Nomination of Semaglutide Products to the Demonstrable Difficulties for Compounding Lists

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Complexity of Formulation

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The Formulations Used for Compounded Semaglutide Expose Patients to Safety and Effectiveness Risks

Semaglutide Bulk Drug Substance Used in Compounding

- Synthetic Semaglutide and Its Impurity Profile
- Factors Impacting Semaglutide's Physical and Chemical Instability
- Semaglutide's Fatty Acid Modifications

Compounded Semaglutide Drug Product: Co-Active Ingredients

- Varied, including BPC-157, NAD+, Levocarnitine, Cyanocobalamin, Glycine, Chromium PIC
- Semaglutide-Co-Active Interactions with BPC-157 and NAD+

Compounded Semaglutide Drug Product: Inactive Ingredients

- Missing absorption enhancer like SNAC
- Liposome Technology

Safety and Effectiveness Risks

Note: The semaglutide bulk drug substance used by compounders is not the same semaglutide used in Novo Nordisk's FDA-approved medicines. For the purposes of this nomination, we will refer to these products as semaglutide, even though these bulk drug substances are meaningfully different than Novo Nordisk's semaglutide.

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Compounders Use Synthetic Semaglutide in their Compounded Drugs, Which Introduces Complexities and Exposes Patients to Safety and Effectiveness Risks

Semaglutide in FDA-approved products is **recombinantly expressed** in yeast

Semaglutide in compounded products is **synthetically produced**

Synthetic semaglutide used in compounding has a **different impurity profile** than recombinantly expressed semaglutide

- Testing results reveal various **types and quantities of impurities**

Differences in impurity profile pose safety and effectiveness risks, including **immunogenicity risks**

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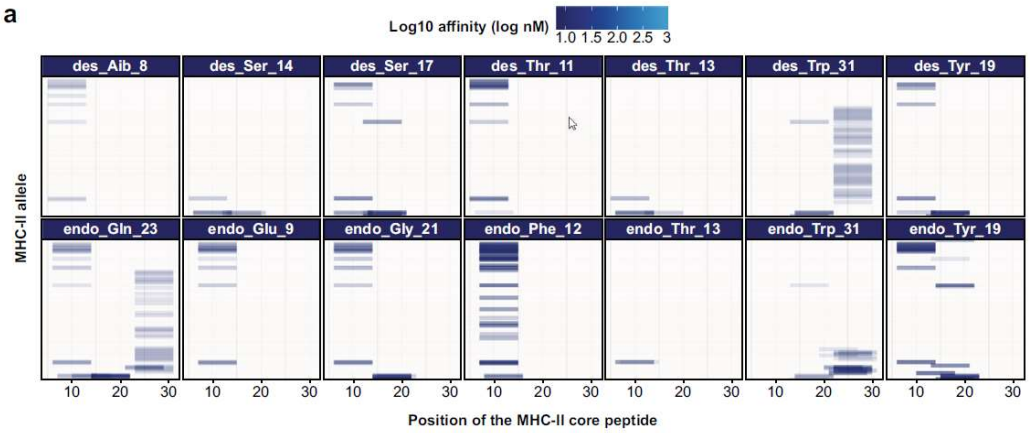
Testing of Bulk and Compounded Semaglutide Revealed Peptide-Related Impurities Not Present in Recombinantly Expressed Semaglutide Used in FDA-Approved Medicines

For example:		
Peptide Backbone	Peptide modifications, such as tert-butyl protection groups	Peptides with amino acid additions and deletions, such as Des Thr and Endo Phe

The above peptide-related impurities can lead to ***immunogenicity*** and a ***shortened half-life*** for the semaglutide in compounded drugs.

In silico Analysis Predicts Peptide-Related Impurities in Bulk and Compounded Semaglutide Pose Immunogenicity Risks

Predicted MHC II-Binding Neoepitopes For the Backbone Sequence of Impurities



Each bar represents a distinct peptide in the backbone sequence (X-axis) and its binding affinity to a given MHC-II allele (Y-axis)

- *In silico* analysis suggests that the peptide-related impurities with amino acid additions and deletions present in the synthetic semaglutide drug substance used in compounding and the compounded semaglutide products have the potential to be immunogenic
- Several of the peptide impurities found in the synthetic semaglutide drug substance used in compounding and compounded semaglutide are predicted to bind to HLA Class II on antigen presenting cells activating antigen-specific T cells and B cells and the production of antidrug antibodies
- *In silico* analysis (using NetMGCIIpan 3.1) identified potential T cell epitopes for peptide sequences with the deletion of Aib-8, Ser-14, Ser-17, Thr-11, Thr-13, Trp-31, or Tyr-19, or the addition of Gln-23, Glu-9, Gly-21, Phe-12, Thr-13, Trp-31, or Tyr-19

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The Differences between Manufacturing Synthetic and Recombinantly Produced Semaglutide and the Differences between Manufacturing FDA-Approved Semaglutide Medicines and Compounding Synthetic Semaglutide Drugs Can Impact Physical and Chemical Stability

Differences in semaglutide manufacturing can result in differences in ***trace metals*** and ***anions***

Physical instability can lead to aggregation and ***subvisible particle formation***

Chemical instability can lead to increased levels of ***stability-indicating impurities*** with reduced or no biological activity

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Bulk Synthetic Semaglutide Used in Compounding Has Trace Metals That Can Impact Semaglutide and Put Patient Safety at Risk

Testing of semaglutide used in compounding revealed ***trace metals*** of various types and levels

Examples include boron, magnesium, chromium, manganese, iron, nickel, copper, potassium, and calcium

The presence of trace metals like iron, copper, and magnesium can cause the formation of ***high molecular weight proteins***, which in turn may impact ***immunogenicity***

Note: The quantity of copper and magnesium found in the bulk synthetic semaglutide samples used in compounding that have been tested to date have not yet reached levels that could cause HMWPs.

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Testing Revealed that the Bulk Synthetic Semaglutide Used in Compounding Had Different And Elevated Levels Of Anions Compared to the Semaglutide in Novo Nordisk's FDA-Approved Medicines

Not Present in Novo Nordisk's Semaglutide

- Acetate
- Nitrate

Present in Elevated Amounts Compared to Novo Nordisk's Semaglutide

- Phosphate

Inclusion of untested anions at untested levels has the potential to ***adversely impact the stability*** of semaglutide

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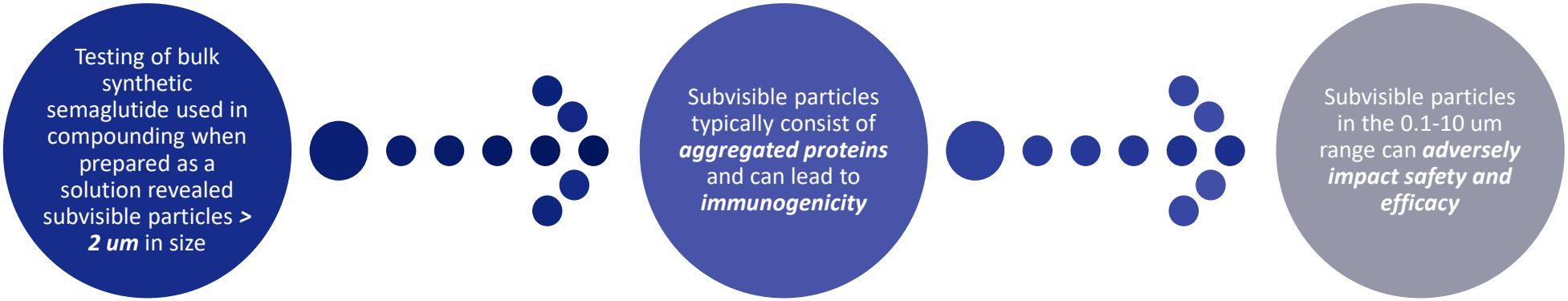
Testing of the Bulk Synthetic Semaglutide Used in Compounding Revealed Subvisible Particles that Threaten Patient Safety



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Impurities Present in Elevated Levels in Many Compounded Semaglutide Products Pose Safety and Effectiveness Risks

- Formaldehyde Adducts (> 15% in multiple samples)
- Oxidations and Di-Oxidations
- Isomers
- Dimers

Note: Formaldehyde adducts of peptides are known to pose immunogenicity risks

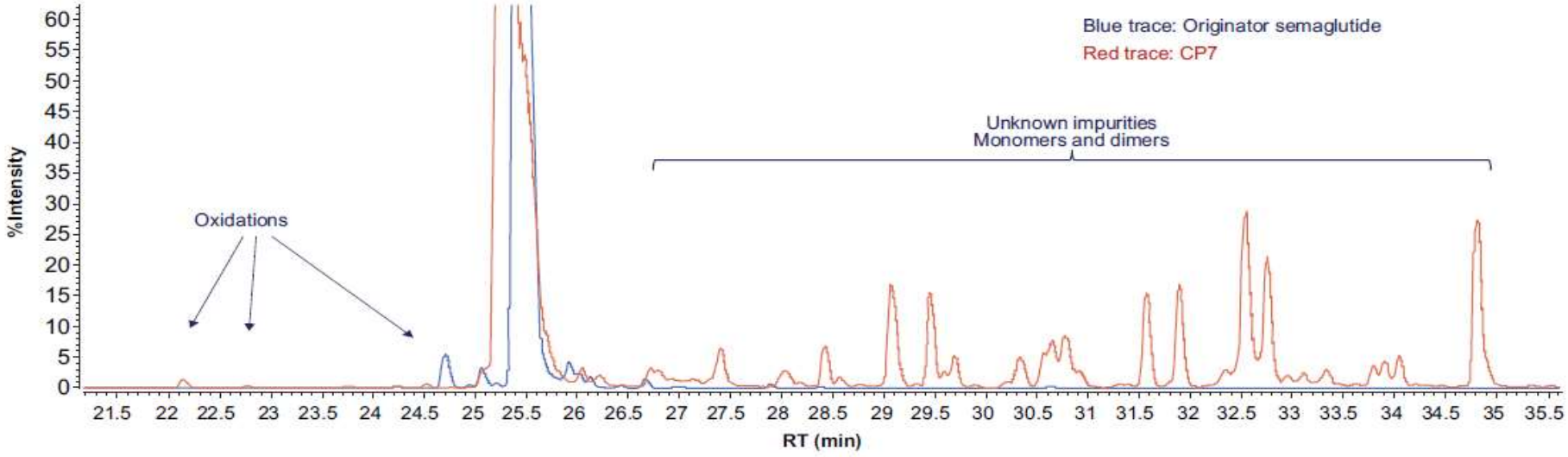
Bulk and Compounded Semaglutide Testing Revealed Unknown Impurities

Many samples of bulk and compounded semaglutide were found to contain ***unknown impurities*** not found in the semaglutide in the FDA-approved products

One of the tested compounded drug samples contained ***33% unknown impurities***

These unknown impurities have ***not been characterized or justified***.

LC–MS Analysis of the Semaglutide in Novo Nordisk's FDA-Approved Medicines ("originator semaglutide") with Compounded Drug Product ("CP7")



The Manufacturing Differences between Bulk Synthetic Semaglutide Used in Compounding and Semaglutide in the FDA-Approved Medicines May Impact the Pharmacological Effectiveness and Impurity Profile

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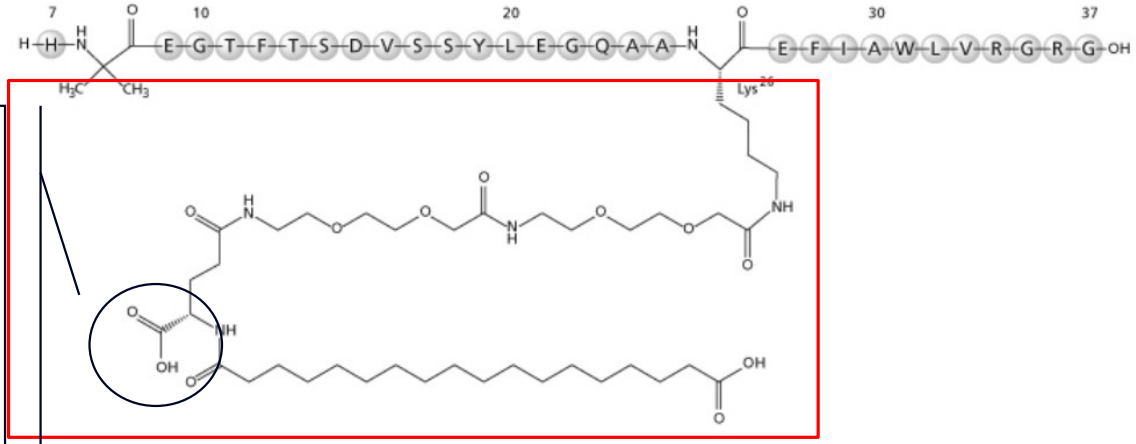
- Manufacturing the chemical modifications in semaglutide correctly is critical to semaglutide's pharmacological action
  - Inclusion of A8Aib (unnatural amino acid) and K34R substitutions
  - Presence of K26-deactivated γGlu-2xOEG linker and C18 fatty-diacid moiety
- Suppliers of synthetic "semaglutide" used in compounding attach the linker and fatty-diacid moiety using a different chemical process than the one used for recombinantly produced semaglutide in FDA-approved medicines, which may impact the ***pharmacological effects*** of the semaglutide and the ***impurity profile***

Testing has identified isomeric impurities at this site in "semaglutide" used by compounders



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Compounders Are Needlessly Co-Formulating Semaglutide With Co-Active Ingredients that Put Patients at Risk

Variety of Examples

- Levocarnitine or L-Carnitine
- Cyanocobalamin, Methylcobalamin, or Vitamin B12
- Pyridoxine
- Tirzepatide
- Chromium PIC
- BPC-157
- NAD+

BPC-157

- Body Protection Compound-157 is an ***investigational*** synthetic peptide
- Semaglutide and BPC-157 form a ***heterodimer impurity***
- FDA does not permit its use in compounding due to its complexities related to ***peptide-related impurities*** and API characterization and significant safety risks, including ***immunogenicity***

NAD+

- NAD+ is an oxidized form of NAD
- Both are ***unstable*** when exposed to light, moisture, or standard room temperatures
- Testing showed ***high levels of oxidations and di-oxidations***, likely due to NAD+ oxidizing semaglutide, which can adversely impact efficacy and potentially ***induce or enhance immune responses***

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Non-Injectable Compounded Semaglutide Drugs Lack the Critical Ingredient to Ensure Bioavailability (SNAC) and Utilize a Liposomal Technology that Has Never Been Subjected to Necessary Clinical Testing

Missing Absorption Enhancer

- SNAC is critical absorption enhancer and key contributor to efficacy in FDA-approved oral formulation
- Omitted from compounded oral formulations

Liposomal Technology

- Liposomal technology has never been clinically tested in humans with semaglutide or any other comparable peptide
- FDA proposed that liposome drug products present demonstrable difficulties in compounding

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The Safety Risks Associated with Compounded Semaglutide Are Significant

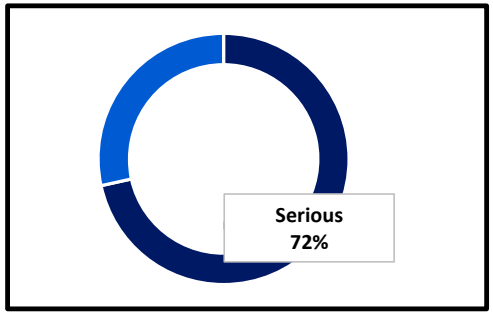
Adverse Events in FAERS Database

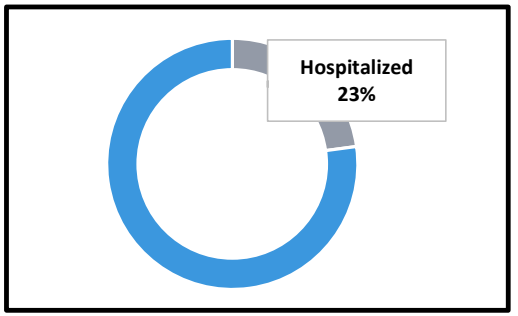
542 Cases

October 2018 – June 2024

10 Deaths

October 2018 – June 2024





FDA alerts health care providers, compounders and patients of dosing errors associated with compounded injectable semaglutide products

FDA has received reports of dosing errors involving compounded semaglutide injectable products dispensed in multiple-dose vials. Some patients sought medical attention or required hospitalization. Adverse events included gastrointestinal effects (e.g., nausea, vomiting, abdominal pain), fainting, headache, migraine, dehydration, acute pancreatitis and gallstones.

The purpose of this letter is to bring to the attention of the Federation of State Medical Boards (FSMB) information related to injectable compounded drug products containing semaglutide or tirzepatide. We encourage you to share the information in this letter with your members for their awareness and consideration.

- Prescribers started patients on doses that were approximately two to four times higher than the recommended starting doses of FDA-approved semaglutide
- Compounded semaglutide products were prescribed to be administered twice a week instead of once weekly, which is the recommended frequency of administration for FDA-approved semaglutide
- Prescribers titrated the patients' doses every one to two weeks instead of every four weeks, which is the recommended titration schedule of FDA-approved semaglutide

Note: Unlike sponsors of FDA-approved medicines, compounding pharmacies do not do surveillance, evaluation, or reporting of adverse events to FDA. The FDA has warned that "adverse events from compounded versions of these drugs are underreported." As a result, the number of adverse events associated with compounded "semaglutide" in FAERS likely reflects a small portion of the actual number of adverse events patients are experiencing after taking compounded "semaglutide.

Compounded Semaglutide Exposes Patients to Serious Immunogenicity Risks and May Make FDA Approved Semaglutide Medicines Ineffective for Those Patients

Compounded semaglutide poses potential ***immunogenicity risks*** not posed by Novo's tightly controlled, FDA-approved semaglutide medicines

Compounded semaglutide may lead to significant hypersensitivity reactions, including ***type I immediate hypersensitivity*** responses like anaphylaxis and potentially ***type III hypersensitivity reactions***, characterized by fever, rash, arthralgia, myalgia, hematuria, proteinuria, serositis, central nervous system complications, and hemolytic anemia

Patients using a drug compounded with synthetic semaglutide may develop ***anti-drug antibodies*** (ADAs). ADAs can bind semaglutide and ***neutralize*** its activity, making ***semaglutide medicines ineffective***. ADAs can bind to native GLP-1 and neutralize the activity of endogenous GLP-1 incretin, which could have severe/long-term consequences on patient health

02 Complexity of Delivery Mechanism

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The Delivery Mechanisms for Compounded Injectable Semaglutide Drugs Lack the Safety and Effectiveness Assurances Provided by FDA Approved Drugs

Ozempic® or Wegovy®		Compounded Vials and Needles	Compounded Prefilled Syringes	Compounding Kits
Prefilled, disposable, pen injector	*vs.*	Syringe, needles, and multi-dose vial with solution	Compounders send patients various doses preloaded into an insulin syringe	Syringe, needles, multi-dose vial of lyophilized powder, and other co-administered products (e.g., MICC)
Pen accurately dispenses precise dose based on labeled titration schedule		Patient must determine proper dose and self-administer with syringe	Several shipments of prefilled syringes lacked dates of compounding or beyond use dates	Patient must resuspend powder, determine dose, and self-administer with syringe
Semaglutide solution in prefilled cartridge is not exposed to air or light		Semaglutide solution exposed to air and light	Semaglutide solution exposed to light and temperature changes and silicone oil leaches	Semaglutide solution exposed to contaminants, air, and light

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There Are Published Reports of Overdosing from Compounded Injectable Semaglutide

50-year-old male with Type 2 diabetes incorrectly self-administered 50 units of compounded semaglutide co-formulated with cyanocobalamin and consistently vomited for 2 days and had ongoing nausea for 1 week

37-year-old female with a history of obesity incorrectly self-administered 10 times the correct dose of compounded semaglutide co-formulated with cyanocobalamin and experienced frequent vomiting, a persistent headache, decreased appetite, weakness, and fatigue

33-year-old female went to a hospital's emergency department with intractable nausea, vomiting, and abdominal pain after receiving a subcutaneous injection of what was reported to be compounded semaglutide of an unknown source

FDA Issued a Risk Alert Related to Dosing Errors for Compounded Semaglutide

FDA alerts health care providers, compounders and patients of dosing errors associated with compounded injectable semaglutide products

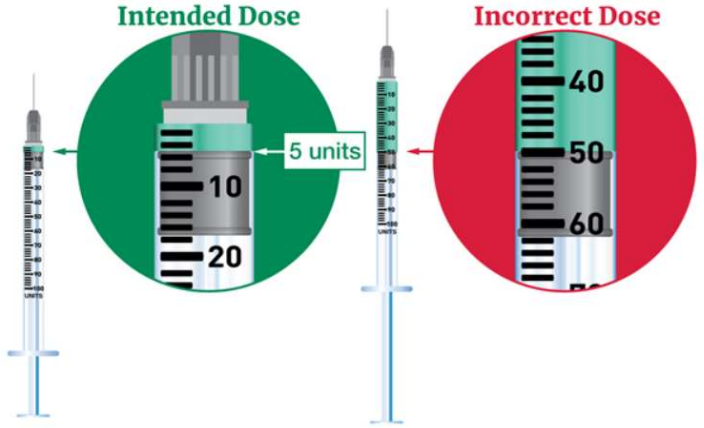
FDA has received reports of dosing errors from patients and health care providers related to these compounded products. There may be a risk of medication dosing errors due to conversion from milligrams to other units of measurement, availability of compounded semaglutide products in varying concentrations and use of multiple-dose vials.

- One provider intended to dose 0.25 milligrams (5 units), but prescribed 25 units instead, leading to a patient receiving five times the intended dose and experiencing severe vomiting.
- Another provider prescribed 20 units instead of 2 units, affecting three patients who, after receiving 10 times the intended dose, experienced nausea and vomiting.
- Additionally, a patient, who is a health care provider, attempted to recalculate their own dose in units and inadvertently self-administered a dose 10 times higher than intended.

In several reports, patients were instructed to use a U-100 (1 milliliter) insulin syringe to draw small doses, such as a 5-unit (0.05 milliliter) dose, from a multiple-dose vial.

As depicted in the figure below, these patients were directed to administer 5 units from a vial. However, these patients mistakenly administered 50 units instead.

Figure 1. **U-100 insulin syringe with fill volume of 5 units and 50 units**



The Oral, Sublingual, and Transmucosal Delivery Mechanisms of Compounded Drugs Lack the Safety and Effectiveness Assurances Provided By Rybelsus®

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Rybelsus®		Compounded Oral Products	Sublingual or Transmucosal Products	Liposomal Drug Products
Oral tablet stored in bottle equipped with a drying agent to protect tablets from moisture	*vs.*	Oral troches or tablets/capsules	Sublingual tablets, sublingual solutions, or buccal/transmucosal films	Sublingual solutions formulated with anhydrous base that uses liposomes to deliver semaglutide
Co-formulated with SNAC, which facilitates absorption of semaglutide after oral administration		Oral products lack SNAC, a necessary ingredient to achieve bioavailability orally	Semaglutide molecule is likely too large to be fully absorbed sublingually	Flux rates of liposomal drug products likely do not allow for any meaningful absorption of semaglutide
Stored in bottle equipped with a drying agent to protect tablets from moisture		Packaging for oral products may expose semaglutide to moisture	Packaging or compounding may expose semaglutide to air, light, moisture, or temperature changes	FDA has proposed that liposome drug products are too complex for compounding

03 Complexity of Dosage Forms

The Dosage Forms for Compounded Injectable Semaglutide Drugs Put Patients at Risk

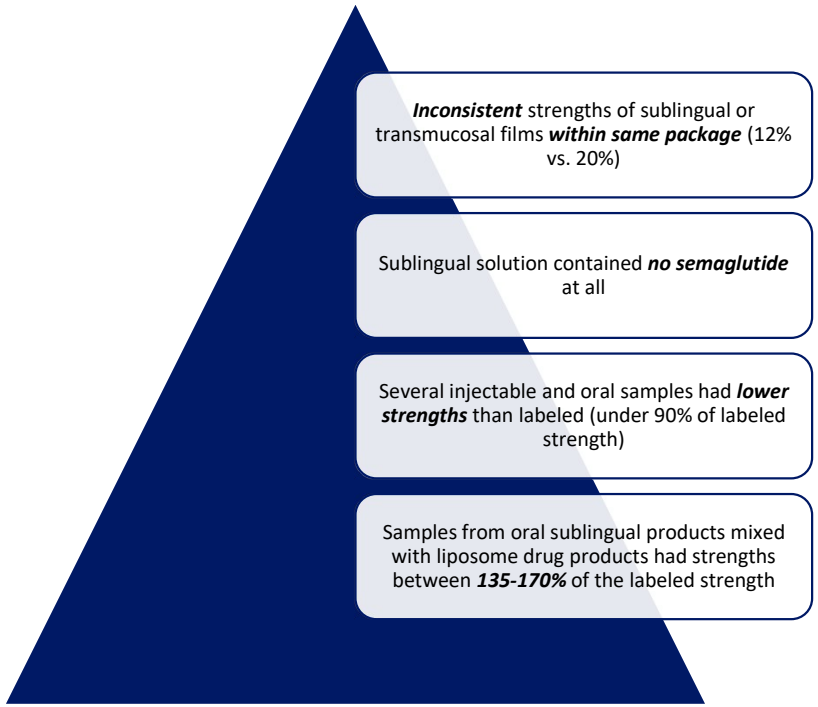
Failing to Ensure Sterility of Products Coupled with Bypassing Body's Natural Defenses Against Toxic Ingredients, Toxins, or Dangerous Organisms

Difficulty in Achieving an Accurate or Consistent Dose Due to Multi-Dose Vial and Insulin Syringe

Possibility of Over-or-Under Dosing with Self Administration

Difficulty in Calculating Correct Dose for New Titration Without Proper Instructions

The Inconsistencies In Compounded Semaglutide Drugs Expose Patients to Significant Safety and Efficacy Risks



Risks to Patients

Superpotent compounded drugs may increase likelihood of ***serious adverse events*** if the drugs are at a consistently higher dose than labeled

Subpotent compounded drugs or compounded drugs with no semaglutide at all may have ***reduced efficacy or lack efficacy***

Patients taking compounded semaglutide products may ***forego safe and effective therapeutic alternatives***

Patients taking variable amounts of semaglutide due to ***inconsistent strengths*** will experience ***safety and efficacy risks***

04

Complexity of Achieving Bioavailability

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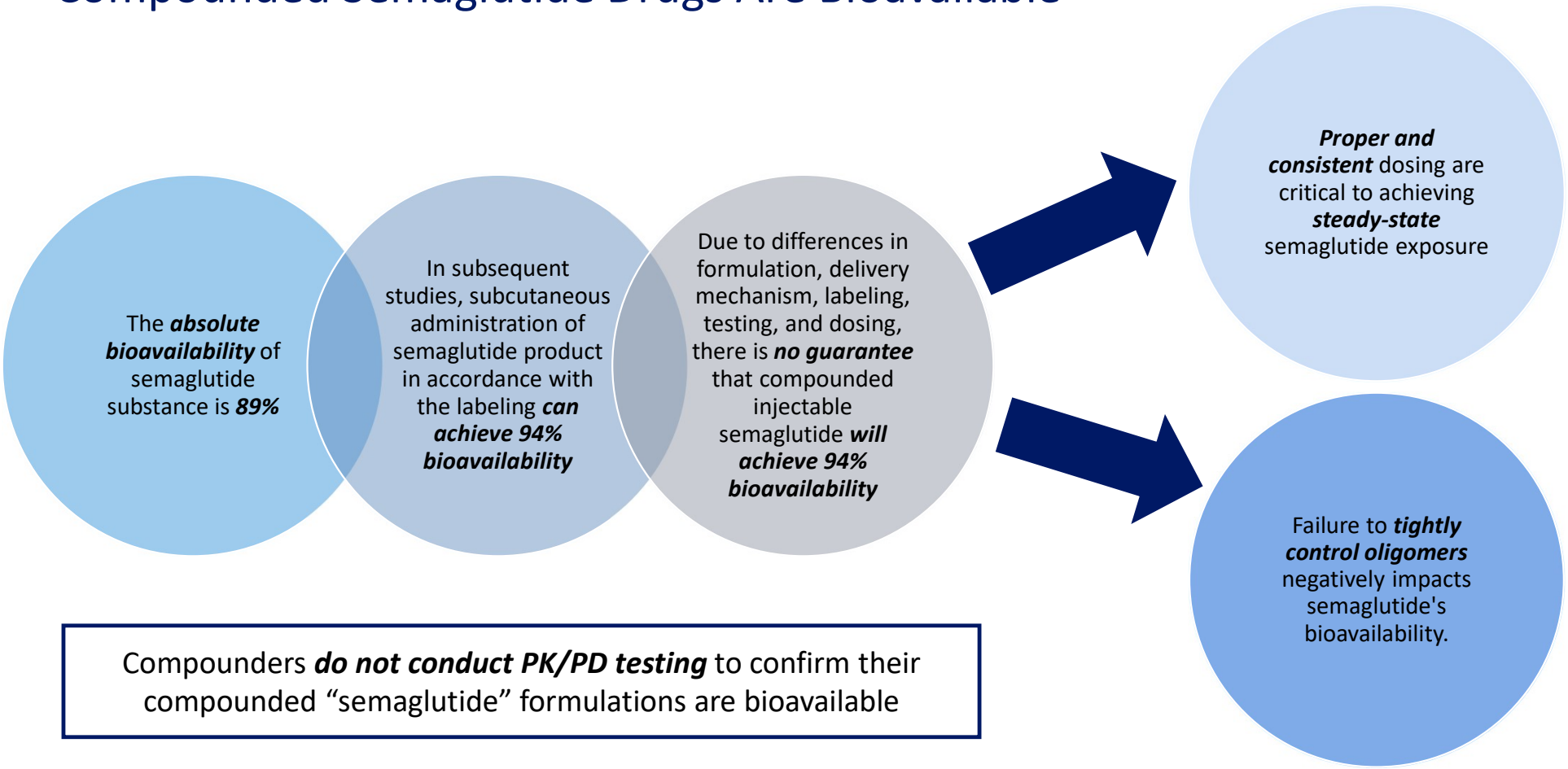
Compounders Do Not Perform the Requisite Testing to Confirm that Their Compounded Semaglutide Drugs Are Bioavailable



Compounders ***do not conduct PK/PD testing*** to confirm their compounded “semaglutide” formulations are bioavailable

Oral Semaglutide Drugs Likely Have Little to No Bioavailability Because They Lack the SNAC Ingredient Present in FDA-Approved Semaglutide Medicines

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Bioavailability is ***particularly difficult*** to achieve for oral semaglutide formulations

Peptides are associated with a low rate of oral availability due to:

- their ***limited membrane permeability*** in the GI tract,
- ***degradation*** in the stomach's low pH,
- ***degradation*** by microorganisms in intestine, and
- food-***impaired absorption***

Semaglutide is a Biopharmaceutics Classification System ***Class 4*** drug, and the bioavailability of semaglutide following oral dosing is approximately 0.8%

RYBELSUS®, the only FDA-approved oral semaglutide formulation, ***overcomes the absorption barriers*** in the GI tract by inclusion of SNAC

Oral formulations of compounded semaglutide ***do not include SNAC*** or other ingredients clinically tested to improve semaglutide's bioavailability

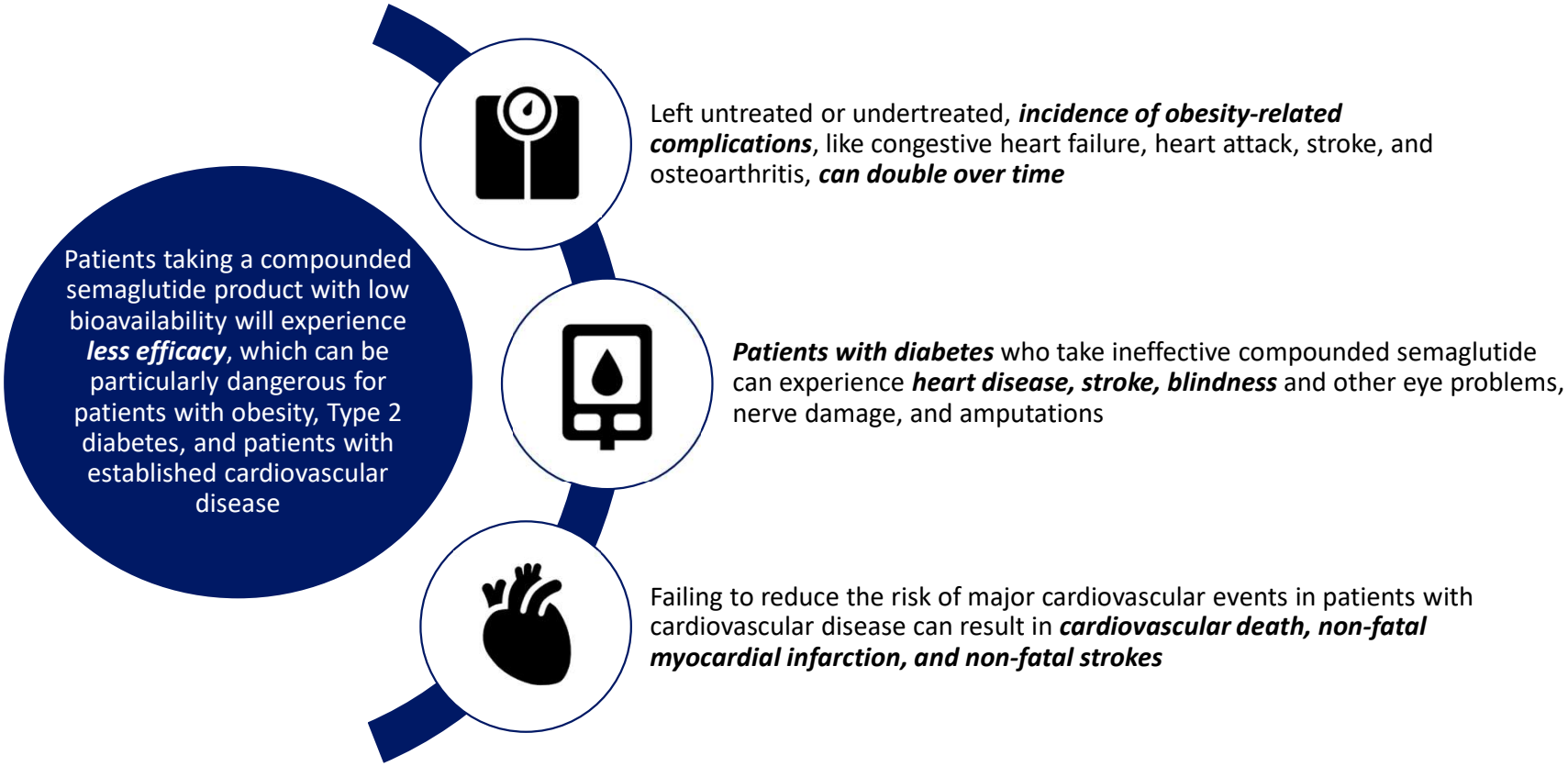
Evidence of Bioavailability for Sublingual and Transmucosal Semaglutide Products Is Lacking

There is ***no approved form*** of sublingual or transmucosal semaglutide or other comparable peptide

Compounded drugs ***do not undergo PK/PD testing*** to ensure that the active ingredient is bioavailable when delivered sublingually or transmucosally

Without a comparator or appropriate testing, patients may receive an ***ineffective product*** and risk leaving their underlying condition untreated, which could have ***life-threatening consequences***

Nonexistent or Low Bioavailability Exposes Patients to Serious Efficacy and Safety Risks



05 Complexity of Compounding Process

The Compounding Process Causes Challenges with Instability, Reconstitution, and Cross-Contamination

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Stability in "Semaglutide" Used in Compounding

- Stability-indicating peptide-related impurities are observed in compounded "semaglutide" samples, including formaldehyde adducts and oxidations
- pH, exposure to air, agitation, temperature, exposure to surfaces, light, and other sources of physical stress all affect stability
- Small changes in the pH of the semaglutide formulation can induce the formation of fibrils

Reconstitution of Lyophilized Powder

- Formulation of solution needs to be suitable for reconstitution
- Testing should be done to confirm reconstitution
- Uncontrolled agitation to reconstitute semaglutide may promote its degradation
- Risk of microbial contamination, especially for physicians compounding in med spas or clinics

Cross-Contamination

- Inadequate cleaning of equipment
- Detected tirzepatide in compounded "semaglutide" drug product

The Compounding Process Causes Challenges with Purification and Processing, the Container Closure System, and Storage

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Purification and Processing

- Semaglutide-related impurities with acetaldehyde adducts and butyraldehyde adducts were detected in tested compounded samples and are known to have no biological activity and may impact HMWP formation and immunogenicity
- Semaglutide-related impurities with acrylonitril additions were found in tested compounded samples and have unknown impacts

Container Closure System

- Vials and prefilled syringes do not adequately protect semaglutide from light
- Exposure to air is evident from oxidation and di-oxidation peptide-related impurities
- Silicone oil leached into semaglutide solution stored in plastic prefilled syringes

Storage

- Temperature instructions may be contrary to approved labeling, such as an instruction to store semaglutide in the freezer
- Beyond use dating is often absent or excessive for injectable products (e.g., 120 days to 364 days)

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Complex Compounding Processes Can Trigger a Series of Risks

- Stability-indicating peptide-related impurities
- Partially reconstituted semaglutide
- Degraded semaglutide
- Oxidized semaglutide
- Contaminated semaglutide
- Aggregated semaglutide

06 Complexity of Physicochemical and Analytical Testing

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Bulk and Compounded Semaglutide Is Not Tested to Ensure Safety, Quality, and Effectiveness

- Glu-C peptide mapping (for Rybelsus) and H^1-NMR
- Chemical stability monitored by RP-HPLC and physical stability by Thioflavin T assay
- Evaluation of hydrophobic and hydrophilic impurities
- Characterization of HMWP formation
- Immunogenicity testing using a semaglutide antibody assay
- Cell-based assay to measure specific bioactivity
- Product bioavailability and physical stability assessments
- Trace metals testing using ICP-MS/ICP-OES

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The Under-Testing of Compounded Semaglutide Drugs Can Mask Many Safety and Effectiveness Risks to Patients

Effectiveness and safety risks, including immunogenicity, caused by:

- Wrong peptide sequence
- Peptide-related impurities
- Formation of Oligomers
- Low bioavailability
- Incorrect strength
- Batch heterogeneity

07

Risk/Benefit Analysis

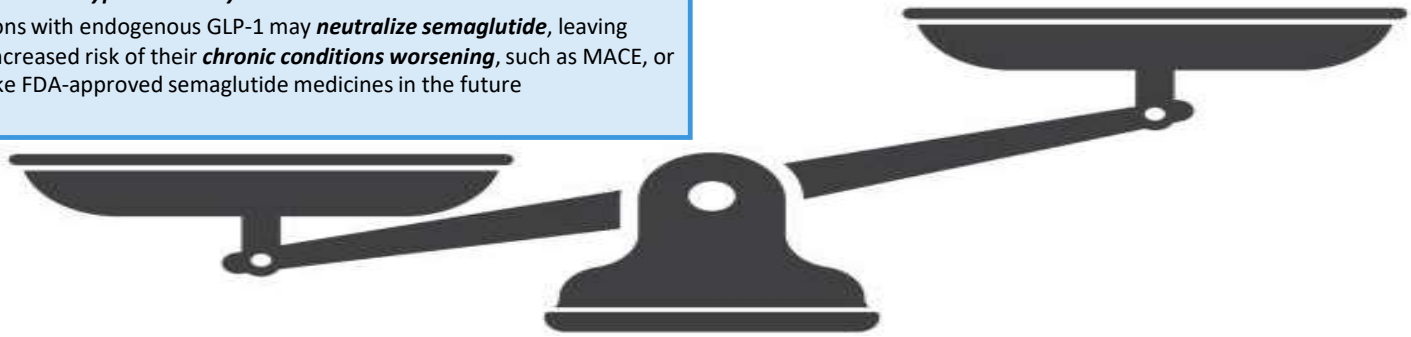
The Significant Risks to Public Health Posed by Compounded Semaglutide Drugs Outweigh Any Alleged Actual or Potential Benefit

Risks

- Complex Formulation
- Complex Drug Delivery Mechanism
- Complex Dosage Form
- Complexities in Achieving Bioavailability
- Complex Compounding Process
- Complex Physicochemical or Analytical Testing
- Numerous Safety Risks
  - Over ***500*** reported adverse events, including ***10 deaths***
    - Reports of ***liver cirrhosis*** after taking compounded "semaglutide" in combination with NAD+
  - Subpotent drugs may lead to ***reduced or no efficacy*** in treating chronic conditions, which can be ***life-threatening***
  - Superpotent drugs may increase likelihood of ***serious adverse events*** if compounded drugs are at a consistently higher dose than labeled
  - ***Immunogenicity issues*** caused by peptide-related impurities
    - Serious type I and III ***hypersensitivity*** reactions
    - Cross-reactions with endogenous GLP-1 may ***neutralize semaglutide***, leaving patients at increased risk of their ***chronic conditions worsening***, such as MACE, or unable to take FDA-approved semaglutide medicines in the future

"Benefits"

- Claim compounded semaglutide are equivalent to FDA-approved drugs (despite ***insufficient evidence*** to support that claim)
- Claim there is a clinical need to compound semaglutide products that do not resemble the FDA-approved drugs ***without any meaningful evidence*** showing that there are patients who cannot take ***FDA-approved medications*** to meet their medical needs and without adequate evidence to support the quality, safety, effectiveness, and historical use of the compounded drugs



International Regulators Agree The Risks of Compounded Semaglutide Outweigh the Benefits

"We recognise there is a valid place for compounding in certain circumstances.

"To keep Australians safe, new regulations will remove GLP-1RA, such as those being misrepresented and sold as replica Ozempic® or Mounjaro®, from the pharmacy compounding exemptions.

"This action will not affect compounded medicines other than GLP-1 receptors.

"While I understand that this action may concern some people, the risk of not acting is far greater.

"You only have to look to the recent reports of individual impacted by large-scale compounding to realise the dangers posed."

"This action will protect Australians from harm and save lives."

"As set out in the *Therapeutic Goods Regulations 1990* [effective Oct. 1, 2024] at the time of issuing these Guidelines, a pharmacist may (subject to compliance with all other relevant laws and guidelines):

- extemporaneously compound medicine (other than medicines that are used for gene therapy, that are medicinal cannabis products ***or that contain glucagon-like peptide-1 (GLP-1) receptor agonist analogues***) 'for a particular person for therapeutic application to that person'."

https://www.pharmacyboard.gov.au/Codes-Guidelines.aspx