharmacists in a State licensed pharmacy or a Federal facility, or by licensed physicians), the drug product must be compounded using bulk drug substances that (1) comply with the standards of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph, if a monograph exists, and the USP chapter on pharmacy compounding; (2) if such a monograph does not exist, are components of drugs approved by FDA; or (3) if such a monograph does not exist and the bulk drug substances are not components of a drug approved by FDA, appear on a list developed by FDA through regulations (the 503A Bulks List). Semaglutide salts are not the subject of an applicable USP or NF monograph, are not components of an FDA-approved drug product, and do not appear on the 503A Bulks List."

503B outsourcing facilities produce and distribute large batches of compounded drugs that are on the FDA drug shortage list or appear on the 503B Bulk Drug Substance list. As opposed to 503A compounding pharmacies, 503B compounding pharmacies can prepare medications without a patient specific prescription. Again, according to the same October 10, 2023 letter from the *U.S. Food & Drug Administration* to the National Association of Boards of Pharmacy:

> "For compounded drug products to qualify for the exemptions under section 503B, they must be compounded in an outsourcing facility that does not compound drugs using bulk drug substances unless the bulk drug substance (1) appears on a list established by FDA identifying bulk drug substances for which there is a clinical need (the 503B Bulks List), or (2) the drug compounded from such bulk drug substances appears on FDA's drug shortage list at the time of compounding, distribution and dispensing. Semaglutide salts do not appear on the 503B Bulks List, nor do products containing semaglutide salts appear on FDA's drug shortage list."

10. What safeguards are in place to mitigate the potential compromise of efficacy and safety issues of compounded peptides?

Three processes that may help mitigate potential compromise of the efficacy and safety of compounded peptides include.

a The production of the API provided to the compounding pharmacist should be by an FDA-registered manufacturing facility, which

undergoes periodic inspection by the FDA, state boards of pharmacy, and other regulatory agencies. It is suggested that some API provided to compounding pharmacies may be from the same FDA-registered manufacturing facilities used by pharmaceutical companies. https://www.npr.org/2024/05/30/nx-s1-4973307/compounding-pharmacies-are-making-their-own-versions-of-blockbuster-weight-loss-drugs#:~:text=SCOTT%20BRUNNER%3A%20Pharmacy%20compounders%20are,that%20the%20drug%20manufacturers%20use. That said, pharmaceutical manufacturers of glucagon-like peptide-1 receptor agonists often do not directly sell such drugs for use in compounding.

b As part of quality assurance, a "Certificate of Analysis" must accompany the receipt of the API by the compounding pharmacy. https://www.artsyltech.com/certificate-of-analysis#:~:text=The%20purpose%20of%20a%20Certificate,required%20quality%20standards%20and%20specifications. A Certificate of Analysis helps verify the API's quality, safety, and compliance with regulations.

c The compounding pharmacy should adhere to best practices. The compounding pharmacy should engage in compounding processes compliant with federal, state, and local regulations. Another best practice is for the compounding pharmacy to periodically send a batch of received API out for third-party testing, to ensure sterility, potency, and lack of endotoxins and impurities.

11. Once FDA-approved anti-obesity peptide medications are no longer on the FDA drug shortage list, will compounding pharmacies still be able to supply compounded versions of these medications?

The current rationale for a compounding pharmacy to supply compounded versions of some anti-obesity peptide medications is because they are on the FDA drug shortage list. When these AOM are no longer on the FDA drug shortage list, then the justification no longer exists, and (presumably), compounding pharmacies will discontinue production. However, even when no longer on the FDA drug shortage list, some physicians may determine that combination products, doses different than FDA-approved formulations, or preservative-free formulations, may be more appropriate for certain patients and provide clinically meaningful benefits. Identifying the circumstances when such a decision might best occur, and determining the clinical benefit of combining semaglutide or tirzepatide with additives such as vitamin B12 (which currently lacks proven clinical evidence) is beyond the scope of this commentary.

12. Are the interests of obesity medicine clinicians, compounding pharmacists, pharmaceutical companies, and the Food and Drug Administration in conflict or in alignment?

If, based upon scientific evidence, a clinician determines that highly effective anti-obesity medication peptides are in the best interest of their patients with obesity, then the objective of the clinician and applicable stakeholders should be to maximize patient access to the safest and most effective AOMs (See Fig. 1). Thus, during times of AOM drug shortage, obesity medicine clinicians, compounding pharmacists, pharmaceutical companies, and the FDA should all be aligned toward ensuring patient access to safe and effective care that is in the best interest of patients.

13. What have pharmaceutical companies done to help ensure the safety of compounded, highly effective anti-obesity medications?

Unless explicitly stated otherwise, pharmaceutical companies have no research, manufacturing, or distribution relationships with compounding pharmacists. Therefore, it would be challenging to imagine a situation where a pharmaceutical company would have legal liability regarding compounded peptides that are manufactured and distributed without its involvement. Pharmaceutical company manufacturers of the two most common compounded peptide, anti-obesity medications (i.e., Eli Lilly for tirzepatide and Novo Nordisk for semaglutide) have taken actions that include suing certain spas, clinics, and pharmacies over "copycat" drugs. https://www.reuters.com/business/healthcare-pharmaceuticals/wegovy-maker-novo-nordisk-sues-nine-spas-clinics-pharmacies-over-copycat-drugs-2024-05-30/In fact, while this news report acknowledged that "legitimate compounded drugs should not be confused or conflated with counterfeit or sub-par substances created by entities looking to exploit patient demand," at the time of this writing, it was reported that Novo Nordisk had filed 21 lawsuits, with accusations that.

- Non-FDA-approved compounded drugs claiming to contain semaglutide with high levels of known impurities and unknown impurities pose significant risks to patients and may lead to serious and life-threatening reactions.
- Some companies were selling products claiming to contain semaglutide directly to patients without any prescription from a medical professional.
- Some companies were selling products claiming to contain semaglutide at standard doses, but which contained minimal to no active drug.
- Some companies sold products containing impurities up to 24 %, including formaldehyde adduct, dimers, and other unknown impurities.

Novo Nordisk has also provided updated information on responsible use of semaglutide and "latest compounding and counterfeit information" and "our position on responsible use" (https://www.novomedlink.com/semaglutide/medicines.html).

Similarly, Lilly has also reportedly sued several medical spas, weight-loss clinics and compounding pharmacies. In addition, in June 2024, Eli Lilly issued: "An Open Letter From Eli Lilly and Company Regarding Certain Practices Related to Mounjaro® and Zepbound®" (https://investor.lilly.com/news-releases/news-release-details/open-letter-eli-lilly-and-company-regarding-certain-practices). This online letter in the public domain extensively discusses inappropriate use, unsafe online and social media ads, fake or unsafe compounded products, and identifying "genuine Lilly Products." Some of the essential points of this letter regarding branded tirzepatide (Mounjaro® for type 2 diabetes mellitus and Zepbound® for patients having overweight with increased adiposity complications or obesity) include.

13.1. Unsafe online posts, videos, and ads put people at risk

- The use of tirzepatide should be restricted to the indicated use and not used for cosmetic weight loss.
- Illegal online pharmacies "sell substandard and falsified versions" of incretin medications and put people at risk.
- People should never put products labeled "research purposes only" or "not for human consumption" into their bodies.
- Social media is not a replacement for a healthcare professional.

13.2. Non-Lilly tirzepatide can put people at risk

- Fake products designed to look like Lilly's medicines put people at risk.
- FDA recognizes that compounded drugs pose a higher risk than FDA-approved medicines.
- Compounded versions of tirzepatide can put people at risk.
- Online ads may be inaccurate or misleading.
- Patients/clinicians are encouraged to help stop illegal sales by reporting suspected fake or unsafe "tirzepatide" products.

Additionally, Lilly has posted a website entitled: "Protect Yourself

Against Counterfeit, Fake, and Unsafe or Untested Compounded Products." https://www.lilly.com/safety/real-medicine.

Among the topics included.

- What are the risks of counterfeit or fake products?
- How significant of a problem is counterfeiting?
- How do I know if my medicine is counterfeit or fake?
- What are the risks of compounded products?
- Is there evidence of counterfeit tirzepatide products?
- Is there evidence of unsafe or untested compounded tirzepatide?
- Should I believe advertisements about compounded tirzepatide products?
- What is "research purposes only" tirzepatide?
- How to report counterfeit products?

14. Conclusion: what guidance can the Obesity Medicine Association provide for clinicians who prescribe compounded anti-obesity medications and how can the Obesity Medicine Association help improve access to AOMs during times of peptide anti-obesity medication shortages?

During times of AOM shortages, defined as being listed on the FDA drug shortage list respective to a specific AOM, dose, and formulation, and if stakeholders (Fig. 2) determine that compounded peptides are in the best interest of the patient, then the process of compounded peptide use should proceed in a manner consistent with patent laws and ethical prescribing. Clinicians should have a bona fide relationship with the patients and should ***NOT*** prescribe compounded peptides solely: (a) to avoid a prior authorization process for the branded formulation, (b) to derive profit or "kickbacks" in return for prescriptions, (c) to use the medication "off label" without sufficient evidence for efficacy and safety regarding the use for this purpose; (d) to avoid FDA oversight; (e) for convenience of administration; (f) to cut costs by choosing a lesser quality compounding pharmacy, potentially increasing safety risks to the patient. Additionally:

- A clinician who prescribes, and/or compounding pharmacist who sells, compounded anti-obesity medications assumes the responsibility of the content, quality, and safety of the API to be administered. Clinicians can become more informed by interviewing the applicable pharmacist about staffing, training, and compounding procedures.
- The Obesity Medicine Association does not recommend for, or against, compounding peptides. That said, Table 1 provides a checklist for clinicians who prescribe compounded drugs, which may better ensure documentation of due diligence in ensuring adequate informed consent, safety, efficacy, and lawful regulatory practices.
- The OMA calls on the major stakeholders to work together regarding the establishment of clear guidance pertaining to compounding peptides for the purpose of treating patients with obesity, especially during times of drug shortages (see Fig. 2).

Author contributions

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Declaration of artificial intelligence

Artificial intelligence was used to gather research for this submission. Artificial intelligence was not used to write this manuscript and the authors accept responsibility for the manuscript content.

Declaration of competing interest

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AKF has participated on advisory boards for Jenny Craig, Novo Nordisk, Eli Lily, Sidekick Health, and Vivus.

CFB has served as a speaker for Eli Lilly, has investments in Eli Lilly and Novo Nordisk.

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LCA has consulted for the Novo Nordisk Obesity Advisory Board and is on the Speaker's Bureau for Eli Lilly.

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