

Engineering Epistemic Resilience: Overcoming Ontological Fragmentation in Pharmaceutical AI

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DOI:10.37819/Jaike.26.0019

Article history:

Received : 15.03.2026

Revised : 14.08.2026

Accept : 15.08.2026

Published : 21.10.2026

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Abstract: Pharmaceutical quality regulatory oversight remains constrained by legacy ontologies that collapse complex engineered drug products and manufacturing processes into static legal descriptors. This ontological fragmentation generates persistent epistemic vulnerabilities, as demonstrated by recurring therapeutic equivalence failures and the inability of current systems to detect clinically meaningful divergence between regulatory assertions and real-world performance. This Perspective proposes Forced-Contradiction Retrieval (FCR) embedded within a five-layer CMC-GraphRAG architecture as a conceptual mechanism to address these limitations. FCR introduces an antithesis pathway that systematically juxtaposes regulatory assertions with structured mechanistic priors and patient-reported outcomes, quantifying divergence through Semantic Friction (ΔSF), a continuous conceptual measure of ontological misalignment. The framework integrates foundational pharmaceutical ontologies (POPE and COPE), the NIPTE-FDA Excipients Knowledge Base, and New Prior Knowledge (NPK) to enable proactive detection of ontological drift and reverse-causal mapping from real-world evidence to critical quality attribute failures. By transforming retrieval from confirmatory to contradiction-seeking, the proposed architecture aims to support more resilient, evidence-aligned regulatory decision-making that reflects the human-centric aspirations of Pharma 5.0. Implementation challenges and a research agenda for formalizing ΔSF and related metrics are outlined. The work invites the JAIKE community to advance epistemically robust, contradiction-aware AI systems for pharmaceutical regulation.

Keywords: Ontological fragmentation, forced-contradiction retrieval, semantic friction, CMC-GraphRAG, new prior knowledge, pharmaceutical AI, antithesis, reverse-causal mapping, patient outcomes

1. INTRODUCTION

More than two decades after the San Francisco Chronicle's investigative series Prescription for Trouble documented systemic failures in generic drug quality, therapeutic equivalence, and FDA oversight (Abate & Wallack, 2002), and the Wall Street Journal warned that pharmaceutical manufacturing had fallen behind even the makers of commodity products (Abboud & Hensley, 2003), the same fundamental questions remain unresolved. In 2025, the U.S. Senate convened hearings under the nearly identical title Generic Drugs: Prescription for

Trouble (U.S. Senate Special Committee on Aging, 2025).

The persistence of these concerns forces a single, disquieting question: why?

These challenges were explicitly acknowledged in FDA's 2004 white paper Innovation and Continuous Improvement in Pharmaceutical Manufacturing (U.S. FDA, 2004), which highlighted the industry's lag in manufacturing science, fragmented knowledge management, and the systemic inability to translate scientific understanding into reliable product performance. Yet despite two decades of awareness

and repeated calls for modernization, the underlying regulatory ontology has remained largely static. As Russell Ackoff observed, the answer to “why?” for any system lies outside the system itself (Ackoff, 1991), and as W. Edwards Deming emphasized,

quality frameworks from 2004 onward and envisions advancing the system toward alignment with Pharma 5.0, the pharmaceutical manifestation of Industry 5.0, which prioritizes human-centric intelligence, epistemic resilience, and sustainable quality systems

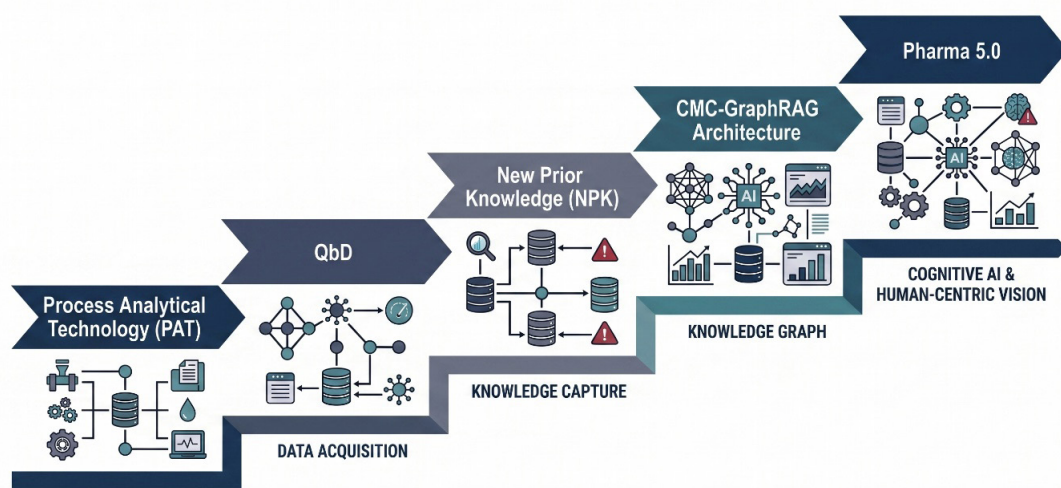


Figure 1. Evolutionary trajectory of regulatory pharmaceutical quality frameworks from 2004 to the present, showing the progression from Process Analytical Technology (PAT) through Quality by Design (QbD) and New Prior Knowledge (NPK) to the proposed CMC-GraphRAG architecture and the human-centric vision of Pharma 5.0

most failures are common-cause failures rooted in the structure and design of the system (Deming, 1993). This Perspective therefore adopts an external vantage point to examine why meaningful solutions have struggled to emerge from within the existing regulatory ontology.

With more than 90 % of U.S. prescriptions filled by generic drugs—many manufactured overseas—and with reshoring efforts accelerating amid geopolitical volatility, the stakes are higher than ever.

This paper reflects on two decades of reform efforts, from FDA’s 2004 Process Analytical Technology (PAT) initiative and its later call for “One Quality Voice” (U.S. FDA, 2004, 2015) to the persistent struggle to move pharmaceutical manufacturing beyond Industry 2.0 thinking (Arden et al., 2021). In this context, the present work traces the evolutionary trajectory (Figure 1) of regulatory pharmaceutical

over purely technological optimization (European Commission, 2021).

Using a contemporary case example, this Perspective illustrates the ontological limits, fragmentation, and structural contradictions embedded in the regulatory language of pharmaceutical quality and therapeutic equivalence. Building on foundational developments in pharmaceutical engineering ontologies from the Venkatasubramanian group—including the POPE (Hailemariam & Venkatasubramanian, 2010) and subsequent work on domain-specific CMC ontologies, such as the SUSIE framework (Mann et al., 2023)—as well as recent advances in ontology-driven CMC information extraction (Taskiran et al., 2025), this paper introduces a conceptual five-layer CMC-GraphRAG architecture. While systems such as SUSIE demonstrate the value of ontology-based extraction of structured knowledge from

unstructured CMC documents, the present work extends that foundation by proposing FCR as an antithesis-generating mechanism. FCR computes Semantic Friction (ΔSF) between regulatory assertions and real-world patient-reported outcomes supported by mechanistic failure modes (Hussain et al., 2026). The proposed framework aims to enable more robust integration of real-world evidence, support proactive detection of ontological drift, and facilitate reverse-causal mapping from real-world signals to underlying material-science and process-engineering criticalities.

2. THERAPEUTIC EQUIVALENCE: EPISTEMIC VULNERABILITIES IN ONTOLOGICAL FRAGMENTATION

The regulatory ontology governing pharmaceutical quality was effectively hard-coded in the Federal Food, Drug, and Cosmetic Act of 1938 and Title 21 of the Code of Federal Regulations (CFR). Enacted in response to the Elixir of Sulfanilamide tragedy—in which more than one hundred people, mostly children, died after ingesting a liquid formulation containing diethylene glycol—the statute classified excipients as “inactive ingredients,” a framing that persists to this day. Although FDA reviews and approves finished drug products, the regulatory ontology remains centered on the active ingredient, reflected in the very name “New Drug Application” (NDA and Abbreviated NDA, ANDA). The agency’s own historical account continues to refer to the episode as the “Sulfanilamide Disaster,” even though enforcement authority was triggered not by toxicity itself, but by misbranding: the product was labeled an “elixir,” a statutory term for a hydroalcoholic solution, yet contained no ethanol (U.S. FDA, n.d.).

This ontological rigidity is carried forward into contemporary practice. In the NDA/ANDA context, placebo-controlled trials are the gold-standard pathway because subtle differences in appearance, sensory cues, or user experience can influence patient perception, adherence, and reported outcomes. Yet in the generic space, the same regulatory system asserts that differences in color, shape, and appearance are inconsequential—even though real-world evidence shows that such variations can disrupt adherence, trigger confusion, and alter patient behavior. The pattern extends to more complex delivery systems. For example, the adhesive performance of a transdermal system—an attribute that directly affects

dose delivery and should clearly qualify as a critical quality attribute—remains only a draft regulatory proposal more than a decade after being identified as such (Wokovich et al., 2006; U.S. FDA, 2021b).

These observable effects on adherence and patient behavior function as real-world proxies for gaps in the assurance of therapeutic equivalence (Kesselheim et al., 2013). They reveal a deeper contradiction within the regulatory framework: while the NDA context demands rigorous empirical and perceptual control, the generic pathway tolerates semantic looseness and categorical ambiguity in determinations of pharmaceutical equivalence to maximize competition and reduce costs. Quality assurance thus becomes inseparable from real-world effectiveness via evidence of Therapeutic Equivalence. Nevertheless, recurring CGMP violations and ineffective CAPA investigations frequently conclude with “root cause unknown,” leaving underlying failure modes uncorrected. This persistent inability to trace, explain, and remediate failures is not merely an operational shortcoming—it is a predictable consequence of an ontology that treats sameness as a regulatory assertion rather than a mechanistic or experiential truth.

The following subsections use case examples to illustrate how these ontological limits and embedded fragmentations create, reinforce, and often lock in epistemic vulnerabilities across the product life cycle.

2.1. Pharmaceutical Equivalence of OROS and Non-OROS Mechanisms

By regulatory definition, pharmaceutical equivalents contain the same active ingredient, in the same amount, and in the same dosage form and route of administration (21 CFR § 314.3; U.S. FDA, 2014). In the methylphenidate case, the dosage form is an extended-release tablet.

The OROS reference listed drug (RLD) is engineered as a rigid, semi-permeable cellulose acetate membrane surrounding a tri-layer core: two active layers with different methylphenidate concentrations and a third “push” layer of osmotically active polymers. Water enters through the membrane, swelling the push layer and forcing drug out through a laser-drilled orifice, producing a precisely ascending release profile over 10–12 hours. The RLD delivers an immediate-release overcoat (~22% of the total dose) followed by a steadily increasing

osmotic release. In late 2012 and early 2013, FDA approved two non-OROS generic versions—Generic A (diffusion-controlled polymer matrix) and Generic B (extended-release bead technology)—under Abbreviated New Drug Applications. The ANDA pathway permits reliance on FDA’s prior findings of safety and effectiveness for the RLD, requiring only demonstration of therapeutic equivalence (21 U.S.C. § 355(j)). Both generics incorporated an immediate-release component intended to deliver a comparable early burst. For the extended phase, Generic A used a hydrophilic polymer matrix, while Generic B used multi-particulate beads with varying coating thicknesses. Although optimized to meet then-current bioequivalence criteria (C_{max} and total AUC within 80–125% of the RLD), subsequent FDA investigations revealed that some of these non-OROS mechanisms could not reproduce the ascending release profile under real-world gastrointestinal conditions, resulting in significantly lower exposure in the critical 7–12-hour window. In 2014, the FDA downgraded both products from AB-rated (substitutable) to BX-rated (evidence of equivalence insufficient) and issued revised bioequivalence guidance requiring partial AUC metrics (U.S. FDA, 2014). In October 2016, FDA proposed full withdrawal of the ANDAs, citing lack of substantial evidence that the products would produce the effects claimed in their labeling (U.S. FDA, 2021a).

2.2. External Observations and the Need for External Reform

This case echoes earlier episodes, such as the cyclosporine “modified solution” controversy, in which the reference product formed a microemulsion upon dilution while a particular generic formed solid dispersions—yet both were deemed pharmaceutically equivalent under the same legacy ontology (Abate & Wallack, 2002). In both instances, the regulatory construct of “sameness” preserved an ontological fiction long after real-world performance had diverged. Historically, sponsors could legally cherry-pick and withhold unfavorable bioequivalence studies. The system responded only when whistleblowers or self-disclosure exposed discrepancies. Only in 2009 did FDA mandate submission of all bioequivalence studies, closing one avenue of ontological manipulation (U.S. FDA, 2009).

The AB-to-BX (not interchangeable) downgrade is rare and consequential. It effectively revokes automatic substitutability and signals that FDA has determined the evidence of therapeutic equivalence to be insufficient. In the methylphenidate extended-release case, the downgrade reflected a mechanistic design failure: two non-OROS generics could match early pharmacokinetic parameters but could not reproduce the ascending release profile required for therapeutic performance in the later dosing window. The decision formally acknowledged that a legacy regulatory ontology centered on legal sameness had failed to capture clinically meaningful divergence (U.S. FDA, 2021a).

The FDA Adverse Event Reporting System (FAERS) itself illustrates the downstream consequences of this fragmentation. As a passive, voluntary reporting system, it suffers from profound underreporting, reporting biases, missing denominator data, and inconsistent manufacturer and lot identification (Hazell & Shakir, 2006). These structural limitations mean FAERS can detect only the largest or most obvious failures—and even then, often only after substantial delay. Because it captures patient-reported events without mechanistic linkage, FAERS becomes a downstream reflection of upstream ontological errors.

2.3. Global Manufacturing Geography and Systemic Quality Risk

Epistemic vulnerabilities created by ontological fragmentation extend beyond isolated cases. Large-scale empirical evidence confirms that these risks are systemic and closely linked to manufacturing (Noh et al., 2025). Analyses of serious adverse event rates across thousands of generic drugs, using exact matching based on FDA therapeutic equivalence criteria, show that generics manufactured in certain emerging-economy locations are associated with significantly higher rates of serious adverse events than equivalent generics manufactured in higher-regulation environments. The disparity is most pronounced for mature generic products subject to aggressive cost-reduction pressures—precisely the segment where narrow therapeutic index drugs are most vulnerable (Hussain et al., 2019).

A profound language barrier compounds this risk. Ontology and language are inseparable: what one culture or regulatory tradition regards as an “inactive ingredient” or a “minor process deviation” may carry

entirely different conceptual weight elsewhere. This mismatch is amplified by behavioral defaults—such as habitual reliance on arbitrary 10× scale-up factors or treating a single bioequivalence trial as “pivotal” evidence—that unconsciously anchor interpretation of quality and risk across global teams. These patterns reinforce the conclusion that a regulatory ontology anchored in legal “sameness” fails to capture life-cycle variation in drug quality.

2.4. Ontological Fragmentation Requiring External Solutions

The totality of evidence demonstrates that these structural blind spots are not abstract or theoretical; they manifest as measurable patient harm and, increasingly, as national security concerns. The Fiscal Year 2023 National Defense Authorization Act directed the Department of Defense to identify vulnerabilities in the sourcing, manufacturing, quality, and distribution of medicines it procures—especially generics (Public Law 117-263). In response, DoD entered into a Cooperative Research and Development Agreement with an independent laboratory to conduct quality testing and scoring of generic drugs supplied to military beneficiaries (Bettelheim, 2023).

Such initiatives address acute vulnerabilities but cannot, on their own, repair the underlying ontology. Ontological fragmentation is not merely a technical regulatory flaw; it is a structural threat to patient safety, national security, and the credibility of the pharmaceutical enterprise. Meaningful, system-level solutions must therefore be developed outside the current regulatory architecture—precisely the gap this Perspective seeks to surface and address.

3. NEW PRIOR KNOWLEDGE (NPK): THE THIRD LEG OF THE STOOL

Having diagnosed the structural problem of ontological fragmentation and its cascading epistemic vulnerabilities, this Perspective now turns to the external vantage point from which meaningful reform can begin. At the center of this framework is New Prior Knowledge (NPK)—knowledge that is “new” in that it is continuously updated from real-world evidence, failure modes, and patient-reported outcomes, and “prior” in that it is anchored in the formally reviewed knowledge base underlying legacy FDA determinations of safety and effectiveness, often residing within trade-secret domains (Hussain et al., 2019). In the context of patient-centric efforts under Pharma 5.0, NPK also seeks to empower the voice of patients by

Pharmaceutical Trust Triangle and Federated Governance Model

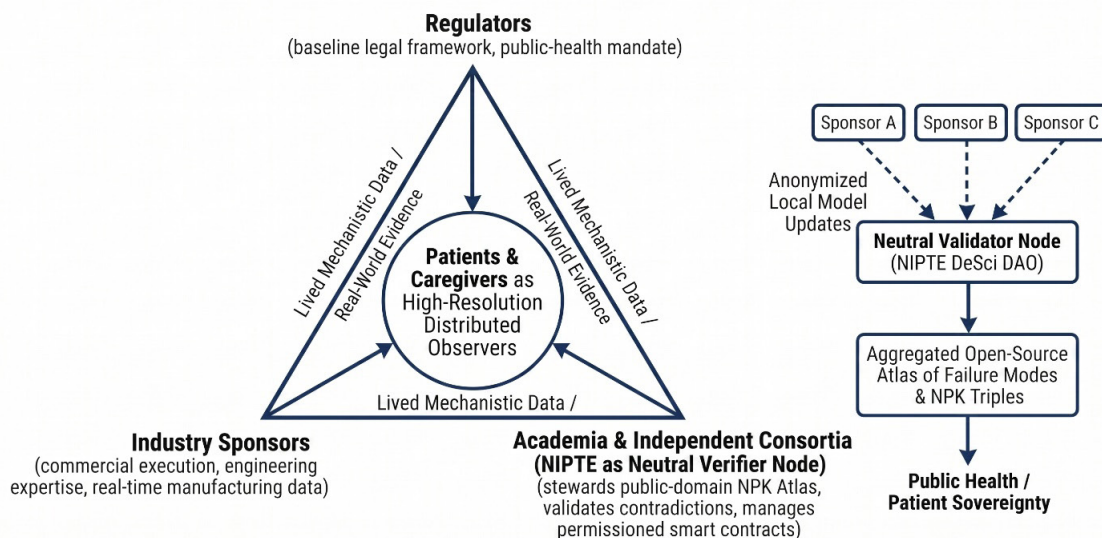


Figure 2. The Pharmaceutical Trust Triangle: A framework for aligning regulatory integration, manufacturer accountability, and patient-centered evidence, supported by federated governance involving neutral validators such as NIPTE.

giving greater weight to their reports. To fulfill this role, NPK must be multidisciplinary and capable of informing FDA; it is therefore best generated and curated by a credible, independent institution such as NIPTE (Hussain et al., 2026).

NPK was first articulated within the National Institute for Pharmaceutical Technology and Education (NIPTE) in 2019 to address a structural impasse: neither FDA nor industry, each confined within its own bounded ontology, could generate the mechanistic insight needed to close the Risk-to-Patient Delta. NIPTE’s decentralized, university-based consortium, established to remedy long-standing blind spots in pharmaceutical engineering science, is positioned here as one option for the neutral “third leg of the stool,” envisioned as the Pharmaceutical Trust Triangle in Figure 2. With neither regulatory authority nor commercial interest, NIPTE can curate “negative knowledge” (what did not work) across corporate-regulatory silos without triggering trade-secret or liability constraints.

NIPTE’s mechanistic focus also complements the United States Pharmacopeia (USP), strengthening independent infrastructure through the development of public standards and monographs. Unlike static regulatory prior knowledge, which effectively freezes at the time of approval, NPK is conceived as a living, life-cycle-aware reference frame. It reframes excipients and delivery systems as dynamic engineering variables rather than static legal placeholders. By systematically integrating failure modes, patient-reported outcomes, and advanced

characterization data into a continuously updated knowledge base, NPK can overcome the ontological constraints embedded in the regulatory frameworks established by the FD&C Act of 1938 and the Hatch-Waxman Act of 1984 and provide the external reference frame required for epistemic humility.

NPK is not intended as a replacement for regulators, USP, or industry. Rather, it is the missing counterweight that enables the system to move beyond legal compliance toward pharmaceutical engineering science. This third-leg architecture sets the stage for the epistemic mechanism introduced in the following section: FCR within a CMC-GraphRAG framework.

4. RELATED WORK

The foundations of this Perspective rest on three complementary streams of prior work. The first concerns domain ontologies for pharmaceutical engineering. The POPE, developed by Hailemariam and Venkatasubramanian (2010), provides a basis for progressing a rigorous conceptual framework for representing materials, processes, and product performance. Subsequent developments, including the SUSIE framework for CMC ontology-based information extraction (Mann et al., 2023) and recent advances in automated extraction from unstructured CMC documents (Taskiran et al., 2025), demonstrate the practical value of structured knowledge representation. Building on this foundation, Venkatasubramanian and Chakraborty (2025) argue for a necessary shift from large language models to

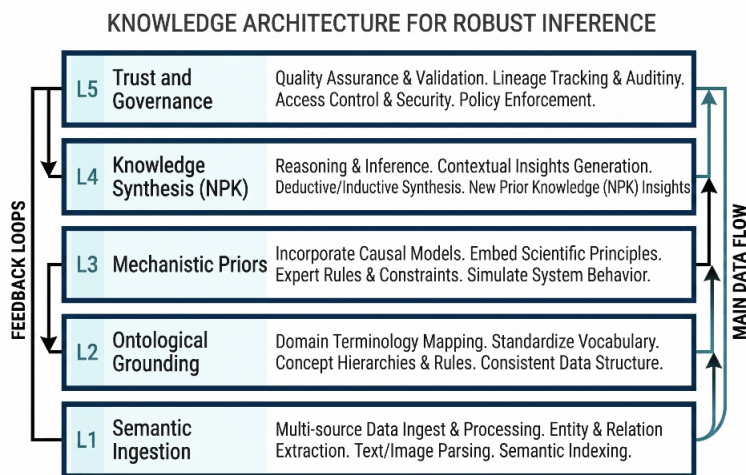


Figure 3. Conceptual five-layer CMC-GraphRAG architecture for engineering epistemic resilience

large knowledge models that embed mechanistic and causal structure.

A second stream of work has advanced retrieval-augmented generation (RAG) and graph-based architecture. GraphRAG approaches, in particular, have shown strong performance on multi-hop, knowledge-intensive tasks by leveraging explicit entity-relationship structures (Edge et al., 2024). However, existing RAG and GraphRAG systems remain fundamentally confirmatory. They are primarily optimized to retrieve supporting evidence, reinforce prior claims, and minimize model drift. As a result, few systems are explicitly designed to surface contradictions or epistemic tension (Mallen et al., 2023).

This gap motivates the present work. Building on the lineage of POPE, SUSIE, and recent advances in large knowledge models (Venkatasubramanian & Chakraborty, 2025), this Perspective proposes FCR within a CMC-GraphRAG architecture. The proposed framework adapts and extends graph-based retrieval into a five-layer, CMC-specific design that treats regulatory assertions, mechanistic priors, and patient-reported outcomes as first-class nodes. In parallel, the NPK framework (Hussain et al., 2019, 2026) provides the epistemic and institutional rationale for an independent, continuously updated knowledge base capable of challenging legacy regulatory assumptions without commercial or jurisdictional capture. Together, these streams motivate the development of FCR as a novel mechanism for surfacing Δ SF and supporting life-cycle-aligned regulatory decision-making. The proposed FCR and CMC-GraphRAG architecture is presented as a high-level conceptual framework for a Perspective article, intended to inspire rigorous community critique and empirical development rather than serving as a fully specified technical implementation.

5. ENGINEERING EPISTEMIC HUMILITY: CONCEPTUAL MECHANICS OF FORCED-CONTRADICTION RETRIEVAL

The core contribution of this Perspective is FCR, an antithesis-generating mechanism embedded within a five-layer CMC-GraphRAG architecture. Conventional retrieval-augmented generation systems are inherently confirmatory: they retrieve passages that support a given query while minimizing divergence from existing knowledge. In contrast,

FCR is designed to deliberately retrieve both a thesis (the regulatory assertion) and an antithesis (mechanistic or real-world counterevidence) and then quantify the divergence between them through Δ SF.

This shift from confirmatory to contradiction-seeking retrieval constitutes both a conceptual advance in AI epistemology and a structural advance in pharmaceutical quality science. The proposed FCR and CMC-GraphRAG architecture is presented here as a high-level conceptual framework appropriate to a Perspective article—intended to invite rigorous community critique and empirical development rather than to serve as a fully specified technical implementation. Rather than reinforcing prevailing regulatory narratives, FCR functions as a computational conscience that actively searches for evidence capable of challenging dominant assertions. By surfacing epistemic tension, the proposed architecture aims to support more resilient and evidence-aligned regulatory decision-making across the product life cycle. To operationalize this approach, the proposed CMC-GraphRAG architecture integrates five interlocking layers, each addressing a distinct epistemic gap (Figure 3):

- Layer 1 – Semantic Ingestion: Transforms unstructured CMC documents, batch records, and stability studies into structured knowledge graphs using schema-based extraction frameworks such as SUSIE (Mann et al., 2023).
- Layer 2 – Ontological Grounding: Provides logical and causal scaffolding through established pharmaceutical engineering ontologies, including the POPE and its extension, the Columbia Ontology for Pharmaceutical Engineering (COPE) (Hailemariam & Venkatasubramanian, 2010; Remolona, 2018).
- Layer 3 – Mechanistic Priors: Anchors the system in physical and material science through resources such as the NIPTE-FDA Excipients Knowledge Base, which catalogs excipient properties and variability across vendors and over time (Basu et al., n.d.).
- Layer 4 – Knowledge Synthesis: Maintains a living repository of NPK by continuously integrating academic pharmaceutical engineering science research, real-world evidence, failure modes, pharmacokinetic and pharmacodynamic data, adverse event trends, and patient-reported outcomes (Hussain et al., 2019, 2026).

- Layer 5 – Trust and Governance: Establishes a neutral validation layer that employs privacy-preserving federated architectures and decentralized governance models to curate, certify, and update the knowledge base.

Within this architecture, FCR operates by executing bipolar queries against regulatory claims or quality-related questions (Figure 4). The thesis pathway retrieves the static baseline—approved label language, bioequivalence claims, and legacy regulatory descriptors—while the antithesis pathway simultaneously searches the NPK Atlas for anomalies such as viscoelastic drift (signaling potential adhesive failure), phase-behavior mismatches, process capability or stability issues, ineffective CAPA investigations, and patient-reported signals that contradict the thesis. The system does not prematurely reconcile these pathways. Instead, it quantifies the resulting tension through ΔSF , introduced here as a continuous conceptual measure of ontological misalignment between a regulatory assertion and a verified counterevidence. ΔSF

integrates semantic similarity to both supporting and opposing evidence along with the degree of logical inconsistency between them (Figure 4).

Elevated values of ΔSF may indicate potential therapeutic equivalence failures at individual and population levels and may provide an early signal of divergence that may escalate into large-scale patient harm or national security vulnerabilities. Formal definition, operationalization, and open benchmarking of ΔSF are listed as a high priority in the proposed research agenda.

Operationalizing ΔSF and the broader FCR framework, however, presents several implementation challenges. These include the limited availability of high-quality “negative” knowledge (failure modes), the development of privacy-preserving mechanisms for federated access to patient-reported data, and the cultural shift required for regulators and sponsors to treat contradiction as a diagnostic signal rather than a liability.

Forced-Contradiction Retrieval (FCR)

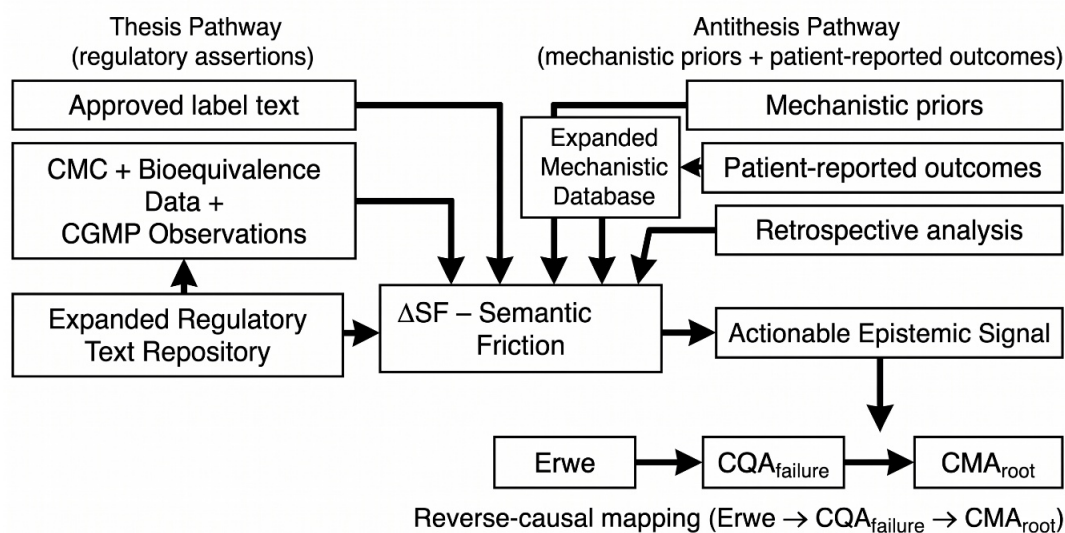


Figure 4. Forced-Contradiction Retrieval (FCR) process illustrating the Thesis and Antithesis pathways and the computation of ΔSF . When ΔSF exceeds a calibrated Pharma 5.0 threshold, the detected contradiction is surfaced as an actionable epistemic signal. This enables reverse-causal mapping from real-world evidence (Erwe) to critical quality failures (CQA_{failure}) and their underlying critical material attribute root causes (CMA_{root}).

6. IMPLEMENTATION CHALLENGES, RESEARCH AGENDA, AND CALL TO THE COMMUNITY

Realizing FCR within the five-layer CMC-GraphRAG interaction faces several practical and institutional hurdles.

First, high-quality mechanistic failure-mode data remain siloed behind corporate trade-secret barriers. Independent validator consortia—such as NIPTE—paired with permissioned decentralized science (DeSci) and decentralized autonomous organization (DAO) frameworks, provide a credible mechanism to curate ‘negative knowledge’ across organizational boundaries without compromising proprietary protections or incurring liability (Hussain et al., 2026). Second, patient-reported outcomes are inherently noisy and subject to bias; hybrid human–AI curation pipelines, supported by reverse-causal mapping from real-world evidence to underlying critical material and process attributes, can meaningfully improve signal-to-noise ratios. Third, regulatory ontologies must evolve from static legal descriptors into dynamic, machine-actionable knowledge graphs capable of incorporating life-cycle updates. Fourth, robust evaluation metrics for epistemic resilience—extending well beyond conventional accuracy or surface-level semantic similarity—remain immature and require dedicated development.

A concrete research agenda for the JAIKE community includes: (a) formalization and open benchmarking of Δ SF measures as a principled approach to quantifying ontological misalignment; (b) development of a public CMC contradiction corpus to support rigorous evaluation of contradiction-aware retrieval systems; (c) pilot deployments of the five-layer CMC-GraphRAG architecture on high-risk product classes, including narrow therapeutic index drugs, complex generics, and transdermal delivery systems; (d) integration with ongoing FDA knowledge-aided assessment and structured application initiatives (Wang et al., 2026); and (e) exploration of constitutional, governance, and incentive structures capable of embedding epistemic humility into AI-mediated regulatory decision-making.

The field of pharmaceutical AI stands at a critical inflection point. Scaling language models alone will not resolve the ontological fragmentation that undermines therapeutic equivalence and

regulatory trust. Only the deliberate engineering of contradiction-seeking, first-principles-grounded knowledge systems can restore epistemic resilience in pharmaceutical oversight. This Perspective offers one architectural blueprint and invites the JAIKE community to engage in rigorous critique, empirical extension, and collaborative implementation.

Acknowledgements

No external funding was received for this work. The author gratefully acknowledges the intellectual community of the National Institute for Pharmaceutical Technology and Education (NIPTE) and colleagues who are advancing pharmaceutical engineering science. The author also thanks the JAIKE peer reviewers and editorial team for their constructive feedback and the opportunity to contribute to this Perspective.

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