FINAL PAPER

From Approval to Recall:

The SUSVIMO® Implant's Odyssey Through FDA's Benefit-Risk Framework

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Table of Contents

1. Introduction: Navigating the Risky Waters of FDA Safety Oversight

When it comes to healthcare products, the U.S. Food and Drug Administration (FDA) plays the dual role of gatekeeper and watchdog. Its mission, as described in the Federal Food, Drug, and Cosmetic Act, is to ensure that drugs, biologics, and medical devices entering the market are both safe and effective for public use. But "safe and effective" is hardly a static benchmark. It's a balancing act, a dynamic assessment that evolves throughout a product's lifecycle—starting from the laboratory bench, through clinical trials, and into the hands of millions of patients.

The FDA's regulatory authority stretches across a vast landscape—prescription drugs, biologics, medical devices, vaccines, gene therapies, combination products, and more. As technologies advance and therapeutic innovations outpace traditional paradigms, the complexity of safety assessment has grown exponentially. Enter the field of safety sciences and pharmacovigilance—disciplines dedicated to evaluating, mitigating, and managing risk before and after product approval. These practices are governed by a robust framework of federal regulations, such as 21 CFR Parts 312 (drugs), 600 (biologics), and 814 (medical devices), alongside global harmonisation efforts led by ICH, WHO, and CIOMS.

The FDA's Benefit-Risk Framework, officially adopted into its review process in the early 2010s, provides structured guidance on how safety (risk) is contextualised relative to benefit. It doesn't demand a zero-risk scenario—that would stall all innovation—but rather insists on clarity, mitigation, and continuous reassessment. Importantly, the framework varies between product categories. For drugs and biologics reviewed by CDER and CBER, risk often hinges on systemic toxicity, immune response, or long-term effects. For devices and combination products overseen by CDRH, risks may stem from mechanical failure, user error, or implantation site complications.

Through the lens of SUSVIMO, a novel intraocular drug delivery implant for age-related macular degeneration, we will examine how the FDA's risk oversight function pre and post approval. SUSVIMO's journey- from a promising innovation to facing safety setbacks post-market- offers valuable insights into how the FDA regulates risk and how these frameworks might be improved to keep pace with innovation without compromising patient safety.

2. The FDA's Benefit–Risk Framework for NDAs/BLAs (Drugs and Biologics)

When it comes to new drug and biologic approvals, the FDA is not just weighing clinical data, it's orchestrating a complex calculus of safety, efficacy, and unmet need. The Benefit–Risk Framework for NDAs and BLAs offers a formal structure through which the FDA's CDER and CBER can make scientifically justified, transparent, and patient-centered decisions.

2.1 Defining Risk in the Context of Drugs and Biologics

"Risk," in FDA parlance, refers to the potential for harm resulting from the use of a product, ranging from predictable side effects (e.g., nausea, fatigue) to rare but serious adverse events (e.g., hepatotoxicity, cardiac arrhythmias). Risks are considered in the context of magnitude, likelihood, reversibility, and population vulnerability.

Risk assessment begins in preclinical development, where toxicology studies (per 21 CFR 312.23) help identify organ-specific toxicity and establish safe starting doses for human studies. During clinical trials, the sponsor must collect safety data, conduct safety monitoring committees, and report SUSARs as well as SAEs. In the pre-approval phase, safety reporting is primarily captured through Development Safety Update Reports (DSURs), a globally harmonized tool standardized by ICH E2F. These annual reports, required under ICH E2C(R2) guidelines, provide regulators with an ongoing safety profile of investigational products, compiling clinical trial data, emerging risks, and potential safety signals. DSURs are

essential for maintaining the benefit-risk balance during clinical development, ensuring that both regulators and sponsors can make informed decisions about study continuation or design modification. Although not mandated in the U.S. under 21 CFR, they are often aligned with IND safety reports (21 CFR 312.32) for global trial harmonisation.

2.2 The Benefit–Risk Framework in Practice

The FDA's formal Benefit–Risk Framework for drug and biologic approvals was codified in 2018 via PDUFA VI and includes four key components:

1. **Analysis of Condition** – What is the disease's severity, prevalence, and burden?
2. **Current Treatment Options** – Are there alternative effective and safe therapies?
3. **Benefit** – What are the clinical outcomes achieved with the new therapy?
4. **Risk and Risk Management** – What are the known and potential risks, and what strategies are in place to mitigate them?

A classic example is the approval of Zolgensma (onasemnogene abeparvovec) for spinal muscular atrophy. Despite concerns about liver toxicity and long-term gene therapy effects, the drug was approved based on the devastating nature of the disease and absence of curative alternatives—demonstrating how Benefit:Risk can tip favorably even in the presence of serious risks.

2.3 Tools for Risk Management and Post-Market Surveillance

Once a product is approved, the FDA requires continued vigilance through post-marketing requirements (PMRs) and post-marketing commitments (PMCs). The FDA Amendments Act (FDAAA) of 2007 gave the agency authority to mandate Risk Evaluation and Mitigation Strategies (REMS) for products with serious safety concerns.

The REMS program may include:

- Medication Guides, Communication Plans, Elements to Assure Safe Use (ETASU) – e.g., restricted distribution, provider certification and Implementation Systems – verification and compliance monitoring

For example, isotretinoin (Accutane) has a robust REMS due to teratogenicity, requiring pregnancy testing and provider certification under the iPLEDGE program.

The FDA Sentinel Initiative, launched in 2008, further exemplifies how real-world data (RWD) is harnessed to monitor product safety post-approval, using claims data and electronic health records (EHRs) to detect adverse events that might not appear in clinical trials.

3. Benefit–Risk Framework for New Medical Devices

In the realm of medical devices, the FDA's approach to benefit–risk assessment is shaped by both product classification and intended use. The device classification system—Class I, II, or III—directly reflects the risk level associated with the product and determines the appropriate regulatory pathway (510(k), PMA, or De Novo). Risk, in this context, is evaluated not only in terms of direct harm (e.g., device malfunction or injury) but also in how misuse, complexity, or failure to perform as intended might impact the patient population.

The FDA's guidance titled *"Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications"* outlines key elements such as the severity and likelihood of adverse events, the ability to mitigate risks, and the extent of available alternatives. These benefit-risk determinations are pivotal during the premarket stage but must also adapt post-market as real-world data surfaces.

To support this adaptive framework, FDA's *Benefit-Risk Framework for Medical Device Product Availability, Compliance, and Enforcement Decisions* emphasises a lifecycle approach, recognising that product risk evolves over time. The FDA also mandates risk

management systems under 21 CFR Part 820, requiring manufacturers to conduct risk analysis, establish controls, and monitor field performance. Safety surveillance is also supported by adverse event reporting systems like MedWatch and MAUDE (Manufacturer and User Facility Device Experience), which gather data that can trigger label changes, recalls, or even device withdrawal. Additionally, Human Factors Engineering (HFE) is increasingly required in submissions to ensure usability and reduce user-related errors—critical in devices such as implantable or combination products like SUSVIMO.

Layered atop regulatory expectations, the medical device industry often applies quality and performance improvement methodologies like Six Sigma to proactively identify and mitigate risks. Six Sigma's DMAIC (Define, Measure, Analyse, Improve, Control) framework supports rigorous problem-solving and data-driven decision-making—particularly useful during design, manufacturing, and post-market monitoring phases. For combination products such as SUSVIMO, Six Sigma could have facilitated early identification of septum dislodgement or leakage issues by minimising process variation and ensuring consistent device performance. While not required by regulation, Six Sigma complements FDA’s expectations of robust quality systems and aligns with global standards such as ISO 13485, enhancing the safety profile of devices from conception through market lifecycle.

In essence, while the core regulatory structure provides a foundation for risk management, tools like Six Sigma and HFE offer added layers of assurance, especially when real-world variables challenge assumptions made in controlled trials. Together, they form a multilayered safety net that reflects both regulatory discipline and engineering excellence.

SUSVIMO, bridging both drug and device domains, must navigate dual-level oversight. Its risk profile is shaped not only by the pharmacology of ranibizumab but also the engineering

and surgical risks of its implantable reservoir. That duality is key to understanding its safety challenges—and lessons for the future.

4. SUSVIMO – A Case Study in Post-Marketing Risk Revelation

4.1. Overview of SUSVIMO and Its Regulatory Pathway

SUSVIMO (ranibizumab injection) was approved by the U.S. Food and Drug Administration (FDA) on October 22, 2021, as a combination product—a biologic delivered via a novel implantable ocular port delivery system (PDS). Developed by Genentech, part of the Roche Group, SUSVIMO was designed to treat neovascular (wet) age-related macular degeneration (nAMD), a leading cause of blindness among older adults.

The approval came through a Biologics License Application (BLA) under section 351(a) of the Public Health Service Act. SUSVIMO represented a breakthrough in patient convenience: by surgically implanting a refillable reservoir that delivered ranibizumab directly into the vitreous humor, patients would only need refills every six months, compared to monthly intravitreal injections. This innovation positioned SUSVIMO as a disruptive product with significant patient-centric value—on paper.

However, as with many novel delivery mechanisms, real-world clinical utility introduced complexities not fully captured in controlled clinical trials. Within a year of approval, the device encountered a post-market crisis.

4.2 Post-Market Safety Challenges and Voluntary Recall

But soon after its release, cracks began to appear in SUSVIMO's benefit-risk facade—literally. By late 2022, Genentech voluntarily recalled the SUSVIMO implant and refill-exchange needle components due to reports of septum dislodgement. The septum—the seal inside the implant through which the drug is refilled—was found to be mechanically unstable, leading to potential underdelivery, exposure of drug contents, or complete device failure. These incidents,

though rare in clinical studies, surpassed expected frequencies in post-market use, signaling a risk that was initially underestimated. This development shifted SUSVIMO from a marvel of convenience to a reminder that innovation, while necessary, is rarely risk-free.

In addition to mechanical concerns, adverse event reports to the FDA's MedWatch and FAERS systems revealed ocular complications including Endophthalmitis (intraocular infection), Hypotony (low intraocular pressure), Conjunctival erosion and retraction, Device dislocation and Inflammatory reactions. These risks were listed in the original product labeling, but labeling alone proved insufficient to mitigate the frequency and severity of events seen post-approval.

4.3 REMS: The Missing Safety Net?

Interestingly, SUSVIMO was *not* approved with a formal Risk Evaluation and Mitigation Strategy (REMS) despite its novel delivery system and potential for serious ocular complications, including endophthalmitis, retinal detachment, and hypotony. This raises a key regulatory question: Should it have been? FDA guidance suggests REMS are required when a product's risk cannot be adequately managed through labeling alone. Given the implantable nature of SUSVIMO and its surgical insertion requirements, some experts argue that a REMS could have enforced standardised training for ophthalmic surgeons, patient registries, or structured follow-up programs—measures that might have preemptively identified device fragility and mechanical failure rates.

Although no REMS was in place, the label included specific warnings about procedural risks, proper handling techniques, and adverse event profiles. Still, real-world use highlighted risks that the clinical trials may have underrepresented, bringing to light the often-quoted maxim: "The trial tells you *if* a drug works. The market tells you *how* it works."

According to FDA guidance, a REMS is required when a product's risks "outweigh the benefits unless additional risk mitigation strategies are implemented". While SUSVIMO's clinical trial data (ARCHWAY trial, NCT03677934) showed non-inferiority in efficacy and manageable safety, it may have underestimated user-dependent procedural risk—an area REMS programs are specifically designed to address.

For example, a REMS could have included Certified surgeon training programs, Restricted distribution to trained ophthalmic facilities, Patient education mandates for post-op care and symptom reporting and Mandatory adverse event reporting for certain complications

Instead, Genentech relied on labeling, device instructions, and procedural training materials, which, while thorough, lacked the regulatory weight of REMS enforcement.

4.5 Safety Signal Detection: FAERS and Literature Insights

A review of the FDA Adverse Event Reporting System (FAERS) and peer-reviewed publications indicates a pattern of mechanical failures and surgical complications surfacing after commercial launch. A 2023 article in *Ophthalmology Retina* reported real-world rates of endophthalmitis and hypotony to be higher than trial data, suggesting a discrepancy between controlled vs. real-world device handling.

This aligns with concerns from the broader regulatory science community that Phase 3 trials of combination products may under-power safety endpoints, especially for mechanical failures that manifest over time and with diverse operator techniques. The FDA's own Benefit-Risk Framework (FDA, 2018) emphasises the role of "uncertainties in evidence"as a core component of risk assessment—an area clearly demonstrated here.

4.6 Combination Product Oversight and Regulatory Gaps

SUSVIMO's regulatory journey also exposes grey zones in the regulation of combination products. It was reviewed under the biologics pathway (BLA), with CBER as the lead center, even though the device component was crucial to its administration and safety. The FDA's Office of Combination Products (OCP) coordinates such reviews, but regulatory experts have long noted that oversight of mechanical reliability and human factors in biologic-device combinations often lacks clarity compared to stand-alone devices.

Had SUSVIMO been classified as a device-led product, the Center for Devices and Radiological Health (CDRH) may have imposed more stringent design validation, usability testing, and real-world simulation requirements before approval. This raises important regulatory science questions: Does our current regulatory structure sufficiently accommodate hybrid products? And if not, how can it evolve to better forecast risk?

Table 1: Summary of SUSVIMO's Risk Profile Evolution

Phase	Benefits	Expected Risks	Underestimated Risks / New Risks	Actions Taken / Notes
At Approval	- Long-acting drug delivery - Reduces injection burden - High patient satisfaction	- Surgical complications - Infection risk - Hypotony	- Mechanical device failure - Refill needle compatibility issues - Post-market user variability	- No REMS required - No mandated training or restricted access
Post-Approval	—	—	- Septum dislodgement - Higher incidence of AEs in real-world settings	- Voluntary recall - Temporary pause in commercial distribution

Had SUSVIMO followed a PBRER-style post-marketing pharmacovigilance model, as recommended in ICH E2C(R2), the early onset of mechanical failure signals might have been captured more systematically. The Periodic Benefit-Risk Evaluation Report (PBRER), unlike traditional PSURs, incorporates both efficacy and safety data to offer a holistic evaluation of a product's evolving benefit-risk profile. For a combination product like SUSVIMO, which merges biologic delivery with device mechanics, the application of such a model—though not currently required by the FDA—could enhance proactive risk communication and regulatory decision-making.

Key Takeaways from the SUSVIMO Case:

- Post-market performance may differ dramatically from trial-based expectations, especially for combination products with complex user interfaces.
- The FDA's Benefit-Risk Framework, while robust, is only as effective as the input assumptions and data modeling used during pre-market review.
- REMS, while not universally necessary, can serve as a valuable regulatory scaffolding for novel delivery mechanisms—bridging gaps between risk perception and reality.
- Safety signal detection must go beyond spontaneous reporting; integration with EHR-based surveillance systems and patient-reported outcome monitoring could provide earlier alerts.
- The regulatory architecture for combination products may need to evolve to reflect their dual nature, with both biologic and device risks playing integral roles.

5. Section 4: Conclusions – Lessons from SUSVIMO and Strategic Recommendations

The post-market journey of SUSVIMO is emblematic of the evolving complexity in regulating combination products. Positioned at the intersection of biologics and medical devices, SUSVIMO's promise was transformative—offering a long-acting, refillable ocular implant for

wet AMD that could drastically reduce treatment burden. Yet, its real-world rollout revealed the limitations of traditional pre-market safety assessments and underscored the need for stronger, more adaptive post-market risk mitigation strategies.

The FDA's Benefit-Risk Framework, while comprehensive in its structure, still faces challenges in real-time risk anticipation—especially in cases where device performance is heavily operator-dependent, and long-term outcomes hinge on real-world variability. SUSVIMO's mechanical failures, which ultimately led to a voluntary recall, could have potentially been mitigated with enhanced human factors testing, more rigorous post-approval surveillance, or even a proactive REMS program that incorporated mandated training and restricted use protocols.

On a broader scale, SUSVIMO raises important questions about how the Benefit:Risk paradigm must evolve in the face of innovation:

- Should combination products automatically trigger REMS considerations when novel delivery mechanisms are introduced?
- Can the FDA mandate real-world evidence collection within the first 6–12 months post-launch as a conditional approval strategy?
- Are existing signal detection systems—such as FAERS—robust enough to identify subtle trends in mechanical failure, or do we need enhanced tools that integrate electronic health records and wearable/device data?

These are not just academic questions. They reflect the urgent, practical challenge of translating medical innovation into safe, effective, and sustainable therapies. As we move toward more sophisticated delivery systems, personalised therapies, and digital-health-integrated treatments, the regulatory science must keep pace.

5.1 Strategic Recommendations:

1. Strengthen Combination Product Oversight:

   Define clearer regulatory pathways for biologic-led vs. device-led combination products. Mandate integrated reviews between CBER/CDRH with shared post-market responsibilities.

2. Risk-Based REMS Triggers for Novel Devices:

   Require REMS or risk management plans for all first-in-class implantable devices unless explicitly exempted. Include mandated surgeon certification, real-world data submission, and periodic safety updates.

3. Bolster Post-Market Surveillance Infrastructure:

   Expand Sentinel-type systems to device-based combination products. Incentivise patient-reported outcome and wearable-based adverse event reporting.

4. Promote Human Factors and Systems Thinking in Pre-Market Review:

   Make human factors testing a mandatory part of biologic-device approvals. Incorporate principles of Six Sigma and Design Failure Mode Effects Analysis (DFMEA) during development and FDA review.

6. Codify Labeling and Training Requirements Beyond Static Instructions:

   Introduce live digital tools (e.g., mobile-based apps or interactive visual training modules) to assist clinicians and patients in using novel devices safely.

SUSVIMO's story is not one of regulatory failure—it is a cautionary tale about the limits of even well-structured frameworks when faced with real-world variability and the unpredictability of novel delivery systems. It is also a case study in the power of post-market vigilance and the need for a regulatory ecosystem that is responsive, proactive, and centered on the patient experience.

Table 2: Drugs vs. Devices: Risk Science at a Crossroads

	Drugs/Biologics	Medical Devices
Regulatory Centre	CDER/CBER	CDRH
Risk Origin	Molecular mechanisms, toxicity	Mechanical failure, user error
Data Requirements	Robust clinical trial data	May rely more on bench- usability studies
Post-market Oversight	REMS, PMRs, MedWatch	MDR, UDI, PAS, Safety Alerts
Regulatory Guidance	21 CFR 312, REMS (21 CFR 314.520)	21 CFR 803, 21 CFR 812, ISO standards

Table 3: Here's a comparison of Benefit vs. Risk attributes in the pre-approval vs. post-approval phases of a drug or medical device's lifecycle. This highlights how benefit-risk assessment evolves with more data, broader populations, and real-world context.

	Pre-Approval (Before FDA Approval)	Post-Approval (After FDA Approval)
Primary Goal	To establish a favourable benefit-risk profile for initial marketing approval	To monitor, update, and refine the benefit-risk profile over time
Benefit Assessment	Based on clinical trial efficacy outcomes (e.g., endpoints, biomarkers)	Based on real-world effectiveness, quality of life, and patient-reported outcomes
Risk Assessment	Limited to short-term, trial-based risks; known adverse events under controlled conditions	Expands to include long-term, rare, and population-specific risks (e.g., geriatrics, pediatrics)
Data Sources	Randomised controlled trials (RCTs), preclinical studies	Observational studies, spontaneous reports, electronic health records, registries

Population Representativeness	Narrow; highly selected populations with exclusion criteria	Broad; includes diverse, real-world patient demographics
Uncertainty Level	High; limited exposure and sample size	Lower; cumulative exposure and broader evidence base
Regulatory Tools	IND safety reports, Advisory Committees, benefit-risk assessment frameworks (e.g., CDER's BR Framework)	REMS, post-marketing commitments (PMCs), post-marketing requirements (PMRs), label changes
Risk Management	Trial protocols, safety monitoring boards, limited distribution or patient access	REMS programs, boxed warnings, targeted surveillance, market withdrawal if needed
Benefit-Risk Outcome	Determines initial approval	Can lead to continued approval, restricted use, or withdrawal
Examples	Approval of a cancer drug with promising Phase III results but high toxicity	Post-market withdrawal of Vioxx due to cardiovascular risks despite pain relief benefits

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