Harmonization of the FDA's Quality Management System Regulation with ISO 13485

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Executive Summary

This paper examines the implications of the U.S. Food and Drug Administration's (FDA) recent regulatory reforms, which amend the existing Quality System Regulation (21 CFR Part 820) by introducing the Quality Management System Regulation (QMSR) in February 2026, aligned with ISO 13485:2016. The objective of this paper is to review these reforms, assess their alignment with international standards, and analyze their impact on key stakeholders in the medical device manufacturing industry, including startups, established firms, regulators and physicians. The research also explores historical changes in the regulatory landscape, schemes such as the Medical Device Single Audit Program (MDSAP), and the uncertainty surrounding future implementation under the current administration.

The methodological approach involves a qualitative review of regulatory texts, amendments published in register, a comparative analysis of the former and revised frameworks, and an examination of case studies from international contexts—such as the European Union, Canada, Japan, and India—where ISO 13485 has already been implemented. The paper also draws on secondary literature to understand regulatory intent, changes in stakeholder roles, and the projected economic and operational impacts.

The findings indicate that while the shift toward ISO 13485 promotes global harmonization, operational efficiency, and risk mitigation, its implementation presents distinct challenges, particularly due to terminology changes and structural adjustments. These challenges are quite burdensome for startups, which may lack the resources and regulatory familiarity needed for compliance. In contrast, established corporations are generally better positioned to adapt. Furthermore, the new framework has a potential to redefine stakeholder roles and market dynamics, requiring increased alignment with formal quality management protocols—particularly for manufacturers and designers engaged in device development. The paper concludes that the new QMSR is a critical and promising step toward alignment of the U.S. medical device sector with the rest of the world; however, there are different implementation challenges making transitional support to ensure inclusive and effective compliance across the industry highly important.

1. Introduction

The roots of modern medical device regulation can be traced back to a simple idea: ensuring that devices work as intended and don't harm the people who rely on them. But getting there took decades of trial, error, and reform. In both the United States and the international regulatory community, the initial push toward formal quality management systems came in response to real-world problems: device failures, inconsistent manufacturing practices, and a lack of clear oversight. What followed was the gradual construction of regulatory frameworks designed to bring order, accountability, and safety to a rapidly growing industry. In the United States, the first major step came with the Medical Device Amendments of 1976, which gave the FDA the authority to regulate medical devices. Two years later, the agency issued its first Current Good Manufacturing Practice rule for devices, codified as 21 CFR Part 820 [1]. That original rule focused on manufacturing controls such as cleanliness, equipment calibration, and recordkeeping. It applied lessons learned from drug manufacturing but didn't include any requirements for design. At the time, the assumption was that quality problems would show up in the factory, not in the engineering [2], [3].

That assumption didn't hold up. Through the 1980s, the FDA saw a steady rise in recalls involving life-sustaining or life-supporting devices. Pacemakers malfunctioned. Heart valves failed. And over time, it became clear that many of these problems weren't caused by sloppy assembly or bad materials. They were baked into the product during design. The tipping point came when FDA studies found that nearly half of all recalls between 1983 and 1989 were due to design-related deficiencies [3,4]. These were failures that couldn't be caught by inspection because they were structural, systemic, and invisible unless you were involved in the product's development process. In response, Congress passed the Safe Medical Devices Act of 1990, giving the FDA the legal authority to require design controls in its device regulations. This kicked off several years of rulemaking and industry consultation, eventually leading to the creation of the QSR. Finalized in 1996 and implemented in 1997, the QSR completely overhauled Part 820. It introduced a set of requirements that forced manufacturers to document user needs, define design inputs and outputs, verify and validate designs, conduct design reviews, and maintain a Design History File [1,2]. These controls ensured that quality was built into the device from the start. The QSR also required manufacturers to establish Corrective and Preventive Action systems, management oversight processes, and internal audit functions to create a full loop of accountability across the organization.

Around the same time, the international community was developing its own framework. The International Organization for Standardization had already released ISO 9001, a generic quality management standard used across industries. But there was growing recognition that medical devices presented unique challenges that required a more targeted approach. In 1996, ISO published the first version of ISO 13485, built on ISO 9001 but tailored specifically for medical device manufacturers. It focused on consistent design, production, installation, and servicing, offering regulators a structured model that could be adopted across borders. ISO

13485 launched alongside a companion standard, ISO 13488, which was designed for manufacturers that didn't perform design activities. Together, they formed the basis for what would become the global medical device quality standard.

In both cases, the push for regulation was reactive. These systems weren't built in a vacuum. They were direct responses to real failures that exposed how dangerous a weak quality system could be. However, the solutions were forward-looking. The QSR and ISO 13485 both emphasized systems thinking, risk awareness, and the need for documented processes that could be audited and improved [2,4]. Over time, these principles became the foundation of modern device regulation, influencing how manufacturers all over the world approach safety, consistency, and compliance. What started as national and international efforts to stop bad products from reaching patients evolved into a broader movement to create a culture of quality in medical device development. And while the two systems started separately, the groundwork laid during this early period made their eventual convergence not just possible, but inevitable.

2. Key Revisions and Evolving Focus

Over time, both ISO 13485 and the FDA's QSR have been revised to keep pace with emerging risks, new technologies, and the growing pressure for global harmonization. While their core intent has stayed consistent, to ensure that medical devices are safe, effective, and built through a controlled process, the details have shifted in meaningful ways. These changes reflect a broader trend in regulation: moving from reactive oversight toward proactive risk management and continuous quality assurance throughout the product lifecycle [5]. For ISO 13485, the biggest shift came in 2016, when the standard was substantially overhauled. The new version didn't just update language or tighten a few clauses. It restructured the framework to embed risk management at every stage of product development, from design through distribution. It required manufacturers to plan for regulatory compliance, validate software used in QMS processes, and put systems in place for post-market surveillance and feedback loops. It also broadened expectations for supplier controls, device traceability, and documentation of design transfer [6]. Compared to the earlier 2003 edition, the 2016 standard presented a more mature and globally relevant model of quality, one that expected manufacturers to be thinking several steps ahead rather than just meeting minimum benchmarks. Importantly, ISO 13485:2016 removed the continual improvement requirement from ISO 9001, recognizing that medical device regulations prioritize maintenance of effectiveness over experimentation or change for its own sake [6]. That removal marked a subtle but important divergence from general manufacturing standards, tailoring ISO 13485 more clearly to a regulated environment.

Meanwhile, the FDA's QSR, implemented in 1997, held steady for over two decades with only minor edits. But its original design was already forward-thinking. It introduced design control requirements that forced companies to trace device development from user needs through verification and validation. It added requirements for management review, internal audits, and CAPA. These features created accountability at every level of the organization, helping ensure

that quality issues weren't isolated to the factory floor. The QSR also introduced the idea of requiring formal risk analysis during product development, which was cutting-edge at the time [5]. While it didn't match the full breadth of ISO 13485's later expectations, it laid the groundwork for many of the practices that eventually became global norms.

By the 2010s, both systems had begun to look more alike than different. But there were still practical challenges for manufacturers who needed to comply with both. Terminology differed, document structures didn't line up, and FDA inspections often looked for items that ISO 13485 audits didn't touch and vice versa. Companies had to maintain dual quality manuals, train staff on both frameworks, and prepare for separate audits that covered almost the same ground in slightly different ways [5,7]. This wasn't just inefficient. It risked misalignment within organizations, especially when compliance teams had to choose which framework to prioritize in ambiguous situations. That's what made the FDA's 2024 QMSR so significant. The final rule didn't just tweak the QSR. It replaced it with a new framework that formally incorporates ISO 13485:2016 by reference. The QMSR acknowledges that ISO 13485 already does the heavy lifting and adds only what's necessary to preserve alignment with U.S. law. This includes retaining definitions that match the Federal Food, Drug, and Cosmetic Act, such as the U.S. legal meaning of "device" and "labeling." It also clarifies that certain FDA-specific rules still apply, including requirements around Unique Device Identification, medical device reporting, and corrections and removals [7]. Perhaps most controversially, the QMSR eliminates a long-standing exception in the QSR that kept management reviews, internal audits, and supplier audit reports out of FDA's routine inspection scope. FDA reasoned that since international regulators already look at these documents under ISO 13485, U.S. rules should follow suit to remain aligned. While some in industry objected to the change, it reflects a broader trend toward transparency and harmonization across regulatory systems [2,7].

These revisions reflect more than just technical updates. They signal a shift in mindset. The goal is no longer to force companies to navigate two slightly different sets of rules but to make it possible to operate under one global quality system. For companies that sell devices internationally, that means less time interpreting differences and more time improving processes. For regulators, it means greater ability to share oversight responsibilities, build mutual confidence, and focus on areas of real risk rather than procedural mismatches. Together, the changes in ISO 13485 and the QMSR represent the next step in the evolution of quality regulation. They preserve what works, update what no longer serves the market, and open the door to a more connected, efficient, and resilient medical device ecosystem [2,5]. While the implementation process still brings challenges, the direction of travel is clear and it reflects lessons learned over nearly thirty years of regulatory progress.

2.1. Global Adoption and Use of ISO 13485

While ISO 13485 was originally developed as a voluntary international standard, over time it has become the foundation for regulatory systems across nearly every major medical device market. What makes it unique is that it offers a shared language for quality management, giving manufacturers a clear path to compliance across different jurisdictions. This has made it more than just a best practice. In many countries, it is now a de facto requirement for selling medical devices at scale [8,9].

In Canada, ISO 13485 compliance is written into law. Since 2003, Class II, III, and IV device manufacturers have been legally required to implement a quality system that meets ISO 13485 standards. As of 2019, Canada enforces this through the MDSAP, which builds directly on ISO 13485 and adds country-specific requirements. Companies that want to sell into the Canadian market must provide a valid MDSAP audit report, which Health Canada uses instead of doing its own inspections. Without this, a license to sell devices is not granted [9,10]. This approach puts ISO 13485 compliance at the center of regulatory approval and has streamlined oversight while holding manufacturers to a consistent standard.

In the European Union, ISO 13485 plays a slightly different role. It is not mandatory by name, but it is recognized as a harmonized standard under the EU's Medical Device Regulation (MDR). That means if a manufacturer uses ISO 13485 to structure its quality system, it is presumed to comply with the relevant quality system requirements of the MDR. In practice, companies aiming for CE marking typically seek ISO 13485 certification because it simplifies the Notified Body review process. Notified Bodies use ISO 13485 as a baseline in their audits and layer on MDR-specific checks [8]. So while ISO 13485 is not formally mandated in Europe, it is deeply embedded in the process of bringing a device to market.

Japan also incorporates ISO 13485 principles directly into its national QMS law through MHLW Ordinance No. 169. This regulation mirrors ISO 13485 in structure and content but includes some local modifications, such as documentation requirements in Japanese and additional expectations around records. Japan participates in MDSAP and often accepts MDSAP audit reports in place of its own inspections, provided those reports cover the Japan-specific additions [11]. Manufacturers seeking to enter the Japanese market are generally expected to pass a conformity assessment based on ISO 13485, either through MDSAP or direct audit by the Pharmaceuticals and Medical Devices Agency (PMDA).

In Australia, the Therapeutic Goods Administration (TGA) uses ISO 13485 as the baseline for QMS compliance. Manufacturers can provide evidence of ISO 13485 certification, a CE certificate, or a MDSAP audit report as part of the registration process. TGA does not routinely conduct its own audits unless there is a specific reason, such as a compliance concern or lack of acceptable documentation. For higher-risk devices, having an ISO 13485 certificate is effectively a requirement, even though the law does not state it outright [8,11]. In practice, ISO certification is the most straightforward way to meet Australia's regulatory expectations.

The United States, for years, stood apart. While ISO 13485 was widely accepted internationally, the FDA continued to enforce its own QSR under 21 CFR Part 820. This created

a dual burden for manufacturers who had to build and maintain parallel systems. With the upcoming QMSR, that is finally changing. Once the rule goes into effect in February 2026, ISO 13485 will become the official quality system framework for the U.S. as well, bringing the country into closer alignment with its global counterparts [8].

Despite the shared use of ISO 13485, enforcement models still differ across countries. In Canada, conformity is certified through MDSAP and required before market entry [9]. In the EU, ISO 13485 is used as a shortcut to demonstrate MDR compliance through Notified Body audits [8]. Japan accepts ISO 13485 but may require audits in Japanese or PMDA-specific forms [11]. In the U.S., compliance will be enforced through FDA inspections rather than certificates, meaning a company might be fully compliant with ISO 13485 but still be cited if it falls short of FDA-specific interpretations. This reflects the FDA's decision not to rely on ISO certificates alone, even under the QMSR. However, the agency will continue to accept MDSAP audits in place of routine FDA inspections, which offers companies a streamlined path for satisfying multiple regulators at once [8].

The MDSAP plays a key role in all of this. MDSAP allows a single audit, conducted by an approved auditing organization, to satisfy the requirements of multiple countries at once, including the U.S., Canada, Japan, Australia, and Brazil [9,11]. This has dramatically reduced audit fatigue and simplified compliance planning for multinational manufacturers. Even though the European Union is not formally part of MDSAP, many of its Notified Bodies also serve as MDSAP auditing organizations. That allows manufacturers to combine audits and stretch their resources further, making ISO 13485 not just a standard but a platform for global operational efficiency [11].

In short, ISO 13485 has moved from being a recommended best practice to a foundational part of regulatory compliance in nearly every major device market. Its wide adoption has reduced fragmentation, improved consistency in device safety standards, and created a pathway for smarter, more predictable global expansion. Now that the U.S. is aligning its regulatory system through the QMSR, manufacturers will finally be able to operate with a single quality management language, dramatically simplifying the task of bringing safe and effective medical devices to patients around the world [8].

2.2. The 2026 Transition: A Strategic Realignment of U.S. Medical Device Regulation

February 2, 2026, is not just another regulatory deadline. It marks a foundational shift in how the United States defines, inspects, and enforces quality in the medical device industry. After nearly three decades, the FDA's domestically built QSR will be replaced by the QMSR, which formally incorporates ISO 13485:2016 into U.S. law [12]. On paper, the FDA insists that "nothing is fundamentally changing"—that the core expectations of safe design, risk management, traceability, and corrective action remain intact. But for manufacturers, the framework around those expectations is changing completely: in structure, in source, and in spirit.

At the center of this shift is the incorporation by reference of ISO 13485:2016 into 21 CFR Part 820, making it a legally binding quality standard for U.S. device manufacturers [12]. That decision is remarkable not just because it ties U.S. regulation to a non-domestic document, but because it represents a fundamental rebalancing of authority. The FDA is no longer the sole author of its quality system rulebook. Instead, it becomes an interpreter and enforcer of a broader, international consensus, one where it still holds a seat at the table, but not the only pen. This isn't a wholesale abdication of sovereignty. The FDA surrounds ISO 13485 with targeted modifications: inserting its own legal definitions, preserving expectations unique to U.S. law like Unique Device Identification and corrections/removals, and emphasizing regulatory concepts like design transfer that ISO leaves implicit [5,13]. Crucially, the FDA also removes the long-standing QSR carve-out that kept internal audits and management reviews outside the scope of inspections. Under QMSR, those documents are fair game [12]. In effect, the agency has built a hybrid system, structurally ISO, but with FDA's fingerprints throughout.

For global manufacturers already certified to ISO 13485, the shift offers long-overdue relief. These companies have long maintained parallel systems, adjusted terminology, and weathered duplicative audits to satisfy both U.S. and international regulators [14]. QMSR promises to eliminate that redundancy and streamline compliance under a single, harmonized framework. But for smaller, U.S.-focused firms, especially those that grew up under QSR, the change may feel more like a forced migration. It's not just a new checklist. It's a new language of quality. Risk-based thinking must extend across the entire product lifecycle. Supplier controls must be traceable and proportionate to risk. Documentation must show intent and logic, not just compliance [13].

The two-year transition period, ending in February 2026, is not a grace period. It is a high-stakes runway. Granted after industry pushback against a one-year phase-in, the timeline reflects a compromise between long-term efficiency and short-term readiness [5]. Larger companies may only need to revise policies or reporting formats. But smaller firms could face significant lift: retraining staff, overhauling documentation, conducting gap analyses, and in some cases investing in entirely new quality tools. The issue is not that these firms suddenly became noncompliant. It's that the format and structure of evidence demanded by FDA have

changed, moving from rule-following to systems thinking, from static procedures to dynamic justification.

Inspection practices will also evolve. Under QSR, FDA inspections followed the relatively predictable QSIT model, focusing on a few critical subsystems. ISO 13485, by contrast, offers no fixed roadmap. Inspectors will have broader discretion, and access to documents previously off-limits: internal audits, management reviews, supplier evaluations. The scope expands, and with it, the expectations. FDA will no longer be satisfied with a complete binder. It will expect a coherent, defensible quality system that reflects thoughtful risk management, organizational accountability, and continual alignment with ISO principles. Whether field inspectors are uniformly trained for this new audit model remains uncertain. The real risk is inconsistency, inspection variability that undermines the predictability industry relies on [14].

The FDA is walking a fine line in this transition, and the QMSR reflects multiple tradeoffs:

- **Clarity vs. Flexibility**: QSR's specificity gave companies certainty. ISO's flexibility gives them autonomy. By declining to issue a clause-by-clause mapping from QSR to ISO, the FDA has made clear that compliance will now require interpretation, not just documentation.
- **Global Alignment vs. Regulatory Sovereignty**: By linking U.S. law to ISO 13485, the FDA has ceded partial control over the evolution of quality standards. If ISO updates the standard in 2028, FDA must either engage in a new round of rulemaking or fall out of sync [14]. Harmonization now means complexity later.
- **Efficiency vs. Enforcement Philosophy**: Even as the FDA aligns its regulations with ISO, it will not accept ISO certification as proof of compliance. That decision reflects a core belief: quality is not a certificate; it's a continuous outcome. A firm can be ISO-compliant on paper and still fail FDA's expectations in practice.

Still, the strategic logic behind QMSR is sound. FDA is recognizing that medical devices are no longer national products. They are global technologies, and the systems that govern them must operate on a global stage. Harmonization reduces duplication, lowers barriers to innovation, and improves consistency across markets [13], [14]. For manufacturers, this means fewer audit silos and more scalable compliance. But it also means a heavier burden of interpretation, especially during the early years when norms are still forming and enforcement practices are untested. In tone and content, the FDA's 2024 final rule is not a revolution. It is a recalibration, a methodical, cautious shift toward shared global oversight without abandoning the agency's core enforcement role. QMSR does not dilute FDA's authority. It retools it for a world where convergence is not just a convenience, but a necessity. For industry, the message is clear: the rules may look familiar, but the logic, expectations, and inspection style are all changing. The next two years will determine whether this harmonization effort delivers on its promise or whether the complexity of global alignment creates new frictions in place of the old ones.

3. Impact of ISO 13485 Reforms on Key Stakeholders in the Medical Device Ecosystem

The FDA's Center for Devices and Radiological Health regulates the firms involved in the manufacture, repackaging, labeling, and import of medical devices in the United States. As explained in the introductory part, medical devices are classified into categories such as Class I, II, and III, with increasing levels of regulatory control from Class I to Class III. This categorization forms the foundation for the regulatory mechanisms applied to various devices and their manufacturers. A detailed classification of medical devices, along with their descriptions and regulatory categories, is available on the FDA's website. Deep dive shows that in regulatory requirements for medical devices, in general, include establishment registration, device listing, premarket notification under Section 510(k) (unless exempt), premarket approval, investigational device exemptions for clinical studies, quality system regulation, labeling requirements, and medical device reporting.

As stated in the above introduction of the new regulatory regime, in February 2026, amendments to Part 820—pertaining to the Quality Management System—will take effect. These changes incorporate the requirements of ISO 13485, which are considered substantially similar to the current Quality System Regulations (QSR). ISO 13485 is expected to provide an equivalent level of assurance in quality management systems, ensuring that manufactured devices are safe, effective, and compliant with the Federal Food, Drug, and Cosmetic Act (FD&C Act). While several amendments will be introduced through these new regulations, it is important to note that the overall scope of the QSR will be retained. The updates will revise the title of the regulation, establish additional requirements, clarify certain expectations, and streamline the concepts found in ISO 13485. The revised Part 820 will be referred to as the Quality Management System Regulation (QMSR). According to the summary document, these amendments will not affect combination products [5].

3.1. Medical Device Companies: Central Stakeholders in Manufacturing and Compliance

Initially, manufacturers and medical device companies registered with the FDA were required to comply with Part 820. In addition to these requirements, registered manufacturers in many other jurisdictions that export devices were also required to comply with ISO 13485, which is substantially like the FDA's Quality System Regulation (QSR). This dual compliance created a redundancy of effort for manufacturers obligated to meet both QSR and ISO 13485 standards. This overlap has been identified as a source of inefficiency. Aligning the requirements of QSR and ISO 13485 is expected to reduce the regulatory burden on device manufacturers and lower the workload for stakeholders responsible for recordkeeping, document preparation, inspections, and audits. Harmonizing these regulations will minimize the need for separate compliance efforts, thereby reducing costs across the industry. These cost savings would

otherwise have been spent on streamlining internal training and establishing mechanisms to separately address both the regulatory frameworks. One key benefit of adopting ISO 13485 as a reference standard is that establishment of uniformity, significantly reducing duplication of effort and enhancing overall regulatory efficiency.

According to the Federal Register publishing the rule making process and inviting comments from the stakeholders before legislating, ISO 13485 document regulations are intended to help manufacturers maintain records demonstrating that their products meet both customer and regulatory requirements, as mandated by law in 1996. That same year, the first version of Regulation ISO 13485 was issued, titled *"Quality Systems – Medical Devices – Particular Requirements for the Application of ISO 9001."* It is important to note that these requirements are voluntary consensus standards designed to be used by manufacturers in conjunction with ISO 9001. Since its inception, ISO 13485 has undergone several revisions and amendments. It is clear that there are many similarities between the FDA's Quality System Regulation (QSR) and the requirements of ISO 13485. These similarities enabled the FDA to harmonize the regulatory structure for medical devices more effectively.

The regulations are structured as a mandatory yet flexible framework, requiring manufacturers to develop their own procedures for designing and producing specific medical devices. Successful compliance with ISO 13485 enables manufacturers to achieve and maintain high quality standards within their organizations. The scope of ISO 13485 implementation includes original equipment manufacturers (OEMs), contract manufacturers, repackagers, relabelers, reprocessors, manufacturers of single-use devices, and manufacturers of accessories and components sold directly to end users. This broad applicability brings nearly all the stakeholders in the medical device manufacturing sector under the regulation purview, making compliance essential across the industry [2]. The impact of implementing ISO 13485 in the United States can be assessed by examining the experiences of various stakeholders, informed by international case studies and research conducted within the medical device industry.

A Quality Management System (QMS) requires manufacturers to ensure that their products meet applicable requirements, without micro-managing the specific requirements for each type of medical device. It forms part of a broader set of requirements that are the part of the original Current Good Manufacturing Practice (CGMP) standards. To accommodate the wide variety of medical devices, the regulations were intentionally designed to be flexible, allowing manufacturers to develop and follow procedures best suited to their specific products. This system enables manufacturers to have flexibility, apply their experience and sound judgment in the design and production of medical devices. The QMS operates as a framework, providing broad guidelines within which manufacturers can define detailed procedures based on their unique device requirements. The use of the phrase “where appropriate” throughout the regulation offers manufacturers the necessary flexibility to tailor processes as needed[2].

According to ISO, the application of the term “as appropriate” is intended to allow organizations the flexibility to define their own requirements—unless they can provide a justified reason for not doing so. There is a framework to determine when a requirement is considered

appropriate. This includes situations where it is necessary for the product to meet specified requirements, to comply with applicable regulatory obligations, or for the organization to manage associated risks effectively. The ISO standards also clarify the meaning of certain terms used within the framework: “Shall” indicates a requirement, “Should” implies a recommendation, and “Can” denotes permission or indicates a possibility. Manufacturers thus have to comply with detailed quality compliance framework provided by the ISO 13485. Henceforth once these regulations are live, there might need to be a change in their charter of quality [15].

3.2. Stakeholders in the Medical Device Manufacturing Industry: Physicians, Patients, and Regulators

A multiphase empirical field study was conducted at Stanford University which explored the critical role of physicians/user inputs in the medical device development process [16]. The initial phase of this study created an analytic framework for case-based research, which served as the conceptual foundation for a pilot case study focused on an entrepreneurial device company. The analysis done through this research identified key development practices involving physicians that significantly influenced both clinical and financial outcomes, in other words development of medical devices. The pilot case underscored the value of engaging a diverse kind of physicians to fully understand user experience, thereby enhancing medical product relevance and performance. It also demonstrated how physician interaction shapes risk perceptions among both surgeons and developers, reinforcing the value of a systems-based design approach over a narrow focus on technical endpoints.

Methodologically, this study has emphasized the importance of analyzing physician involvement within its broader organizational and developmental context, rather than through isolated variables. This approach can not only reveal deeper insights into the dynamics of actual user interaction but also laid the groundwork for case-based investigations into physician engagement in medical device innovation. This research can be understood as a testimony of the role of health care professionals in the development of medical devices, in a limited sense for the purpose of investigating the role of physicians in the wake of new rules. Thus, the development of medical devices is significantly shaped by the dynamic interplay between users—particularly physicians—and device developers. With the introduction and increasing adoption of ISO 13485 in US, physicians will now be required not only to provide input but also to adapt to formalized quality management systems regulation given their significant role in the development of medical devices. This integration might require them to align clinical practices with regulatory protocols, thus necessitating changes to procedural workflows and documentation standards. With the stringent QMS requiring elaborate documentation, physicians are not just end-users, but strategic collaborators and their inputs will be highly valued. This integration of actual users into evolving regulatory frameworks post ISO 13485 can bring positive impact for the product’s success and further changes in future development.

4. Case studies: How should companies adjust to an internationally diverse regulatory framework?

US will be having implementation of new rules in 2026 but EU already have alignment with ISO 13485 and there are some examples which show that the impact on innovations through start up and through established companies can be different. The detailed development of QMS required by ISO can be tough work for a new start up and may be even capital-intensive process, when compared with the well-established corporates. A compelling example of ISO 13485 implementation is found in a Belgian start-up specializing in orthopedic medical devices, including braces and post-operative bandages [17]. Despite beginning its operations in 2009 with CE-marked products as required in EU, the company did not achieve ISO 13485 certification until 2016—demonstrating the high barriers that start-ups could face in aligning with international quality standards. Unlike established companies that typically possess dedicated compliance teams and structured documentation practices, this start-up had to navigate the complex process internally, relying on newly hired quality personnel and hands-on involvement from top management. The certification process required the development of a comprehensive Quality Management System (QMS), built around ISO 13485 guidelines. Central to this was the creation of a Quality Manual (QM), titled "General Design Procedure," which laid out the design, documentation, and review processes across five stages. The documentation included 3 core procedures and 23 individual forms covering project planning, customer requirements definition, risk analysis , functional requirements, and verification and validation steps. This documentation effort, while essential for compliance, was resource-intensive, require highly specialized experience and also required extensive coordination across departments, often a significant burden for short, staffed start-up teams lacking institutional support. This case study reveals that start-ups are at a disadvantage compared to established firms when adopting ISO 13485 due to limited manpower, insufficient prior knowledge of regulatory requirements, and constrained financial resources. While large manufacturers can allocate specialized compliance units and outsource certification efforts, start-ups must internalize both the technical and procedural aspects of QMS development. The burden is compounded by the need to document every stage of the product lifecycle in a traceable and auditable manner, which requires dedicated forms, records, and continuous updates to remain compliant.

However, the study also demonstrates that with clear documentation, managerial commitment, and strategic alignment of ISO requirements with internal design processes, start-ups can successfully achieve certification. In this circumstance, time factor becomes very essential given the fact the innovation in this sector requires a lot of patience and investment. These investments after all will demand return at a given point of time. For early-stage innovators, this often means tailoring their design documentation directly around ISO's structure, integrating forms and reviewing mechanisms from the outset rather than retrofitting them later. Thus, while ISO 13485 can be demanding for start-ups, it also provides a structured path toward

operational excellence, beneficial internal processes, and market credibility, particularly when it comes to reducing risks of failure and recalls.

Following table compiles the diversity and complexity of regulatory mechanisms and standards across some important medical device markets. Each country has its own classification systems and regulatory authorities and agencies, creating challenges for global harmonization. However, ISO 13485 emerges as a unificatory and acceptable standard, offering a common QMS framework that enhances consistency and facilitates cross-border regulatory alignment.

Country	Regulator	Classification	QMS/ISO Standard
USA	FDA/CDRH	Class I–III	21 CFR 820
Canada	Health Canada	Class I–IV	ISO 13485:2016
India	CDSCO	Partial list (not standardized) Bill in process	ISO 13485 (recommended)
EU	EMA/NBs	Class I, IIa, IIb, III	ISO 13485 (baseline)
Japan	PMDA/MHLW	Class I–IV	ISO 13485-equivalent

A research paper discussing different medical equipment and relative complexity involved in its approval has emphasized the importance of harmonization and reduction of red tape[18]. The case studies on connected insulin pens in the EU and digital patient monitoring (DPM) systems in cancer care reveal how rapidly evolving device functionalities increasingly intersect with software, clinical data, and pharmaceuticals. Regulatory divergences such as how software modules are classified or how apps are certified, poses challenges for innovators trying to scale solutions globally. In that scenario, flexibility offered by ISO 13485 might be a very efficient system. The insulin pen system, for instance, required both device and medicinal product review in Europe, depending on whether the app or injector was integrated or separate. In contrast, the lack of equivalent integration pathways in India or the U.S. could delay the product's entry. ISO 13485, by requiring structured documentation, traceability, and risk analysis, becomes a baseline that countries can use to recognize device safety and quality, even when digital configurations vary. Without this harmonized structure, many medical device companies face a lot of process redundancy, duplicative procedures and unclear expectations from regulators—slowing innovation and patient access[18].

In many ways, the emergence of ISO 13485 will bring significant changes to the roles and relationships among the numerous stakeholders involved in the medical device industry. Furthermore, a careful balance must be maintained between promoting and encouraging innovation in the sector and addressing the potentially stringent requirements of the QMSR, which may involve considerable administrative work. While the QMSR offers a framework for operational excellence and provides assurance to the market that a consumer-focused and ethics-

based quality management system is in place, the transition to this new regulatory mechanism may require substantial support and guidance for manufacturers, auditors, and regulators alike.

5. International Medical Device Regulators Forum

The adoption of ISO 13485 by the FDA is a significant harmonization milestone in a broad landscape of global harmonization efforts. The Global Harmonization Task Force was established in 1993 with the aim of outlining best practices for medical regulatory agencies. The founding members of this task force were the European Union, the United States, Canada, Australia, and Japan. The Global Harmonization Task Force had five study groups which addressed different stages of medical device regulation; these study groups focused on Premarket Evaluation, Post-Market Surveillance/Vigilance, Quality Systems, Auditing, and Clinical Safety/Performance. The Global Harmonization Task Force was eventually replaced by the International Medical Device Regulators Forum, which has eleven members and many more affiliate members. The study groups described above were replaced by working groups which are created to harmonize different aspects of medical device regulation, and which produce guidance documents that outline how agencies can harmonize their regulations. Some working groups focus on standardizing terminology and best practices in existing areas such as quality management systems or adverse event terminology, and others are dedicated to more emerging areas of device regulation such as artificial intelligence as a medical device or personalized medical devices. The adoption of ISO 13485 by the United States Food and Drug Administration can be seen through the broader context of harmonization efforts undertaken by the International Medical Device Regulators Forum. The timeline of harmonization milestones leading toward the adoption of ISO 13485 is summarized in Figure 1.

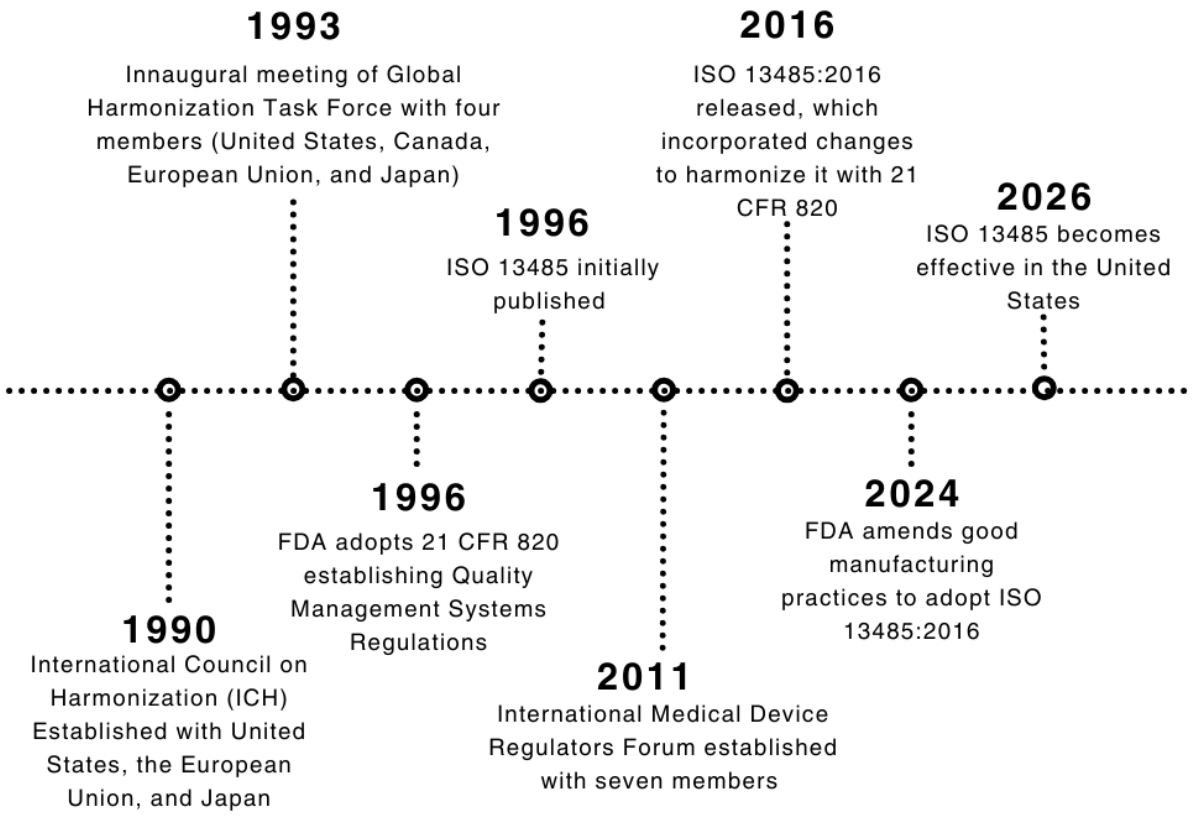

Figure 1: *Timeline of major milestones in the global harmonization of medical device regulation.*

The International Medical Device Regulators Forum has created many working groups which release guidance documents relevant to their focus area. Here, we will discuss some of the previous and current working groups in order to contextualize past and future harmonization efforts. One past working group was focused on unique device identification. Harmonizing device identification is important because it allows medical device manufacturers to use a single device identifier per device and simultaneously satisfy regulations in many jurisdictions. Unique device identification is important because it allows for tracking of all medical device units that are in circulation, and it streamlines the process of reporting adverse events or enacting corrective actions. The guidance document released by this working group outlines how devices should be labeled, namely that a device identifier should be present on the medical device itself and on all levels of packaging. Furthermore, it recommends that national and local regulatory agencies adopt the conventions outlined by the International Medical Device Regulators Forum without modification, such that a single device identifier can be valid in all jurisdictions. This harmonization effort is of great importance as previous studies have shown the challenges and confusion that companies have faced as a result of poor harmonization between unique device identifier policies in the United States and Europe [19]. Furthermore, even with harmonized standards, there exist challenges for companies in adopting these standards, especially for software as a medical device.

Another past working group is the cybersecurity working group, which has released documents that apply both to software as a medical device and software or firmware that will run on a physical medical device. These documents outline risk management frameworks that consist of identifying risks, evaluating their severity, controlling the risk with mitigation measures, monitoring the risk as devices are used, and communicating risks to end users. It also recommends regulatory pathways for medical device companies to bypass regulatory review for software updates that solely improve cybersecurity, or which remedy an unacceptable cybersecurity risk. Harmonization of cybersecurity regulations is important as new medical devices which rely on wireless communication or the internet are increasingly common. As a result, it is important for regulatory agencies and international organizations to provide guidance for medical device companies, and to institute regulatory pathways to ensure that the guidance is followed. Another key aspect is to not examine cybersecurity risks in isolation, but to instead compare the risks to the relative benefits, both when designing the device and once the device is on the market [20]. This can even be applied to risk mitigation strategies, as introducing additional security measures could affect a patient's ability to use their device in an emergency [21].

Current working groups exist to address new technological areas or areas which are growing rapidly, including in vitro diagnostics, personalized medical devices, and artificial intelligence as a medical device. The in vitro diagnostics working group is working on updating guidelines on the risk classification of in vitro diagnostics. Such guidelines were originally published in 2008 by the GHTF and have since been updated in 2020. The most recent guidelines recommend a risk classification system that takes into account both the individual and public health risks associated with a device. The particular recommended scheme for identifying the risk class is outlined in table 1. As a result, diagnostic devices which diagnose life-threatening infectious diseases are considered the highest risk, while a lower risk is assigned to diagnostics for either non-transmissible life-threatening diseases or for non-life-threatening transmissible diseases [22]. Harmonization of regulations regarding in vitro diagnostics is particularly important as in vitro diagnostics are critical for limiting spread of infectious diseases in developing countries; in these countries, having international standards helps expedite access to critical diagnostic tests [23].

Artificial intelligence as a medical device is an area that has received a lot of attention from academics, investors, and the public. The International Medical Device Regulators Forum has also addressed regulation of such devices through a new working group which has published guidelines on the best practices for developing artificial intelligence algorithms. These best practices include technical guidelines that are used throughout machine learning but which are particularly relevant in medical contexts, such as ensuring that test sets and training sets are independent, and mitigating the possibility of dataset drift [24]. It is similarly important to prevent the model from learning non-causal correlations between the training data and the predicted outcome, as was observed in one study where a neural network predicted that a photo with a ruler in it was more likely to be cancerous [25]. In addition, these guidelines recommend focusing

not only on technical performance, but also on how the algorithm will be used by a human, whether that is a healthcare professional or the patient.

The working group that is focused on Personalized Medical devices has published guidance documents classifying devices based on how much they are personalized to a particular patient and suggesting how each class of devices should be regulated. A custom-made device is defined as one which is made for a specific individual at the direction of a physician. Due to the uniqueness of each device, these devices are not subject to the same quality management regulations mass-produced medical devices. However, these devices should only be used when products available on the market are insufficient to treat a patient, and physician is responsible for the specifications of the product. On the other hand, an adaptable medical device is one which is mass-produced, meaning that all instances of the product are identical, but which is adjusted based on the patient's anatomy or disease at the point of care. Finally, in between an adaptable device and a custom-made device is a patient-matched device, which has some design parameters matched to the patient's anatomy or physiology, but where these design parameters are constrained to lie within a particular design envelope [26]. When conducting verification and validation tests on such devices, it is critical that the "worst" case values for each of the design parameters are tested in order to ensure the device will work on all patients [27]. Unlike custom-made medical devices, patient-matched medical devices are subject to the same premarket approval and postmarket surveillance requirements as other medical devices, and the manufacturer rather than the physician is responsible for the safety and effectiveness of the device. Included in the domain of personalized medical devices are devices which are made using additive manufacturing techniques which can be made rapidly by individual clinics instead of a central factory [28]. The International Medical Device Regulators Forum outlines how in such cases, the device designer is responsible for creating a Medical Device Production System, which outlines all variables in the creation of a medical device including the materials, equipment, software files, and instructions for fabrication and assembly. Figure 2 shows the components of Medical Device Production System that are combined to form a resultant medical device. Once a Medical Device Production System is approved by a regulatory agency, any clinic should be allowed to manufacture a medical device by adhering to its requirements. This represents a significant change for many regulatory agencies which require strict requirements to be satisfied by any facility involved in the manufacturing of medical devices [29].

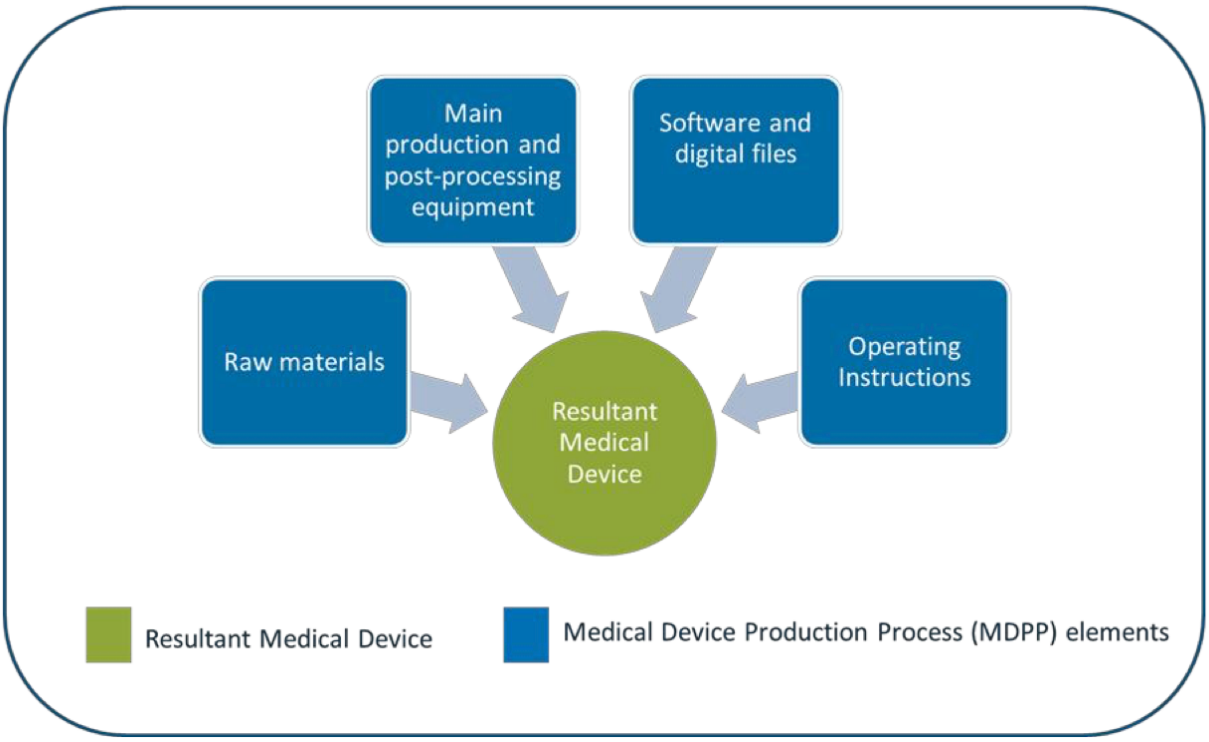

Figure 2: *Description of Medical Device Production Processes. This figure was extracted from the International Medical Device Regulators Forum guidance document for regulatory pathways for personalized medical devices* [28].

In parallel with the International Medical Device Regulators Forum, the International Council for Harmonization was founded in 1990 in order to harmonize regulation of pharmaceuticals between different national and international agencies. It initially focused on harmonizing regulations between the United States, Europe, and Japan, but has since expanded to a much broader scope [30]. While the guidance from the international council for harmonization typically does not apply to medical devices, there regulations may apply to medical devices which incorporate the use of pharmaceuticals such as insulin pumps or drug eluting stents.

One remaining challenge with harmonization efforts put forth by the International Medical Device Regulators Forum is that the time between initial creation of a working group and ultimate adoption by major regulatory agencies can be quite lengthy. For instance, ISO 13485, which will be enforced by United States Food and Drug Administration starting in 2026, was published in its final form in 2016, and was initially published in 1996. Similarly, the working group focused on unique device identifiers formed in 2011, and it wasn't until 2021 that the United States Good Manufacturing Practices and the European Medical Device Regulations were updated to reflect the recommendations of the working group [31]. Such delays are unsurprising given that there are bureaucratic challenges both within international organizations such as the International Medical Device Regulators Forum and within national regulatory agencies. This is concerning for current working groups that seek to regulate emerging technologies such as personalized medical devices or artificial intelligence as a medical device.

In the next decade, many revolutionary technologies will be developed that fall into one of these categories, and if regulations are not harmonized among regulators in the major medical device markets then there will be an unnecessary burden of regulation on these new devices. This burden could delay such devices from reaching a global audience and could ultimately diminish their lifesaving impact.

6. Software as a Medical Device

Software as a Medical Device refers to medical devices which have no physical component and does not include software or firmware that runs on a physical medical device. This instead includes algorithms that are meant to inform medical care, either by assisting physicians or patients directly. Such technologies vary significantly in the risk that they pose to patients, and as such are classified by the International Medical Device Regulators Forum into four categories. These categories are distinct from the three risk classes used by the United States Food and Drug Administration [32]. Two factors determine which category a software device will fall into: the first factor is how serious the condition being treated is, which is rated as either non-serious, serious, or critical. The second factor is how significantly the information delivered by the software will affect care, which is categorized as either diagnosing / treating disease, driving clinical treatment, or informing clinical management. Table 1 shows how risk class is decided based on these two factors. The International Medical Device Regulators Forum then recommends different regulatory pathways for software systems in different risk categories.

State of Healthcare situation or condition	Significance of information provided by SaMD to healthcare decision		
	Treat or Diagnose Disease	Drive Clinical Management	Inform Clinical Management
Critical	Risk Class 4	Risk Class 3	Risk Class 2
Serious	Risk Class 3	Risk Class 2	Risk Class 1
Non-serious	Risk Class 2	Risk Class 1	Risk Class 1

Table 1: *Table extracted from the International Medical Device Regulators Forum guidance document for risk categorization of Software as a Medical Device. Devices are assigned to a risk class between 1 (least risk) and 4 (most risk) based on the condition that they are used to treat and the extent to which they affect diagnosis, treatment, or prevention of that disease .*

In addition, software is not developed in the same way as physical devices, and thus different quality systems regulations should be implemented throughout the lifecycle of a software product [33]. First, the requirements for the software must be identified, which includes any requirements from ISO 13485 or other regulations. Next, in the design phase, one must identify major components in the software and outline how data will flow between them. In this stage, it is also critical to ensure that sensitive data including personal health information is handled in a way that is secure and complies with relevant legislation. Next, in the coding phase, each component of the software is implemented while following best coding practices. Then, in

the testing phase, various levels of verification and validation tests are performed to ensure that individual components of the software work and that they integrate well together. These begin with unit tests to assess the function of the smallest components of the software, and end with user acceptance tests that ensure that end users are satisfied with the completed device. Next, in the release phase, the software is deployed to its users along with appropriate documentation and instructions for use. Finally, in the maintenance phase, a system must be in place for users to report bugs and updates to be released to users.

In the United States, the Food and Drug Administration also regulates software as a medical device differently from other types of medical device. In particular, the Food and Drug Administration has created a program called the Digital Health Software Precertification Pilot program which attempts to promote innovation by relaxing regulatory requirements for software companies which have demonstrated a "culture of quality and organizational excellence" [34]. For organizations that qualify, their software would be allowed to bypass some of the standard pre-market regulations and instead rely more heavily on post-market surveillance. The intention of this program is to recognize that the pace of software development is often faster than that of hardware development, and that standard regulatory review timelines may be overly burdensome. Upon completion of this pilot program, the food and drug administration recommended passing legislation that permanently streamlines the way software as a medical device is regulated. In spite of this, some studies have argued that thorough premarket approval is equally important in software and hardware, as there have been major software recalls in the past, including a diabetes app that recommended inaccurate insulin doses [35]. In particular, between 2011 and 2015, there were 627 device recalls due to software-related issues which affected over 1 million individual devices [36].

7. The Medical Device Single Audit Program

The Medical Device Single Audit Program (MDSAP) is a particularly relevant topic that highlights how the global harmonization of QMS regulations can facilitate other harmonization efforts. MDSAP offers a pathway through which medical device manufacturers can demonstrate compliance with the QMS requirements of all participating regulatory agencies, thus reducing redundant audits and giving manufacturers rapid access to multiple markets. While MDSAP is not directly related to the FDA's adoption of ISO 13485, given that MDSAP audits are designed to inspect compliance with multiple QMSR guidelines, any changes to the QMS regulations in the United States will have significant implications for both auditors and medical device manufacturers. What follows is an overview of MDSAP's development, structure, and impact on global regulatory harmonization, with a focus on its challenges, adoption patterns, and implications of ISO 13485 alignment.

7.1. History of MDSAP and Pilot Program

The origin of MDSAP can be traced back to the first meeting of the International Medical Device Regulators Forum (IMDRF) in 2012, where a working group was appointed to develop the concept of a single globally harmonized audit. The goal of MDSAP was to reduce the regulatory burden on industry by eliminating redundant audits from multiple authorities and to facilitate the IMDRF's mission to promote the use of international standards and best practices to globally align regulatory approaches. The group proposed a single audit that would examine quality system compliance for a variety of regulatory agencies, performed by an approved third-party auditing organization. The manufacturer would sign a contract agreeing to pay the auditing organization for conducting the audit. The structure of the audit would closely resemble that of ISO 13485:2003 (later adapted to ISO 13485:2016) and included additional requirements imposed by the regulatory authorities of participating countries [37].

An MDSAP pilot program was conducted from January 2014 to December 2016, during which manufacturers could choose to enroll in the program to undergo a single series of audits by an approved auditing organization of their choice to certify that they had met the QMS requirements of the regulatory authorities participating in the pilot [38]. Five countries/regulatory agencies elected to join the pilot program and remain the five current participants of MDSAP to date [37]:

- The United States of America - U.S. Food and Drug Administration (FDA)
- Canada - Health Canada
- Brazil - Agencia Nacional de Vigilancia Sanitaria (ANVISA)
- Australia - Australian Therapeutic Goods Administration (TGA)
- Japan - Ministry of Health, Labour and Welfare (MHLW)

Throughout the pilot program, the MDSAP regulatory authority council (consisting of representatives from the five participating regulatory authorities) assessed seven proof of concept criteria (PoCC), to ensure audit quality and operational feasibility. These metrics assessed whether audit reports met formatting standards and supported the decisions of regulatory authorities, whether audits durations were appropriate, and whether sufficient participation was reached from both auditing organizations and manufacturers [39].

Of the seven proof-of-concept criteria, all were met except for two. The first related to the use of MDSAP audit reports to substantiate audits by participating regulatory authorities. Of the evaluated MDSAP audits, only 59% agreed with the decisions of all four regulatory authorities (Health Canada was excluded due to prior proof of substantiation) compared to the goal of 80%. The criterium was considered a partial success as it was met when only requiring substantiation of three of the four participating authorities. As a result, the standardized audit template was revised to follow a more logical and specific process-based flow.

The second unmet criterium related to medical device manufacturers participation, with only 161 of the target 330 manufacturers participating in the pilot program by its conclusion at

the end of 2016. Despite this underperformance, a steady increase in the number of participating manufacturers convinced the MDSAP working group to recommend the program to become fully active in 2017. In fact, as seen in Figure 3, the number of participating manufacturing sites doubled in the six-month period following the completion of the pilot program [39].

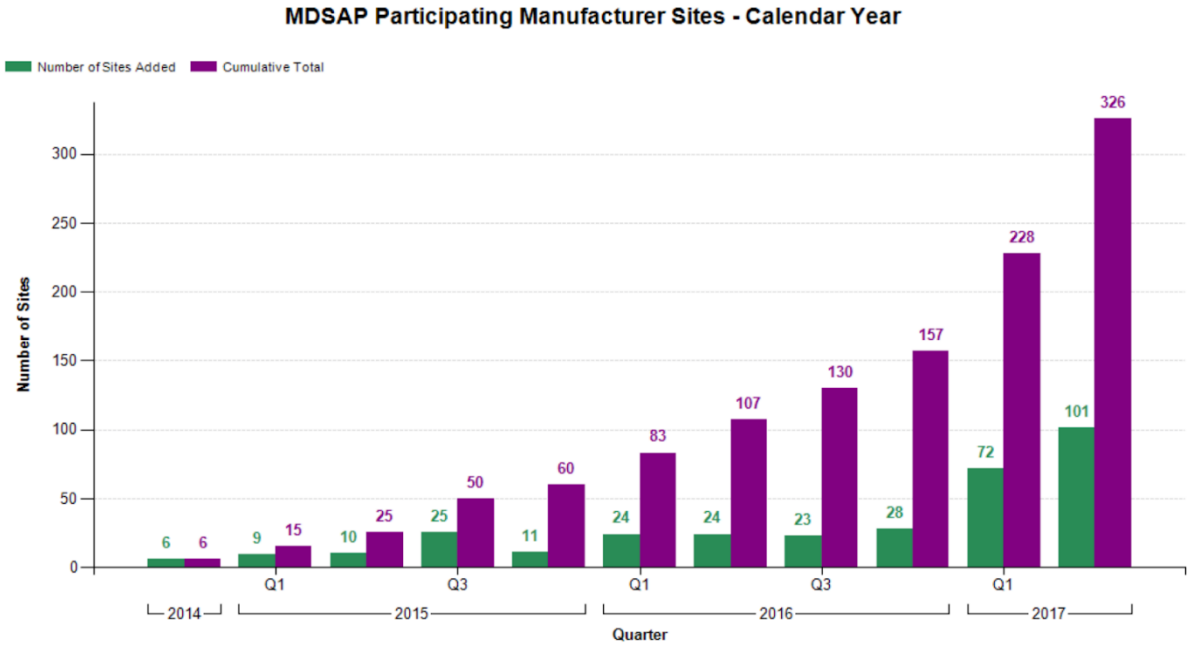

Figure 3: *Growth of MDSAP during the pilot program and following six months* [39].

7.2. MDSAP Auditing Organizations

With audits satisfying the requirements of five different regulatory authorities, one may wonder which country should be responsible for conducting these audits. MDSAP avoids favoring or burdening one regulatory authority over another by outsourcing audits to third-party auditing organizations approved by the five participating regulatory authorities. To date, fifteen auditing organizations have been considered for MDSAP approval, of which thirteen were given approval to conduct MDSAP audits and grant certification [40].

As is often a challenge with international regulatory efforts, MDSAP has no real power to enforce the outcomes of audits in each country, so audit reports and certifications are instead submitted by third-party organizations to the countries' own authorities who then review the outcomes to make regulatory decisions [41].

This is not an entirely new concept, as the use of third-party certification bodies rather than regulatory agencies themselves to inspect medical device manufacturers is actually common in many countries and regions. For example, the European Union primarily relies on third-party notified bodies to conduct audits of medical device companies, and the FDA has accredited third parties to inspect class II and class III device manufacturers since 2002 [42,43].

7.3. Structure of MDSAP Audits

The MDSAP audit sequence is designed to ensure efficient and comprehensive coverage of the necessary regulatory requirements to grant market access to the participating countries. These requirements include ISO 13485:2016 (Canada), TG(MD)R Sch3 (Australia), RDC ANVISA 665/2022 (Brazil), MHLW Ministerial Ordinance No. 169 (Japan), and 21 CFR Part 820 (USA). Additionally, each medical device regulatory authority may mandate specific requirements for manufacturers located within its jurisdiction. For example, the United States requires that electronic records and documents have backups [44].

The MDSAP audit sequence is structured in a process-based approach rather than a clause-by-clause approach outlined by regulatory authorities. This method allows auditors to evaluate the compliance of different quality systems within the operations of a manufacturer instead of following a checklist of isolated regulations. It is especially important that the audit structure for MDSAP flows in a logical and detailed manner to ensure consistency between the many third-party auditing organizations that are not under the control of a single regulatory authority. Furthermore, a process-based approach eases the integration of multiple regulatory approaches by allowing the individual requirements of participating MDSAP countries to be grouped into their appropriate processes. The seven processes outlined in the MDSAP audit approach are:

- **Management** - For example, quality policy and objectives, organizational structure, and internal communication procedures.
- **Device Marketing Authorization and Facility Registration** - Significant country specific requirements related to licensing and registration of facilities, and evidence of market approval.
- **Measurement, Analysis, and Improvement** - For example, internal audit schedules, nonconformity reports and investigations, and feedback mechanisms.
- **Design and Development** - For example, design history, documentation of design inputs and outputs, and risk analyses.
- **Production and Service Controls** - For example, manufacturing process validation reports, equipment maintenance and calibration logs, and service records and returned product evaluations.
- **Purchasing** - For example, supplier qualification files and audit reports, approved supplier lists, and purchase agreements/contracts.
- **Medical Device Adverse Events and Advisory Notices Reporting** - For example, recall decision-making procedures, advisory notices and customer communications, and recordkeeping and timelines for reporting [44].

7.4. MDSAP Audit Cycle

MDSAP audits occur on a three-year cycle consisting of an initial certification audit followed by surveillance audits in years two and three and a recertification audit at the start of year four to begin a new cycle.

The initial certification audit is split into two stages. A stage 1 audit may be performed partially off-site and reviews QMS documentation to determine the manufacturer's preparedness for a full audit. The stage 2 audit is conducted on-site and is significantly more comprehensive than the first stage, evaluating all processes outlined above. In practice, these two stages are often assessed in a single on-site visit.

The two surveillance audits over the next two years do not need to address every process but primarily focus on any changes to the medical device organization, their products, and documentation thereof. Furthermore, certain QMS documentation may be reviewed in the context of any relevant legislative changes if deemed necessary by the auditing organization.

Finally, the recertification audit for the following year closely resembles a stage 2 certification audit and consists of a comprehensive on-site review of the manufacturer's QMS. If the manufacturer passes this audit, their MDSAP certification is renewed, and the cycle continues [44].

7.5. MDSAP Membership

Throughout the five members of MDSAP there exists significant variation between inspection methods and the degree to which MDSAP audits can substitute them. Countries can be broadly categorized in three types by who primarily carries out inspections [41]:

- **Regulatory authority-led**: Inspections are conducted by governmental regulatory agencies such as the FDA in the United States and ANVISA in Brazil.
- **Certification body-led**: Inspections are conducted by certification bodies such as MDSAP. Examples include Canada and the European Union.
- **Certification body co-use**: Inspections may be carried out by either regulatory authorities or certification bodies. Japan and Australia can be classified as such.

Given that all three inspection method types can be found in the MDSAP members, several interesting trends can be drawn between how the primary inspection method in a country influences the utilization rate of MDSAP. This information is summarized in Table 2.

Country	Primary Inspection Organization(s)	Methods of Utilizing MDSAP	Utilization rate of MDSAP if available
United States	Regulatory authority (FDA)	Substitute for FDA routine inspections	46%
Canada	Certification body (MDSAP)	Required for class II, III, and IV devices	100%
Brazil	Regulatory authority (ANVISA)	Can replace ANVISA inspections for class III and IV devices	55%
Japan	Certification body co-use (PMDA + certification body)	Can exempt from on-site new and periodic inspections	33%
Australia	Certification body co-use	Can exempt from inspection by authority	NA

Table 2: *Comparison of MDSAP use among member countries* [41].

The country with the highest utilization rate is Canada as MDSAP audits are required for all class II, III, and IV medical device manufacturers. This was a somewhat controversial decision by Health Canada, as it placed considerable regulatory pressure on small medical device manufacturers who only sought access to the Canadian market yet had to adapt to the more complicated and stringent requirements of the MDSAP audit regardless [45].

In all other member countries MDSAP participation is voluntary, although the degree to which MDSAP audit reports exempt manufacturers from routine audits from regulatory agencies varies. In the United States, MDSAP audits reports can be submitted to the FDA as a direct substitute for on-site FDA-led inspections [37].

Other factors influencing the MDSAP utilization rate between countries include industry confidence in regional regulatory authorities to perform predictable and timely audits, number of manufacturers seeking to export to the markets of other MDSAP countries, and the cost associated with audits [41].

Since MDSAP has consisted of the same five member countries since its inception, it is important to ask why other countries have not sought membership given the program's numerous benefits. In fact, there are several factors, both internal and external, that explain why no additional countries have joined.

For prospective members, the criteria to join MDSAP are currently quite stringent. Integrating a new regulatory system into the already convoluted MDSAP audit process

represents a significant regulatory challenge that can only be justified if the country or region has a sufficiently large market and organized regulatory system to justify the effort to amend the MDSAP audit process [46]. Furthermore, a country would only seek membership to MDSAP if a significant number of manufacturers in its own jurisdiction would be interested in undergoing the transition to MDSAP certification for more efficient access to the markets of MDSAP members. Many countries may not have sufficient demand to export, and MDSAP would likely not be widely adopted.

One region that is notably missing from MDSAP is the European Union which opted not to join MDSAP due to funding and research constraints but has participated as an observer (along with several other countries) since 2014 [37]. Instead, the EU permits its own certification bodies to use MDSAP audit reports as part of their surveillance audits to streamline the process [47].

7.6. Impact of ISO 13485 Adoption on MDSAP

Given that MDSAP audits already cover ISO 13485 QMS requirements, any changes to the audit process after the FDA's adoption of these regulations will be mostly semantic. Manufacturers in the United States that are currently MDSAP certified will have already demonstrated compliance with ISO 13485 requirements, so the shift to a new QMS standard will be relatively straightforward [44].

While changes to the MDSAP itself will be minimal, the FDA's alignment of its QMS regulations with ISO 13485 may encourage greater participation in MDSAP by U.S. companies. Since the ISO 13485 guidelines form the backbone of the MDSAP audit process, manufacturers familiar with the FDA's revised standard will face fewer regulatory barriers to MDSAP certification. This shift could enable more American medical device manufacturers to pursue access to the markets of other MDSAP countries, opportunities they might have previously avoided due to the complexity of meeting diverging QMS requirements.

Furthermore, the FDA audit system is currently overworked and lacks sufficient resources to conduct timely audits of medical device manufacturers under its jurisdiction [48]. MDSAP offers an alternative inspection pathway to alleviate this burden, especially in a time when increased funding is unlikely to be approved by Congress.

These benefits of ISO 13485 adoption are not exclusive to the United States. One of the primary barriers to expanding MDSAP membership has been the challenge of reconciling QMS requirements across regulatory authorities. If additional countries were to harmonize their QMS regulations with ISO 13485, it would become significantly more feasible to integrate their requirements into the MDSAP framework, enabling a more efficient, harmonized audit system for medical device companies around the world.

8. Uncertainty Moving Forward: The Role of Politics, Policy, and Global Signals

As 2026 approaches, the QMSR sits at a crossroads. On paper, it's final. The rule is codified, the timeline is set, and the agency has laid out its intention to move forward. But regulation doesn't exist in a vacuum. Implementation depends not just on what the rule says, but on who's steering the agencies, how global partners respond, and whether domestic political priorities stay aligned with technical goals. The most significant unknown right now is whether the current administration will allow the QMSR to unfold as planned or whether it will slow-walk, revise, or even reverse course [49,50].

Signals from the Trump administration so far have been mixed. There's been no explicit attempt to repeal or freeze the rule, which is telling. That silence may reflect a broader consensus: the QMSR doesn't expand government authority or add burdens, it reduces redundancy and costs. On its face, it aligns with the administration's deregulatory messaging. But recent executive orders instructing agencies to reassess any regulation that shifts control to international bodies have introduced friction [49,51]. Internally, officials at HHS and the Office of Management and Budget have reportedly begun reviewing whether the QMSR's reliance on ISO 13485 raises sovereignty concerns, not because they question the rule's content, but because they question the principle of outsourcing regulatory language to a non-U.S. entity [49].

Public statements from administration officials have hedged. In one interview, the new FDA Commissioner called the QMSR "consistent with global best practices," but also emphasized that "American oversight must never be diluted by foreign consensus" [52]. That framing keeps options open. If industry support remains strong, the administration can claim credit for cutting red tape. If political winds shift or if small manufacturers complain of transition costs officials can argue for a pause or reevaluation without appearing anti-business. This ambiguity has left manufacturers, consultants, and even FDA field staff in a holding pattern, unsure how aggressively to prepare or how much discretion they will be given [53].

Meanwhile, other governments are watching closely. For regulators in Europe, Canada, and Australia, the QMSR is welcome news. It suggests that U.S. oversight is finally converging with global norms. But convergence only works if it's stable. If the U.S. were to backtrack, confidence in mutual reliance efforts, such as MDSAP, could weaken. Global manufacturers, too, are waiting for confirmation that the U.S. intends to stay the course. A sudden shift would not only disrupt compliance planning, it could also harm the credibility of ISO 13485 as a universal standard. Countries that modeled their systems around ISO may question whether the U.S. sees harmonization as a real commitment or a temporary alignment [52]. This tension cuts to the heart of the policy tradeoff. The QMSR promises long-term efficiency, with potential cost savings estimated at over $500 million annually. It reduces duplication, streamlines audits, and simplifies global expansion. But it also ties U.S. regulation more closely to international standards, and in doing so, limits the FDA's unilateral control over how those standards evolve [49,52]. That's not a technical flaw; it's a strategic decision. The question is whether the current

political climate will allow that decision to stand. For now, it's holding. But as the transition deadline nears, and as FDA begins inspecting under the new framework, the balance between global integration and domestic independence will remain a live issue. What happens next depends not just on regulations, but on politics, perceptions, and power within the FDA, across the executive branch, and around the world. Industry is betting that the shift will go forward. But they're also preparing for turbulence because in today's regulatory environment, even a rule designed for stability can become a flashpoint[50].

8.1. Efficiency, Cost Savings, and the Question of Regulatory Independence

One of the most compelling arguments for the QMSR is efficiency. For years, device manufacturers have had to straddle two quality systems, FDA's QSR and ISO 13485, often rewriting procedures, training staff twice, and undergoing separate audits to satisfy nearly identical requirements. The QMSR removes that barrier. By aligning with ISO 13485, the FDA is not just modernizing, it's effectively consolidating a fragmented system. And that consolidation has real economic weight. Industry groups like AdvaMed have cited over $500 million in annual cost savings, mostly from reduced duplicative audits, streamlined documentation, and harmonized supplier oversight [54]. In that sense, the QMSR isn't just a regulatory change, it's an operational upgrade.

But the efficiencies come with a price, and it's not just upfront transition costs. The deeper question is about control. By incorporating ISO 13485 into U.S. law, FDA is choosing to outsource the structure of its quality system framework to an international body, one where the U.S. is just one of many voices [55]. The ISO standard can't be changed unilaterally by FDA. If ISO decides in 2028 to revise the standard to reflect new concepts like machine learning validation or real-time risk monitoring, FDA will have to re-engage in rulemaking to adopt it or choose not to and start diverging from the global norm again. Either path introduces friction. The efficiency gained in 2024 could be offset by regulatory ambiguity in a few years. This isn't just a theoretical concern. Regulatory independence has long been part of FDA's identity. Unlike other agencies, FDA doesn't typically defer to private standards without adaptation. It has always written its own rules, built its own inspection frameworks, and defended its authority to enforce them. The QMSR softens that stance. It signals a shift from being the author of quality regulation to being an interpreter and enforcer of a broader consensus. That may be fine when the consensus is strong. But if future ISO revisions introduce requirements that clash with U.S. statutory definitions, industry practices, or political priorities, FDA will face difficult decisions. The efficiency of harmonization could quickly become the burden of inconsistency [55].

There's also a geopolitical lens to consider. In a moment where American policy is increasingly framed through the lens of economic nationalism, relying on an international standard might seem out of step. Critics could argue that ceding ground to ISO weakens U.S. sovereignty, or that it gives too much influence to non-U.S. regulators or standards

organizations. So far, those critiques have been muted. But if geopolitical tensions rise, particularly around global trade, supply chain resilience, or standards-setting, the FDA's alignment with ISO 13485 could become a talking point, especially if it's seen as disadvantaging American firms in favor of global harmonization [54].

Still, most of the industry seems to believe the tradeoff is worth it. The old QSR was becoming a bottleneck. The world had moved on. ISO 13485 had become the de facto global standard, and firms were already building systems to meet it. FDA's decision to align isn't just about saving money, it's about keeping U.S. regulation relevant in a global market [55]. By adopting the language everyone else is speaking, the agency is positioning itself to better influence that conversation moving forward. But that only works if the U.S. stays engaged, not just with ISO, but with its own commitment to the principles behind QMSR. The efficiency is real. The savings are tangible. But the independence question is not going away. It's embedded in the structure of this shift. How the FDA, Congress, and future administrations navigate that balance will shape not just how QMSR is enforced, but whether it endures.

9. Conclusion

The FDA's incorporation of ISO 13485:2016 is an important moment in the evolution of medical device regulation in the United States. By harmonizing with global standards, the FDA's new QMSR will streamline global market access, create a unified language of quality across jurisdictions, and reduce redundancies. This shift will be particularly beneficial to large, multinational manufacturers who currently invest considerable effort to comply with multiple diverging regulatory systems, and it represents a strategic opportunity for the FDA to strengthen its regulatory and industry influence.

Yet, global harmonization is not without its challenges. Medical device startups and small companies may struggle to navigate the transition to a new QMSR as they lack the resources and institutional knowledge of larger firms. Moreover, harmonization requires international collaboration and the sacrifice of some sovereignty over regulatory affairs. As a result, the success of the FDA's regulatory shift will hinge not only on the policy itself, but on inter-agency cooperation and global confidence the United States' long-term commitment to harmonization.

The importance of international regulatory standardization is evident in the rapidly evolving medical device landscape. As new technologies like software-based devices, artificial intelligence, and personalized medical devices expand into the market, regulatory authorities will need to act with cooperation, flexibility, and foresight to maintain harmonization.

The FDA's decision to adopt ISO 13485 is not merely an update to policy. It represents a deliberate prioritization of global collaboration and market expansion over isolation and regulatory autonomy. Although the success of its implementation will depend on the adaptability of stakeholders and political uncertainties, ISO 13485 has the potential to create a more efficient, collaborative, and innovation-friendly regulatory ecosystem for medical device companies worldwide.

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