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REVIEW ARTICLE

Rationality over convenience: The CDSCO's regulatory ban on irrational antidiabetic fixed-dose combinations in India and its clinical-pharmacological imperatives

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Abstract

Background Fixed-dose combinations (FDCs) have become a mainstay in managing type 2 diabetes in India, offering potential benefits such as simplified regimens, improved adherence, and better glycemic control. However, several irrational FDCs—lacking validated pharmacodynamic synergy or compatible pharmacokinetic profiles—have raised serious safety concerns. In April 2025, the Central Drugs Standard Control Organisation (CDSCO) issued a regulatory ban on multiple antidiabetic FDCs, highlighting critical lapses in drug approval processes.

Objectives To evaluate the regulatory and pharmacological rationale for the CDSCO's ban, assess the evidence gaps in the banned FDCs and outline actionable strategies to strengthen FDC oversight in India and similar low- and middle-income countries (LMICs).

Executive summary In April 2025, the Central Drugs Standard Control Organisation (CDSCO) banned 35 fixed-dose combinations (FDCs), including several commonly prescribed antidiabetic formulations. These products bypassed mandatory central evaluation by entering the market through state licensing authorities (SLAs), in violation of the New Drugs and Clinical Trials (NDCT) Rules, 2019. The regulatory breach underscored the urgent need for centralized oversight to uphold uniform safety and efficacy standards across the country.

Several banned antidiabetic FDCs lacked pharmacological rationale. For instance, the fixed-dose combination of metformin, glimepiride, and dapagliflozin combined drugs with divergent pharmacokinetic profiles and overlapping adverse effect potentials-particularly hypoglycemia and renal complications. Critically, these combinations were not supported by validated evidence of pharmacodynamic synergy. Models such as isobologram analysis or Chou–Talalay combination index were not used to demonstrate any additive or synergistic benefit.

The CDSCO emphasized that irrational combinations pose significant public health risks, including adverse drug reactions, therapeutic failure, and avoidable polypharmacy-especially among elderly and comorbid patients. The 2025 ban represents a decisive step toward restoring scientific rigor in the approval of FDCs.

Recommendations

- Mandate preclinical synergy validation for new FDC approvals using established pharmacodynamic models.
- Strengthen pharmacovigilance systems focused on post-marketing surveillance and real-world effectiveness.
- Develop and maintain a publicly accessible registry of approved FDCs to support rational evidence-based prescribing.

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Methods This review synthesizes regulatory documentation from CDSCO, established pharmacodynamic synergy models (e.g., Chou-Talalay index, isobologram analysis), and clinical pharmacology literature. FDCs were evaluated for pharmacokinetic incompatibility, lack of synergy, overlapping toxicity, and regulatory bypass under the New Drugs and Clinical Trials Rules (2019).

Results Most banned FDCs bypassed CDSCO review, gaining approval through state licensing authorities (SLAs) despite qualifying as "new drugs." These combinations lacked synergy validation and often paired agents with overlapping toxicity profiles. The CDSCO's regulatory intervention reasserts the importance of centralized approval, pharmacological compatibility, and scientific rigor in FDC evaluation.

Conclusions The ban marks a turning point in India's approach to rational pharmacotherapy, with implications for regulatory harmonization, pharmacovigilance, and evidence-based prescribing. It serves as a model for LMICs aiming to balance accessibility with safety and scientific integrity in chronic disease management.

Keywords Fixed-dose combinations (FDCs) · CDSCO regulation · Pharmacokinetics · Drug synergy · Type 2 diabetes · State licensing authorities · LMICs

Introduction

India has emerged as one of the largest global markets for antidiabetic medications, with over 100 million individuals living with diabetes [1, 2]. As the prevalence of chronic diseases continues to rise, the use of fixed-dose combinations (FDCs) has gained popularity due to their potential to improve medication adherence, reduce pill burden, and simplify therapeutic regimens [3–5]. When developed based on sound pharmacological principles—specifically, pharmacodynamic synergy and pharmacokinetic compatibility—FDCs can offer meaningful clinical advantages and support better long-term disease management.

However, the pace at which antidiabetic FDCs have proliferated in India has often outstripped scientific validation and regulatory oversight [6]. Many of these combinations entered the market through approvals granted by state licensing authorities (SLAs), bypassing evaluation by the Central Drugs Standard Control Organisation (CDSCO) [7]. As a result, numerous formulations were made available without adequate evidence of added therapeutic benefit, proper dose titration capabilities, or matching pharmacokinetic profiles. Most critically, they lacked evaluation through established methods of synergy analysis, such as isobologram modeling or the Chou–Talalay Combination Index [8–12].

Recognizing these concerns, the CDSCO issued a pivotal directive in April 2025 (File No. 4-01/2023-DC (Misc. 3)), banning the manufacture, sale, and distribution of several irrational antidiabetic FDCs [13]. Notably, combinations like metformin + glimepiride + dapagliflozin and metformin + voglibose were found to pose serious risks due to fixed-dose inflexibility, pharmacokinetic mismatches, and overlapping adverse effect profiles—particularly in vulnerable populations, such as the elderly and those with renal impairment.

This review aims to examine the regulatory basis, scientific deficiencies, and clinical risks associated with the banned FDCs. It also explores the broader implications for rational FDC development, regulatory harmonization, and public health policy in India and other low- and middle-income countries (LMICs). Ultimately, the goal is to provide a framework for reform that prioritizes pharmacological justification, patient safety, and evidence-based regulation.

Methodology and scope of review

This review was developed through a focused appraisal of regulatory documents, scientific literature, and pharmacological models relevant to the CDSCO's 2025 ban on irrational oral antidiabetic fixed-dose combinations (FDCs).

We began by reviewing the official CDSCO circular issued on April 11, 2025 (File No. 4–01/2023-DC (Misc. 3)), which listed the banned combinations and outlined the reasons for the regulatory action [6, 13]. We also referred to the New Drugs and Clinical Trials (NDCT) Rules, 2019, framed under the Drugs and Cosmetics Act, 1940 [7].These documents provided the legal and procedural basis for evaluating how the banned FDCs bypassed central regulatory approval.

To understand the pharmacological rationale, we conducted a selective literature search on PubMed and Google Scholar. Search terms included the following: "antidiabetic FDCs," "drug synergy models," "isobologram," "Chou–Talalay," and "pharmacokinetic compatibility." We included studies that explained methods for assessing drug combinations or discussed India's FDC policy history.

Each banned combination was assessed across four areas:

1. Pharmacokinetic alignment—whether the drugs had compatible absorption, half-life, and metabolism

2. Pharmacodynamic synergy—whether any published or conceptual models show additive or synergistic effects
3. Dose flexibility—whether the fixed combination allowed titration based on patient needs
4. Clinical evidence—whether supporting trial data or real-world outcomes were available

No primary data were collected. Instead, this review integrates information from official policy circulars, pharmacological standards, and selected published literature. The aim was to assess the scientific and regulatory basis for the banned combinations and understand their potential impact on diabetes care in India.

The regulatory action and legal foundation

On April 11, 2025, the Central Drugs Standard Control Organisation (CDSCO) issued a landmark directive (File No. 4–01/2023-DC (Misc. 3)) instructing all State and Union Territory Drug Controllers to prohibit the manufacture, sale, and distribution of several unapproved fixed-dose combinations (FDCs), including widely prescribed oral glucose-lowering agents [13]. This regulatory action was triggered by findings that many of these FDCs had entered the market through state licensing authorities (SLAs) without the mandatory evaluation and approval from the Drugs Controller General of India (DCGI), in violation of the New Drugs and Clinical Trials (NDCT) Rules, 2019, framed under the Drugs and Cosmetics Act, 1940 [7].

The circular highlighted three key areas of regulatory failure:

- Violation of central approval protocol: These formulations qualified as "new drugs" under Indian law and were therefore required to undergo central evaluation by the CDSCO. However, several were approved at the state level without central review, undermining regulatory consistency and scientific scrutiny.
- Lack of scientific evaluation: The banned FDCs were introduced into the market without being subjected to rigorous clinical trials or pharmacological assessments. In the absence of safety, efficacy, and synergy data, patients were exposed to combinations whose risk–benefit profiles remained unverified.
- Potential public health hazard: The CDSCO raised serious concerns about the possibility of adverse drug reactions, drug-drug interactions, and treatment failures stemming from unreviewed FDCs. It emphasized that the presence of such irrational formulations posed a direct threat to patient safety and public health.

Upon issuance of show-cause notices, many pharmaceutical companies admitted that the licenses had been obtained through SLAs, claiming ignorance of the requirement for central clearance. However, the CDSCO did not accept this rationale, underscoring the importance of national-level regulatory compliance to maintain uniform standards of drug approval across India. The directive also called upon all state authorities to reassess their licensing procedures and to strictly align with central drug laws in the interest of safeguarding public health [14, 15].

Overview of banned oral glucose-lowering agent fixed-dose combinations

The 2025 CDSCO circular included a detailed annexure listing the specific oral glucose-lowering agent FDCs banned from manufacture and sale. These combinations were either voluntarily withdrawn by manufacturers or formally canceled by state regulators following the directive. Each of the listed formulations raised distinct pharmacological concerns, particularly in terms of mismatched pharmacokinetics, overlapping adverse effects, and absence of validated synergy.

Some of the most clinically relevant combinations included:

A. **Metformin + glimepiride + dapagliflozin**

- **Formulation:** Extended-release metformin 500 mg, glimepiride 3 mg, dapagliflozin 10 mg (**Regulatory Reference:** *Sr. No. 3, Annexure, CDSCO Circular, 2025*)
- **Concern**: This triple combination merges three distinct mechanisms—insulin sensitization, insulin secretagogue action, and SGLT2-mediated renal glucose excretion—without any evidence of synergistic efficacy. The lack of titration flexibility and pharmacokinetic misalignment, particularly between sustained-release metformin and immediate-release glimepiride/dapagliflozin, raises safety concerns such as hypoglycemia and renal stress

B. **Glimepiride + metformin**

- **Formulation:** Glimepiride 1 mg, metformin 500 mg (**Regulatory Reference** *Sr. No. 29*)
- **Concern:** While commonly co-prescribed, this combination in fixed ratio has not been subjected to CDSCO evaluation for pharmacokinetic compatibility or clinical benefit in the proposed strengths

C. **Glimepiride + metformin + voglibose**

- **Formulation:** Glimepiride 2 mg, metformin 500 mg (sustained release), voglibose 0.3 mg (**Regulatory Reference:** *Sr. No. 30*)
- **Concern:** This triple FDC heightens the risk of gastrointestinal intolerance and hypoglycemia. The formulation combines agents with non-aligned pharmacokinetic profiles and does not allow for individual dose adjustmen, which is crucial in elderly or renally impaired patients

D. **Metformin + voglibose**

- **Formulation:** Metformin 500 mg (prolonged release), voglibose 0.2 mg (**Regulatory Reference** *Sr. No. 31*)
- **Concern:** Despite being a frequent combination in clinical practice, the fixed-dose version lacks justification through synergy studies and does not accommodate patient-specific glycemic variability

These examples underscore the primary concern: That combinations were being marketed in fixed ratios without adequate scientific support or individualized dosing flexibility. The inclusion of both short-acting and long-acting agents within the same formulation further complicates glycemic control, as mismatches in duration of action can compromise both efficacy and safety.

In all the listed FDCs, there was no evidence presented to CDSCO regarding superior outcomes when compared to sequential or tailored monotherapy. These combinations failed to meet basic regulatory expectations for new drugs under Indian law, justifying their removal from the market.

Scientific evaluation of fixed-dose combination rationality

Fixed-dose combinations (FDCs) are expected to be grounded in rigorous scientific rationale. For oral glucose-lowering agents, this entails demonstrating both pharmacokinetic (PK) compatibility and pharmacodynamic (PD) synergy. The primary scientific justification for any FDC lies in the premise that combining two or more agents offers either enhanced efficacy, improved safety, or both—beyond what can be achieved with each drug administered separately [9, 10, 16].

In the case of the banned combinations, several critical scientific shortcomings were noted:

(1) Pharmacokinetic incompatibility.

Rational FDCs require that the component drugs possess harmonized pharmacokinetic properties, particularly with respect to absorption, half-life, and metabolism. In several banned formulations, such as metformin (extended-release) combined with voglibose (short-acting), the mismatch in onset and duration of action compromised the predictability and consistency of glycemic control. Similar concerns were raised for combinations involving glimepiride (immediate-release) and dapagliflozin, which differ in their peak activity windows. This lack of PK alignment not only undermines therapeutic efficiency but may also heighten the risk of adverse effects.

(2) Absence of synergy validation.

Scientific validation of pharmacodynamic synergy is central to justifying FDC use. Established models such as the Chou–Talalay Combination Index, isobologram analysis (Loewe additivity model), and Bliss independence are widely accepted frameworks for quantifying whether two drugs act synergistically, additively, or antagonistically. None of the banned oral glucose-lowering agent FDCs had undergone such evaluations. Without this data, claims of additive or synergistic benefit remain speculative and unproven. [17]

(3) Fixed-dose rigidity.

Another significant limitation was the absence of titration flexibility. In clinical practice, antidiabetic therapies often require careful dose adjustment based on patient age, renal function, body weight, and glycemic profile. Fixed-dose products that lack individual component adjustability limit a physician's ability to optimize therapy, leading to either subtherapeutic effects or increased toxicity. This rigidity is particularly problematic in elderly or comorbid populations.

(4) Lack of comparative clinical outcomes.

There was no evidence that the banned FDCs offered better clinical outcomes than their individual components administered separately. No head-to-head randomized controlled trials or real-world data analyses were submitted to demonstrate superiority or non-inferiority of the combinations in terms of HbA1c reduction, adverse event profiles, or patient adherence.

Collectively, these deficiencies reveal that the banned combinations were introduced without fulfilling the essential scientific conditions that define rational FDC development. The lack of PK/PD harmony, synergy validation, and dose flexibility undermines the therapeutic justification for their fixed-dose co-formulation. These gaps were central to CDSCO's decision to withdraw these products from the Indian market. These scientific concerns are summarized in Table 1, which outlines the core pharmacological models for assessing synergy in FDCs and the key deficiencies identified in the banned formulations.

Clinical impact of irrational oral antidiabetic FDCs

In clinical practice, the appeal of fixed-dose combinations (FDCs) lies in their potential to simplify treatment regimens, especially in chronic conditions like type 2 diabetes.

Table 1 Key Pharmacological models for assessing FDC synergy and common deficiencies in banned combinations

Concept	Explanation
Isobologram analysis (Loewe additivity)	Predicts whether two drugs act additively or synergistically when combined. Synergy is demonstrated when the combined doses (c1 and c2) are lower than the doses needed individually (C1 and C2) to achieve the same effect: $c1/C1 + c2/C2 < 1$
Combination index (Chou–Talalay method)	Quantifies whether drug combinations are synergistic, additive, or antagonistic based on how effective a dose is at reaching a certain level of response (e.g., ED50, ED75, ED90 — the dose required to produce 50%, 75%, or 90% of maximum effect)
Key issues with banned FDCs	– No proven synergy between components – Overlapping side effects (e.g., low blood sugar, gastrointestinal discomfort) – No option to adjust individual doses for patient-specific needs

Key pharmacological models for evaluating synergy in fixed-dose combinations and common deficiencies in banned formulations. This table outlines core scientific tools used to assess drug synergy—such as the isobologram and Chou–Talalay models—and summarizes common pharmacological flaws in the banned oral antidiabetic FDCs.

ED50, ED75, ED90: effective doses to achieve 50%, 75%, and 90% of a drug's maximum effect. c1, c2: doses of drugs used in combination; C1, C2: doses needed individually to achieve the same effect.

By reducing pill burden and potentially improving adherence, rationally designed FDCs can contribute to better glycemic control. However, when combinations are introduced without scientific justification or flexibility, the risks may outweigh the intended benefits—particularly in vulnerable patient populations.

The oral glucose-lowering agent FDCs banned by CDSCO in 2025 presented several such concerns:

(A) Hypoglycemia risk from sulfonylurea combinations.

Many of the withdrawn formulations involved glimepiride, a sulfonylurea known for its insulin-secretagogue effect. When combined in a fixed ratio with drugs like dapagliflozin or metformin, glimepiride can cause an unpredictable drop in blood glucose levels, particularly when dose titration is not possible. The lack of flexibility in such fixed combinations increases the likelihood of symptomatic and severe hypoglycemia, especially among elderly patients or those with poor nutritional intake.

(B) Lactic acidosis concerns in at-risk groups.

Metformin is a cornerstone of type 2 diabetes management, but its use must be carefully monitored in patients with impaired renal function, heart failure, or advanced age due to the rare but serious risk of lactic acidosis. When combined with other agents in a fixed formulation—such as voglibose—without the ability to tailor doses based on renal function or tolerability, the risk of adverse events may increase. In fixed-dose settings, even a single agent's contraindication becomes a barrier to the entire regimen's safe use.

(C) Gastrointestinal intolerance with combined agents.

Both metformin and voglibose are associated with gastrointestinal side effects, including bloating, abdominal discomfort, and diarrhea. When administered together in a fixed-dose format, these effects may become amplified and intolerable for many patients. Importantly, clinicians are unable to adjust or discontinue one component without discontinuing the entire combination, often leading to poor adherence or premature discontinuation of therapy.

(D) Pharmacokinetic mismatch and therapeutic inefficiency.

Some of the banned FDCs combined drugs with non-aligned pharmacokinetic profiles. For example, extended-release metformin formulated with immediate-release glimepiride or voglibose results in inconsistent glucose-lowering activity throughout the day. This mismatch can lead to suboptimal postprandial control or increase the risk of hypoglycemia at non-targeted times. Clinical decisions require precision, and when drugs with mismatched kinetics are combined in a fixed ratio, that precision is lost.

Taken together, these issues underscore the importance of individualized care in diabetes management. FDCs that limit clinical judgment, restrict dose adjustment, or increase side effects can interfere with effective chronic disease management. The CDSCO's ban was not just a regulatory action; it was a necessary step to protect patients and promote safer, more individualized care.

Indian FDC policy framework: regulatory loopholes

India's pharmaceutical industry is globally recognized for its manufacturing capabilities and cost-effective drug supply [14]. However, the regulatory framework governing fixed-dose combinations (FDCs)—particularly for chronic diseases like diabetes—has long faced scrutiny for inconsistencies in enforcement. [18] Although policy guidelines exist to ensure scientific and clinical rigor in the approval of

FDCs, their implementation has been uneven. This disconnect, between regulation and practice, has allowed irrational combinations to enter and remain in the market.

The CDSCO's 2025 ban on several oral glucose-lowering agent FDCs exposed long-standing structural weaknesses in the approval system, especially regarding the conflicting roles of central and state authorities. Despite clear procedural requirements, many FDCs bypassed the central review process altogether, highlighting gaps in regulatory coordination and oversight.

The 2013 CDSCO policy guidelines: scientific and regulatory requirements

In June 2013, the CDSCO released detailed guidelines outlining the requirements for FDC approval in India. These were designed to ensure that any fixed-dose combination entering the market would be supported by sound scientific and clinical justification. The core expectations include:

- Clearly defined therapeutic need: The combination must serve a specific, well-characterized patient population, with a clinical rationale justifying the simultaneous use of its components.
- Pharmacokinetic and pharmacodynamic compatibility: All active pharmaceutical ingredients (APIs) should have compatible profiles—particularly in terms of absorption, metabolism, and half-life—to ensure synchronized therapeutic action.
- Evidence of enhanced efficacy or safety: The FDC must demonstrate either improved clinical outcomes or a superior safety profile compared to individual agents, supported by clinical trials or strong pharmacodynamic modeling.
- Justification of fixed-dose ratios: The chosen strengths of each component should be justified through dose-finding studies, synergy analysis (e.g., Chou–Talalay or isobologram methods), and population-based pharmacokinetics.
- Stability and bioavailability testing: The final formulation must undergo thorough bioequivalence and stability testing to ensure consistent pharmacological performance over time.

While these requirements provide a robust framework for rational FDC development, their application has often been inconsistent, particularly at the level of state licensing.

Regulatory oversight mechanism: central vs. state conflict

A major contributor to the unchecked proliferation of irrational FDCs in India has been the fragmented regulatory structure. While the CDSCO, through the Drugs Controller General of India (DCGI), is the central authority for approving new drugs, state licensing authorities (SLAs) have often granted manufacturing licenses for FDCs independently, without CDSCO consultation [19].

This regulatory dichotomy has enabled companies to bring fixed-dose combinations to market without central review or compliance with national scientific standards [14, 15]. The CDSCO's 2025 circular explicitly notes that many banned combinations were:

- Not classified or reviewed as "new drugs" under Rule 122E of the Drugs and Cosmetics Rules
- Never submitted for preclinical, pharmacological, or clinical evaluation by the DCGI
- Approved solely by SLAs in contravention of the NDCT Rules, 2019, and the Drugs and Cosmetics Act, 1940

This breakdown in coordinated oversight allowed irrational FDCs to reach patients without adequate scientific justification or risk assessment.

Path forward: strengthening scientific oversight and policy coordination

To prevent such failures from recurring, structural reforms are urgently needed. Based on the lessons of the 2025 ban, the following actions are recommended:

- Centralize All FDC approvals: All fixed-dose combinations—especially those involving chronic disease treatments—must receive mandatory CDSCO-level clearance, regardless of SLA involvement.
- Create a public FDC database: A transparent, regularly updated registry of approved FDCs, including pharmacological data and approval rationale, should be made publicly accessible to clinicians, pharmacists, and researchers.
- Strengthen post-marketing surveillance: A robust pharmacovigilance system is essential to monitor the real-world safety and effectiveness of FDCs, particularly those targeting high-risk populations.
- Standardize SLA training and oversight: State authorities should receive formal training on FDC evaluation protocols and work in close alignment with central regulatory bodies to avoid jurisdictional inconsistencies.
- Educate prescribers and stakeholders: Awareness campaigns for healthcare professionals should reinforce the principles of rational FDC use and help prevent the re-emergence of irrational combinations through off-label promotion or substitution.

While the 2013 policy guidelines were conceptually sound, their fragmented implementation left patients

exposed to unvalidated therapies [20, 21]. The 2025 CDSCO ban marks a significant course correction and offers an opportunity to rebuild regulatory credibility by embedding scientific discipline and transparency into India's drug approval ecosystem (Box 1). The core regulatory challenges, case findings, and proposed reforms discussed above are summarized in Table 2.

Box 1 Case examples of irrational antidiabetic FDCs withdrawn by CDSCO in 2025, reflecting key failures in regulatory vetting and clinical justification

Box 1. Illustrative Examples of Policy Failure: Oral Glucose-Lowering FDCs

Several withdrawn FDCs, such as Metformin + Glimepiride + Dapagliflozin and Metformin + Voglibose, exemplify the intersection of pharmacological irrationality and regulatory oversight failure. These combinations were introduced without central synergy validation, featured mismatched pharmacokinetic profiles (e.g., extended-release metformin with short-acting voglibose), and lacked clinical trial data demonstrating superior outcomes versus individual or stepwise therapies. Their widespread availability despite these shortcomings underscores gaps in regulatory enforcement and highlights the risks posed to patient safety and confidence in national drug policy.

Clinical impact and implications for diabetes care

Fixed-dose combinations (FDCs) have seen growing acceptance in diabetes management due to their potential to simplify treatment regimens, improve patient adherence, and enhance glycemic control. However, their clinical value depends entirely on rational design—anchored in pharmacological compatibility, safety, and flexibility for patient-specific needs.

Best practices recommend starting therapy with individual agents, allowing titration based on clinical response, side effects, and comorbid conditions. Only after achieving stable glycemic control should a switch to an FDC be considered, provided its components are pharmacokinetically and pharmacodynamically compatible.

Unfortunately, many of the banned oral glucose-lowering combinations did not meet these criteria. Their rigid dosing, mismatched pharmacokinetics, and overlapping toxicities posed avoidable risks—especially to older adults and

Table 2 Summary of Indian FDC policy framework and regulatory challenges

Subsection	Focus	Key points
2013 CDSCO Guidelines	Scientific & Regulatory Requirements	– Clearly defined therapeutic need – PK/PD compatibility – Evidence of improved efficacy/safety – Justified fixed-dose ratios – Stability and bioavailability data
Central vs. State Conflict	Regulatory Loopholes	– SLAs granted licenses without CDSCO review – No DCGI clearance despite "new drug" status – Violations of NDCT Rules, 2019
Case Study: Banned FDCs	Real-World Policy Failure	– No synergy or dose optimization evidence – PK mismatches (e.g., metformin SR + voglibose) – No supporting clinical trial data
The Way Forward	Reforms & Recommendations	– Centralized CDSCO clearance – Public FDC registry – Post-marketing surveillance – SLA training and alignment – Prescriber education

Summary of key regulatory challenges and recommendations related to oral glucose–lowering agent fixed-dose combinations in India

patients with renal or cardiovascular disease. The clinical consequences were not theoretical—they were tangible and potentially harmful in everyday practice.

Patient-level risks of irrational FDCs

Hypoglycemia risk

Combinations like glimepiride (a sulfonylurea) with dapagliflozin (an SGLT2 inhibitor) created an exaggerated glucose-lowering effect without glucose-dependent regulation. In fixed doses, especially in older or underweight patients, this led to a heightened risk of symptomatic or severe hypoglycemia [22].

Lactic acidosis with metformin-based FDCs

Metformin carries an established risk of lactic acidosis, especially in patients with renal or hepatic impairment. When combined in a fixed-dose with short-acting agents, such as voglibose, the lack of dose adjustability and duration mismatch increased the chance of drug accumulation and toxicity [23, 24].

Gastrointestinal intolerance and adherence issues

Both metformin and voglibose can cause gastrointestinal side effects. Their co-formulation, especially in extended- and short-acting mismatched forms, compounded GI symptoms—leading to poor tolerability and reduced long-term adherence [25].

Pharmacokinetic discordance

Several banned FDCs paired drugs with mismatched onset and duration of action (e.g., sustained-release metformin with immediate-release glimepiride). As previously established from a pharmacological and regulatory standpoint, many of these banned combinations suffered from pharmacokinetic mismatches. Clinically, this translated to erratic glycemic control, particularly during postprandial periods.

Broader system-level benefits of the CDSCO ban

Encouraging individualized therapy

The removal of irrational FDCs nudges clinicians back toward patient-specific treatment planning. Stepwise therapy—guided by renal function, age, body weight, and glycemic profile—remains the cornerstone of safe and effective diabetes care.

Realigning practice with evidence-based standards

This regulatory action shifts clinical priorities away from convenience and toward validated pharmacological reasoning. It reinforces the importance of dose titration, safety monitoring, and rational sequencing in chronic disease management.

Rebuilding trust in regulatory oversight

India's regulatory framework has at times faced credibility challenges due to inconsistencies and state-level discrepancies. The 2025 ban reflects a renewed commitment to pharmacovigilance, transparency, and scientific accountability—restoring faith among prescribers and patients alike.

Final takeaway

FDCs should support—not override—clinical judgment. When poorly designed, they risk undermining the very goals they aim to achieve. The CDSCO's decision is not just regulatory—it is a shift toward safer, evidence-informed, patient-centered diabetes care.

Actionable recommendations by stakeholder group

The CDSCO's move to ban irrational fixed-dose combinations (FDCs) in antidiabetic therapy offers a critical opportunity for systemic reform in how FDCs are developed, evaluated, and regulated in India. To ensure the long-term success of this initiative, a collaborative framework involving regulators, researchers, industry, and prescribers is essential. Below are specific, actionable recommendations for each stakeholder group:

(A) For regulatory authorities

(i) Centralize approval processes under CDSCO
All FDC approvals should be routed exclusively through the Central Drugs Standard Control Organization (CDSCO). State licensing authorities (SLAs) should not independently approve FDCs, especially when such combinations meet the definition of "new drugs" under current regulatory frameworks.

(ii) Require evidence of pharmacodynamic synergy
FDC applications must include robust experimental data demonstrating synergy or justified additivity. Validated models, such as isobologram plots, Chou-Talalay Combination Index,

or Bliss Independence models, should be mandated to prevent the approval of ineffective or antagonistic combinations [8, 9, 12, 16].

(iii) Implement real-time pharmacovigilance

Strengthen pharmacovigilance by establishing real-time adverse drug event (ADE) surveillance systems specific to FDCs. Integration with electronic medical records and national ADR databases can enable proactive safety monitoring and faster regulatory action [26, 27].

(iv) Launch a public registry of approved FDCs

Develop a transparent, regularly updated national database of all CDSCO-approved FDCs. Each entry should include the pharmacological rationale, clinical trial data, PK/PD compatibility, and approval status to guide prescribers and reduce misinformation.

(B) For researchers and the pharmaceutical industry

(i) Use Validated Models to Demonstrate Synergy

(ii) All FDC development efforts should include quantifiable synergy assessment using methods like Chou-Talalay, bliss independence, or response surface models. This scientific rigor ensures objective evaluation and regulatory credibility.

(iii) Generate pharmacokinetic and drug interaction data

Comprehensive pharmacokinetic studies must accompany FDC proposals, with particular emphasis on compatibility in absorption, metabolism, elimination, and half-life alignment—especially for chronic therapies [8].

(iv) Design comparative clinical trials

Randomized controlled trials comparing the FDC against individual monotherapies or sequential regimens are essential. Such studies should evaluate meaningful outcomes, including glycemic control (e.g., HbA1c), adverse effects, adherence, and quality of life.

(v) Focus on rational FDCs for NCDs

Given the escalating burden of non-communicable diseases in India, research and development should prioritize FDCs that support long-term disease control, minimize adverse effects, enhance adherence, and offer cost-effective treatment options. A coordinated strategy for evidence-based FDC regulation and development is outlined in Tables 3 and 4, detailing actionable recommendations for regulatory authorities and the pharmaceutical industry, respectively [28].

Conclusion

The recent ban on selected antidiabetic FDCs in India marks more than a regulatory intervention—it signals a pivotal turning point in national pharmaco-policy. For years, scientific oversight in the approval of FDCs allowed irrational combinations to enter clinical practice, often justified by perceived convenience or cost-effectiveness. The CDSCO's decision directly addresses this long-standing gap, reaffirming that scientific validity, clinical rationale, and patient safety must remain the cornerstones of drug approval processes.

In a country with the world's second-largest diabetic population, the stakes are especially high. Irrational FDCs—particularly those with incompatible pharmacokinetics or unproven synergistic claims—not only jeopardize therapeutic outcomes but also contribute to adverse events, reduced adherence, and an increased burden on the healthcare system.

India's action offers a compelling model for other low- and middle-income countries (LMICs), where regulatory oversight is often inconsistent. Moving forward, establishing

Table 3 Recommendations for regulatory authorities (CDSCO)

Recommendation area	Action point	Rationale/goal
Centralized approval system	Route all FDC approvals exclusively through CDSCO	Ensures uniform scientific scrutiny and prevents unregulated approvals by State Licensing Authorities
Evidence of synergy	Mandate submission of synergy data using validated models (e.g., Chou-Talalay, Bliss Independence) [8–10, 12]	Prevents approval of irrational, ineffective, or antagonistic combinations
Pharmacovigilance enhancement	Implement real-time ADE surveillance linked to national ADR platforms and EHRs	Enables early detection of adverse events and timely regulatory response
Public FDC registry	Develop a national, publicly accessible database of CDSCO-approved FDC	Promotes transparency, informed prescribing, and reduces confusion among clinicians

This table presents targeted recommendations for regulatory authorities, particularly the Central Drugs Standard Control Organization (CDSCO), to improve oversight, transparency, and scientific rigor in FDC approvals. It emphasizes the need for centralized approval, synergy validation, enhanced pharmacovigilance, and a national FDC registry.

Table 4 Recommendations for researchers and the pharmaceutical industry

Recommendation area	Action point	Rationale/goal
Scientific synergy assessment	Use validated models (Chou-Talalay, Bliss Independence, response surface mapping) to quantify synergy	Provides objective, reproducible evidence of pharmacodynamic compatibility for regulatory review
Pharmacokinetic compatibility	Conduct detailed PK/PD and drug interaction studies	Ensures aligned absorption, metabolism, and elimination; reduces risk of drug accumulation or inefficacy
Comparative clinical trials	Undertake high-quality RCTs comparing FDCs with monotherapy or sequential therapy	Demonstrates real-world effectiveness, safety, and adherence benefits
Focus on NCDs and rational design	Prioritize FDC development for major NCDs with clear therapeutic rationale and long-term disease control	Supports India's healthcare priorities while enhancing adherence and reducing costs

This outlines key recommendations for researchers and the pharmaceutical industry, highlighting the importance of scientifically grounded synergy models, pharmacokinetic compatibility studies, comparative clinical trials, and rational FDC development tailored to the Indian non-communicable disease (NCD) burden.

rigorous scientific criteria for FDC evaluation, aligning state and central approval processes, and embedding evidence-based prescribing into clinical practice are essential steps.

By placing scientific integrity above commercial expediency, India has taken a decisive step toward reshaping the global standards for FDC development and use—especially in the context of chronic disease care. Future regulatory pathways must not only prevent irrational FDCs, but also proactively support rational ones that meet India's unique therapeutic needs.

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Author contribution Shambo Samrat Samajdar (SSS), Shashank R. Joshi (SRJ), and Noor Husain (NH) conceptualized the manuscript and led the regulatory and policy analysis. SRJ and SSS contributed clinical expertise in diabetes pharmacotherapy and critically revised the manuscript for medical accuracy. NH, Shatavisha Mukherjee (SM), and Shravan Venkatraman (SV) conducted the pharmacological synergy evaluation and drafted content on pharmacokinetic incompatibilities.

SSS, NH, SV, Khushboo Bisht (KB), and SM performed detailed reviews of CDSCO communications and regulatory documentation, supporting the legal-policy synthesis. SRJ, KB, SM, NH, and SV conducted literature reviews, synthesized pharmacodynamic models, and contributed to figure and table drafting.

Rajeev Chawla (RC) provided senior clinical oversight and played a key role in the final review and integration of clinical perspectives into the manuscript. SSS, NH, SM, and SV supported scientific writing, reference management, and ensured consistency in methodology throughout the draft. All authors reviewed the final version, contributed important intellectual content, and approved the manuscript for submission.

Data availability All data relevant to this review are publicly accessible and referenced throughout the manuscript. Supporting documents, such as CDSCO circulars and regulatory guidelines, are cited within the text. No additional datasets were generated or analyzed during the current study.

Declarations

Ethics approval Not applicable. This study is a non-interventional policy and scientific review based solely on publicly available regulatory documents and published literature. No human participants, patient data, or institutional permissions were involved.

Competing interests The authors declare no competing interests.

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