International Journal of Basic and Applied Sciences, 14 (8) (2025) 702-709

International Journal of Basic and Applied Sciences

Website: www.sciencepubco.com/index.php/IJBAS
https://doi.org/10.14419/n99q9v48
Research paper

Adverse Event Label Expansion for GLP-1 Medications Due to Off-Label Use: Regulatory Implications and Challenges

Deepaben Bhavsar *

Northeastern University- Boston, MA, USA
**Corresponding author E-mail: deepa.bhavsar590@gmail.com*

Abstract

The high-velocity growth of off-label administration of glucagon-like peptide-1 (GLP-1) receptor agonists that were initially approved to be used as Type 2 diabetes medications has raised new safety issues and initiated regulatory procedures for developing adverse event label expansions. Since these agents are becoming popular in weight reduction, the treated population has become less homogenous, and therefore, the risk of adverse events that were not seen during the pre-approval trials is more probable. The paper critically evaluates the pharmacological justification of off-label use, the role of post-marketing surveillance in identifying safety signals, and the regulatory frameworks of various jurisdictions regarding the correction of the labeling of that product. It also deals with regulatory communication obligations of regulators, manufacturers, and prescribers to communicate changing risks; and with operational impediments to the successful implementation of label changes in a timely and consistent manner. It outlines the evidential challenges in demonstrating causality among various patient groups as well as recommending approaches to future regulation, including the development of dynamic labeling systems, streamlined global pharmacovigilance, and enhanced safety research. Analysis indicates that the adaptive, coordinated, and evidence-based strategies are essential to ensure the protection of public health and, at the same time, maintain access to therapeutics in the new reality of changing prescription patterns at a blistering pace.

Keywords: *GLP-1 Receptor Agonists; Off-Label Drug Use; Adverse Event Label Expansion; Pharmacovigilance; Regulatory Harmonization.*

1. Introduction

The increased use of glucagon-like peptide-1 (GLP-1) receptor agonists has changed the treatment options in the management of Type 2 diabetes and, more recently, in weight loss treatment. Liraglutide, Semaglutide, and Dulaglutide, initially authorized to treat glycemic failure, are used more and more in conditions far outside their initial approved indications. This is a global tendency of increased off-label use, especially among populations that intentionally want to lose weight or improve their metabolism in groups outside the standard diabetic populations. The pharmacological effect of the GLP-1 agents on satiety and gastric emptying slowing, together with cardiovascular and metabolic advantages, has led to an increased patient exposure in a short time frame [1] [2]. Nevertheless, this increasing penetration of patients has also been linked with an increase in reported adverse events that perhaps may not have been expected in situations where the same drugs are given to other groups of people who may have or present a different background or comorbid condition [3]. The term "adverse event label expansion" describes the formal regulatory procedure undertaken to revise and update product safety labeling in order to incorporate newly validated adverse event signals identified during post-marketing surveillance. Regarding GLP-1 receptor agonists, the rapid rate of off-label use has led to an increase in new safety issues like increased severity of gastrointestinal complications, gallbladder and liver biliary pathologic disorders, possible psychiatric effects, as well as unusual and severe adverse outcomes like pancreatitis or bowel obstruction [4] [5]. There has been a growing momentum among regulatory bodies to change product labels within a reasonable time to accommodate these facts, protect the health of the populace, and also keep the utility of such drugs available to relevant patients. The interactions of pharmacovigilance and real-world use, epidemiological information, with regulatory intervention would comprise the main issue of concern in this discussion. This involves high demographic changes brought about by off-label prescribing, thus making the challenge even greater. The exclusion criteria of clinical trials of the GLP-1 receptor agonists have, in the past, excluded people without Type 2 diabetes, with eating disorder care, adolescents, or with severe gastrointestinal disease. However, the same groups of individuals in the real-world environment are now being exposed to GLP-1 treatment at an increasing rate, and potentially revealing previously undocumented adverse effects that had never been properly evaluated during the initial clinical development program [6] [7]. Adverse event label expansion, therefore, has to straddle the constraint of original evidence and the regulatory requirement to incorporate emerging real-world adverse-event hints into labeling text. The issue of adverse event label expansion in GLP-1 agents should not be minimized or treated merely as a matter of regulatory nuance, as it marks a significant milestone in the ongoing lifecycle management of these therapies. Its implications deal with pharmacovigilance infrastructure, procedures of post-marketing surveillance, and harmonization of regulatory policies, as well as the ethical responsibilities of prescribers. An examination of the regulatory regimes governing such updates reveals that the phenomenon is shaped both by global and local approaches to safety communication, as well as by the scientific frameworks used to establish causality between GLP-1 therapy and newly observed adverse events [8][9]. Moving to the second part of the analysis, it is vital

to discuss the pharmacological basis of GLP-1 receptor agonists and clinical reasoning behind their off-label application since these are the contexts implicit in the development of adverse events upon their application to the non-approved population.

2. Pharmacological Mechanism of GLP-1 Receptor Agonists and their Relevance to Off-Label Use

One of their mechanisms is their effectiveness in terms of imitating a hormone known as glucagon-like peptide-1, which is elevated by the ingestion of nutrients. They work at the level of glucose-stimulated insulin release, inhibition of glucagon secretion, delayed gastric emptying, and increased action on the central nervous system to promote satiety as depicted in Figure 1 [10] [11]. The effects increase their applicability in managing glycemic control in Type 2 diabetes and also lead to a remarkable amount of weight loss, which has been one of the main factors that has led to their off-label application in non-diabetic individuals in an attempt to reduce obesity [12]. The mechanism of action of GLP-1 receptor agonists does not just stop at glycemic benefits, as there is also data on cardiovascular risk protection, hepatic steatosis, and even neuroprotective effects [13]. Pleiotropic effects have led to interest in their use to treat certain diseases, including polycystic ovary syndrome, non-alcoholic fatty liver disease, and even neurodegenerative diseases [14]. Although this expansion can be seen as a sign of exciting therapeutic utility, it also serves to further diversify the patient population being treated and, thus, brings diversity to drug metabolism, comorbidity load, and concomitant therapy. All these factors may affect the occurrence and the extent of adverse events [15]. Safety-wise, off-label use of GLP-1 receptor agonists poses different problems. The adverse gastrointestinal events, like severe nausea, vomiting, and diarrhea, are potential concerns and can be increased in the non-diabetes population since baseline gastrointestinal and metabolism adaptation and motility patterns are already altered in these groups of people [16]. In addition, gallbladder events and uncommon instances of pancreatitis have been reported more frequently in some real-life groups than in pre-approval studies, and low disease burden and poorer glycemic control are also plausible risk modifiers related to the combination of underlying health risk and GLP-1 pharmacology [17]. Psychiatric adverse events, such as reports of depression and suicidal thoughts, happen infrequently but have become an area of growing regulatory concern, especially when combined with a greater mental health susceptibility present in some off-label patient groups [18]. It is against this mechanistic and clinical background that the reasons why off-label use of GLP-1 receptor agonists can be described as a driver of the realization of new types of adverse events and, as a result, new types of regulatory label expansion should become evident. This pharmacological premise establishes the setting needed to consider how these safety signals are identified, tested, and used in the decision-making process of regulators, which is taken up in the section presented next.

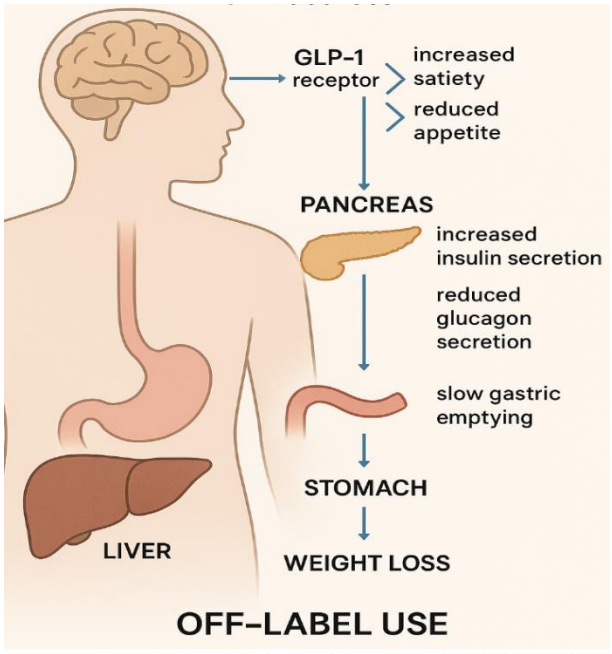

Fig. 1: Pharmacological Mechanism of GLP-1 Receptor Agonists and Their Relevance to Off-Label Use, Showing Their Effects on Insulin and Glucagon Secretion, Gastric Emptying, and Appetite, Along with Clinical Benefits, Cautions, and Potential Applications Beyond Diabetes Management.

3. Post-Marketing Surveillance and Adverse Event Signal Detection for GLP-1 Medications

Post-marketing surveillance is essential for the ongoing safety assessment of GLP-1 receptor agonists after they enter routine clinical practice. This process utilizes diverse data sources such as spontaneous adverse event reports, structured pharmacovigilance initiatives, patient registries, and real-world evidence from electronic health records and claims databases to help identify unfavorable or rare events that may emerge outside the controlled environments of pre-approval trials [19] [20]. Within GLP-1 receptor agonists, spontaneous reporting registries administered by regulatory bodies, like the FDA Adverse Event Reporting System, or the EudraVigilance database, have played a significant role in raising red flags in regards to safety issues connected with the off-label applications. Singularly, there have been reports of elevated-than-anticipated gastrointestinal obstruction, development of gallbladder stones, and biliary tract ailments in populations using these agents to treat obesity compared to diabetes [21]. The signals provide early warning without being causative since they encourage subsequent, more detailed analysis, both through pharmaco-epidemiological investigation and adverse reaction-specific safety reviews. A number of methodological issues complicate the detection procedure. First, stratification of risk based on indication may not always be captured in the medical records with regard to off-label use. Second, adverse events can be underreported based on the opinion that the benefit the drug is perceived to give to a patient exceeds the harms that it causes when it comes to cosmetic/lifestyle-oriented use cases. Third, and related to the above, confounders like a quick weight loss, in itself, may contribute to the occurrence of adverse outcomes and confound the causal relationship toward the drug [22]. There is an increasing use of signal detection techniques of data-mining algorithms and disproportionality analyses to detect events written up at an unexpectedly high frequency in comparison to the background drug

database [23]. In the case of the GLP-1 drugs, the methods have strengthened the relationship between treatment with gastrointestinal adverse reactions, and also, in rare cases, pose psychiatric risks of potential connections. For regulatory agencies, the decision of whether to officially expand a drug's label based on available evidence is far from straightforward, requiring a careful balance between the statistical robustness of the findings, the biological plausibility of the association, and the potential public health implications of the proposed risk [24]. Off-label usage also becomes more complex globally because, beyond the quality of adverse event reports, jurisdictions vary in regulatory conditions precedent to action. To illustrate, a safety signal that is identified in the European Union does not automatically translate to immediate updating of labels in the United States and the other way around. Such an asynchrony may induce confusion among the population and question clinicians who practice in various areas with varying labeling requirements [25]. Post-marketing surveillance can be used to update the emerging safety profiles; the next regulatory step, which requires scientific rigor and procedural visibility, is how to convert such information into formal changes on labels. This section examines the regulatory frameworks governing the adverse event label expansion of GLP-1 receptor agonists, highlighting how tensions between the need for rapid risk communication and the requirement for robust evidence emerge within these systems. While narrative analysis is essential for understanding the nuances of safety signal development, a structured summary of key adverse events emerging specifically from off-label GLP-1 use helps clarify the breadth of post-marketing findings and the diversity of detection mechanisms.

Table 1: Emerging Adverse Events Linked to Off-Label GLP-1 Receptor Agonist Use and Their Detection Pathways

Adverse Event Type	Detection Source	Population Context	Regulatory Response Stage
Severe gastrointestinal obstruction	Disproportionality analysis in FDA FAERS	Non-diabetic obese adults	Under PRAC review (EU)
Gallbladder disease (cholelithiasis)	National spontaneous reporting databases	Mixed diabetic/non-diabetic	Label warning in several EU states
Rapid-onset pancreatitis	Targeted case–control studies	Patients with rapid weight loss	Ongoing risk assessment (FDA)
Psychiatric symptoms (e.g., ideation)	Electronic health record (EHR) mining	Adolescents and young adults	Signal validation stage
Intestinal ischemia	Hospital discharge registry analysis	Non-diabetic bariatric patients	No formal action yet

Source: Compiled by the author through synthesis of data and concepts from the literature [19-25].

As illustrated above, the heterogeneity of detection methods reflects the multi-source nature of pharmacovigilance, which in turn influences the speed and certainty of regulatory action. This operational complexity becomes even more pronounced when these safety signals enter the formal framework for label expansion, as discussed in the next section.

4. Regulatory Frameworks Governing Adverse Event Label Expansion

The intent to expand the safety label of a drug is not only a scientific judgment carried out, but a legal as well as administrative step that is under the control of the local regulatory frameworks. With GLP-1 receptor agonists, the processes of adverse event label expansion vary across authorities (FDA, EMA, and other regulatory health authorities). In every instance, nonetheless, the essence of the expectation is that prescribing information correctly channels the contemporary understanding of the hazards of a drug so that clinicians and patients can make decisions based on the same information [26]. Most of the changes in the safety labeling in the United States are initiated either by the data submitted by manufacturers, by the studies conducted after the marketing, or by review of reported adverse events. In cases where a new risk is discovered, the FDA could either ask the manufacturer to submit a "Changes Being Effected" supplement that would permit some of the more urgent safety-related changes to be made without prior agency review or seek formal negotiations with the label in more complicated situations [27]. Concerning GLP-1 receptor agonists, label expansion has traditionally involved pancreatitis and thyroid C-cell cancer (in experimental animals), and most recently, possible psychiatric effects after reports of off-label use in obesity. The EMA in the European Union uses a more centralized mechanism that follows the same pattern, except that safety signals are initially evaluated by the Pharmacovigilance Risk Assessment Committee (PRAC). This body analyzes the evidence and, when it is justified, advises on the label changes that have to be introduced in all EU member countries. This process of harmonization is beneficial to maintain consistency, which may be slow when it comes to the update process in case of the signals with marginal value in statistical terms of significance [28]. The issue with GLP-1 receptor agonists in both systems is the fact that regulatory stringency and the rate of accruing real-world data overlap. Since off-label use is rapidly growing, new adverse events can come up more swiftly than the regulatory mechanisms will be able to keep up. In addition, the agencies have to negotiate between the timeliness of warnings and risk in changing labels before sufficient evidence is obtained, which would subvert public trust or unnecessarily limit potentially helpful therapy [29]. Coordination on an international scale is not complete. The Program for International Drug Monitoring operated by the World Health Organization (WHO) enables the sharing of data on the products in more than 130 countries, but regulatory measures are defined within guiding jurisdictions. Consequently, patients residing in various regions of the world might be provided with significantly different material on one and the same drug, which is the most alarming in the case of globally marketed agents, such as Semaglutide and Liraglutide [30]. Such complexity of regulation directly contributes to the larger issue of ethics and policy regarding GLP-1 label expansions, especially where off-label usage promotes new risks to emerge. These issues present difficult questions and dilemmas on the role that manufacturers, regulators, and prescribers need to play in the safe introduction of these common drugs, as will be discussed in the next section.

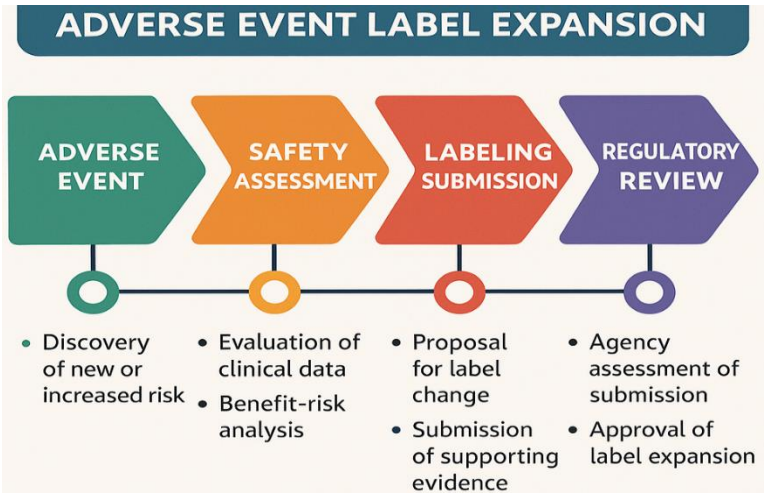

Fig. 2: Regulatory Process for Adverse Event Label Expansion, Outlining the Sequential Steps from Risk Identification to Regulatory Approval Across Major Agencies Such as the FDA And EMA.

5. Ethical and Policy Challenges in GLP-1 Adverse Event Label Expansion

The increase in adverse events of GLP-1 receptor agonists, particularly in off-label contexts such as obesity management, presents complex ethical and regulatory challenges that reach beyond traditional pharmacological assessments. At the core is the need to balance the protection of public health with the preservation of individual autonomy and equitable access to promising therapeutic options. Although mechanistic links have been proposed between these agents and gastrointestinal events (e.g., gastroparesis), psychiatric symptoms (e.g., suicidal ideation), and other side effects, definitive causal relationships remain unconfirmed. Several systematic reviews and pharmacovigilance studies, such as recent real-world data analyses from the FDA Adverse Event Reporting System and international surveillance platforms, have identified recurring safety signals, but also highlighted significant reporting bias and confounding factors. In parallel, clinical and professional associations have underscored the ethical obligation of prescribers to ensure shared decision-making, sound clinical justification, and transparency when recommending therapies outside their licensed use [26-28]. Ethically, the precautionary principle remains a cornerstone in regulatory decision-making, urging action in the face of uncertainty; however, its application becomes contentious when safety data are limited, inconsistent, or mechanistically unclear. Rushing to expand safety warnings or alter labels prematurely may inadvertently limit access for on-label populations such as those with Type 2 diabetes and provoke disproportionate concern among the public, especially in sensitive areas like mental health. Current policy frameworks emphasize that safety warnings should be proportionate and grounded in solid evidence to avoid unintended miscommunication. Meanwhile, manufacturers are expected to uphold robust post-marketing surveillance and report risks with transparency and objectivity [26-29]. Independent health policy organizations have warned that industry-sponsored studies may delay the identification or disclosure of potential harms, especially when financial stakes are significant. These dynamics highlight the need for more independent pharmacovigilance systems and consistent regulatory scrutiny. Ultimately, ethical governance in this space depends on a collective commitment from regulators, healthcare providers, and industry stakeholders to ensure timely, clear, and balanced communication about emerging risks while maintaining patient access to clinically valuable therapies.

The prescribers stand in a special ethical role as the first line of patient care. With off-label treatment using GLP-1 agents, clinicians face the unknown risk profile and potential metabolic or weight-loss benefits, and in many cases, lack robust evidence on the long-term safety of these interventions. From an ethical standpoint, this places an increased responsibility on the process of informed consent, ensuring that patients are made aware not only of the known risks outlined in the current drug label but also of the limitations and uncertainties surrounding the evidence for off-label use [30].

These dialogues are further complicated by patient-driven demand, often fueled by media coverage and the amplification of personal experiences shared on social media platforms. This form of indirect marketing has accelerated public interest in GLP-1 medications for off-label uses such as weight loss, sometimes outpacing the available clinical evidence. The resulting enthusiasm places additional ethical pressure on prescribers to balance patient expectations with clinical appropriateness. The absence of clear communication about the off-label nature of such use, whether due to lack of guidance or discretion in practice, can undermine trust, especially if future label updates introduce new safety warnings that reveal previously undisclosed risks specific to off-label populations. When patients later learn that certain adverse effects were known but not communicated at the time of prescription, even if disclosure was not formally required, it can erode confidence in both providers and the broader healthcare system [27].

Policymakers are thus faced with the challenge of developing regulations that promote transparency while preserving clinical autonomy. Another conceptual ethical issue is caused by the situation of accessibility to new safety information, which is unequal globally. The regulatory measures implemented in a specific region can be imitated and repeated in other regions in months or years, and, as a result, patients in particular countries remain uninformed of the possible dangers. Such delays may lead to real and concrete social health impacts in the face of the soaring use of off-label GLP-1. This creates the policy consideration as to whether international standardization of safety labeling, despite the challenging logistics, warrants prioritization in the case of most high-impact drugs that may be prevalently used internationally [28]. Ethical and policy complexities indicate that the process of adverse event labeling expansion of GLP-1 drugs is not merely a mechanistic regulatory exercise but rather a highly value-laden exercise. This sector is especially vulnerable to the risks in the communication and mitigation of risks since there is a need to balance the maintenance of clinical innovation and patient choice with a parallel need to protect the population. Since these ethical issues are inseparably knitted to the scientific dilemma of evaluating causality, the following section will discuss the evidence burden regulators must jump to affirm and place adverse events associated with off-label use of GLP-1 in a proper context, and how such a burden affects the speed and accuracy of label revisions.

6. Evidentiary Challenges in Establishing Causality for Label Expansion

The question of whether a new adverse event discovered will be sufficient reason to be included in the safety labeling of a GLP-1 receptor agonist depends on adequate evidence of causality. Nevertheless, the nature of the evidence used to make such judgments tends to be inconsistent and logistically complicated, especially where off-label use comes into the picture. The gold-standard clinical trial data, which are based on authentic efficacy and safety assessment, provide little direction here, as most clinical trials focus on a tightly defined population, and exclude most of the very groups where off-label use patterns prevail [19] [20]. With GLP-1 agents, it implies that signals that are identified in the real-world context, e.g., gastrointestinal obstruction, psychiatric, or hepatobiliary complications that are quite rare, can now become apparent in a population in which the pharmacology of the drug works differently as compared with trial subjects. It is also compounded by the situation that off-label users may have a wider spectrum of comorbidities, other medications taken, and lifestyle issues, which may confound a simplistic appraisal of adverse event reports [21]. Pharmaco-epidemiological research, observational-based cohort research, and case-control research can provide useful work in reinforcing causality, though these types of research are prone to bias. Confounding by indication, especially, is an ongoing issue: the reason a patient is off-label prescribed a GLP-1 agonist (e.g., obesity, metabolic syndrome) may be correlated with the greater prior risk of experiencing the adverse event in question. Unless they are statistically controlled, such background risks may be confused with the effects of the drug [23]. The need to balance biological plausibility and statistical robustness is also an issue that regulators have to solve. In other instances, the adverse event may show at least a plausible mechanistic relationship to the effects of GLP-1 receptor agonist activity, e.g., delayed gastric emptying that predisposes to intestinal obstruction, but the epidemiological data may be limited or show discrepancies. On the other hand, statistically significant results can be obtained as a result of large-scale data-mining activities that have no clear pathophysiological explanation, and the examination presents the possibility that they might be spurious correlations based on reporting bias [24]. Another hurdle is the time lag between the detection of the signal and the synthesis of evidence. The active assessment of a safety signal usually takes years of data collection, especially when dealing with infrequent outcomes. Regulators during this time have to make a choice on whether to take preliminary actions to change labels with parts of evidence or wait until more evidence can be obtained to take the stronger measures, which leads to the eventual delays of inflicting damage. These choices are subject to increased scrutiny by the general population and the medical community in the commercial highly ministry market of GLP-1 medications [25]. Regulatory bodies have increasingly resorted to such concepts of adaptive pharmacovigilance, where warnings may be added temporarily with pledges of post-marketing research. The method allows communicating risks in time and leaves possibilities for refinement in the future due to newly obtained data. These adaptive strategies may be critical in the case of GLP-1 medications that have seen the fast development of safety profiles as a result of off-label use. Having established the evidentiary field of play, the question now shifts to the logistical and practical challenges in carrying out those expansions of labels in the context of GLP-1 receptor agonists, at least when such expansions have to be accomplished across more than one jurisdiction and more than one healthcare system.

7. Operational Challenges in Implementing Global Label Changes for GLP-1 Medications

Although scientific and ethical constraints in the approach of adverse event label expansion of GLP-1 receptor agonists are very demanding, carrying out such changes is an equally complicated affair. The modification of a drug label does not involve merely writing some text somewhere on a package insert but actually planning and organizing the efforts of regulatory agencies, manufacturers, healthcare providers, and, in some cases, even payers. When applied in the context of GLP-1 drugs sold globally, the functional complexity increases with the introduction of multi-jurisdictional coordination and harmonization communications [26] [27]. Regulatory asynchrony is one of the most urgent operating problems. Although a safety signal identified on the international level may seem identical to the regulatory counterparts of various countries, the rate at which individual regulatory agencies process and grant label changes may differ significantly. As an example, a warning about an adverse event can be added to the European label of Semaglutide within weeks after the PRAC decision, whereas the corresponding change in the U.S. label will take months because of further evidence assessment or negotiations with the manufacturer [28]. Such inconsistency in markets confuses due to differences in the information provided, leaving prescribers with no means to make an informed judgment on making a treatment decision based on up-to-date risk profiles, particularly in cross-border telemedicine cases. The second obstacle to operations presents itself in distribution logistics. Whenever a label change has been adopted, the manufacturers should update all packaging of the products, leaflets accompanying the prescribed information, and any online references to the product. In the case of GLP-1 drugs, with complex supply chains and administered in various formulations (pens, vials, combination kits), every medicine in the global marketplace must be updated to the current language of safety, a challenge that is not trifling [29]. Old or new labels might be seen together during the transition time, which may expose inconsistent counseling of the patients. The other vital operational aspect is healthcare provider education. Label changes do not limit risk in a situation where prescribers do not know about them and do not use the new information when making clinical decisions. In the case of GLP-1 agents, where off-label prescribing is so prevalent, conventional methods of dissemination like continuing medical education programs and bulletins will not necessarily reach non-specialists making these prescriptions, in a general practice setting, weight management clinic, or even the cosmetic clinics setting [30]. This emphasizes how specialist-blinded communications that have a particular focus on the clinical utility of new safety communication messages by indication can be required. Operational problems are further confounded when the label expansions deal with complex or nuanced adverse events. As an illustration, there is a caution with gastrointestinal obstruction in users of GLP-1, necessitating prescribers to evaluate symptomological patterns, which might not be easily noticed or harmonize with the anticipated result of the drug, i.e., hindering gastric emptying. There is a need to deliver such risks clearly to prevent fear or confusion without alarm, and this should be done through carefully tailored messaging and training of clinicians. Moreover, there is an opportunity, but also a challenge, that is embodied by digital health systems. In theory, electronic prescribing systems and clinical decision support systems could be modified to warn prescribers of new warnings of adverse events in real time. Nevertheless, the processes of integration between different healthcare IT infrastructures tend to be slow, and in most jurisdictions, the updates are not mandated centrally. The outcome is a checkerboard of varying levels of awareness, with one prescriber informed, literate, and on the ball, and others still plowing away with obsolete knowledge. Lastly, the operational considerations are at the patient level. When the change is about labeling, it has to be conveyed in a manner that patients can interpret, especially in cases where there are complex, uncommon negative events. Considering the subjective interest of the media in GLP-1 drugs as a weight-loss tool, label changes may be misinterpreted due to media reports on excessive safety concerns or safety insufficiencies. Systematic evidence-based communication strategies with patients are thus needed to ensure that the lack of safety and adherence is not triggered by misinformation. Such practical realities imply that in a case where there is no confusion about the scientific rationale behind the label expansion, the effect might not necessarily translate into real life. By resolving such problems, it is essential not only to coordinate the efforts of regulation but

also to involve the active participation of the healthcare systems and consumer advocacy groups. As these issues demonstrate, adverse event label expansion of GLP-1 receptor agonists is a layered activity with science, policy, ethics, and implementation dimensions. An obvious next question is: how may regulatory systems change to better respond to these overlapping needs, a point that is covered in the following section regarding future regulatory strategies.

Beyond the scientific assessment of new risks, the operational reality of implementing label changes reveals a set of recurring bottlenecks that hinder timely global alignment. The table below distills these challenges, their downstream impacts, and strategies that have been proposed to address them.

Table 2: Operational Bottlenecks in the Global Implementation of GLP-1 Adverse Event Label Changes.

Operational Challenge	Impact on Safety Communication	Potential Mitigation Strategy
Regulatory asynchrony between regions	Confusion among multinational prescribers	Joint regulatory review task forces for high-impact drugs
Dual presence of old and new labels	Inconsistent patient counseling	Centralized label version control in supply chains
Limited provider outreach in non-specialist fields	Missed warnings in off-label prescribers	Targeted multi-specialty educational campaigns
IT lags in updating e-prescribing systems.	Delayed clinical decision support alerts	Mandated rapid integration into certified Electronic Health Record (EHR) platforms
Media misrepresentation of label changes	Public misperception of drug safety	Coordinated regulator–manufacturer public statements

Recognizing and addressing these operational bottlenecks is critical to ensuring that label expansions translate into meaningful patient protection. These same operational lessons also inform the design of future regulatory strategies, which aim to enhance responsiveness and coordination across all stages of pharmacovigilance.

8. Future Regulatory Strategies for Managing Adverse Event Label Expansion

This rising rate and severity of adverse event label additions to GLP-1 drugs demonstrate why regulatory approaches should be more flexible and anticipatory, capable of tracking the changing nature of real-world application. The timely pharmacovigilance models currently based on the use of rigid reporting mechanisms and conjunctive updating of the labels are increasingly inadequate in response to immediate changes in prescribing practices, especially concerning high-value agents with high off-label potential [19] [20]. The dynamic labeling systems are one of the promising moves. Dynamic labeling would be used through digital platforms, whereas, in contrast to paperwork, which would need manual updating after some time, even where the information of safety becomes available in real-time to both prescribers and patients. In the case of GLP-1 receptor agonists, it can imply that new adverse events acknowledged by regulators spontaneously get reflected into electronic prescribing systems, patient applications, and official drug information portals [21]. This type of solution would go a long way towards decreasing the amount of time necessary between the identification of risks and the dissemination of the same, effectively eliminating the regulatory asynchrony discussed above. Integrated global pharmacovigilance networks are the other strategy. Although the framework of the WHO Programme for International Drug Monitoring covers the sharing of data, a more organized, real-time collaboration plan between the main regulatory authorities may facilitate the achievement of a consensus and harmonized response. As an example, the GLP-1 safety task force, possessing the ability to collectively review emerging signals and issue unanimous recommendations, could help in assessing the implementation of label changes consistently across jurisdictions [22]. Regulatory bodies can also develop conditional labeling measures for drugs with off-label use that is fast-growing. Within the framework of such a system, the label might include provisional warnings accompanied by attributive notices regarding the degree of evidence and the continuity of the investigation. This gives the ability to ship information on the possibility of risk without an implication of certainty in terms of causality, which can be saved until later when data are more conclusive [23]. Improved post-marketing study requirements are also another area of improvement. In case of GLP-1 agents, regulators should be able to institute specific safety studies in off-label populations, which may include non-diabetic obese individuals, adolescents, or patients with pre-existing disease in the GI tract. These studies would serve to give more firsthand evidence on which to base label expansions and to be less reliant on extrapolations to diabetic cohorts [24]. Cooperation of the people with the state also plays an important role in the former. The manufacturers also have a large amount of real-life data about the use of their products via prescription tracking, patient support programs, and pharmacovigilance operations. It is proposed that further open sharing of these data sets with regulators and independent researchers may improve the rates of evaluation and accuracy of adverse events. In practice, this type of transparency might be useful in describing the actual rate of occurrence of such complications as gallbladder disease or psychiatric symptoms in off-label populations concerning GLP-1 drugs [25]. Last, regulatory approaches should take into consideration risk communication science, which is the science of communicating safety in accurate, accessible, and actionable ways. In the case of GLP-1 receptor agonists, with high levels of media interest, it will involve the need to develop messages that neither sensationalize nor obscure risk, and place new warnings into the context of the known benefit-risk position of the drug [26]. Collectively, these measures serve as a transition towards proactive pharmacovigilance, to guarantee that labels are expanded on adverse events in a coordinated and timely fashion, and by providing substantial evidence. With the GLP-1 agents continuing to innovate the traditional expectations of therapeutic classifications, these sorts of regulatory innovations will be vital to protecting the safety of patients amidst the ongoing discoveries of therapeutic innovation. Under such forward-thinking intentions, it is now possible to draw a conclusion that synthesizes the scientific, ethical, operational, and policy-related facets of adverse event label expansion to GLP-1 receptor agonists in the context of off-label use.

9. Conclusion

An example of the adverse event label expansion of GLP-1 receptor-agonist in the case of off-label use will present a current case study in the mix of pharmacological knowledge, regulatory science, and ethical concerns in the field of clinical ethics. Originally created to manage Type 2 diabetes, these agents have since come to be seen as an example of how even advances in therapeutics can be racing ahead of the systems in place aimed to promote safe and appropriate use. Increasing off-label prescribing, especially for weight loss, has not only widened the demographic and clinical scope of affected patients but has also hastened the development of adverse events once considered infrequent or not observed during trials. Although label expansion seems to be a grounded process based on the scientific review of safety data from post-marketing, it is hardly a technical exercise. It is framed by the uncertainty of evidence, practical circumstances of the drug distribution on the world market, and ethical duties of several stakeholders. Whether it is a precautionary approach to regulators,

commercial openness of producers and manufacturers, or subscriber duties of informed consent, each of the participants acts in a system of obligations, which, in some cases, are mutually reinforcing, and in some cases, they are conflicting. Post-marketing surveillance systems are critical in detecting safety signals associated with GLP-1 medications; however, this success is due to their timeliness, accuracy, and completeness of the report. Under-reporting and confounding by indication are important methodological difficulties in the off-label setting. Regulators should, consequently, walk the fine line between making precautionary alarms that safeguard the health of the population and making such alarms with enough security-based evidence to prevent unjustified alarms or limitations. The coordination of jurisdictional elements of label changes is a significant lynchpin operationally. Asynchronous regulatory processes, unequal provider awareness of strategic options, and disjunctive patient outreach processes can thwart the efficacy of even the most well-founded label expansions in practice. Long chains of distribution of GLP-1 and the variety of execution environments in which prescribers of these drugs operate contribute to further logistical fatigue, and the attention of the general population to these medicines results in an amplification of any safety messaging latency or inconsistency. In the future, we urgently require greater flexibility of regulatory systems that can keep up with the speed of therapeutic uptake and the appearance of safety signals. Real-time/dynamic digital labeling, global networks of pharmacovigilance, conditional warnings, targeted post-marketing research, and better risk communication are all designs that can improve responsiveness and coherence of the label expansion processes. In the end, the history of GLP-1 receptor agonists reminds us of a more universal lesson about pharmacovigilance in this era: the end of a drug does not mark approval. In a world where social, commercial, and clinical pressures have the capacity to transform prescribing environments in a matter of months, regulatory systems have to become real-time as well as internationally collaborative in terms of safety monitoring and communication. It is only by evolving in this way that we can be sure that with the growth in opportunity to provide treatment, we keep pace with a commensurate increase in our ability to guard against harm to the patient.

Table of Abbreviations

Abbreviation	Full Form
GLP-1	Glucagon-like peptide-1
FDA	U.S. Food and Drug Administration
EMA	European Medicines Agency
PRAC	Pharmacovigilance Risk Assessment Committee
FAERS	FDA Adverse Event Reporting System
EHR	Electronic Health Record
WHO	World Health Organization
REMS	Risk Evaluation and Mitigation Strategies

References

[1] Liu, Q. K. (2024). Mechanisms of action and therapeutic applications of GLP-1 and dual GIP/GLP-1 receptor agonists. *Frontiers in Endocrinology*, 15, 1431292. https://doi.org/10.3389/fendo.2024.1431292.

[2] Butler, P. C., Elashoff, M., Elashoff, R., & Gale, E. A. (2013). A critical analysis of the clinical use of incretin-based therapies: Are the GLP-1 therapies safe? *Diabetes Care*, 36(7), 2118-2125. https://doi.org/10.2337/dc12-2713.

[3] Alenzi, K. A., Alsuhaibani, D., Batarfi, B., & Alshammari, T. M. (2024). Pancreatitis with use of new diabetic medications: a real-world data study using the post-marketing FDA adverse event reporting system (FAERS) database. *Frontiers in Pharmacology*, 15, 1364110. https://doi.org/10.3389/fphar.2024.1364110.

[4] Jalleh, R. J., Rayner, C. K., Hausken, T., Jones, K. L., Camilleri, M., & Horowitz, M. (2024). Gastrointestinal effects of GLP-1 receptor agonists: mechanisms, management, and future directions. *The Lancet Gastroenterology & Hepatology*, 9(10), 957-964. https://doi.org/10.1016/S2468-1253(24)00188-2.

[5] Jarow, J. P., & Moscicki, R. (2017). Impact of expanded access on FDA regulatory action and product labeling. *Therapeutic Innovation & Regulatory Science*, 51(6), 787-789. https://doi.org/10.1177/2168479017707800.

[6] Guo, X., Zhou, Z., Lyu, X., Xu, H., Zhu, H., Pan, H., ... & Gong, F. (2022). The anti-obesity effect and safety of GLP-1 receptor agonist in overweight/obese patients without diabetes: a systematic review and meta-analysis. *Hormone and Metabolic Research*, 54(07), 458-471. https://doi.org/10.1055/a-1844-1176.

[7] Li, Y., Wu, Y., Jiang, T., Xing, H., Xu, J., Li, C., ... & Liu, Y. (2023). Opportunities and challenges of pharmacovigilance in special populations: a narrative review of the literature. *Therapeutic Advances in Drug Safety*, 14, 20420986231200746. https://doi.org/10.1177/20420986231200746.

[8] Gupta, S. K., & Nayak, R. P. (2014). Off-label use of medicine: Perspective of physicians, patients, pharmaceutical companies, and regulatory authorities. *Journal of Pharmacology and Pharmacotherapeutics*, 5(2), 88-92. https://doi.org/10.4103/0976-500X.130046.

[9] Bessesen, D. H., & Van Gaal, L. F. (2018). Progress and challenges in anti-obesity pharmacotherapy. *The Lancet Diabetes & Endocrinology*, 6(3), 237-248. https://doi.org/10.1016/S2213-8587(17)30236-X.

[10] Hayes, M. R., Borner, T., & De Jonghe, B. C. (2021). The role of GIP in the regulation of GLP-1 satiety and nausea. *Diabetes*, 70(9), 1956-1961. https://doi.org/10.2337/dbi21-0004.

[11] Hankir, M. K., & Lutz, T. A. (2025). Novel neural pathways targeted by GLP-1R agonists and bariatric surgery. *Pflügers Archiv-European Journal of Physiology*, 477(2), 171-185. https://doi.org/10.1007/s00424-024-03047-3.

[12] Ryan, D., & Acosta, A. (2015). GLP-1 receptor agonists: Nonglycemic clinical effects in weight loss and beyond. *Obesity*, 23(6), 1119-1129. https://doi.org/10.1002/oby.21107.

[13] Rizzo, M., Nikolic, D., Patti, A. M., Mannina, C., Montalto, G., McAdams, B. S., ... & Cosentino, F. (2018). GLP-1 receptor agonists and reduction of cardiometabolic risk: Potential underlying mechanisms. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, 1864(9), 2814-2821. https://doi.org/10.1016/j.bbadis.2018.05.012.

[14] Bednarz, K., Kowalczyk, K., Cwynar, M., Czapla, D., Czarkowski, W., Kmita, D., ... & Madej, P. (2022). The role of GLP-1 receptor agonists in insulin resistance with concomitant obesity treatment in polycystic ovary syndrome. *International Journal of Molecular Sciences*, 23(8), 4334. https://doi.org/10.3390/ijms23084334.

[15] Onoviran, O. F., Li, D., Toombs Smith, S., & Raji, M. A. (2019). Effects of glucagon-like peptide 1 receptor agonists on comorbidities in older patients with diabetes mellitus. *Therapeutic Advances in Chronic Disease*, 10, 2040622319862691. https://doi.org/10.1177/2040622319862691.

[16] Stonehouse, A. H., Darsow, T., & Maggs, D. G. (2012). Incretin-based therapies. *Journal of Diabetes*, 4(1), 55-67. https://doi.org/10.1111/j.1753-0407.2011.00143.x.

[17] He, L., Li, J., Cheng, X., Luo, L., & Huang, Y. (2025). Association between GLP-1 RAs and DPP-4 inhibitors with biliary disorders: pharmacovigilance analysis. *Frontiers in Pharmacology*, 16, 1509561. https://doi.org/10.3389/fphar.2025.1509561.

[18] Chen, W., Cai, P., Zou, W., & Fu, Z. (2024). Psychiatric adverse events associated with GLP-1 receptor agonists: a real-world pharmacovigilance study based on the FDA Adverse Event Reporting System database. *Frontiers in Endocrinology*, 15, 1330936. https://doi.org/10.3389/fendo.2024.1330936.

[19] He, L., Li, Q., Yang, Y., Li, J., Luo, W., Huang,Y., & Zhong, X. (2024). Pharmacovigilance study of GLP-1 receptor agonists for metabolic and nutritional adverse events. *Frontiers in Pharmacology*, 15, 1416985. https://doi.org/10.3389/fphar.2024.1416985.
[20] Moiz, A., Filion, K. B., Tsoukas, M. A., Yu, O. H., Peters, T. M., & Eisenberg, M. J. (2025). The expanding role of GLP-1 receptor agonists: a narrative review of current evidence and future directions. *EClinicalMedicine*, 86. https://doi.org/10.1016/j.eclinm.2025.103363.
[21] Fusaroli, M., Salvo, F., Begaud, B., AlShammari, T. M., Bate, A., Battini, V., ... & Khouri, C. (2024). The Reporting of A disproportionality analysis for Drug safety signal detection using individual case safety reports in Pharmacovigilance (READUS-PV): explanation and elaboration. *Drug Safety*, 47(6), 585-599. https://doi.org/10.1007/s40264-024-01423-7.
[22] Gravel, C. A., & Douros, A. (2023). Considerations on the use of different comparators in pharmacovigilance: a methodological review. *British Journal of Clinical Pharmacology*, 89(9), 2671-2676. https://doi.org/10.1111/bcp.15802.
[23] Agbabiaka, T. B., Savović, J., & Ernst, E. (2008). Methods for causality assessment of adverse drug reactions: a systematic review. *Drug Safety*, 31(1), 21-37. https://doi.org/10.2165/00002018-200831010-00003.
[24] Pore, A. V., Bais, S. K., & Kamble, M. M. (2024). Pharmacovigilance in clinical research. *International Journal of Pharmacy and Herbal Technology*, 2(1), 759-775.
[25] Olsson, S. (1998). The role of the WHO program on International Drug Monitoring in coordinating worldwide drug safety efforts. *Drug Safety*, 19(1), 1-10. https://doi.org/10.2165/00002018-199819010-00001.
[26] Thomson, R., Edwards, A., & Grey, J. (2005). Risk communication in the clinical consultation. *Clinical Medicine*, 5(5), 465-469. https://doi.org/10.7861/clinmedicine.5-5-465.
[27] Dellgren, J. L., Persad, G., & Emanuel, E. J. (2024). International coverage of GLP-1 receptor agonists: a review and ethical analysis of discordant approaches. *The Lancet*. https://doi.org/10.1016/S0140-6736(24)01356-4.
[28] Singh, A., Twomey, K., & Baker, R. (2018). Global pharmacovigilance regulations: call for re-harmonization. *Clinical Trials*, 15(6), 631-632. https://doi.org/10.1177/1740774518801592.
[29] Garg, S. K., Snell-Bergeon, J., Kaur, G., & Beatson, C. (2024). Challenges of GLP analog use for people with type 1 diabetes: Issues with prior approvals and tips for safer use. *Diabetes Technology & Therapeutics*, 26(6), 363-366. https://doi.org/10.1089/dia.2024.0023.
[30] Davis, T. C., Federman, A. D., Bass III, P. F., Jackson, R. H., Middlebrooks, M., Parker, R. M., & Wolf, M. S. (2009). Improving patient understanding of prescription drug label instructions. *Journal of General Internal Medicine*, 24(1), 57-62. https://doi.org/10.1007/s11606-008-0833-4.