Beyond Patents in Diabesity Care: An Indian Expert Commentary on Semaglutide

Semaglutide in Indian Diabesity Care

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Abstract

India is experiencing a rapid rise in the burden of type 2 diabetes and obesity, driven by urbanization, lifestyle transitions, and demographic shifts. With over 100 million individuals living with diabetes and a steadily increasing prevalence of obesity, the demand for effective therapies such as glucagon-like peptide-1 (GLP-1) receptor agonists has grown substantially. Semaglutide, a long-acting human GLP-1 analogue with proven benefits in glycemic control, weight reduction, and end organ outcomes, has emerged as a key therapeutic option. Semaglutide was first approved by the U.S. Food and Drug Administration (U.S. FDA) in 2017 and has since received regulatory approval in more than 75 countries worldwide. The end of patent period of semaglutide in March 2026 in India marks a critical turning point, enabling the entry of multiple follow-on products developed predominantly via synthetic pathways. Unlike small-molecule generics, follow-on versions of semaglutide may potentially present unique challenges due to their structural complexity, sensitivity to manufacturing processes, and potential variability in impurity profiles. Differences in production methods, quality control standards, and regulatory pathways may influence safety, efficacy, immunogenicity, and overall clinical performance. Furthermore, India's climatic conditions and infrastructural variability pose additional challenges related to cold-chain maintenance and product stability. While follow-on semaglutide products are expected to improve affordability and access, they also introduce uncertainties regarding comparability, interchangeability, and long-term outcomes. In this evolving landscape, there is a need for generating real-world evidence to assess clinical effectiveness, safety, adherence, of follow-on products.

This narrative review aims to evaluate the impact of semaglutide patent expiry in India, with a focus on manufacturing differences, regulatory considerations, and potential implications for clinical outcomes and real-world practice.

Keywords

Semaglutide, GLP-1 receptor agonist, Synthetic peptides, rDNA technology, SPPS, Biosimilars, Generics, Cold chain, India, Ozempic®, Rybelsus®

I. INTRODUCTION

The burden of diabetes in India is rising at an alarming rate. According to the Indian Council of Medical Research–India Diabetes (ICMR-INDIAB) study (2023), nearly 101 million individuals are currently living with diabetes, a number projected to increase to approximately 124.9 million by 2045 as per the International Diabetes Federation (IDF) Diabetes Atlas [1]. This rapid escalation is largely driven by socioeconomic transitions, including urbanisation, increased affluence, dietary changes, and increasingly sedentary lifestyles [2]. Obesity plays a significant role in driving the type 2 diabetes mellitus (T2DM)

epidemic, with nearly 88% of individuals with T2DM classified as overweight or obese (falling into the category of 'diabesity') [3,4].

Growing evidence supporting the multifaceted benefits of glucagon-like peptide-1 receptor agonists (GLP-1 RA) has led to their increased use and has substantially reshaped the management of both T2DM and associated weight issues. semaglutide, a potent long-acting GLP-1 RA, is approved in India as a first-line anti-diabetic agent, to be used along with diet and exercise [4]. Semaglutide for use in diabetes management is available in both injectable and oral formulations as Ozempic® and Rybelsus® respectively [5].

Patent protections on semaglutide, lapsed on March 20, 2026 in few countries, opening the door for domestic pharmaceutical companies to manufacture and market their own versions of the drug [6]. In this evolving landscape, follow-on semaglutide products have begun to emerge across those markets. However, regulatory authorities have raised concerns regarding semaglutide formulations, particularly those involving unapproved modifications. After this loss of patent protection in March 2026, multiple brands of semaglutide have been approved and launched in India [7,8]. Variability in manufacturing processes and process controls for such products may lead to differences in impurity profiles, potentially impacting the quality, safety, and consistency of the drug substance and finished product [9].

This narrative review evaluates the impact of loss of patent of semaglutide in India, focusing on differences between innovator and follow-on products in diabetes management in terms of manufacturing, quality, and clinical outcomes. It also highlights evidence gaps and the need for real-world data to inform clinical practice.

II. MATERIALS AND METHODS

Electronic databases, like PubMed, Scopus, Scribd, and Google Scholar, were searched to identify literature on biologics, biosimilars, generics, and synthetic peptides, along with their regulatory frameworks. Keywords included biologics, biosimilars, generics, synthetic peptides, solid-phase peptide synthesis (SPPS), recombinant DNA (rDNA) technology, cold chain, immunogenicity, manufacturing processes, impurity profiles, Central Drugs Standard Control Organization (CDSCO), U.S. Food and Drug Administration (U.S. FDA), and European Medicines Agency (EMA).

Relevant review articles, original studies, and regulatory documents were screened to extract definitions, classification criteria, and regulatory considerations, with emphasis on differences in structure, manufacturing dependency, and approval pathways. Supporting literature on semaglutide's structure, manufacturing, and loss of exclusivity was included for context. Only English-language articles from the past 18 years were considered.

III. Defining Biologics, Biosimilars, Generics, and Synthetic Peptides

Biologics are approved therapeutic products composed of proteins, nucleic acids, their combinations, or even living systems such as cells and tissues. They are typically derived from natural sources, including humans, animals, or microorganisms, and are produced using biotechnology (particularly r-DNA technology) and other advanced technological processes. Typical examples in the diabetes therapy area include Mixtard, NovoMix, Tresiba, Ryzodeg, Ozempic, Rybelsus, Wegovy, Victoza, etc [8,10,11].

Biosimilars are biologic products designed to be highly similar to an approved reference product, produced by biotechnology (particularly r-DNA technology) with no clinically meaningful differences in safety, purity, or efficacy. This is established through comprehensive comparability studies. However, they are not identical, and minor variations in manufacturing processes may lead to differences in structure, impurity profiles, or post-translational modifications. Examples include biosimilars of insulins (like basaglar, basalog, etc.) or liraglutide (lirafit, etc.) [8,10,11].

In contrast, generic drugs are small molecules, low molecular weight, chemically synthesized compounds with simple, well-defined structures. Their characteristics are independent of the manufacturing process, allowing complete and easy characterization. These typically include generic versions of sitagliptin and dapagliflozin [8,10,11].

Synthetic peptides are sequences of amino acids generated through chemical methods, most commonly using solid-phase peptide synthesis (SPPS). While traditional SPPS techniques significantly boost peptide production, they are often limited by a progressive decline in purity as the number of coupling steps increases. Although chemical synthesis can achieve high yields and purity, it is associated with substantial costs, particularly for peptides that require post-translational modifications. In addition, the synthesis of peptides and proteins is technically challenging and susceptible to sequence-related errors due to the stepwise assembly process. Given these complexities, such products undergo stringent regulatory scrutiny under pathways like the Abbreviated New Drug Application (ANDA) overseen by the U.S. FDA, as well as guidelines set by the EMA. In India, the requirements are quite relaxed as compared to the global mandates. Recent examples include follow-on synthetic versions of semaglutide that have been introduced in India [12-15].

IV. Regulatory Landscape for Peptide Therapeutics in India: A CDSCO Perspective

In India, peptide therapeutics are regulated by the CDSCO under the framework of the Drugs and Cosmetics Act, 1940 and its associated rules. However, the absence of dedicated peptide-specific regulatory guidelines has led to reliance on a composite framework derived from general drug, biologic, and biosimilar regulations.

In contrast to the size-based classification approach adopted by the U.S. FDA, CDSCO follows a more process-driven and risk-based evaluation paradigm. Synthetic peptides are required to showcase data related to pre-clinical safety, characterization and a phase 3 clinical trial in India unlike the innovator biologic, which comes with a long legacy of clinical trial data.

The lack of peptide-specific guidance in India further contributes to interpretational variability, thereby increasing regulatory complexity for both domestic manufacturers and multinational sponsors [15,16].

V. Semaglutide as a Molecule — Key Structural and Pharmacological Features

Semaglutide (C187H291N45O59; 4,113.58 g/mol) is a modified analogue of human GLP-1, designed for prolonged activity and increased enzymatic stability. Its structure is composed of 31 amino-acids. Semaglutide retains 94% sequence homology with the native GLP-1 hormone. Semaglutide incorporates specific structural modifications that enhance its pharmacokinetic and pharmacodynamic properties. Substitution of alanine with 2-aminoisobutyric acid (Aib) at position 8 confers resistance to degradation by dipeptidyl peptidase-4 (DPP-4), thereby prolonging its activity. Additionally, a C18 fatty diacid chain is conjugated to Lys26 via a γGlu–2xOEG hydrophilic linker, which facilitates reversible albumin binding, reduces renal clearance, and extends the half-life to approximately 7 days. Furthermore, substitution of lysine with arginine at position 34 is incorporated to optimize recombinant production and prevent mis-acylation by ensuring that the fatty acid chain attaches at the intended site [17].

Semaglutide is available in both oral and injectable formulations. The oral formulation is co-formulated with the absorption enhancer sodium N-(8-(2-hydroxybenzoyl) amino) caprylate (SNAC) at a strength of 300 mg (this strength has been found to be the most ideal – with lower of higher strengths being inadequate for semaglutide doses of 3, 7 or 14 mg), which protects the peptide from gastric degradation and facilitates its absorption across the gastric mucosa by locally increasing pH [18].

VI. Patent loss timelines in India

Since 2019, India has experienced over 25 loss of patent events, particularly within cardio-metabolic therapies, including dipeptidyl peptidase 4 (DPP-4) inhibitors (vildagliptin, sitagliptin), sodium-glucose cotransporter 2 inhibitors (SGLT2) inhibitors (dapagliflozin, empagliflozin), as well as agents like ticagrelor and sacubitril/valsartan. Specifically, patent loss milestones include Dapagliflozin in late 2020, sacubitril/valsartan in March 2021, sitagliptin in July 2022, Apixaban in September 2022, Empagliflozin in March 2025, and most recently, semaglutide in March 2026 [19]. For semaglutide in diabetes

management, this means that several companies have now been permitted to launch their follow-on versions of the original semaglutide brands of Ozempic® and Rybelsus® [8].

VII. Manufacturing Pathways: rDNA vs SPPS Approaches

Biological peptides play key physiological roles such as hormone regulation, neurotransmission, and immune modulation. rDNA technology, enzymatic synthesis, and high-throughput methods have enhanced the production of complex peptides, improving yield while reducing impurities. On the other hand, SPPS is a technique used by most companies to synthetically manufacture semaglutide [20,8].

VII A. rDNA Technology for Innovator semaglutide

Semaglutide received approval from the U.S. FDA in 2017 [21]. The innovator semaglutide is manufactured through a specifically designed multistep process that employs rDNA technology using *Saccharomyces cerevisiae*, followed by recovery, purification, peptide synthesis/acylation, and subsequent purification to obtain the final drug substance (DS). Each stage of this process is tightly controlled to ensure consistent product quality [9]. This represents a hybrid manufacturing approach that combines recombinant expression technology with subsequent chemical modification steps to incorporate the N-terminal oligopeptide and the C18 fatty acid side chain [17].

The advent of r-DNA technology has revolutionized the production of biologic therapeutics by enabling the safe, consistent, and large-scale manufacture of proteins that closely mimic naturally occurring human molecules. This approach not only minimizes immunogenicity but also eliminates the risk of infections associated with animal- or cadaver-derived sources [22].

VII B. SPPS for Synthetic Follow-On Products

Most follow-on semaglutide products are developed using total chemical synthesis, wherein the peptide is assembled amino acid by amino acid through SPPS, followed by chemical attachment of the fatty acid side chain. This approach eliminates the need for recombinant yeast-based fermentation, offering advantages such as improved process control, reproducibility, and scalability. However, semaglutide's relatively long peptide chain of 31 amino acids approaches the practical limits of SPPS at a commercial scale, making it challenging to consistently achieve the high purity required. As a result, differences in impurity profiles and structural attributes may arise when compared with innovator semaglutide brands, potentially impacting overall quality and consistency [8].

VII C. Why Manufacturing Pathway Matters — Quality, Safety, and Immunogenicity Risks

As mentioned earlier, the innovator brands (Ozempic® and Rybelsus®) are developed using rDNA technology [23]. These complex, multi-step processes are specifically optimised and tightly controlled to ensure consistent product quality. Given the intricacy of this approach and the potential for impurity formation, stringent quality control measures are essential to maintain purity, efficacy, safety and batch-to-batch consistency [17].

The manufacturing of GLP-1 peptides, such as semaglutide is highly complex and a significant barrier to entry, as it demands stringent control at multiple levels. These peptides require precise sequence fidelity, where even a single incorrect amino acid can compromise biological activity, along with correct three-dimensional folding and accurate chemical modification, including attachment of the fatty acid side chain. Additionally, achieving extremely high purity levels (typically >98%) is critical to ensure safety and efficacy. Beyond the drug substance, maintaining stability in the final formulation and ensuring uninterrupted cold-chain storage and distribution are essential to preserve product integrity. Given these challenges, not all manufacturers possess the technical capability and infrastructure required to consistently meet these standards [8]. Variations in manufacturing approaches may influence the clinical profile of these products. Even minor process-related changes can affect the chemical and physical stability of the molecule and alter its impurity profile, potentially impacting immunogenicity [24,25].

With advances in peptide chemistry, large-scale chemical synthesis has emerged as a viable alternative, facilitating the development of both innovative and generic peptide drugs. Differences in manufacturing processes, production scale, equipment, host systems, and raw materials can result in physicochemical variability between originator products and follow-on versions of semaglutide. Evidence from case studies indicates that the same peptide, when produced by different manufacturers or via different techniques (recombinant versus synthetic), can exhibit markedly different impurity profiles [24]. Hach M et al. conducted an analysis comparing follow-on oral and injectable semaglutide products with the originator formulations, identifying notable differences in impurity profiles, potential stability concerns, reduced active pharmaceutical ingredient (API) content, and possible immunogenic risks. These findings highlight the inherent complexities in replicating such formulations, particularly when they involve novel excipients like SNAC, which possesses intrinsic biological activity [9,26].

While the clinical significance of these variations is yet to be fully established, they emphasize the need for further evaluation through well-designed clinical studies. Collectively, these observations reinforce the importance of rigorous regulatory scrutiny of follow-on GLP-1 analogues, including follow-on formulations, to ensure consistent quality, safety, and therapeutic efficacy.

VIII. Oral Semaglutide Enabled by SNAC Absorption Enhancement

In 2019, the U.S. FDA approved Rybelsus® (oral semaglutide), as the first orally administered GLP-1 receptor agonist for T2DM, with subsequent approval by the EMA and Indian CDSCO. It is the first GLP-1 RA designed for oral delivery (offering the power of semaglutide in a convenient oral formulation), formulated as a combination of semaglutide and the absorption enhancer, SNAC, which enables effective peptide absorption despite the acidic gastric environment. This represents a major advancement in peptide drug delivery [27,28]. Commercially available oral semaglutide tablets contain 3 mg, 7 mg or 14 mg of semaglutide co-formulated with 300 mg of SNAC, which was found to be the ideal concentration for adequate absorption. The follow-on versions have been reported to have a lower SNAC concentration at ~160 mg for equivalent oral semaglutide doses of 3 mg, 7 mg and 14 mg [29].

In the PIONEER 1 trial, once-daily oral semaglutide at doses of 3, 7, and 14 mg demonstrated clear superiority over placebo in reducing glycated Hemoglobin (HbA1c) over 26 weeks [30]. In another study by Granhall C et al, pharmacokinetic evidence further showed that co-formulation with 300 mg of SNAC was the optimal strength to enhance semaglutide absorption and subsequently, improved bio-availability (150 mg and 600 mg were found to be inadequate in comparison with 300 mg of SNAC) [31].

SNAC has generally regarded as safe (GRAS) status and is U.S. FDA-approved as a permeation enhancer (PE). SNAC has been extensively studied, with multiple clinical trials supporting its role in improving oral bioavailability of poorly permeable drugs [26].

IX. Cold-Chain Integrity — India's Operational Realities

Pharmaceutical stability is fundamental to drug safety, efficacy, regulatory approval, and defined storage conditions, reflecting a product's ability to remain potent, pure, and of consistent quality throughout its shelf life. Environmental factors such as temperature, humidity, and light significantly influence the degradation of API and excipients. In tropical and temperate regions, pronounced seasonal variations, particularly high heat and humidity or fluctuating storage conditions due to poor infrastructure, pose added risks, especially in resource-limited settings with inadequate climate control [32]. Furthermore, climate change–related events, including floods and power outages, can disrupt supply chains, compromise storage conditions, and delay transportation, thereby affecting the availability and integrity of temperature-sensitive medications [33]. Maintaining strict temperature control is essential for cold-chain pharmaceuticals, which are typically required to be stored within a 2–8 °C range to preserve their chemical stability and therapeutic efficacy. Deviations from this range, even if brief (temperature excursions),

can occur during transportation, especially across long distances or in extreme climates, and may compromise product quality. To address this, continuous monitoring using temperature data loggers and real-time tracking systems is employed, enabling prompt detection and corrective action. Additionally, robust cold chain logistics, including well-maintained and properly calibrated refrigeration units in transport and storage, are critical to ensuring consistent temperature conditions throughout the supply chain [34]. In this context, the storage requirements of semaglutide highlight the importance of maintaining strict temperature control across its lifecycle [35]. Robust cold-chain infrastructure, supported by regular audits and temperature monitoring, is essential to ensure consistent temperature control and preserve product quality throughout distribution, including last-mile delivery. Pharmaceutical companies that have been managing cold chain compliance for decades, have the upper hand in this context vis-à-vis companies that are foraying fresh into this game [36].

X. Injection Device — Enhancing Usability and Adherence

Drug delivery devices are a critical component of injectable semaglutide therapy, as their design can significantly influence dosing accuracy, ease of administration, and overall treatment experience. In clinical practice, prefilled pen devices, are widely used and often preferred by both healthcare professionals and patients due to their established reliability and familiarity. Modern pen devices incorporate features such as spring-assisted injection mechanisms that reduce the force required for administration, eliminate push-button extension, and simplify the injection process. Additional design elements, including large and clear dose displays, end-of-dose confirmation clicks, and color-coded pens for dose differentiation, further enhance usability, reduce handling errors, and improve user confidence.

Beyond convenience, accurate and consistent dose delivery across the approved dosing range remains a fundamental requirement, particularly for peptide therapies with dose-dependent pharmacological effects. These attributes are especially relevant for patients requiring long-term therapy, including elderly individuals or those with impaired manual dexterity, who may face challenges with traditional vial-and-syringe methods or conventional pen devices. While device design alone does not determine clinical outcomes, it represents an important practical consideration, alongside drug quality, regulatory evidence, and clinical efficacy, that can influence real-world use. Improved ease of use, simplified training, and strong user preference, particularly for devices used in Ozempic® dosing, may enhance treatment acceptance, support long-term adherence, and potentially reduce diabetes-related complications and associated healthcare burden through better disease management [37,38].

XI. Evidence Base and Indication Breadth — Where Follow-Ons Are at a Disadvantage

Early phase 2 and phase 3 trials of semaglutide were conducted to establish optimal dosing, and to evaluate its safety and efficacy in individuals with T2DM. Phase 2 data demonstrated a clear dose-dependent response without unexpected safety concerns, supporting the selection of 0.25 mg, 0.5 mg and 1.0 mg once-weekly subcutaneous doses with stepwise escalation for phase 3 studies, and 3 mg, 7 mg and 14 mg for the oral dosing. For injectable and oral semaglutide, trial program were named as SUSTAIN and PIONEER clinical trials respectively. Across the phase 3 SUSTAIN trials, injectable semaglutide, Ozempic® 1.0 mg demonstrated superior reduction in HbA1c and body weight compared with placebo and active comparators including DPP-4 inhibitors, SGLT2 inhibitors, other GLP-1RAs, and basal insulin. Similarly, in the PIONEER program, oral semaglutide, Rybelsus® 14 mg demonstrated superior reduction in HbA1c and body weight compared with placebo and active comparators including DPP4 inhibitors, SGLT2 inhibitors and GLP-1 receptor agonists [5].

The strength and consistency of evidence generated from these landmark programs have translated into broad regulatory approvals. Ozempic® and Rybelsus® have received indications in India that extend beyond glycemic control in T2DM. Ozempic® carries multiple on-label indications, including its use as an adjunct to diet and exercise to improve glycemic control, reduction in the risk of major adverse cardiovascular events (MACE) in patients with established cardiovascular disease, and lowering risk of sustained decline in estimated glomerular filtration rate (eGFR), progression to end-stage kidney disease, and

cardiovascular death in adults with T2DM and chronic kidney disease. Similarly, Rybelsus® is approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM and is also indicated for reducing the risk of major adverse cardiovascular events in adults with T2DM who are at high cardiovascular risk. These expanded indications highlight the broader cardiometabolic and organ-protective benefits of semaglutide beyond glucose lowering [23,39].

It is important to underscore that the robust evidence demonstrated in these clinical outcomes has been generated exclusively with the innovator brands Ozempic® and Rybelsus® in T2DM, and not with any follow-on semaglutide products. To date, both injectable and oral follow-on versions have been evaluated only in small-scale clinical trials of short duration (24–26 weeks), involving limited patient populations (ranging between 100 and 300 patients on an average). Consequently, the long-term cardiovascular and renal benefits associated with semaglutide remain unestablished for these follow-on formulations. Furthermore, most Phase 3 non-inferiority trials comparing innovator and generic semaglutide have primarily focused on key endpoints such as glycemic control and weight reduction in patients with diabetes and obesity. These studies have not comprehensively assessed the broader cardiometabolic and organ-protective effects that were demonstrated in landmark programs such as PIONEER and SUSTAIN [40,41]. In addition, the cardiovascular benefits observed with oral semaglutide in the SOUL trial may not be directly extrapolated to follow-on oral formulations, as differences in SNAC concentration between the innovator and copy products could potentially influence drug absorption and clinical outcomes [5].

In line with these evidence gaps, currently available follow-on semaglutide brands have limited regulatory approvals, which are largely restricted to improving glycemic control in T2DM (as add-on to metformin), with only a subset approved for chronic weight management [42]. Notably, these products do not carry approved on-label indications for cardiovascular, renal, or other long-term outcome benefits, further highlighting the gap between innovator evidence and follow-on data.

XII. Future Directions

With the entry of multiple synthetic and biosimilar versions, each with potential differences in manufacturing processes, impurity profiles, and formulation, there will be an inherent need to evaluate how these variations translate into real-world outcomes. In this context, India presents a strong opportunity for real-world evidence (RWE) generation to compare clinical effectiveness, safety, and adherence, between innovator and follow-on semaglutide products. Given the country's large, diverse patient population and increasing adoption of digital health records, such data can provide critical insights beyond controlled clinical trials, helping bridge existing gaps in comparability, inform clinical decision-making, and build confidence in the use of follow-on peptide therapies. In addition, this also means there is a need to educate physicians and patients on the critical clinical differences between the original and follow-on semaglutide brands, in order to ensure informed decision-making [8,19].

XIII. CONCLUSION

The transition into the post-patent loss era for semaglutide in India underscores the critical importance of maintaining manufacturing process fidelity, particularly for complex peptides where even minor variations can impact purity, stability, and clinical performance. Equally, in the context of India's climatic conditions, robust cold chain infrastructure is indispensable to preserve product quality across the distribution pathway.

The breadth of clinical indications established by the innovator, across T2DM, cardiovascular disease, and chronic kidney disease, reflects a depth of evidence that follow-on products must rigorously and independently demonstrate. As multiple versions enter the market, a comprehensive and discerning evaluation of manufacturing approaches, impurity profiles, delivery device reliability, and the strength of regulatory and clinical evidence will be essential. Such diligence will be key to ensuring consistent quality, safeguarding patient safety, and maintaining therapeutic efficacy in real-world clinical practice. As of today, Ozempic® and Rybelsus® remain the gold standard GLP-1 therapeutic options in the space of diabesity and T2DM management

in India, considering multiple factors including assured quality, consistent manufacturing, improved patient safety and robust cold chain compliance.

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