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The Authority of Doubt Regulatory Culture, Knowledge, and the Re-Making of Pharmaceutical Governance after Thalidomide

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Abstract

The thalidomide disaster (1957–1962) is often narrated as a biomedical tragedy caused by inadequate testing. This paper argues that its deeper historical significance lies in how it transformed the epistemic and moral foundations of pharmaceutical governance. The decisive variable separating catastrophe from containment was not superior scientific knowledge, but regulatory culture—specifically, whether institutions treated uncertainty as tolerable risk or as grounds for restraint. In the United States, FDA medical officer Frances Oldham Kelsey withheld approval for thalidomide amid incomplete evidence, legitimizing delay as a protective act. In contrast, West Germany and much of Europe operated within trust-based regulatory systems that normalized limited premarket proof and dispersed responsibility across manufacturers, physicians, and courts. By integrating institutional history, comparative regulatory analysis, and regulatory theory, this paper reconstructs how doubt became a form of state authority, how that authority was codified in the 1962 Kefauver–Harris Amendments, and why this transformation remains central to contemporary debates over accelerated approvals, emergency authorizations, and public trust.[1]Methodologically, the article employs comparative historical analysis across the United States and West Germany, drawing on statutory texts, FDA institutional materials, parliamentary records, and contemporaneous medical literature to explain why similar scientific uncertainty produced divergent regulatory outcomes.

INTRODUCTION: WHEN UNCERTAINTY BECOMES A DECISION

In modern pharmaceutical governance, the principle of "proof before permission" is often treated as self-evident. Drugs are assumed to require demonstrated safety and effectiveness before reaching the public. Historically, however, this principle is neither ancient nor inevitable. It emerged out of crisis. The thalidomide disaster rendered it politically and morally unavoidable.[2]

Between 1957 and 1962, thalidomide was prescribed to pregnant women across dozens of countries and promoted as a mild, non-toxic sedative. When infants were born with severe limb malformations—most notably phocomelia—physicians assembled causal suspicion while regulators confronted a more difficult question: should uncertainty justify restraint, or should access continue until harm was conclusively proven?[3]

The United States largely avoided mass catastrophe because thalidomide never received FDA approval for general marketing. This outcome was not an accident of fate, nor the result of superior scientific foresight. It was the contingent product of institutional practices that allowed uncertainty to halt authorization rather than merely delay warning. This paper advances three claims. First, thalidomide represents a crisis of regulatory epistemology rather than simply a failure of pharmacology. Second, Frances Oldham Kelsey's refusal mattered because it enacted a model of regulatory authority in which delay itself functioned as protection. Third, post-thalidomide reforms did more than tighten standards: they relocated the burden of proof onto manufacturers and embedded skepticism as a legal obligation.

In this paper, "the authority of doubt" refers to a form of regulatory power that treats unresolved uncertainty as actionable. It is not merely delay as bureaucratic inertia, but a legitimized capacity to withhold market permission until evidentiary thresholds are met—thereby shifting the burden of proof from the public to the sponsor.

LITERATURE REVIEW: FROM TRAGEDY TO GOVERNANCE

Early scholarship on thalidomide focused on clinical recognition and biological mechanism. William McBride's 1961 letter in *The Lancet* marked the first public warning

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connecting thalidomide to congenital abnormalities.[4] Subsequent medical research examined why animal testing failed to predict human teratogenicity, emphasizing species-specific vulnerability and the mistaken assumption that the placental barrier protected the fetus.[5]

A second body of literature situates thalidomide within regulatory history. FDA retrospectives emphasize the episode as the catalyst for reform, culminating in the Kefauver–Harris Amendments of 1962.[6] Daniel Carpenter's institutional history reframes thalidomide as a turning point in the construction of FDA authority and bureaucratic reputation, highlighting how restraint generated legitimacy rather than backlash.[7] Jeremy Greene extends this analysis by examining how pharmaceutical trust, branding, and therapeutic optimism shaped regulatory expectations before and after the crisis.[8]

More recent scholarship examines how regulatory systems govern uncertainty itself. Rather than assuming that more data automatically produces better outcomes, political scientists and public-health scholars analyze precaution, negative regulatory power, and the consequences of evidentiary thresholds for innovation and risk.[9] This paper contributes to that literature by foregrounding **doubt** as an analytic category and tracing how it became a legitimate form of state authority.

METHOD AND APPROACH

This study employs comparative historical analysis, drawing on FDA institutional records, statutory texts, parliamentary debates, scientific literature, and public history syntheses. The aim is not exhaustive archival reconstruction but institutional explanation: why the same scientific uncertainty produced radically different outcomes across governance regimes.[10]

THE POSTWAR PHARMACEUTICAL ORDER

Therapeutic Optimism and Regulatory Speed

In the decades following World War II, pharmaceuticals symbolized scientific progress and national recovery. Antibiotics, sedatives, and hormones promised control over disease and discomfort. Regulatory institutions often prioritized access and innovation, while fetal risk and long-term toxicity remained scientifically marginal and politically inconvenient. Speed itself acquired moral valence: rapid approval signaled modernity, competence, and economic vitality.[11]

What "Safety" Meant before Thalidomide

Before thalidomide, safety was defined narrowly as the absence of immediate, observable harm. Chronic toxicity, reproductive effects, and long-term outcomes were rarely central to approval decisions. The fetus was assumed to be shielded by the placental barrier—an assumption that lowered evidentiary burdens and accelerated approvals. These were not merely scientific errors but institutional conveniences embedded in regulatory routine.[12]

THALIDOMIDE'S RISE AND COLLAPSE

Thalidomide was marketed as a gentle alternative to barbiturates, praised for its apparent lack of toxicity and promoted for use by pregnant women. Its credibility rested on narratives of harmlessness rather than systematic fetal testing. By 1961, clinicians began reporting clusters of congenital abnormalities. Withdrawal followed unevenly across countries, revealing the absence of clear decision rules for acting under uncertainty.[13]

THE U.S. CASE: AUTHORITY WITHOUT PROOF AND THE POWER TO DELAY

Before 1962, the authority of the U.S. Food and Drug Administration rested less on statutory coercion than on professional judgment exercised within a permissive legal framework. Under the Federal Food, Drug, and Cosmetic Act of 1938, manufacturers were required to demonstrate drug safety, but approval was largely automatic unless the FDA could affirmatively prove that a product was unsafe.[14] In practice, this structure normalized uncertainty: absence of evidence was treated as an acceptable residue of innovation rather than a barrier to market entry.

Within this institutional environment, FDA medical officer Frances Oldham Kelsey reviewed Richardson–Merrell's New Drug Application for thalidomide. The company anticipated routine approval, citing the drug's extensive circulation in Europe and its reputation as a mild, non-toxic sedative.[15] Rather than producing new evidence, Richardson–Merrell's strategy relied on reframing evidentiary absence as adequacy. Repeated resubmissions and references to foreign approval functioned as a form of procedural pressure, testing the FDA's willingness to sustain skepticism without definitive proof of harm.[16]

Kelsey's review did not uncover conclusive teratogenic evidence. Instead, it revealed systematic gaps: incomplete neurological assessments, inconsistent clinical summaries, and a near-total absence of data regarding fetal exposure.[17] These deficiencies were not anomalous by the standards of the period; they reflected a regulatory culture in which missing knowledge was routinely tolerated. What distinguished Kelsey's intervention was her refusal to translate uncertainty into permission.

Rather than allowing market entry to proceed by default, Kelsey repeatedly returned the application for further data. This act constituted what may be termed negative authority: the exercise of institutional power through delay and refusal rather than affirmative authorization.

Although thalidomide circulated in the United States through investigational distribution channels—resulting in a small number of documented congenital injuries[18]—delay prevented commercial normalization and mass exposure.

The significance of Kelsey's refusal therefore lies not in absolute prevention, but in prevented scale. Delay did not eliminate risk; it constrained its magnitude.

While Kelsey's regulatory decision was grounded not in demonstrated harm but in the absence of critical evidence, the full biological consequences of thalidomide exposure would only become intelligible decades later. At the time of review, regulators lacked fetal toxicity studies, comprehensive neurological assessments, and long-term outcome data capable of predicting downstream systemic effects. As a result, the potential scope of harm remained fundamentally unknowable.

Although Kelsey's decision unfolded in advance of definitive scientific proof, it is important to note that the regulatory uncertainty she confronted was not merely procedural but epistemic in nature. At the time of review, the evidentiary record lacked not only conclusive demonstrations of safety, but also the analytical frameworks necessary to anticipate downstream effects. The absence of such knowledge did not signify regulatory failure; rather, it defined the limits of what could be responsibly known at the moment of decision. Kelsey's refusal thus reflected an institutional judgment about the boundaries of acceptable ignorance, transforming evidentiary absence into a legitimate basis for delay within a permissive legal framework.

THE GERMAN CASE: REGULATORY FRAGMENTATION AND THE ABSENCE OF CENTRALIZED RESTRAINT

In contrast to the United States, postwar West Germany lacked a centralized regulatory authority capable of exercising premarket restraint over pharmaceutical approval. Drug oversight was distributed across regional authorities and professional bodies, creating a fragmented regulatory environment in which responsibility for risk assessment was diffuse rather than institutionally concentrated. This regulatory fragmentation limited the state's capacity to impose uniform evidentiary standards or to delay market entry in the absence of definitive proof of harm.[19]

Within this decentralized system, pharmaceutical approval operated largely through professional self-regulation and ministerial notification rather than through centralized, adversarial review. Manufacturers were not required to submit comprehensive preclinical or clinical data to a single national authority prior to marketing, and the absence of coordinated oversight reduced incentives for precautionary delay. As a result, uncertainty was not systematically translated into regulatory restraint but was instead absorbed within a permissive approval environment.[20]

The approval and widespread distribution of thalidomide in West Germany reflected these structural conditions. Grünenthal's applications were reviewed within a regulatory framework that emphasized post hoc correction over anticipatory control. Without a centralized authority empowered to suspend approval on the basis of unresolved evidentiary gaps, early warning signals—such as emerging reports of peripheral neuropathy—failed to trigger meaningful regulatory intervention. Responsibility for action remained dispersed across institutions, weakening the capacity for coordinated response.

Legal accountability similarly reflected this fragmentation. Subsequent prosecutions and civil proceedings focused on individual culpability rather than institutional failure, reinforcing a regulatory culture oriented toward retrospective adjudication rather than preventative governance. In the absence of a centralized mechanism for delaying approval, uncertainty did not function as a trigger for restraint but as a residual condition tolerated within the system.[21]

The German case therefore illustrates not regulatory negligence but structural limitation. The absence of centralized oversight and delay authority meant that doubt could not be operationalized as a governing principle. Where the American system—through the discretionary actions of individual regulators—converted uncertainty into delay, the West German framework lacked the institutional architecture necessary to perform a comparable function. The resulting divergence was not a matter of regulatory strength versus weakness, but of organizational capacity: the ability, or inability, to translate evidentiary absence into coordinated restraint.

CODIFYING DOUBT: THE KEFAUVER–HARRIS AMENDMENTS (1962)

The significance of regulatory delay became fully apparent only in retrospect, as subsequent scientific inquiry revealed dimensions of pharmaceutical risk that had not been foreseeable within the evidentiary regimes of the early 1960s. These later findings did not retroactively validate or invalidate individual regulatory decisions; rather, they exposed the structural inadequacy of approval systems that treated uncertainty as tolerable by default. The Kefauver–Harris Amendments of 1962 responded to this recognition by embedding skepticism directly into the regulatory architecture, converting uncertainty from a residual condition into a formal trigger for restraint. What had previously depended on discretionary judgment was thus codified as institutional obligation.

The regulatory logic embodied in Frances Kelsey's refusal did not remain an isolated administrative episode. In the wake of the thalidomide disaster, Congress moved to formalize skepticism as a governing principle of pharmaceutical regulation. The Kefauver–Harris Amendments of 1962 fundamentally restructured the legal architecture of drug approval by reversing the burden of proof and embedding evidentiary requirements directly into the approval process.[22]

Where the pre-1962 framework operated on a default-permission model—allowing drugs to enter the market unless

regulators could demonstrate harm—the Amendments required manufacturers to affirmatively demonstrate both safety and efficacy prior to approval. This shift transformed uncertainty from a tolerable residue of innovation into a legally consequential condition demanding resolution. Doubt was no longer incidental; it became institutionalized.

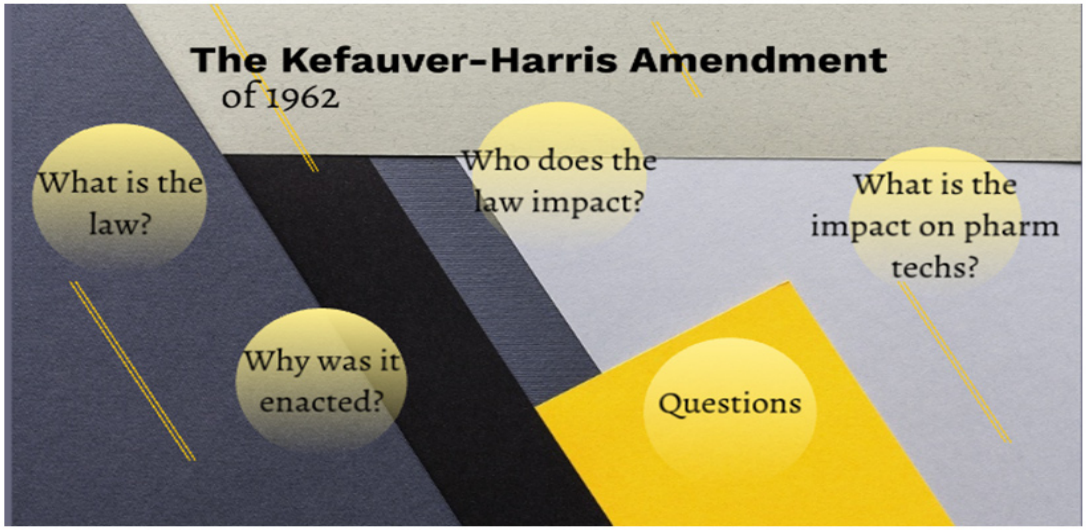

Figure 1. Conceptual Questions Raised by the Kefauver–Harris Amendments of 1962.

This figure presents a conceptual mapping of the regulatory questions introduced by the Kefauver–Harris Amendments, including the scope of the law, the rationale for its enactment, the actors affected, and its implications for pharmaceutical development. Rather than depicting procedural approval logic, the figure frames the Amendments as a reorientation of regulatory authority—shifting pharmaceutical governance away from trust-based assumptions and toward structured skepticism and evidentiary accountability.

Following this conceptual reorientation, the Amendments translated skepticism into concrete institutional mechanisms. Proof requirements were no longer abstract expectations but formal prerequisites enforced at multiple stages of drug development.

After 1962, doubt was operationalized through three linked mechanisms: (1) affirmative evidentiary burdens on sponsors, (2) staged premarket testing that forces uncertainty to be resolved sequentially, and (3) FDA's authority to withhold permission when evidence remains incomplete. Figure 2 visualizes how this logic matured into the modern IND–NDA pipeline.

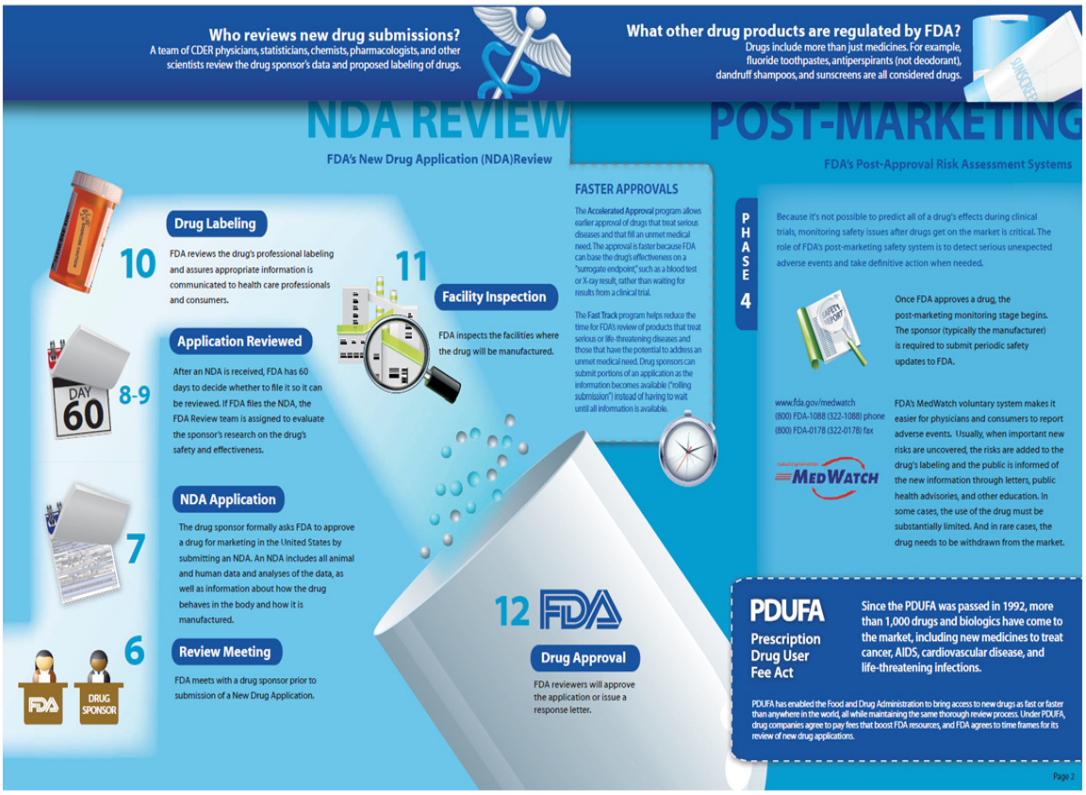

Figure 2. Institutionalization of Evidentiary Gatekeeping in the FDA Drug Approval Process.

(*Source: U.S. Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), "Drug Approval Process" infographic (PDF))*

This figure illustrates the post-1962 FDA drug approval pathway, emphasizing the sequential evidentiary thresholds governing market entry. The process delineates preclinical testing, Investigational New Drug (IND) authorization, phased clinical trials, New Drug Application (NDA) review, and post-marketing surveillance. By requiring affirmative demonstrations of safety and efficacy at each stage, the approval architecture converts uncertainty into a basis for regulatory delay rather than a justification for market entry, thereby institutionalizing doubt as a core feature of pharmaceutical governance.

Through these reforms, regulatory delay ceased to be an improvised administrative tactic and became a legally mandated feature of the approval process. The Amendments thus codified the logic that Kelsey had enacted in practice: that unresolved uncertainty itself constitutes a legitimate ground for restraint. Authority was no longer exercised primarily through post hoc intervention, but through anticipatory gatekeeping designed to prevent irreversible harm before market normalization occurred.[23]

This reform codified the logic that Kelsey had enacted administratively. Doubt was no longer an inconvenience to be overcome but a legally enforceable condition of market entry.

Table 1 summarizes the structural shift in FDA regulatory authority following the Kefauver–Harris Amendments, highlighting the reversal of burden of proof and the institutionalization of evidentiary skepticism.

Table 1. Transformation of FDA Regulatory Authority Before and After 1962

Feature	Pre-1962 FDA Authority (1938 Act)	Post-1962 FDA Authority (Kefauver–Harris)
Primary Approval Basis	Safety only	Safety and efficacy
Burden of Proof	On FDA	On manufacturer
Approval Mechanism	Passive notification	Active premarket approval
Clinical Trials	Minimal regulation	Adequate and well-controlled studies; informed consent
Manufacturing Oversight	Limited	Enforced GMP standards
Advertising Authority	Minimal	Expanded FDA oversight
Core Philosophy	Trust-based, reactive	Doubt-based, proactive

THE POLITICS OF DELAY AND THE DRUG LAG DEBATE

Critics argued that stricter regulation produced a "drug lag," delaying access to beneficial therapies. Subsequent analyses complicated this claim, showing ambiguous evidence of net harm and significant reductions in ineffective or dangerous drugs.[24]

MEDIA, MEMORY, AND LEGITIMACY

Media coverage transformed thalidomide into a moral scandal and reframed regulatory restraint as ethical commitment. Kelsey's refusal became emblematic of bureaucratic integrity, shaping public trust and legitimizing regulatory expansion.[25]

CONCLUSION: THE AUTHORITY OF DOUBT

The thalidomide episode reveals that modern regulatory authority is not founded on certainty, but on disciplined uncertainty. The transformation of pharmaceutical governance after 1962 did not eliminate risk; rather, it reallocated it. Instead of allowing uncertainty to be absorbed by the public after harm occurred, post-thalidomide reforms required manufacturers to resolve doubt before exposure. This shift fundamentally altered how societies negotiated the relationship between innovation, evidence, and vulnerability.

Seen in this light, thalidomide should not be understood simply as a tragedy narrowly averted in the United States by individual virtue. Frances Oldham Kelsey's refusal mattered not because it was heroic in isolation, but because it demonstrated that restraint could function as legitimate state action even in the absence of definitive proof. Her insistence that evidentiary gaps themselves constituted a public hazard challenged a deeply embedded assumption of mid-century pharmaceutical culture: that access should proceed unless danger was conclusively shown. In doing so, she enacted—before it was codified—a model of regulatory authority grounded in refusal rather than facilitation.

The subsequent legal reforms, most notably the Kefauver–Harris Amendments of 1962, embedded this logic into statutory form. By shifting the burden of proof onto manufacturers and formalizing requirements for safety, efficacy, and informed consent, the law transformed doubt from an administrative inconvenience into a legally enforceable condition of market entry. Regulation thus became not merely a mechanism for controlling dangerous products, but a system for governing uncertainty itself.

Comparative cases underscore the stakes of this transformation. In regulatory environments characterized by fragmented authority and trust-based oversight, uncertainty functioned as an excuse for delay without restraint, allowing harm to diffuse before decisive action could be taken. Where authority was centralized and willing to act on incomplete knowledge, uncertainty triggered caution rather than paralysis. The divergent outcomes associated with thalidomide were therefore not accidents of scientific ignorance, but consequences of institutional design.

Thalidomide's enduring relevance lies in this broader lesson. Contemporary debates over accelerated approvals, emergency authorizations, and reliance on surrogate endpoints continue to hinge on how uncertainty is interpreted and allocated. When institutions treat doubt as tolerable residue, the burden of risk tends to migrate toward the most vulnerable. When doubt is treated as actionable, delay becomes a form of care rather than a failure of governance.

Ultimately, the authority of doubt represents a moral as well as institutional achievement. It affirms that protection need not wait for catastrophe, and that restraint can be a legitimate expression of democratic responsibility. Thalidomide endures not only as a warning about pharmaceutical harm, but as a foundational case in the history of how modern states learned to govern the unknown.

Notes

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