

FROM GRAS TO CONTINUOUS EVIDENCE

Is Food-Ingredient Regulation Entering a New Era of Regulatory Life-Cycle Management?

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Core thesis — The strategically important regulatory asset of the future may not be an ingredient that was once authorised, notified or considered GRAS, but an ingredient whose identity, manufacturing history, exposure, safety evidence and jurisdiction-specific legal status can be continuously reconstructed and defended.

Abstract

Food-ingredient regulation is undergoing a structural transition. For decades, the central regulatory question was whether a substance had crossed a legally defined market-entry threshold: food-additive approval, inclusion in a positive list, a novel-food authorisation, a Generally Recognized as Safe (GRAS) conclusion, a traditional-use pathway, or another recognised legal basis. That architecture remains legally decisive, but it is increasingly insufficient as a description of how modern safety governance actually works. New analytical methods, changing exposure patterns, more complex manufacturing technologies, systematic post-market reassessment, data-rich supply chains and regulatory digitalisation are pushing authorities and industry toward a different operating logic: safety and compliance are becoming continuously defensible evidence positions rather than one-time administrative events.

The United States provides the most visible 2026 example. On 10 August 2026 the U.S. Food and Drug Administration (FDA) announced a proposed rule, published in the Federal Register on 11 August 2026 as 91 FR 51834, that would require submission of GRAS notices for certain uses of substances in human and animal food, replacing a major element of the current voluntary notification architecture. The proposal does not abolish GRAS as a statutory concept. Its significance lies elsewhere: it would materially increase regulatory observability of substances entering commerce under GRAS conclusions and would reduce the informational asymmetry created by independent GRAS determinations that never reach FDA. The same agency has also finalised a systematic post-market assessment programme for food chemicals and launched reassessments of selected substances, illustrating that market entry and market permanence are becoming distinct regulatory questions. [1–5]

The European Union already operates within a more centralised authorisation architecture, yet its continuing re-evaluation of legacy food additives shows that positive-list systems also require life-cycle governance. As of 10 September 2026, the European Commission reported 315 pre-2009 additives subject to re-evaluation, 245 covered by 137 EFSA opinions and 70 still awaiting completion. Great Britain, meanwhile, has converted regulated-product authorisations into official electronic registers following reforms effective from 1 April 2025, creating a more administratively updateable regulatory infrastructure. [6–10]

This article develops the concept of regulatory life-cycle management for food ingredients and analyses its consequences for scientific evidence, manufacturing comparability, biotechnology, data architecture, artificial intelligence, intellectual property, SMEs, international market access and corporate strategy. It proposes several research concepts—regulatory observability, manufacturing drift, evidence readiness, the regulatory digital twin, the regulatory evidence graph and Regulatory Evidence Engineering—and distinguishes clearly between established law, analytical interpretation and prospective research hypotheses.

Evidence-status convention used in this article

Label	Meaning
ESTABLISHED FACT	A proposition directly grounded in legislation, an official regulatory document, an authoritative scientific opinion or a well-supported published scientific source.
ANALYTICAL INTERPRETATION	A reasoned conclusion derived from established facts but not itself a statutory or agency conclusion.
RESEARCH HYPOTHESIS / PROPOSAL	A prospective concept advanced here for investigation, validation or industrial development; it should not be presented as an existing legal requirement.

1. The Regulatory Status of an Ingredient Is No Longer a Static Asset

Food companies still tend to store regulatory status as a binary field: authorised/not authorised; GRAS/not GRAS; novel/non-novel; additive/non-additive; permitted/not permitted. That representation is administratively efficient, but scientifically crude. Safety is conditional on identity, specifications, intended use, exposure, manufacturing method, relevant population, analytical capability and the state of scientific knowledge. If any of these variables changes, a historical regulatory conclusion may remain legally valid while becoming scientifically incomplete or commercially vulnerable.

The distinction is crucial. A legal authorisation is a normative act; a safety conclusion is an evidentiary judgment. The first can persist until amended, suspended or revoked. The second depends on the evidence and assumptions that supported it. Regulatory systems are increasingly designing mechanisms that reconnect those two layers through reassessment, calls for data, change-control expectations, post-market review, searchable registers and improved regulatory transparency.

ANALYTICAL INTERPRETATION — The most important 2026 development is therefore not the reform of one procedure. It is the progressive separation of three moments that were historically treated as a single event: market entry, continued scientific defensibility and continued regulatory permission. Once those are treated separately, regulatory affairs becomes a life-cycle discipline.

Under a traditional market-entry model, the regulatory function peaks before commercialisation: classify the product, build the dossier, obtain the necessary status and then maintain routine compliance. Under a life-cycle model, initial status is only the first checkpoint. Evidence must be capable of being reassembled when the material changes, when the market changes, when analytical methods improve, when exposure grows, when new toxicological endpoints emerge or when authorities revisit old assumptions.

2. GRAS as a Legal Concept: What It Is—and What It Is Not

Under sections 201(s) and 409 of the U.S. Federal Food, Drug, and Cosmetic Act, a substance intentionally added to food is generally a food additive requiring premarket approval unless it falls within a statutory exclusion. One of the most consequential exclusions applies where the substance is generally recognised, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use. FDA explains that GRAS status is tied to the intended conditions of use and that general recognition ordinarily rests on publicly available evidence and expert consensus. [1,2]

A common international misunderstanding is to describe GRAS as a corporate declaration of safety. That is legally inaccurate. The substantive standard concerns general recognition by qualified experts and a scientific evidentiary basis comparable in quantity and quality to that required for a food-additive safety determination. What has historically distinguished GRAS is not the absence of a safety standard, but the possibility—under current rules—of reaching a GRAS conclusion independently without mandatory notification to FDA.

This created two different propositions that are often conflated in commercial documents: “this use meets the GRAS standard” and “FDA has reviewed a GRAS notice for this use.” They are not interchangeable. A company can have an independently reached GRAS conclusion without an FDA response letter; conversely, an FDA “no questions” response to a notice does not operate as a food-additive approval and is framed in relation to the notifier’s conclusion and the submitted use conditions.

The distinction matters internationally because distributors, customers and non-U.S. regulators frequently ask for “FDA approval” where the actual U.S. legal status is a GRAS conclusion. Regulatory precision requires identifying the pathway, the intended use, the basis of the conclusion, whether a notice was submitted, and the scope of FDA’s response. Simplifying these elements into a global “approval” statement creates avoidable legal and reputational risk.

3. The 2026 GRAS Proposal: A Change in Visibility, Not the Abolition of GRAS

ESTABLISHED FACT — FDA announced the proposed GRAS reform on 10 August 2026; the proposal was published on 11 August 2026 as 91 FR 51834 under docket FDA-2025-N-3262. FDA describes the proposed rule as requiring submission of GRAS notices for certain uses of substances in human and animal food. Under the current system, notification is voluntary. FDA’s economic analysis states that the principal expected benefit is greater information available to FDA and the public about substances used in food. [3–5]

The legal architecture is therefore more subtle than the phrase “closing the GRAS loophole” suggests. Congress created the GRAS exclusion in statute. An administrative rule can modify notification procedures within statutory authority, but it does not simply erase the statutory category. The key regulatory movement is from a system that tolerates invisible independent conclusions toward one in which certain GRAS uses would become systematically visible to the agency.

This is why the concept of regulatory observability is more useful than the rhetoric of “abolition.” A regulator can only prioritise, compare, reassess and aggregate what it can identify. Mandatory submission converts private safety conclusions into nodes within a regulatory information system. That has consequences for signal detection, duplication analysis, exposure aggregation, identification of related substances, prioritisation of reassessment and public transparency.

FDA’s Regulatory Impact Analysis estimates annualised costs of approximately USD 10.5 million at a 3% discount rate and USD 11.7 million at a 7% rate, with broad uncertainty ranges. These costs represent more than paperwork. They are an early quantification of the economic price of increasing observability: dossier preparation, data assembly, submission, internal review, and the organisational work required to ensure that the scientific basis of a GRAS conclusion is sufficiently documented for regulatory scrutiny. [5]

What the proposal changes strategically

- Independent conclusions would no longer remain structurally invisible for the covered uses; the regulator would receive a formal notice.
- Companies would need stronger control over identity, intended conditions of use, exposure estimates, safety narratives and supporting literature before commercial launch.
- Portfolio-level regulatory intelligence would become more valuable because related uses and substances could be easier for FDA to compare and prioritise.
- Commercial claims such as “self-GRAS”, “FDA notified”, “FDA reviewed” and “FDA approved” would require even more careful differentiation.
- The reform would increase the value of version-controlled evidence because later questions may concern what information supported the original conclusion and whether the commercial material still matches that evidence base.

4. Why a Notification Reform Can Change Industrial Behaviour

Regulation modifies incentives even when it does not change the substantive safety threshold. A voluntary system permits firms to decide whether the benefits of agency engagement outweigh the costs and uncertainty of review. A mandatory system internalises part of the regulatory information cost into every covered market-entry decision. That can alter product-development sequencing.

Large multinational groups are likely to absorb the change through established regulatory teams, external counsel, toxicology functions and dossier systems. Smaller developers may face a sharper marginal cost because the fixed cost of a robust safety package is spread across fewer products and smaller sales. This does not mean the reform is anti-innovation; it means that innovation economics become more dependent on evidence architecture.

ANALYTICAL INTERPRETATION — The likely competitive split will not simply be between “large” and “small” firms. It will be between evidence-native firms and evidence-reactive firms. An evidence-native developer designs identity, manufacturing controls, analytical specifications, toxicology and intended-use boundaries during R&D. An evidence-reactive developer tries to reconstruct those elements after the technology is commercially mature. The latter model becomes increasingly expensive as regulatory visibility rises.

5. Post-Market Reassessment: Market Entry Is No Longer the End of the Scientific Story

In May 2026 FDA finalised a more systematic post-market assessment programme for chemicals in food and launched reassessments of butylated hydroxytoluene (BHT) and azodicarbonamide (ADA). The agency’s prioritisation tool describes a process involving signal detection, triage, prioritisation, scientific assessment and risk management. FDA’s 2026 priorities also identify post-market safety review of marketed food chemicals as a major workstream. [11–13]

This matters conceptually because it institutionalises a second question after market entry: not “was the substance considered safe when it entered commerce?” but “does the current evidence still support safety under current conditions of exposure?” Those conditions may differ materially from the original evidence environment.

Exposure can expand through category proliferation. A substance initially used in a narrow application can become ubiquitous across beverages, supplements, snacks, foods for children or multiple processing categories. A low per-product concentration does not necessarily imply a low aggregate exposure if the ingredient becomes technologically fashionable. Modern dietary-exposure assessment therefore makes market diffusion itself a regulatory variable.

Analytical science can also destabilise historical assumptions. Lower detection limits reveal impurities previously considered absent. Particle-size characterisation can identify nanoscale fractions. Omics technologies can generate mechanistic signals. New epidemiological or toxicological evidence can challenge an old acceptable daily intake, safety factor or assumption about metabolism. Life-cycle regulation is, in part, the legal response to the increasing resolution of science.

6. Historical Proof That “Accepted” Does Not Mean “Permanent”

6.1 Partially hydrogenated oils: GRAS status can disappear

In 2015 FDA issued its final determination that partially hydrogenated oils (PHOs), the principal dietary source of industrial trans fat, were no longer GRAS for use in human food. Compliance dates followed, and in 2023 FDA completed administrative actions revoking residual regulatory references. The case demonstrates that a status grounded in one historical evidence environment can be displaced when cardiovascular evidence and public-health analysis change. [14,15]

6.2 Brominated vegetable oil: authorised use can be revoked

Brominated vegetable oil (BVO) followed a different legal path. FDA had regulated it as a food additive after removing it from a codified GRAS list in 1970. In 2024 the agency revoked the food-additive regulation after concluding there was no longer a basis to consider the authorised use safe, relying in part on newer studies and evidence of bromine accumulation and thyroid effects in rodents. [16,17]

6.3 Titanium dioxide E171: scientific methodology can change the answer

The European experience with titanium dioxide (E171) is equally instructive. EFSA re-evaluated E171 in 2016, identified data gaps, and in 2021 concluded that a concern for genotoxicity could not be ruled out and that E171 could no longer be considered safe as a food additive. The European Commission subsequently withdrew the food-use authorisation through Regulation (EU) 2022/63, with transitional measures. [18,19]

These examples should not be misused to imply that all legacy ingredients are suspect. Their real regulatory lesson is narrower and stronger: legal status can change when the underlying evidence, analytical resolution, exposure context or safety methodology changes. A life-cycle system must therefore preserve the ability to connect current commercial material to the evidence that justifies its status.

7. The European Union: Positive Lists Already Contain a Life-Cycle Logic

The EU architecture is more explicitly pre-authorisation driven than the U.S. GRAS model. Regulation (EC) No 1333/2008 establishes the framework for food additives, while Regulation (EC) No 1331/2008 provides the common authorisation procedure for additives, food enzymes and flavourings. Authorisation rests on safety, technological need and the protection of consumers against misleading practices, with detailed conditions of use and specifications. [6,20]

Yet positive-list systems do not eliminate temporal uncertainty. Commission Regulation (EU) No 257/2010 created a re-evaluation programme for additives authorised before 20 January 2009. As of 10 September 2026, the Commission reported 315 additives within that programme, 245 covered by 137 EFSA opinions and 70 still awaiting re-evaluation. [7]

More importantly, the process does not end when EFSA publishes an opinion. Where data gaps remain, the Commission or EFSA may call for technical, toxicological, usage or analytical data. The Commission explicitly states in several follow-up processes that if requested data are not supplied—or are insufficient—the existing authorisation may be revised and the additive may be removed from the Union list. That is life-cycle evidence governance in operational form. [7]

ANALYTICAL INTERPRETATION — The EU thus makes an important point that is sometimes missed in corporate compliance systems: regulatory permission and evidence maintenance are different assets. A company may not “own” the authorisation of a generic additive, yet the continued practical utility of that additive can depend on industry’s willingness to generate and submit new evidence when authorities reopen the safety question.

8. Novel Foods: Process History Is Part of Regulatory Identity

Regulation (EU) 2015/2283 illustrates why molecular identity alone can be insufficient. The definition of novel food captures, among other categories, foods produced through processes not used for food production within the Union before 15 May 1997 where those processes give rise to significant changes in composition or structure affecting nutritional value, metabolism or levels of undesirable substances. It also addresses foods from microorganisms, fungi, algae, mineral-origin materials and engineered nanomaterials. [21,22]

This structure embeds manufacturing history inside legal classification. Two materials with similar headline composition may not be legally equivalent if one is produced through a materially different process that affects relevant attributes. Modern ingredient development therefore cannot treat process as an internal manufacturing detail detached from regulatory identity.

EFSA’s current novel-food application procedure also explicitly recognises applications to modify existing authorisations. That is an important life-cycle mechanism: once a product is authorised, changes in uses, specifications, production or other conditions may themselves become the subject of regulatory assessment. [23]

For biotechnology-derived ingredients this issue will become increasingly important. Precision fermentation, engineered production organisms, cell-free synthesis, enzymatic conversion and advanced purification create materials whose commercial name may be familiar while the production history, residual host-cell components, impurity spectrum, structural variants or particle characteristics differ materially from legacy sources.

9. Great Britain: From Legislative Instruments to Dynamic Official Registers

On 1 April 2025 reforms to Great Britain's regulated-product authorisation system came into force. For relevant product categories, authorisations can now take effect following ministerial decision and publication in official registers rather than requiring an individual statutory instrument for each authorisation. The Food Standards Agency describes the registers as the primary official source for authorised products and conditions of use. [8–10]

The legal systems remain distinct, and an electronic register should not be confused with deregulation. The significance is infrastructural. Registers can be searched, filtered, updated and increasingly exposed in structured formats. The official food-additive register, for example, presents authorisation status and jurisdictional application; the feed-additive register already contains more than a thousand entries and supports downloadable data formats. [9,10]

ANALYTICAL INTERPRETATION — Once an official regulatory register is digital, a new category of compliance becomes technically possible: machine-assisted comparison between a company's product portfolio and the current regulatory state. That is qualitatively different from a compliance model based on periodically reading consolidated legislation and manually updating spreadsheets.

10. Convergence Without Harmonisation

It would be inaccurate to state that the United States, European Union and Great Britain are converging toward a single ingredient law. They are not. Their statutory categories, institutional structures, evidentiary pathways and administrative traditions remain different. The more defensible claim is that they are facing common governance pressures and are adopting partially analogous tools.

Dimension	United States	European Union	Great Britain
Market-entry architecture	Food additive approval plus statutory exclusions including GRAS; multiple category-specific pathways.	Positive-list authorisations for many regulated substances; novel-food authorisation; harmonised EU risk assessment.	Post-Brexit retained/assimilated framework with domestic risk analysis and ministerial authorisation.
2026 direction	Proposed mandatory GRAS notice submission for certain uses; systematic post-market chemical assessment.	Continuing additive re-evaluation and data-gap follow-up; structured applicant procedures.	Official digital registers are primary sources of authorisation information after 2025 reform.
Life-cycle mechanism	Post-market reassessment; enforcement; proposed improved visibility of GRAS uses.	Formal re-evaluation, calls for data, list updates, modification procedures.	Register updates, domestic risk analysis, status fields and ministerial decisions.
Digital potential	Increasingly structured inventories and assessment processes.	EU databases and centralised application systems, though data remain distributed.	Official searchable/downloadable registers create strong machine-readability potential.
What has NOT converged	Underlying statutory meaning of GRAS and food additive remains U.S.-specific.	Positive-list and precautionary/risk-management architecture remains EU-specific.	GB remains legally separate from EU and may diverge in authorisation management.

The useful common denominator is therefore functional rather than doctrinal: greater visibility, stronger re-assessment capability, faster update mechanisms and more structured regulatory information.

11. Regulatory Observability: The Hidden Variable in Modern Food Law

RESEARCH CONCEPT — Regulatory observability can be defined as the extent to which a regulator can identify a substance, its responsible operator, relevant manufacturing characteristics, conditions of use, exposure, safety basis and subsequent changes with enough resolution to support oversight and reassessment.

A system can be legally demanding yet poorly observable if information is scattered across private dossiers, historical files and inconsistent terminology. Conversely, a well-structured register can make even a complex regulatory system more observable. Observability is therefore not identical to strictness. It is an information property of the regulatory system.

For food ingredients, useful observability requires more than a name and CAS number. A regulator may need to distinguish source organism, production strain, extraction solvent, catalyst, residual enzyme, particle-size distribution, purity profile, carrier, stabiliser, intended technological function, use level and exposed population. The more technologically sophisticated the ingredient, the less adequate a single chemical identifier becomes.

This suggests a policy question for the next decade: which minimum data fields should be standardised across authorisation, notification, register and post-market systems so that regulators can compare ingredients without requiring every assessment to begin with manual dossier reconstruction?

12. What Exactly Is the Ingredient? Identity in the Age of Advanced Manufacturing

Classical food regulation often assumes that identity can be captured by a conventional chemical or compositional description. That works reasonably well for simple, well-characterised materials. It becomes less reliable when production technologies shape impurity patterns, molecular variants, aggregation state, particle morphology or residual process-derived components.

For a modern ingredient, regulatory identity may need to be treated as a multidimensional vector rather than a name. At minimum, that vector can include:

- chemical or biological identity of the principal component(s);
- source organism or raw-material provenance;
- manufacturing process and critical transformation steps;
- purity and impurity profile;
- physical state, particle characteristics or polymorphic form where relevant;
- residual processing aids, catalysts, solvents, host-cell material or enzymes;
- microbiological status where relevant;
- intended technological or nutritional function;
- conditions and levels of use;
- exposure profile and vulnerable populations.

A change in one dimension may be immaterial; a combination of changes may not be. The regulatory problem is therefore not merely “did composition change?” but “did the change alter the relationship between the marketed material and the evidence that supported its safety and legal classification?”

13. Manufacturing Drift: A Regulatory Risk That Often Begins as Continuous Improvement

RESEARCH CONCEPT — Manufacturing drift is the cumulative movement of a commercial ingredient away from the material represented by its original evidence package as a result of successive process, supplier, scale, equipment, formulation or specification changes.

Individual modifications may be scientifically justified and operationally minor: a new raw-material supplier, a different drying profile, increased fermentation yield, tighter filtration, a carrier substitution, a modified catalyst, a strain-improvement step, a different milling distribution or a new plant. The difficulty arises when change control assesses each modification locally but never tests the cumulative distance from the evidence-defined reference material.

The pharmaceutical biotechnology sector offers a useful conceptual analogue. ICH Q5E provides principles for assessing comparability of biological products before and after manufacturing-process changes, focusing on whether quality attributes remain sufficiently comparable that safety and efficacy are not adversely affected. Food ingredients are not medicinal products and should not inherit pharmaceutical requirements by analogy. Nevertheless, the comparability logic is intellectually valuable. [24]

RESEARCH PROPOSAL — Food regulatory science could develop a tiered comparability framework proportionate to ingredient risk. Low-risk changes might require documented equivalence against specifications; intermediate changes could trigger targeted analytical comparability; high-impact changes—such as new production organisms, materially altered impurity profiles or nanoscale attributes—could trigger a formal reassessment of whether existing safety evidence remains transferable.

A practical “regulatory delta” test

1. Define the evidence-critical attributes of the reference material.
2. Characterise the pre-change and post-change material using fit-for-purpose analytical methods.
3. Identify changes in composition, impurities, physical characteristics, process residues and functional behaviour.
4. Assess whether exposure or intended use also changes.
5. Map each change to the assumptions in the existing safety and regulatory dossier.
6. Classify the regulatory delta as immaterial, potentially material or material.
7. Document the scientific rationale and determine whether authority engagement is required.

14. Biotechnology and Precision Fermentation: Where Identity and Process Become Inseparable

Precision fermentation makes the identity problem especially visible. A target molecule may be chemically identical to a conventional analogue, yet the process may involve a genetically modified microorganism, fermentation media, host-cell proteins, nucleic-acid residues, downstream purification and process-specific impurities. Depending on jurisdiction and product category, the legal assessment may focus on the final substance, the production organism, the process, the absence or presence of viable cells/DNA, or combinations of these elements.

The scientific question is not whether “biotech” is inherently more or less safe. It is whether the material is adequately characterised and whether the evidence matches the commercial manufacturing process. A highly purified fermentation-derived molecule may be easier to characterise than a complex botanical extract; a complex biomass ingredient may require far broader compositional analysis. Risk follows the evidence problem, not the marketing category.

This is why regulatory life-cycle management should begin during strain selection and process development. If a later commercial-scale process produces a different impurity spectrum from the pilot material used in toxicology studies, the developer may face a comparability question precisely when scale-up economics are most sensitive.

The same logic applies to engineered enzymes, cell-cultured materials, enzymatic bioconversion and synthetic-biology-derived compounds. The stronger the link between production history and material attributes, the more valuable it becomes to preserve a version-controlled chain from strain or source through process parameters, specifications, analytical data and the lots used in pivotal studies.

15. Exposure Drift: When the Ingredient Does Not Change but the Market Does

Life-cycle risk is not limited to manufacturing. Exposure can drift even when the ingredient remains chemically identical. A substance may migrate from niche use to mass-market use, from one food category to many, from adult products to products consumed by children, or from occasional consumption to daily consumption through beverages and supplements.

Regulatory dossiers typically estimate exposure under defined intended uses. Commercial success can invalidate those assumptions without any single manufacturer exceeding its stated use level. This is a systems problem: aggregate exposure emerges from the market, not from one product specification.

RESEARCH PROPOSAL — Companies should maintain an “exposure envelope” alongside a technical specification. The envelope would record the intended food categories, typical and maximum use levels, target populations and assumptions used in the original safety assessment. New applications could then be tested against that envelope before commercial approval.

For distributors and ingredient suppliers this may require better application data from customers. A supplier that sells the same material into many sectors can otherwise lose visibility over cumulative market expansion. Contractual and technical-documentation systems therefore become part of evidence governance.

16. Analytical Methods Are Part of Regulatory History

An ingredient can appear to change because measurement changes. A contaminant once reported as “not detected” may become quantifiable when detection limits improve. A particle distribution once described by a mean diameter may later require number-based nanoscale characterisation. Chromatographic resolution can reveal previously unresolved congeners. Genomic methods can detect low-level microbial or DNA signatures invisible to legacy assays.

This creates an underappreciated problem: historical specifications may be analytically non-comparable with current specifications even when the product is stable. A life-cycle dossier should therefore preserve not just results, but analytical method versions, limits of detection/quantification, validation status and relevant sample preparation.

The E171 case shows why this matters. EFSA’s 2021 reassessment incorporated newer nanotechnology guidance and a far more detailed understanding of particle characteristics than earlier regulatory eras. The lesson is not confined to titanium dioxide: a changing measurement paradigm can change the regulatory interpretation of a material without any intentional manufacturing change. [18]

17. Evidence Readiness: A New Competitive Variable

RESEARCH CONCEPT — Evidence readiness is the ability of an organisation to rapidly demonstrate why a product remains safe, compliant and technically justified when challenged by a regulator, customer, auditor, insurer, distributor, investor or new scientific publication.

Two ingredients can be chemically similar yet commercially unequal if one supplier can reconstruct its evidence within hours and the other requires weeks of emails across QA, R&D, regulatory affairs, procurement and external laboratories. The difference becomes decisive during customer qualification, due diligence, a regulatory inspection, an incident investigation or a rapid market-access opportunity.

Evidence readiness can be measured. Useful metrics include retrieval time, proportion of claims linked to primary evidence, percentage of specifications with validated change history, completeness of jurisdictional status maps, age of the last literature review, number of unresolved data gaps and time from regulatory change to portfolio impact assessment.

ANALYTICAL INTERPRETATION — As regulatory systems become more observable, evidence readiness may become a market-access capability comparable to quality certification. Customers increasingly ask not only “does it comply?” but “show me why, under my use, in my country, using the material you currently manufacture.”

18. From Regulatory Dossier to Regulatory Digital Twin

RESEARCH HYPOTHESIS — A regulatory digital twin can be defined as a continuously maintained digital representation of an ingredient’s regulatory and scientific identity, linked to the current commercial material and updated as evidence, manufacturing or legal conditions change.

The analogy with industrial digital twins is deliberate but limited. The objective is not to simulate a molecule. It is to maintain a structured model of the evidence state surrounding the product. A mature regulatory digital twin could contain modules for:

- canonical identity and synonyms;
- composition and critical material attributes;
- manufacturing process and version history;
- specifications, methods and trend data;
- safety studies and literature;
- exposure assumptions and approved/intended uses;
- jurisdiction-specific classifications and authorisations;
- claims and labelling constraints;
- supplier and raw-material provenance;
- open regulatory questions and data gaps;
- change-control events and materiality assessments;
- customer declarations generated from controlled evidence.

The digital twin becomes valuable because it preserves state through time. A regulator or customer may ask what supported the product in 2027, not what the company believes in 2030. Version history therefore matters as much as current status.

19. The Regulatory Evidence Graph: From Pages to Relationships

Conventional dossiers are document-centric. Documents are excellent for legal submission and expert reading but weak for computational reasoning because the relevant relationships remain implicit in prose and tables. A regulatory evidence graph would represent those relationships explicitly.

A simplified graph might encode: Ingredient → manufactured by → Process Version 7; Ingredient → has specification → Spec 12; Spec 12 → controls impurity → X; Study 4 → tested batch → Lot A; Lot A → produced by → Process Version 3; Intended Use → produces exposure → Population P95; Jurisdiction J → permits use → Category C at Level L; Publication N → concerns hazard → impurity X.

When one node changes, graph traversal can identify affected evidence. If impurity X becomes a regulatory concern, the system can identify every ingredient, process and dossier linked to X. If a specification changes, it can identify

which customer declarations depend on the old version. If a jurisdiction revises a maximum level, it can identify affected formulations.

Peer-reviewed work already shows the feasibility of large-scale food and chemical knowledge graphs. FoodAtlas, published in 2024, used an LLM-assisted active-learning pipeline to extract more than 230,000 food–chemical composition relationships from over 155,000 papers, illustrating the scale at which structured evidence extraction can operate. The regulatory use case would require substantially tighter validation, provenance and governance, but the underlying computational direction is credible. [25]

20. Artificial Intelligence Changes the Economics of Surveillance—but Not the Allocation of Responsibility

The practical barrier to continuous surveillance has historically been labour. A global ingredient company may need to monitor agency websites, official journals, EFSA opinions, FDA dockets, toxicology databases, scientific literature, customer standards, national implementing measures and emerging analytical guidance. Manual review at high frequency is expensive and inconsistent.

AI can reduce the cost of detection and triage. A governed system can retrieve new items, classify them by ingredient and hazard, identify jurisdiction, compare new statements with stored evidence, summarise changes and route potentially material signals to qualified reviewers. FDA itself identifies technology-enabled risk management and AI-predictive modelling among its 2026 priorities, demonstrating that regulators as well as industry are moving toward data-intensive oversight. [12]

But the governance boundary must be explicit. AI can support retrieval, clustering, extraction, contradiction detection, change comparison, impact mapping and prioritisation. It should not autonomously determine that a use is lawful, that a safety concern is resolved, that an impurity is toxicologically irrelevant or that a process change is immaterial. Those are accountable scientific and legal judgments.

A defensible human-in-the-loop workflow

8. Automated source monitoring retrieves potentially relevant new evidence.
9. Machine classification assigns product, jurisdiction, hazard, legal topic and confidence.
10. Relevance scoring prioritises signals against existing product metadata.
11. A qualified human reviewer validates the source and interpretation.
12. If potentially material, the item triggers a structured impact assessment.
13. Regulatory/scientific leadership determines action: no action, data request, specification review, customer communication, authority engagement or formal reassessment.
14. The decision and rationale become part of the versioned evidence history.

The quality objective is not “AI regulation.” It is augmented regulatory intelligence with traceable provenance and accountable human decision-making.

21. The Data Problem: Machine-Readable Does Not Mean Scientifically Interoperable

Digital registers solve only part of the problem. A downloadable CSV can still be scientifically ambiguous if names, identifiers, functions, food categories and conditions of use do not map cleanly to a company’s internal terminology. Interoperability requires controlled vocabularies and semantic alignment.

For example, one system may identify a material by E-number, another by INS number, another by CAS number, another by a trade name, and another by a broad functional class. Botanical materials can have Latin binomials, plant parts, extraction ratios and solvent histories. Fermentation-derived products may require strain and process identifiers. Without canonical identity resolution, automated compliance can produce confident but false matches.

RESEARCH PROPOSAL — The sector would benefit from an open regulatory ingredient ontology connecting chemical identifiers, biological taxonomy, production source, technological function, food category, legal status, specifications and evidence references. The ontology should preserve jurisdiction-specific meanings rather than collapsing them into a false universal taxonomy.

22. SMEs: The Risk of a New Evidence Barrier—and the Opportunity to Build Better

Increasing evidence intensity can unintentionally create barriers to entry. Large companies can maintain specialists in toxicology, exposure, regulatory law, analytical chemistry and data systems. SMEs often cannot. The cost is particularly acute before revenue exists, when a start-up is deciding whether to fund pivotal safety studies, process scale-up or an authorisation dossier.

EFSA has recognised this structural issue. Its 2026 SME support programme includes dedicated advice mechanisms and a call for novel-food SMEs seeking advice both at early development stages—before studies begin—and at final dossier-preparation stages. This is strategically important because the most expensive regulatory error often occurs before the dossier: the wrong study design, the wrong test material, insufficient characterisation or a process that changes after pivotal testing. [26,27]

The answer is not necessarily regulatory simplification. It may be regulatory sequencing. SMEs should classify first, map evidence gaps second, design studies third and only then lock the commercial process. Doing this in the opposite order creates sunk costs and can force a company to repeat studies using representative material.

A modular evidence architecture can also reduce SME burden. If identity, manufacturing, analytical, safety and exposure modules are maintained independently but linked, the same validated evidence can be reused across customers and jurisdictions without rewriting the entire dossier from scratch.

23. Intellectual Property and Transparency: The Coming Tension

Greater regulatory observability creates an inevitable tension with confidential business information. Manufacturing details, strain engineering, impurity-control strategies, process parameters and supplier architectures can constitute valuable trade secrets. Yet regulators may need precisely those details to determine whether a product is comparable to the material supporting a safety conclusion.

A mature life-cycle system therefore needs layered transparency: public information sufficient to identify the product, legal status and conditions of use; regulator-accessible confidential information sufficient for safety assessment; and internal proprietary detail necessary for process control. Treating all information as either public or secret is too crude.

This has contractual consequences. Ingredient developers should specify ownership, access and continuity rights for critical evidence generated by contract manufacturers, laboratories and research partners. A company that loses access to raw analytical data or strain/process history after changing suppliers may discover that it has lost part of its regulatory evidence asset even though it retains the brand and commercial formula.

24. Distributors, Customers and Auditors Become Part of the Evidence Network

Ingredient suppliers often focus on the regulator, but commercial evidence flows through a wider network. Distributors translate regulatory statements into local markets. Customers define intended applications. Auditors test document control. Insurers and investors assess latent liabilities. Laboratories generate evidence. Contract manufacturers control process variables. Regulatory resilience depends on how these actors exchange information.

The greatest weakness is often not the absence of data but inconsistency: one specification sent to Europe, another to Latin America; a historical declaration still stating “approved worldwide”; a distributor using an obsolete dosage range; a customer applying the product for a function not considered in the original classification. Continuous evidence management must therefore include controlled outward-facing documentation.

RESEARCH PROPOSAL — Every external compliance statement should be generated from a controlled evidence source and carry at least four metadata elements: product version, jurisdiction, intended function/use and document date. This simple discipline could prevent a significant class of avoidable regulatory errors.

25. What This Means for INTABIOTECH

For a company working across functional ingredients, preservation technologies, mineral systems, biotechnology-related solutions and international distribution, the strategic opportunity is not to make broader regulatory claims. It is to become more granular than competitors.

A portfolio-level evidence architecture could link each technology to composition, manufacturing characteristics, critical specifications, analytical evidence, technological function, application, dosage, residual presence, relevant populations, jurisdiction, legal classification, labelling implications, customer documentation and change history. This is especially valuable where the same underlying technology can enter different industries or countries under different legal concepts.

For multifunctional systems, regulatory classification should be built around function + process + residual presence + technological effect + jurisdiction, not trade name alone. The same material can be an ingredient in one context, an additive in another, a processing aid in another, or outside a particular additive framework depending on its technological purpose and legal definition.

The corporate value lies in regulatory precision. A distributor who can receive an application-specific, jurisdiction-specific and evidence-linked statement is less likely to improvise. A customer qualification process becomes faster. Regulatory due diligence becomes auditable. Product-development teams can see evidence gaps before scale-up.

26. A Regulatory Evidence Operating System: Proposed Architecture

RESEARCH & DEVELOPMENT PROPOSAL — The concepts developed above can be operationalised as a Regulatory Evidence Operating System (REOS) for food ingredients. This would not replace official dossiers or quality-management systems. It would connect them.

26.1 Core data objects

- Ingredient master: canonical identity, synonyms, identifiers and trade names.
- Process master: manufacturing flow, critical steps, facilities, outsourced stages and version history.
- Specification master: limits, methods, impurity controls and release criteria.
- Evidence library: studies, opinions, regulatory documents, literature and analytical reports with provenance.
- Use-and-exposure object: application, category, function, dosage, residual presence, population and exposure assumptions.
- Jurisdiction object: classification, authorisation/notification status, conditions of use, labelling and documentary requirements.
- Change object: event, affected attributes, regulatory-delta assessment, decision and approver.
- External statement object: controlled certificate, declaration, technical dossier or customer response generated from current evidence.

26.2 Decision layers

15. Detection — identify scientific, legal, manufacturing or market changes.

16. Triage — determine whether the change is product-relevant.
17. Materiality — assess whether safety evidence, classification, exposure or permitted use may be affected.
18. Action — define testing, dossier update, authority contact, customer communication or no action.
19. Verification — human sign-off and traceable rationale.
20. Propagation — update all dependent documents and downstream users.
21. Audit — preserve who decided what, when, using which evidence.

26.3 Minimum viable pilot

A pilot should not begin with the entire company portfolio. It should begin with three to five technologically different ingredients—for example, a conventional additive, a mineral technology, a fermentation-derived ingredient and a multifunctional processing system. That diversity would expose whether the data model can handle simple chemicals, process-dependent materials and jurisdictionally variable functions.

The objective of the pilot would not be to prove that AI can summarise regulations. It would be to measure whether structured evidence reduces regulatory retrieval time, inconsistent declarations, duplicated dossier work, missed changes and uncertainty during customer qualification.

27. Validation Metrics: How to Test Whether Continuous Evidence Management Actually Works

A research platform should be judged by measurable performance, not presentation quality. Suitable metrics include:

- median time to answer a jurisdiction-specific customer compliance question;
- percentage of regulatory statements traceable to primary evidence;
- number of obsolete or inconsistent declarations detected per quarter;
- percentage of manufacturing changes that receive documented regulatory-delta review;
- mean time from regulatory change to portfolio impact assessment;
- recall and precision of automated literature surveillance;
- false-positive rate for AI-generated regulatory alerts;
- percentage of safety-critical studies linked to the exact tested material/batch;
- percentage of product dossiers with current exposure envelopes;
- number of customer applications outside defined intended-use boundaries;
- audit time required to reconstruct the evidence state at a historical date.

A platform that cannot improve these metrics is a document repository, not evidence engineering.

28. Governance: The Failure Modes Must Be Designed Out

Digitalisation introduces new risks. A copied regulatory error can propagate faster than a paper error. An LLM-generated summary can omit a limiting condition. A poorly resolved synonym can link the wrong substance. A database can preserve an obsolete authorisation while giving users the false confidence of a structured interface.

A serious governance model should therefore require source provenance, effective dates, jurisdiction fields, reviewer identity, confidence classification, immutable version history and explicit supersession rules. Critical legal conclusions should link to the controlling primary source, not only to secondary summaries.

The principle should be simple: automation may accelerate information flow, but it must not erase the chain of accountability. Every consequential compliance statement must remain reconstructible from source evidence through expert judgment to the final document.

29. Regulatory Scenarios to 2030

The precise trajectory will vary by jurisdiction, but three plausible scenarios can be described without pretending to predict legislative outcomes.

Scenario A — Incremental observability

Regulators expand electronic registers, notification requirements and post-market review without fundamentally changing existing legal categories. Companies respond by improving dossier systems and surveillance. This is the most conservative continuation of current trends.

Scenario B — Structured life-cycle obligations

Authorities begin to require more formal post-market data maintenance, change notification or periodic evidence updates for selected ingredient classes, especially novel, biotechnology-derived or high-exposure substances. Comparability concepts become more explicit.

Scenario C — Computational regulation

Regulatory registers, company evidence systems and scientific surveillance become sufficiently structured that significant parts of impact assessment are machine-assisted. Regulators can identify affected products when rules or evidence change; companies can continuously compare portfolio status against official data. Human experts remain accountable for interpretation and decisions.

RESEARCH INTERPRETATION — The present regulatory developments are compatible with all three scenarios. What is already rational, however, is to build evidence architecture that performs well under each of them. Structured identity, versioned manufacturing data, explicit use conditions and traceable evidence are not wasted even if regulation evolves slowly.

30. Strategic Consequences for Ingredient Development

The conventional sequence of product innovation is functionality → manufacturability → economics → regulatory clearance. The emerging evidence environment argues for a different sequence: regulatory classification and identity design should occur in parallel with scientific development, not after it.

A stronger development gate would ask four questions before major scale-up:

22. Can the ingredient be defined with enough precision that the tested material and commercial material are demonstrably connected?
23. Can the manufacturing process evolve without losing the ability to assess comparability?
24. Are intended uses and exposure boundaries explicit enough to prevent uncontrolled use creep?
25. Can the regulatory status be defended separately in each target jurisdiction without resorting to generic “global approval” language?

If the answer to any of these is no, the problem is not merely regulatory documentation. It is product design.

31. Conclusion: From Regulatory Affairs to Regulatory Evidence Engineering

The 2026 GRAS debate is important, but its significance is larger than U.S. food law. FDA’s proposed mandatory notification architecture, its systematic post-market chemical assessment programme, the EU’s continuing re-evaluation and data-gap mechanisms, and Great Britain’s official digital registers all point toward a common governance reality: an ingredient’s regulatory legitimacy increasingly depends on the continued defensibility of the evidence connecting identity, manufacturing, exposure and safety.

This does not mean that authorisations have become temporary by default, nor that the major jurisdictions are legally harmonising. It means that the informational expectations surrounding authorised or otherwise lawful ingredients are becoming more dynamic.

The strategic consequence for industry is substantial. A static PDF dossier is no longer an adequate mental model for long-lived technologies. Companies need evidence systems capable of representing change: the process changed, the specification changed, the market changed, the science changed, the jurisdiction changed—or some combination of them.

The concepts proposed here—regulatory observability, manufacturing drift, exposure envelopes, evidence readiness, regulatory digital twins and evidence graphs—are not universal legal requirements. They are an attempt to describe the infrastructure that a scientifically serious food-ingredient company may need as regulation becomes more data-intensive and more continuous.

The resulting discipline can be called Regulatory Evidence Engineering: the deliberate design of systems that connect product identity, manufacturing, safety science, exposure, legal status and change history so that every material regulatory claim can be reconstructed, tested and updated.

If food regulation continues in the direction visible in 2026, the valuable asset will not simply be an ingredient that once crossed a regulatory threshold. It will be an ingredient accompanied by a living, traceable and continuously validated evidence architecture.

Practical Research Agenda

Research question	Why it matters	Possible validation approach
Can manufacturing drift be quantified?	Would allow proportionate triggers for reassessment.	Define critical evidence-linked attributes; calculate change distances across real process versions; compare expert materiality judgments.
Can an exposure envelope detect use creep?	Commercial diffusion may invalidate original exposure assumptions.	Link sales/application data to food categories and use levels; test whether aggregate exposure warnings appear earlier than conventional review.
Can knowledge graphs reduce compliance latency?	Document-centric systems are slow to update.	Compare time-to-impact-assessment before and after graph implementation across a controlled portfolio.
How reliable is AI literature surveillance?	False negatives may miss safety signals; false positives create workload.	Prospective blinded evaluation against expert-curated monthly literature sets.
Which data fields maximise regulatory observability?	Too little data prevents surveillance; too much creates burden and confidentiality risk.	Cross-jurisdictional ontology study using FDA, EU/EFSA and GB registers/dossiers.
Can comparability principles be adapted to food?	Process changes can decouple commercial material from evidence.	Develop risk-tiered food comparability framework; test retrospectively on ingredient process changes.

References

1. U.S. Food and Drug Administration (FDA). Generally Recognized as Safe (GRAS). Updated 2026.
2. U.S. Food and Drug Administration. Understanding How the FDA Regulates Food Additives and GRAS Ingredients.
3. U.S. Food and Drug Administration. Generally Recognized as Safe (GRAS) Notification Program. 2026.

4. 4. Federal Register. Substances Generally Recognized as Safe. Proposed Rule, 91 FR 51834, 11 August 2026; Docket FDA-2025-N-3262.
5. 5. U.S. Food and Drug Administration. Substances Generally Recognized as Safe (Proposed Rule): Regulatory Impact Analysis. 2026.
6. 6. European Parliament and Council. Regulation (EC) No 1333/2008 on food additives, as amended.
7. 7. European Commission. Re-evaluation of Food Additives. State of play updated 10 September 2026.
8. 8. Food Standards Agency. Reforms to the market authorisation process for regulated products come into force. 1 April 2025.
9. 9. Food Standards Agency. Authorised Regulated Food and Feed Products for Great Britain. Official registers.
10. 10. Food Standards Agency. Guidance on using the Register of Food Additive Authorisations and Register of Novel Food Authorisations. 2025–2026.
11. 11. U.S. Food and Drug Administration. FDA Finalizes Food Chemical Safety Post-Market Assessment Program, Launches Reassessment of BHT, ADA. 12 May 2026 (updated July 2026).
12. 12. U.S. Food and Drug Administration. Human Foods Program 2026 Priority Deliverables. 2026.
13. 13. U.S. Food and Drug Administration. Tool for the Prioritization of Food Chemicals for Post-Market Assessment. May 2026.
14. 14. U.S. Food and Drug Administration. Final Determination Regarding Partially Hydrogenated Oils (Removing Trans Fat). 2015, implementation updates.
15. 15. U.S. Food and Drug Administration. FDA Completes Final Administrative Actions on Partially Hydrogenated Oils in Foods. 2023.
16. 16. U.S. Food and Drug Administration. Brominated Vegetable Oil (BVO). Final revocation effective 2 August 2024.
17. 17. U.S. Food and Drug Administration. Revocation of Authorization for Use of Brominated Vegetable Oil in Food — Final Rule. 89 FR 55040 (2024).
18. 18. European Food Safety Authority (EFSA). Safety assessment of titanium dioxide (E171) as a food additive. EFSA Journal. 2021;19(5):6585.
19. 19. European Commission. Regulation (EU) 2022/63 withdrawing authorisation of titanium dioxide (E171) as a food additive.
20. 20. European Parliament and Council. Regulation (EC) No 1331/2008 establishing a common authorisation procedure for food additives, food enzymes and food flavourings.
21. 21. European Parliament and Council. Regulation (EU) 2015/2283 on novel foods.
22. 22. European Commission. Union list and implementing framework for novel foods under Regulation (EU) 2015/2283.
23. 23. European Food Safety Authority. Novel food application procedure. Last reviewed 6 May 2026.
24. 24. International Council for Harmonisation (ICH). Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process. 2004.
25. 25. FoodAtlas: Automated knowledge extraction of food and chemicals from literature. Computers in Biology and Medicine. 2024; DOI: 10.1016/j.combiomed.2024.109072.
26. 26. European Food Safety Authority. SME support services. Reviewed 22 September 2026.
27. 27. European Food Safety Authority. Call for expressions of interest in EFSA's advice for Novel Food SMEs — 2026 edition. 16 September 2026.

28. 28. U.S. Government Accountability Office. Food Safety: FDA Should Strengthen Its Oversight of Food Ingredients Determined to Be Generally Recognized as Safe (GRAS). GAO-10-246. 2010.
29. 29. U.S. Food and Drug Administration. List of Select Chemicals in the Food Supply Under FDA Review. Updated 2026.
30. 30. Food Standards Agency. Register of Regulated Product Applications. 2026.

INTABIOTECH Knowledge Center

Editorial note: This article distinguishes established regulatory facts from analytical interpretations and prospective research proposals. The latter should not be represented as current legal obligations unless subsequently adopted by the competent authority.

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