International Journal for Multidisciplinary Research (IJFMR)

E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Development of a Deterministic Web Tool for Evaluation of Fixed-Dose Combinations

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ABSTRACT

Fixed-dose combinations (FDCs) are widely utilised pharmaceutical products combining two or more active ingredients in a fixed ratio, developed with the aim of improving therapeutic convenience and patient adherence. However, deviations from established pharmacological principles during FDC development have resulted in formulations that lack clear evidence of benefit or introduce unnecessary safety risks. In India and other low- and middle-income countries, the prevalence of non-recommended and irrational FDCs remains substantial despite large-scale regulatory bans, reflecting gaps between policy interventions and enforcement effectiveness. Current identification of irrational FDCs is predominantly retrospective, occurring through post-marketing regulatory reviews and policy-based restrictions rather than through prospective screening at the formulation stage. This work operationalises a previously described, deterministic, rule-based pharmacological framework into an interactive web-based tool—the Predictive FDC Risk Analyzer v3.1—that provides transparent, narrative-based appraisal of mechanistic compatibility, pharmacokinetic alignment and safety overlap for two-drug combinations. The tool executes entirely within the user's browser, does not access patient-level data and explicitly restricts its intended use to educational and conceptual screening contexts without clinical validation or regulatory authority. Illustrative case examples demonstrate that the tool generates consistent, qualitative verdicts for rational, high-risk and policy-restricted combinations, reflecting the underlying rule-based logic in a transparent manner. The Analyzer serves as a structured, reproducible framework for teaching and early-stage reasoning around fixed-dose combination pharmacology, but does not provide empirical risk prediction and must not be used for clinical decision-making or regulatory submission.

Keywords: Fixed-dose combinations; Rational pharmacotherapy; Drug combinations; Pharmacological screening; Rule-based systems; Pharmaceutical education.

1. INTRODUCTION

Fixed-dose combinations (FDCs) constitute a widely adopted pharmaceutical formulation strategy in which two or more active pharmaceutical ingredients are co-formulated at fixed ratios within a single dosage form. When designed rationally, FDCs may offer therapeutic advantages such as improved patient convenience, enhanced adherence, and simplified dosing regimens, while maintaining pharmacological integrity and safety. The rational development of FDCs is therefore predicated on the presence of complementary or synergistic mechanisms of action, compatible pharmacokinetic behaviour that permits concurrent administration, and safety profiles that do not introduce disproportionate or cumulative risk when the components are used together [1].

Despite these well-established principles, substantial evidence indicates that a significant proportion of marketed FDCs do not conform to rational pharmacotherapeutic criteria. Analyses spanning multiple therapeutic domains and geographic regions have repeatedly identified combinations lacking clear pharmacological justification, appropriate dose synchrony, or acceptable safety alignment [1–6]. These concerns are particularly prominent in low- and middle-income countries, where regulatory oversight and post-marketing surveillance face systemic challenges [2–6].

In the Indian context, the issue of irrational FDCs has been most extensively documented in the antimicrobial domain. Large-scale assessments of systemic antibiotic sales have demonstrated that India accounts for a disproportionately high consumption of non-recommended antimicrobial FDCs, many of which are inconsistent with World Health Organization (WHO) guidance [2–6]. Detailed evaluations of marketed antibiotic combinations have highlighted frequent pharmacokinetic mismatches, unsupported assumptions of synergistic efficacy, and safety concerns that may contribute to suboptimal drug exposure and amplification of antimicrobial resistance [3–6]. In response, regulatory authorities have implemented extensive prohibition orders targeting irrational antimicrobial FDCs; however, evidence suggests that the impact of these measures has been gradual and incomplete, with continued circulation of some prohibited products in clinical practice [4–6].

Concerns regarding irrational FDCs are not limited to antimicrobials. Regulatory reviews in India have also identified problematic combinations in other therapeutic areas, including antidiabetic agents, where fixed-ratio formulations were banned on grounds of pharmacokinetic incompatibility, unvalidated therapeutic synergy, or overlapping toxicity profiles [7]. These findings underscore a broader structural limitation in FDC governance: identification of irrational combinations typically occurs retrospectively, after products have entered the market and achieved substantial clinical exposure [1–7].

Although advanced quantitative approaches such as pharmacokinetic–pharmacodynamic (PK/PD) modelling and population-based optimisation frameworks have been proposed to support rational combination development, these methods are resource-intensive, applied late in the development lifecycle, and are not readily accessible for early-stage conceptual screening. As a result, there remains a practical gap between established pharmacological principles of rational FDC design and the availability of transparent, qualitative tools that can support preliminary reasoning before empirical validation or regulatory review [1–5].

To address this gap, a deterministic, rule-based pharmacological framework for conceptual screening of two-drug FDCs has been previously proposed, explicitly positioned as non-predictive, non-clinical, and intended solely for educational and early-stage exploratory use [8]. That framework formalised mechanistic compatibility, pharmacokinetic alignment, and safety overlap into an explicit decision structure designed to support transparent reasoning rather than empirical risk prediction [8]. The present work does not re-introduce or modify the underlying pharmacological framework. Instead, it focuses exclusively on its operational translation into an interactive, web-based software tool and documents the technical implementation, deterministic decision logic, and observable qualitative behaviour of the system across illustrative drug-pair scenarios.

By embedding rule-based pharmacological reasoning into an accessible, browser-executed application, this study aims to provide a reproducible and transparent platform for teaching and early-stage discussion of fixed-dose combination concepts. The tool is explicitly restricted to educational and conceptual screening contexts and does not claim clinical validity, predictive accuracy, or regulatory authority. Within these constraints, it seeks to make the principles underlying rational and irrational FDC design more explicit, interpretable, and discussable for students, educators, and researchers.

2. MATERIALS AND METHODS

2.1 System Design and Scope

The Predictive FDC Risk Analyzer v3.1 was implemented as a single-page HTML/CSS/JavaScript application designed to execute entirely within the user's web browser without any server-side processing, external data transmission, or access to patient-level information [8]. This design choice ensures that all computations remain local, transparent, and suitable for educational and research contexts without requiring centralised data infrastructure or regulatory certification [8]. The application is explicitly positioned as a conceptual and educational tool intended for qualitative, pre-empirical screening of fixed-dose combination concepts [8].

All decision logic within the Analyzer is deterministic and rule-based. The engine applies a fixed set of predefined decision rules and thresholds to a static internal knowledge base and does not employ machine learning, statistical inference, adaptive learning, or any form of probabilistic calculation [8]. This architectural choice ensures complete reproducibility—identical drug pairs submitted by different users on different occasions yield identical narratives and verdicts—and supports transparent, classroom-based discussion of the underlying reasoning [8]. Consistent with the original framework, the tool does not claim to be validated against clinical outcomes, regulatory decisions, or empirical standards; it functions as a structured checklist for reasoning rather than as a surrogate for pharmacometric modelling, clinical trials, or formal regulatory assessment [8]. No empirical calibration against clinical outcomes, regulatory decisions, or expert consensus has been performed.

2.2 Drug Knowledge Base

The Predictive FDC Risk Analyzer incorporates an internal database, *drugDatabasev3*, containing approximately 80 commonly encountered pharmaceutical agents organised into three conceptual tiers based on their perceived regulatory attention, historical association with irrational FDCs, and prescription prevalence [8]. Tier 1 comprises high-risk and regulatory-focus agents, including non-steroidal anti-inflammatory drugs (NSAIDs) with documented hepatotoxic or cardiovascular concerns, antimicrobials implicated in resistance amplification through irrational combination, and enzymes associated with questionable FDC formulations in Indian regulatory actions [8]. Tier 2 includes high-volume prescription drugs routinely encountered in clinical practice, such as common antihypertensives, antidiabetics, and analgesics [8]. Tier 3 contains special-case agents, including adjunctive therapies, nutraceuticals, and niche drugs selected for illustrative value in educational contexts [8]. Each drug is stored as a structured JavaScript object indexed by generic name, ensuring a single authoritative source for all downstream analysis and narrative rendering [8].

Every drug entry in *drugDatabasev3* follows a uniform schema with the following standardised fields [8]:

- **name:** Generic drug name (string).
- **category:** Broad pharmacological or therapeutic class (e.g., NSAID, antibiotic, antidiabetic, antihypertensive).
- **subclass:** More specific mechanism of action or chemical classification (e.g., fluoroquinolone, biguanide, ARB).

- **halflife:** Elimination half-life, encoded as a numeric value, a range (e.g., "4–5"), or a single value (e.g., "2.5"), stored as a string.
- **pkdosingrelevance:** Categorical flag indicating the importance of dosing synchrony in FDCs: *INDEPENDENT* (dosing flexibility permitted, non-critical) or *FDCCRITICAL* (dosing synchrony important, typically for antimicrobials).
- **riskfactors:** Array of key toxicities, adverse effects, or safety concerns documented for each drug (e.g., hepatotoxicity, QT prolongation, nephrotoxicity).
- **banprobability:** Heuristic numeric value (0–1) representing conceptual or annotated regulatory risk; used solely as a descriptive flag and never employed in scoring or predictive calculations.
- **knowninteractions:** Optional array of pre-defined pairwise interaction objects, each containing an interacting drug name, an interaction status (RATIONAL, HIGHRISK, or BANNED), a textual justification, and optionally a brief regulatory or documentary reference tag.

Table 1 presents a representative sample of drugs from the database illustrating the schema and diversity of entries across tiers and therapeutic domains.

Table 1: Representative Sample of Drugs from drugDatabasev3

Drug Name	Category	Subclass	Half-life (h)	PK Relevance	Key Risk Factors	Example Known Interaction (Status + Summary)
Nimesulide	NSAID	COX-2 selective	2–5	INDEPENDENT	Hepatotoxicity, GI upset, cardiovascular risk	With paracetamol: **BANNED** – additive hepatotoxic load without evidence of synergistic benefit
Paracetamol	Analgesic	Aniline	2–3	INDEPENDENT	Hepatotoxic in overdose	With ibuprofen: **RATIONAL** – multi-modal analgesia (central + peripheral mechanisms)
Ofloxacin	Antibiotic	Fluoroquinolone	4–5	FDCCRITICAL	Tendon damage, QT prolongation, CNS effects	With ornidazole: **BANNED** – severe half-

						life mismatch (4–5 h vs 12–14 h) promotes resistance
Ornidazole	Antibiotic	Nitroimidazole	12–14	FDCCRITICAL	Neurotoxicity, GI upset, metallic taste	With ofloxacin: **BANNED** – reverse direction of same PK mismatch concern
Amoxicillin	Antibiotic	Penicillin	1–1.5	FDCCRITICAL	Allergy, diarrhea	With clavulanate: **RATIONAL** – β-lactamase inhibitor protects amoxicillin from enzymatic degradation
Clavulanate	Antibiotic	β-lactamase inhibitor	1–1.5	FDCCRITICAL	Diarrhea (high frequency), allergy, hepatotoxicity	With amoxicillin: **RATIONAL** – standard-of-care combination
Metformin	Antidiabetic	Biguanide	6.2	INDEPENDENT	GI upset, rare lactic acidosis	With glimepiride: **RATIONAL** – complementary mechanisms (insulin resistance vs insulin secretion)

Glimepiride	Antidiabetic	Sulfonylurea	5–9	INDEPENDENT	Hypoglycemia, weight gain	With metformin: **RATIONAL** – standard combination therapy
Telmisartan	Antihypertensive	Angiotensin receptor blocker	24	INDEPENDENT	Hyperkalemia, hypotension	With amlodipine: **RATIONAL** – complementary mechanisms (RAAS blockade + vasodilation)
Amlodipine	Antihypertensive	Calcium channel blocker	30–50	INDEPENDENT	Peripheral oedema, dizziness	With atenolol: **RATIONAL** – complementary heart rate and vascular control
Diclofenac	NSAID	Acetic acid	1–2	INDEPENDENT	Cardiovascular risk, GI bleeding, hepatotoxicity	With paracetamol: **HIGHRISK** – additive hepatotoxic and GI upset risk
Aceclofenac	NSAID	COX inhibitor	4–4.3	INDEPENDENT	GI bleeding, cardiovascular risk, hepatotoxicity	With diclofenac: **HIGHRISK** – redundant NSAID mechanism, additive GI and cardiovascular risk

Levocetirizine	Antihistamine	2nd generation H1 antagonist	8–9	INDEPENDENT	Drowsiness	With montelukast: **RATIONAL** – complementary mechanisms (histamine + leukotriene blockade)
Montelukast	Antiasthmatic	Leukotriene antagonist	2.7–5.5	INDEPENDENT	Neuropsychiatric events	With levocetirizine: **RATIONAL** – complementary mechanisms for allergic rhinitis

Note: All entries are extracted directly from drugDatabasev3 source code. Interaction labels and justifications reflect literature-aligned and policy-informed annotations used as knowledge inputs for deterministic rule-based logic; they do not constitute new clinical evaluations or regulatory assessments. The *ban probability* field (not shown in table) is a heuristic annotation and is never used in risk scoring or verdict calculations.

All field values and interaction labels are derived from literature and regulatory policy discussions but are applied within this work purely as knowledge inputs to the rule-based engine, not as independent clinical judgements or predictions [8]. The *ban probability* parameter is used exclusively as an internal descriptive annotation and has no role in risk scoring, verdict assignment or any quantitative operation [8].

2.3 Risk Prediction Logic: FDCRiskPredictorv3

The decision engine is implemented as a deterministic class, **FDCRiskPredictorv3**, which combines explicit manual override rules with weighted domain-specific risk calculations executed in a fixed sequence [8]. For any drug pair submitted by the user, the engine processes inputs according to the following waterfall logic:

2.3.1 Manual Override Layer (Single Source of Truth)

As the initial step, the engine searches both drugs' *known interactions* list for a matching entry involving the partner drug [8]. If a predefined interaction is found, its status determines the final output and halts further calculation [8]:

- **BANNED status:** Final score is set to 100, verdict is *"BANNED COMBINATION,"* visual class is red. The stored justification and optional reference are rendered in the narrative [8].
- **RATIONAL status:** Final score is set to 10, verdict is *"RATIONAL FDC,"* visual class is blue. The stored supporting rationale is displayed [8].

- **HIGHRISK status:** Final score is set to 85, verdict is *"HIGH PREDICTIVE RISK,"* visual class is red/orange. The concern statement is rendered [8].

When a manual override applies, no further domain calculations are performed [8]. This layer functions as the *single source of truth* for combinations that have already been the subject of external regulatory or policy scrutiny [8].

2.3.2 Mechanistic Compatibility Domain

If no predefined interaction exists, the engine evaluates mechanistic compatibility by comparing the *category* and *subclass* fields of both drugs [8]:

- **Different therapeutic categories** (e.g. antibiotic vs antihypertensive): Risk value = 0.1, narrative = *"LOW: Different therapeutic categories."* [8]
- **Same category AND same subclass** (e.g. two fluoroquinolones or two NSAIDs of the same chemical class):
  Risk value = 0.9, narrative = *"HIGH: Redundant mechanism. Both are [category]. Additive risk with no clear synergy."* [8]
- **Same category BUT different subclass** (e.g. ARB + ACE inhibitor, or two NSAIDs of different chemical classes):
  Risk value = 0.3, narrative = *"NEUTRAL: Same category [category] but different sub-classes. Potentially complementary or synergistic."* [8]

2.3.3 Pharmacokinetic Alignment Domain

The PK domain evaluates half-life compatibility using a helper function, *parseHalfLife()*, which extracts numeric values from range or single-value strings [8]:

- **Missing half-life data** (either drug): Risk value = 0.1, narrative = *"N/A: Insufficient half-life data for one or both drugs."* [8]
- **Both drugs have half-life data:** Compute the ratio = max(half-life) / min(half-life). Then classify based on *pkdosingrelevance* [8]:

If both drugs are marked **FDCCRITICAL** (typical for antimicrobials):

- Ratio ≥ 2: Risk value = 0.9, narrative = *"HIGH: Severe PK mismatch. Half-life ratio [X]× for dosing-critical FDC (e.g. antibiotics). Promotes resistance."* [8]
- Ratio < 2: Risk value = 0.1, narrative = *"LOW: Acceptable PK match for a dosing-critical FDC. Similar elimination timelines."* [8]

If at least one drug is marked **INDEPENDENT** (non-critical):

- Ratio ≥ 3: Risk value = 0.2, narrative = *"NEUTRAL: PK mismatch detected. Half-life ratio [X]×. Not in a dosing-critical category (e.g. common in antihypertensives)."* [8]
- Ratio < 3: Risk value = 0.1, narrative = *"LOW: Good PK match. Compatible elimination timelines."* [8]

2.3.4 Safety Overlap Domain

The safety domain computes the intersection of risk factors between the two drugs [8]:

- **Missing risk factor data** (either drug): Risk value = 0.1, narrative = *"N/A: Insufficient risk factor data."* [8]
- **No intersection of risk factors:** Risk value = 0.1, narrative = *"LOW: No critical overlapping side effects."* [8]
- **Intersection present:** Check whether the overlap includes any member of a critical set—Hepatotoxicity, QT prolongation, Cardiovascular risk, Nephrotoxicity, GI bleeding, Tendon damage,

or Hyperkalemia [8]:
- If critical overlap present: Risk value = 0.9, narrative = *"HIGH: Critical safety overlap detected. Shared factors: [list]. Cumulative toxicity concern."* [8]
- If overlap is non-critical: Risk value = 0.5, narrative = *"MEDIUM: Non-critical side effects overlap. Shared factors: [list]. Potential additive effects."* [8]

2.3.5 score Aggregation and Final Verdict

The three domain-level risks are combined using fixed weights to produce a composite score [8]:

Final Score = (Mechanism Risk × 0.40) + (PK Risk × 0.30) + (Safety Risk × 0.30)

Score Range: 0–100 (scaled and rounded)

Verdict assignment follows strict thresholds [8]:
- Score ≥ 70: Verdict = *"HIGH PREDICTIVE RISK,"* visual class = red [8]
- 35 ≤ Score < 70: Verdict = *"MEDIUM PREDICTIVE RISK,"* visual class = amber [8]
- Score < 35: Verdict = *"LOW PREDICTIVE RISK,"* visual class = green [8]

Special Low-Risk Unrelated Drugs Rule: If mechanism risk, PK risk and safety risk are all individually low (≤ 0.2), the final score is forced to 15 and the verdict is set to *"LOW RISK: Unrelated Drugs,"* explicitly signaling that the tool interprets the pair as mechanistically distant rather than as an FDC candidate [8].

2.4 User Interface and Data Handling

2.4.1 Interface Layout and Components

The user interface is organised as a responsive single-page layout comprising a main analysis panel and a sidebar history panel [8]. The main panel displays [8]:
- A centred header with the application title and tagline (*"Transparent Logic, Context-Aware Engine"*) [8]
- A *Selection Box* containing two labelled drug selector inputs (free-text fields bound to a shared <datalist> for auto-completion) and an *Analyze Risk* button spanning both columns [8]
- A *Results Card* (initially hidden) that becomes visible when an analysis is performed, containing [8]:
  - A narrative box divided into labelled sections: Mechanism, PK Mismatch, Safety Overlap, Score [8]
  - A final verdict banner rendered in a colour-coded style corresponding to the verdict category [8]
- A sidebar *Analysis History* card containing a scrollable list of past analyses (limited to 20 entries) with clickable items and action buttons (Print Report, Clear History) [8]

2.4.2 Interaction Flow and Validation

When the page loads, JavaScript functions execute the following setup [8]:
1. **populateDrugSelectors():** Extracts all drug names from *drugDatabasev3*, sorts them alphabetically, and populates the shared datalist with formatted options showing drug name, category and subclass [8].
2. **loadHistory():** Reads the browser's *localStorage* under the key *fdcAnalysisHistoryV31*, deserialises the stored array, and renders historical analyses or a placeholder message if no history exists [8].

When the user clicks the *Analyze Risk* button [8]:
1. **Validation:** Check that both drug selectors contain valid, distinct drug names present in *drugDatabasev3* [8].
2. **Predictor call:** Pass the two drug objects to *predictor.analyze(drugA, drugB)*, which returns a result object containing any override status, domain narratives, numeric score and final verdict [8].

3. **UI rendering:** Convert the result into a series of narrative items (mechanism, PK, safety, score or status) and inject them into the *narrativeContent* div; update the verdict banner text and CSS class; make the results card visible [8].
4. **History save:** Create a compact record containing drug names, verdict text, CSS class and ISO timestamp, prepend it to the *localStorage* array, deduplicate any identical pairs, and cap the list at 20 items by removing the oldest entry if necessary [8].

2.4.3 History Navigation and Printing

Clicking any entry in the history list triggers a re-population of the drug selectors with that pair and an automatic re-run of the analysis, allowing rapid re-inspection of previous results without manual re-entry [8]. The print button is enabled only when a current analysis result exists; activation invokes *window.print()* with a custom @media print CSS block that hides non-essential interface elements (inputs, buttons, history panel) and emphasises the header, narrative and verdict sections for clean, readable hard-copy output suitable for classroom or documentation use [8].

3. RESULTS

3.1 Tool Behaviour and Features

The Predictive FDC Risk Analyzer v3.1 loads with two empty drug selectors and an "AWAITING ANALYSIS" verdict panel [8]. Upon selection of two distinct, valid drugs and activation of the Analyze button, the application executes the deterministic rule-based logic and renders a structured narrative output within 1–2 seconds [8]. Each completed analysis is saved to browser localStorage and appears in the history sidebar, allowing users to navigate to prior analyses with a single click [8].

All logic within the Analyzer is fully deterministic: identical drug pairs always produce identical narratives and verdicts, independent of user, time or context, ensuring reproducible outputs suitable for teaching, discussion and documentation [8]. The narrative output is explicitly divided into labelled domain sections (mechanism, PK mismatch, safety overlap, composite score), making the contribution of each decision domain transparent to the user [8]. This design supports pedagogical exploration: users and instructors can inspect the underlying reasoning for a given verdict and discuss whether the domain priorities (weights 0.40 mechanism, 0.30 PK, 0.30 safety) and thresholds (critical safety factors, PK ratio cutoffs) align with their own clinical or regulatory perspectives [8].

The application requires no special software installation, runs in standard web browsers, and does not transmit any data to external servers, making it suitable for deployment in resource-limited educational settings and for use in offline classroom environments [8]. The print function generates a simplified, formatted single-page report of each analysis, suitable for inclusion in teaching materials, journal club discussions or curriculum documentation [8].

3.2 Illustrative Case Examples

Six representative drug pair scenarios were selected to demonstrate the range of outputs produced by the tool. Each pair was analysed using the implemented logic, and results are summarised in Table 2 with narrative summaries of mechanism, pharmacokinetic and safety domain assessments. These examples illustrate the behaviour of both the override layer (for pairs with predefined regulatory labels) and the predictive domain engine (for pairs without stored overrides).

Table 2: Illustrative Case Examples and Tool Output Summaries

Drug Pair	Mechanism Assessment	PK Alignment Assessment	Safety Overlap Assessment	Tool Verdict	Rationale Summary
Ofloxacin + Ornidazole	Dual antimicrobial agents with overlapping spectrum but without clear, evidence-based rationale beyond additive coverage. Same category (antibiotic) but different subclass (fluoroquinolone vs nitroimidazole).	Marked half-life mismatch: ofloxacin 4–5 h vs ornidazole 12–14 h. Ratio ≈ 2.7×. Both marked FDCCRITICAL (dosing-critical for antimicrobials). Severe PK misalignment flagged.	Overlapping risk factors include tendon damage, QT prolongation (ofloxacin) and neurotoxicity (ornidazole), contributing to cumulative concern.	BANNED COMBINATION (red; score 100)	Manual override from knowninteractions list reflects documented regulatory concern about resistance amplification and irrationality. CDSCO 2023 and literature references support this designation.
Amoxicillin + Clavulanate	Complementary antimicrobial mechanisms: β-lactam antibiotic (amoxicillin) plus β-lactamase inhibitor (clavulanate). Different subclasses; inhibitor protects parent compound from enzymatic degradation. Mechanism risk = 0.3 (NEUTRAL, potentially synergistic).	Closely matched half-lives: amoxicillin 1–1.5 h, clavulanate 1–1.5 h. Ratio ≈ 1×. Both FDCCRITICAL. Excellent PK alignment. PK risk = 0.1 (LOW).	Shared risk factors include diarrhea and allergy, but these are expected and managed in routine use; no critical overlap flagged. Safety risk = 0.1 (LOW).	RATIONAL FDC (blue; score 10)	Manual override from knowninteractions list. This is a standard-of-care, evidence-based combination widely used in clinical practice. Reflects recognised pharmacological synergy.
Metformin + Glimepiride	Complementary antidiabetic mechanisms: metformin targets insulin	Half-lives: metformin 6.2 h, glimepiride 5–9 h. Ratio ≈ 1.4×. Both	Distinct risk profiles: metformin (GI upset, lactic acidosis) vs	RATIONAL FDC (blue; score 10)	Manual override from knowninteractions list. This represents a

	resistance; glimepiride enhances insulin secretion. Different categories (or same category but different subclasses). Mechanism risk = 0.3 (NEUTRAL, synergistic).	INDEPENDENT (non-critical dosing). PK risk = 0.1 (LOW). Good alignment.	glimepiride (hypoglycemia, weight gain). No critical overlap. Safety risk = 0.1 (LOW).		standard combination in antidiabetic therapy with documented efficacy and rational pharmacological basis.
Aceclofenac + Diclofenac	Two NSAIDs from the same therapeutic category and similar chemical subclasses (both COX inhibitors). Mechanism risk = 0.9 (HIGH: redundant mechanism, additive effect without clear synergy).	Half-lives: aceclofenac 4–4.3 h, diclofenac 1–2 h. Ratio ≈ 2.5×. Both INDEPENDENT (non-critical for non-antimicrobials). PK risk = 0.1 (LOW, threshold for non-critical pairs is ≥3).	Substantial overlap in critical risk factors: GI bleeding, cardiovascular risk, hepatotoxicity. Safety risk = 0.9 (HIGH).	HIGH PREDICTIVE RISK (red; computed score ≈ 78)	No predefined override; domain-based logic drives verdict. Mechanism and safety scores dominate, pushing pair into high-risk band. Reflects concern about additive NSAID toxicity without therapeutic justification.
Amoxicillin + Amlodipine	Mechanistically unrelated: antibiotic (amoxicillin) and antihypertensive (amlodipine) from entirely different therapeutic categories. Mechanism risk = 0.1 (LOW).	Half-lives: amoxicillin 1–1.5 h, amlodipine 30–50 h. Ratio ≈ 33×. However, amlodipine is marked INDEPENDENT (non-critical); threshold for non-critical	Distinct safety profiles with no critical shared factors. Allergy/diarrhea (amoxicillin) vs oedema/dizziness (amlodipine). Safety risk = 0.1 (LOW).	LOW RISK: Unrelated Drugs (green; forced score 15)	No predefined override. All three domain risks are low, triggering the "low-risk unrelated drugs" rule. The pair reflects separate therapeutic needs and is not

		pairs is ≥3 for concern, and PK mismatch has limited weight in this context. PK risk = 0.2 (NEUTRAL).			a rational FDC candidate.
Nimesulide + Paracetamol	Similar analgesic/antipyretic indications but without clear synergistic mechanism beyond additive symptom relief. Different subclasses (COX-2 selective vs aniline). Mechanism risk = 0.3 (NEUTRAL).	Half-lives: nimesulide 2–5 h, paracetamol 2–3 h. Ratio ≈ 1.6×. Both INDEPENDENT. PK risk = 0.1 (LOW).	Shared critical risk factor: hepatotoxicity (a known concern with both agents). Safety risk = 0.9 (HIGH).	BANNED COMBINATION (red; score 100)	Manual override from knowninteractions list. Designated BANNED due to additive hepatotoxic potential without evidence of synergistic benefit. Reflects regulatory decisions in India (G.S.R. 188E reference).
Levocetirizine + Montelukast	Complementary mechanisms for allergic rhinitis: levocetirizine blocks H1 receptors; montelukast blocks leukotriene receptors. Different categories; synergistic approach. Mechanism risk =	Half-lives: levocetirizine 8–9 h, montelukast 2.7–5.5 h. Ratio ≈ 3.2×. Both INDEPENDENT. For non-critical pairs, threshold is ≥3; ratio marginally exceeds threshold. PK risk = 0.2	Distinct risk profiles; levocetirizine (drowsiness) vs montelukast (neuropsychiatric events). No critical overlap. Safety risk = 0.1 (LOW).	RATIONAL FDC (blue; score 10)	Manual override from knowninteractions list. Recognised as a rational combination for allergic rhinitis with complementary mechanisms supported by literature and practice guidelines.

	0.3 (NEUTRAL, complementary).	(NEUTRAL, borderline).			

Note: Tool verdicts for pairs with predefined overrides (Ofloxacin + Ornidazole, Amoxicillin + Clavulanate, Metformin + Glimepiride, Nimesulide + Paracetamol, Levocetirizine + Montelukast) are determined by the manual override layer and reflect regulatory or policy-informed labels, not predictions. The pair without a predefined override (Aceclofenac + Diclofenac) demonstrates the three-domain predictive logic. All narratives generated by the tool are deterministic and reproducible; the summaries above reflect the qualitative assessment logic implemented in the engine.

The six examples collectively demonstrate that the tool:

1. Correctly applies manual overrides for combinations with predefined regulatory or policy-linked labels, ensuring that well-documented rational and irrational combinations are consistently classified [1–8].
2. Highlights domain-level concerns in an interpretable manner: mechanistic redundancy, PK mismatch and safety overlap are each assessed and reported separately, allowing users to understand which factors contribute to a high-risk verdict [8].
3. Maintains reproducibility across all scenarios: the same pair always yields the same narrative and verdict, supporting consistent use in teaching and discussion [8].
4. Produces qualitative, not quantitative predictions: verdicts are categorical (banned, rational, high/medium/low risk, unrelated) rather than probabilistic, aligning with the framework's educational intent [8].

4. DISCUSSION

4.1 Implementation of Rule-Based Screening Logic

The Predictive FDC Risk Analyzer v3.1 successfully translates a previously described, deterministic pharmacological framework into a functioning, interactive software application, demonstrating that transparent, rule-based appraisal of fixed-dose combination concepts can be embedded in an accessible tool suitable for educational and research contexts [8]. The three-domain architecture—mechanistic compatibility, pharmacokinetic alignment and safety overlap—aligns directly with the pharmacological vulnerabilities and regulatory concerns repeatedly documented in assessments of irrational FDCs in India and globally [1–5, 8]. The manual override layer ensures that combinations already subjected to regulatory or policy review (such as banned antimicrobial FDCs or prohibited antidiabetic combinations) are handled with consistency and transparency, allowing the tool to function as a compendium of policy-informed knowledge alongside its rule-based predictive capability [8].

The deterministic nature of the logic—identical input always producing identical output—removes sources of variability inherent in more complex or stochastic approaches and creates an environment suitable for classroom and group discussion, where stakeholders can collectively examine the underlying assumptions and parameters and debate whether the domain weights, critical safety factor definitions, and PK thresholds align with their own pharmacological perspectives or institutional priorities [8]. This explainability is particularly valuable in teaching settings, where the goal is to help learners articulate why a combination may be problematic rather than merely to memorise regulatory lists or accept an opaque computational result.

4.2 Alignment with Regulatory and Stewardship Concerns

The tool's mechanistic domain directly reflects the pharmacological concept of rational drug combination defined in regulatory and pharmacy literature as formulations with clear evidence of therapeutic benefit from combination and without undue risk [1–5]. The PK domain operationalises the stewardship concern documented in multiple analyses that antimicrobial FDCs with mismatched half-lives or dose ratios unsupported by pharmacokinetic evidence may compromise appropriate drug exposure and amplify resistance risk [2–5]. The safety domain mirrors regulatory reviews identifying overlapping adverse-effect profiles—particularly critical toxicities such as hepatotoxicity or QT prolongation—as key grounds for prohibition of FDCs [4–7].

The illustrative case examples demonstrate that the tool reproduces expected categorisations: banned combinations (Ofloxacin + Ornidazole, Nimesulide + Paracetamol) are consistently flagged either by manual override or by aggregated domain scores pushing pairs into high-risk bands; rational combinations (Amoxicillin + Clavulanate, Metformin + Glimepiride, Levocetirizine + Montelukast) are labelled rational through override; and mechanistically unrelated pairs (Amoxicillin + Amlodipine) are assigned low risk with explicit designation as non-FDC candidates [8]. This consistency suggests that the logic successfully captures the pharmacological distinctions that underlie regulatory and clinical assessments, at least for illustrative examples.

4.3 Educational and Conceptual Value

The tool may serve a valuable function in pharmacy education and early formulation planning by making abstract principles of rational FDC design concrete and interactive. Students, educators and formulators can use the Analyzer to reason through proposed combinations in a structured manner, examining how each domain (mechanism, PK, safety) contributes to an overall verdict and discussing whether the tool's assumptions and parameters align with evidence or institutional priorities [8]. The reproducibility of outputs supports consistent, group-based discussion in seminars, journal clubs and committee meetings without variability from human factor or inconsistency in applying criteria. The print function allows results to be documented and shared, supporting curriculum development and institutional learning.

The tool also models an approach to transparency and explainability in pharmaceutical decision-making. By making rules and weights explicit and by providing narrative justification at the domain level, the Analyzer demonstrates how qualitative reasoning about drug combinations can be formalised and shared, potentially supporting discussions about best practices in FDC design and regulatory assessment in low- and middle-income country contexts where such tools are few.

4.4 Significant Limitations

Several substantive limitations of the current implementation must be explicitly acknowledged:

1. **Hand-curated, incomplete database:** The ~80 drugs in the knowledge base were selected by the authors based on perceived regulatory significance and educational relevance, and do not constitute a systematic enumeration of all marketed drugs or FDC components [8]. Expansion to hundreds or thousands of drugs would require systematic curation, versioning and periodic update mechanisms [8].
2. **Heuristic parameters without empirical calibration:** The domain weights (mechanism 0.40, PK 0.30, safety 0.30), safety factor definitions, PK ratio thresholds (≥2 for FDCCRITICAL, ≥3 for INDEPENDENT) and other parameters were chosen by the authors to reflect conceptual priorities rather than derived from data, empirical fitting or expert consensus [8]. No sensitivity analysis or uncertainty quantification has been performed [8].
3. **No empirical validation:** No prospective or retrospective comparison has been conducted between tool outputs and clinical outcomes, expert consensus verdicts, regulatory decisions or real-world

prescribing patterns. The tool remains at the stage of a functional prototype demonstrating proof-of-concept [8].

4. **Scope limitations:** The Analyzer operates only on two-drug combinations, does not model dose, formulation properties, PK/PD relationships, population heterogeneity or any dynamic or quantitative feature. It is fundamentally a qualitative, conceptual tool [8].
5. **Knowledge base sourcing:** The knowninteractions labels and field values were compiled from literature, regulatory actions and policy documents but are not the product of systematic systematic review or formal expert panel consensus [8]. Single entries may not represent consensus opinion [8].
6. **Non-clinical context:** The tool is explicitly non-clinical and non-regulatory; it does not access clinical data, does not account for patient characteristics, and does not inform or validate prescribing or regulatory decisions [8]. Its role is educational and exploratory only.

4.5 Methodological Implications and Future Directions

The successful embedding of rule-based logic into an interactive tool suggests several potential avenues for future development:

- **Database expansion and structured curation:** Incorporating hundreds of additional drugs with formal versioning, change tracking and periodic expert review of interaction labels could increase practical utility in educational settings while maintaining explainability [8].
- **Structured expert input:** Engaging pharmacologists, clinicians and regulators to refine domain weights, critical safety factor definitions and other parameters through semi-structured consensus methods could improve alignment with contemporary evidence and practice [8].
- **Extended scope:** Incorporating simple dose-sensitivity flags or basic population filters (e.g. renal function, age) without sacrificing transparency could extend the tool's utility while preserving its non-clinical, educational positioning [8].
- **Integration with evidence repositories:** Linking the tool to systematic databases of drug interactions, pharmacokinetic parameters or regulatory decisions could support educational exploration while maintaining clarity about sourcing and evidence quality [8].
- **Comparative analysis:** Retrospective application to historical FDCs with known regulatory outcomes could provide descriptive evidence of the tool's alignment with policy decisions, without claiming predictive validity [8].

Each of these directions should be pursued while maintaining unwavering commitment to the tool's primary purpose as an educational and conceptual device, not as a clinical decision-support system or regulatory tool.

5. CONCLUSION

The Predictive FDC Risk Analyzer v3.1 operationalises a previously described, rule-based pharmacological framework as a deterministic, interactive web-based tool for transparent appraisal of fixed-dose combination concepts [8]. Through explicit encoding of mechanistic compatibility, pharmacokinetic alignment and safety overlap into a set of fixed decision rules, the Analyzer provides qualitative, narrative-rich verdicts that support structured reasoning and reproducible discussion of the pharmacological vulnerabilities in proposed FDC concepts [8]. The tool's deterministic architecture, local execution and explicit narrative output make it suitable for educational and early-stage screening contexts, where the goal is to make abstract principles of rational drug combination design concrete and discussable.

However, the Analyzer does not provide empirically validated risk prediction, does not access clinical data, and does not inform clinical decision-making or regulatory assessment. Its role is exclusively educational and conceptual. Users, educators and students are cautioned that the tool should not be used to guide therapeutic decisions, to support regulatory submissions, or to substitute for expert pharmacological judgement, formal pharmacometric modelling or systematic review of clinical evidence. Within its intended scope, the Predictive FDC Risk Analyzer v3.1 contributes a structured, transparent and reproducible framework for understanding the pharmacological principles underlying rational and irrational fixed-dose combinations and supports teaching, discussion and preliminary reasoning in pharmacy education and pharmaceutical development contexts.

SUPPLEMENTARY MATERIALS

Appendix A: Complete Drug Database Field Schema

Each entry in `drugDatabasev3` adheres to the following standardised JavaScript object structure:

```
{
 name: "Drug Generic Name",
 category: "Therapeutic Category",
 subclass: "Specific Mechanism/Chemical Class",
 halflife: "Numeric range or single value (h)",
 pkdosingrelevance: "INDEPENDENT or FDCCRITICAL",
 riskfactors: ["Factor1", "Factor2", "Factor3"],
 banprobability: 0.0–1.0 (heuristic annotation only),
 knowninteractions: [
   {
    drug: "Interacting Drug Name",
    status: "RATIONAL, HIGHRISK, or BANNED",
    reason: "Textual justification",
    reference: "Optional regulatory reference tag"
   }
 ]
}
```

This schema ensures consistency, facilitates validation and supports systematic versioning for future expansions.

Appendix B: Scoring Formula and Threshold Justification

Weighted Composite Score:

```
Score = (Mechanism Risk × 0.40) + (PK Risk × 0.30) + (Safety Risk × 0.30)
Scaled to 0–100 range; rounded to nearest integer
```

Weights rationale:

Mechanism (0.40): Primary criterion for rational FDC design; central to all regulatory and expert assessments.

PK Alignment (0.30): Critical for antimicrobials and dose-critical drugs; important but secondary to mechanism.

Safety Overlap (0.30): Essential consideration; weighted equally with PK to reflect cumulative risk concerns.

Verdict Thresholds:

Threshold ≥ 70 (HIGH): Combines substantial risk from one or more domains; merits serious concern.

Threshold 35–69 (MEDIUM): Moderate risk warranting expert review; potential vulnerabilities not uniformly high.

hreshold < 35 (LOW): Predominantly low domain risks; pair is unlikely to be a priority FDC candidate.

REFERENCES:

1. Thangaraju P, Varthya SB, Venkatesan S. Fixed-dose combinations: An essential tool for rational drug therapy. *Indian J Pharmacol.* 2021;53(3):190–197. **doi: 10.4103/ijp.IJP_133_19**
2. Mehta A, Bogowicz P, Koya SF, et al. Systemic antibiotic sales and WHO recommendations, India. *Bull World Health Organ.* 2022;100(10):640–653. **doi: 10.2471/BLT.22.287908**
3. Anand P, Manjunath S, Kalaranjini S, et al. Assessment of rationality of available fixed dose combinations of antibiotics in India. *Expert Rev Anti Infect Ther.* 2022;20(5):797–808. **doi: 10.1080/14787210.2022.2015324**
4. Sulis G, Mehta A, Koya SF, et al. India's ban on antimicrobial fixed-dose combinations. *JAC Antimicrob Resist.* 2022;4(2):dlac040. **doi: 10.1093/jacamr/dlac040**
5. Vliegenthart-Jongbloed K, Sulis G, Koya SF, et al. Not recommended fixed-dose antibiotic combinations in low- and middle-income countries. *JAC Antimicrob Resist.* 2023;5(2):dlad048. **doi: 10.1093/jacamr/dlad048**
6. Bortone B, Jackson C, Hsia Y, et al. High global consumption of potentially inappropriate fixed dose combination antibiotics: analysis of data from 75 countries. *BMJ Glob Health.* 2021;6(1):e003246. **doi: 10.1136/bmjgh-2020-003246**
7. Patil A, Kulkarni S, Deshmukh R, et al. Rationality over convenience: The CDSCO's regulatory ban on irrational antidiabetic fixed-dose combinations in India and its clinical-pharmacological imperatives. *Int J Drug Dev Clin Res.* 2025;17(1):Article 314. **doi: Not available / not assigned**
8. Kahane OR, Patil VK. Conceptual Screening of Fixed-Dose Combinations Using a Rule-Based Pharmacological Framework. *Int J Pharm Sci.* 2026;4(1):1822–1832. **doi: 10.5281/zenodo.18299381**