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**Letter to the Editor**

# Semaglutide salt versus base formulations: a regulatory and pharmacovigilance imperative

Sir,

Obesity is one of the most dreaded epidemics in the world, and it is a significant challenge to global public health that must be addressed aggressively through clinical and pharmacological interventions.[1] The unprecedented rise in the global use of glucagon-like peptide-1 receptor agonists for the treatment of obesity and type 2 diabetes has created a critical regulatory and pharmacological challenge related to the proliferation of mass-marketed compounded alternatives.

On 06 February 2026, the U.S. Food and Drug Administration (FDA) issued a definitive enforcement directive to restrict the use of GLP-1 active pharmaceutical ingredients (APIs) in non-approved compounded drugs, specifically targeting companies engaged in large-scale "copycat" manufacturing.[2] This directive highlights a fundamental pharmacological concern that warrants the attention of the global clinical community: the chemical and clinical distinction between semaglutide base and its unapproved salt forms.

A primary issue in the compounding scenario is the use of semaglutide sodium and semaglutide acetate. While the FDA-approved products (Wegovy and Ozempic) use semaglutide in its base form, many compounding pharmacies employ these salt forms, which are chemically distinct and have not been evaluated for safety, efficacy, or quality as finished drug products.[3] The FDA has explicitly stated that it is unaware of any scientific basis for compounding with these salts, hence effectively categorizing them as new, unapproved drug substances. The FDA has even issued warning letters to tele-health providers and companies to remove any misleading advertisements claiming the similarity between the two salts.[4]

From a basic pharmacology point of view, altering the salt form of a peptide can significantly impact the stability, solubility, and pharmacokinetic profile of the drug, sometimes causing serious injury or even death.[5] The 1968 phenytoin intoxication outbreak in Brisbane clearly demonstrated the clinical risk of assuming excipients are pharmacologically inert. In this incident, calcium sulfate had been interacting with phenytoin to form a poorly soluble complex, thereby limiting drug absorption. When calcium sulfate was substituted with lactose as the capsule filler by the manufacturer, in phenytoin sodium formulations, this interaction no longer occurred, resulting in a marked increase in bioavailability. The unintended increase in systemic exposure led to widespread toxicity, with approximately 87% of previously stable patients developing features of phenytoin intoxication, including cerebellar ataxia and nystagmus. This episode underscores a critical pharmacological principle: even seemingly minor formulation changes can significantly alter drug bioavailability and produce serious clinical consequences. It highlights the importance of rigorous evaluation of excipient–API interactions, particularly in contexts such as large-scale compounding, where assumptions of equivalence may pose substantial patient safety risks.[6]

Besides the molecular integrity, the clinical safety of modern compounded products is compromised by vulnerabilities in the "cold chain" and dosing precision. There are reports that have emerged of injectable peptides arriving warm or with inadequate refrigeration, a failure that risks product degradation and potential immunogenicity.[7] Furthermore, the transition of these potent medications from standardized autoinjectors to multi-dose vials has led to widespread dosing errors.

The FDA adverse event reporting system (FAERS) data analysis through early 2026 revealed a disturbing scenario of a significant increase in hospitalizations due to dosing confusion, where patients mistakenly measured doses in "units" rather than milligrams. This controversy is particularly pertinent to the Indian pharmacological landscape.

As primary patents for semaglutide expire in March 2026, the market is pivoting toward local production. While firms like Sun Pharma are introducing standardized versions such as Noveltreat, the interim period remains flooded with "copycat" products using misleading marketing. As we navigate this "obesity revolution," it is imperative for pharmacologists to advocate for a "base-only" standard in GLP-1 therapy. We must educate patients that compounded salt forms are not bioequivalent generics and carry unverified risks of contamination and sub-therapeutic dosing.[8] The 2026 regulatory crackdown serves as a necessary mandate for stricter pharmacovigilance and a return to evidence-based prescribing in metabolic medicine.[9]

Therefore, it is expected that new salts be subjected to stringent regulatory oversight and approved only after the availability of sufficient clinical trial data for these new biosimilars.

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