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Unlocking success in medtech innovation: Regulatory challenges for start-ups and spin-offs

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The journey of a medical device start-up from concept to market is fraught with challenges, particularly when meeting stringent regulatory requirements for clinical data. This article provides a comparative analysis of these requirements between the EU and US, with a particular focus on the unique hurdles faced by start-ups and spin-offs and the resources available to them.

Keywords – clinical data, EU MDR, medical devices, regulatory strategy, start-ups

Introduction

Clinical data demonstrating the safety and performance of a medical device, preferably in a real-world setting, is the bedrock of regulatory submissions in the EU and the US. However, the specific requirements and pathways for generating this data can differ significantly between the two regions depending on the device's risk class.

European Union

- **Clinical investigation –** The EU Medical Devices Regulation (EU MDR), also known as Regulation (EU) 2017/745,[1] places a strong emphasis on clinical investigation for all implantable and Class III devices. It requires manufacturers to conduct a premarket clinical investigation to generate clinical data to demonstrate compliance with the general safety and performance requirements (GSPR; Annex 1 of the EU MDR[1]).
- **Equivalence demonstration –** Although the EU MDR still allows the use of clinical data from a device to which full equivalence can be demonstrated, the requirements to demonstrate equivalence have become more stringent, especially when claiming equivalence to a device manufactured by a competitor, so that this pathway will be almost impossible for a start-up to use.

United States

- **Premarket approval (PMA) –** The US Food and Drug Administration (FDA) requires premarket approval (PMA) for high-risk Class III devices, which necessitates substantial clinical data from well-controlled clinical trials to demonstrate safety and effectiveness.
- **510(k) clearance –** Moderate-risk Class II devices can often leverage the 510(k) pathway, demonstrating substantial equivalence to a predicate device. This pathway may allow for reliance on existing clinical data for the predicate device, reducing the burden on start-ups.
- **De novo pathway –** For novel Class II devices without a predicate, the de novo pathway allows for classification and marketing authorization based on

a robust demonstration of safety and effectiveness, which may involve clinical data.

Clinical data sources

Start-ups can leverage various sources for gathering the necessary clinical data:

- **Clinical investigations –** These are designed to specifically evaluate the safety and performance of the device in a controlled environment. The studies can range from early feasibility studies to large-scale randomized controlled trials. Since many start-ups focus on novel devices or devices for niche indications, a premarket clinical investigation might be a mandatory pathway for the EU and the US.
- **Published literature –** Peer-reviewed publications relevant to the device or its technology can provide valuable scientific evidence when researching and learning about the state of the art for a specific medical device. The clinical evaluation, especially in the EU, must be based on comparing the clinical data for the subject device with the state of the art in consideration of the available alternative treatment options for a specific indication.
- **Postmarket surveillance –** Data collected after the device has been placed on the market, including specific postmarket clinical follow-up activities as required under the EU MDR, and adverse event and vigilance reporting are crucial contributors to the continuous postmarket surveillance.
- **Real-world data (RWD) –** This refers to data collected outside traditional clinical trials, such as electronic health records or patient registries. RWD are increasingly recognized as a valuable source of clinical evidence for demonstrating long-term safety and performance. Active medical devices or medical device software could collect and use data from the device as real-world evidence.

Challenges for start-ups in generating clinical data

Start-ups often face significant hurdles in generating the required clinical data:

- **Limited resources –** Financial constraints and lack of personnel can hinder the ability to design and conduct clinical investigations.
- **Lack of regulatory experience –** Start-ups may lack the regulatory expertise to fully understand the regulatory requirements and data requirements during the planning phase of a premarket clinical investigation.
- **Patient recruitment –** Enrolling an adequate number of patients in clinical investigations can be challenging, especially for devices targeting niche populations or start-ups that might not have a network of physicians when selecting the appropriate clinical study centers.
- **Data management and analysis –** Collecting, managing, and analyzing clinical data requires specialized statistical skills, and start-ups should collaborate with or employ a statistician to ensure that all statistical requirements of ISO 14155:2020[2] and EU MDR and Annex XV[1] are fulfilled.

> *The Horizon Europe funding program offers grants for research and innovation projects, including clinical investigations.*

Support and strategies for start-ups

There are numerous entities and resources that provide support for start-ups. In the EU, these would include,

- **Notified body guidance –** Notified bodies offer guidance documents and technical meetings to help start-ups understand the regulatory process and the clinical data requirements under the EU MDR.
- **Expert panels –** The EU MDR allows for the voluntary consultation of one of the 11 expert panels for Class III implantable and Class IIb active devices intended to administer and/or remove a medicinal product on regulatory and clinical strategies of start-ups. Currently, this program is in a pilot phase.
- **Horizon Europe –** This EU funding program

offers grants for research and innovation projects, including clinical investigations.[3]

In the US, the following may provide support,

- **FDA presubmission program –** This voluntary program allows medical device and in vitro diagnostic manufacturers to obtain feedback from the FDA before submitting a marketing application. This program can help start-ups identify potential problems early on, clarify regulatory requirements, and improve their final submission to the FDA.
- **FDA small business determination program –** This program by the Center for Devices and Radiological Health provides reduced user fees for small businesses.[4]
- **FDA breakthrough devices program –** A program for expediting the development and review of devices with significant clinical advantages, potentially facilitating access to clinical trial resources.
- **Voluntary total product lifecycle advisory program pilot –** This initiative has been designed to accelerate the development of innovative medical devices. It offers enhanced interaction and guidance from the FDA throughout the product lifecycle, from concept to commercialization. It aims to reduce the time to market and improve the predictability of the regulatory process for breakthrough designated devices.

Start-ups should consider leveraging existing data from published literature, predicate device data (for 510(k)), and real-world data to support clinical evaluation.

Strategic approaches for clinical data challenges

- **Early regulatory planning –** Engage with regulatory authorities early in development to obtain feedback on clinical data requirements and study design.
- **Leverage existing data –** Explore using published literature, predicate device data (for 510(k)), and real-world data to support clinical evaluation.
- **Strategic partnerships –** Collaborate with research institutions, hospitals, or larger companies to access clinical trial expertise and infrastructure.
- **Pilot studies –** Conduct smaller-scale pilot studies to gather preliminary data and refine the device design before embarking on more extensive clinical investigations.
- **External funding –** Seek grants, venture capital, or angel investors to support clinical data generation.
- **Expert consultation –** Engage with experts in clinical trial design, biostatistics, and regulatory affairs to optimize study design and data analysis.

Generating robust clinical data is a critical step in bringing a medical device to market. Start-ups face unique challenges in meeting these requirements, so sufficient regulatory guidance is key for them. In general, the EU MDR seems to have raised the bar for clinical data requirements, especially for implantable and Class III devices, and more novel and innovative devices might end up being approved in other markets first, such as in the US. Clinical data collected in these markets in a PMS setting could be used as premarket clinical data for the EU. It might also be easier to conduct a clinical investigation, which is required for CE-marking in the EU in a country where the device has already been approved.

Regarding clinical data obtained outside their regulatory jurisdiction, the EU and US allow the use of clinical data obtained outside their jurisdictions as long as the data are obtained according to regulatory and scientific standards. Ideally, the study should follow ISO 14155:2020.[2] In addition, there has to be justification for why the data would be fully transferable to the target patient population in the EU and the US. That justification, besides the differences in patient demographics, should also consider any differences in the standard of care or healthcare systems that could significantly affect data transferability.

Having covered the clinical aspects of the medical device start-up journey, the next part of the article will examine the experiences from within a start-up.

Regulatory challenges for start-ups and spin-offs

Start-ups typically begin with a small group of enthusiastic, motivated people with big dreams and high ambitions. It is unquestionably tempting to chase these dreams, fulfill one's ambitions, and secure a place among successful entrepreneurs. However, the reality is that most start-ups eventually fail to bring their medical innovation to the market.

Start-ups have few resources but are subject to the same stringent timelines and regulatory approval processes as medium-sized and large enterprises, which are better resourced and have access to a greater pool of experienced, expert professionals. Especially in the very early phase of product development, it is not unusual for the founders of a start-up company to divide the top titles and become "top management." Lower-level positions may be filled with younger, ambitious, and talented resources.

> *The regulatory challenges of a start-up depend heavily on the type and skill set of the regulatory professionals responsible for managing and executing the regulatory requirements.*

Guiding a start-up through the complex regulatory requirements is as challenging as keeping up to date with all changes and updates of regulations, standards, and guidelines that may or may not vary by region. Possibly the most challenging of all are the efforts to keep the various stakeholders, such as investors, top management, and the engineering and marketing teams, involved and focused on the project and goals at all stages of the process. Therefore, the regulatory challenges of a start-up depend heavily on the type and skill set of the regulatory professionals responsible for the management and execution of the regulatory requirements.

Regulatory experience

A start-up must have individuals with the appropriate regulatory experience on board from the beginning. The regulatory assessment of the possibilities should be started with more senior and experienced regulatory professionals, either internally or as consultants. Working within the complex regulatory landscape and managing all staff requires experience and a broad knowledge of the regulations, standards, and guidelines for the medical device industry.

Start-ups that anticipate recruiting relatively inexperienced professionals to be solely responsible for setting up the regulatory strategy and ensuring compliance with regulatory requirements should consider the associated implications. Learning on the job, especially in the dynamic, fast-moving start-up setting, can be extremely expensive if there are compliance- or regulatory-related setbacks that could cause significant delays and require additional, costly involvement of consultants.

Regulatory strategy

It is not evident that all decision makers within a start-up are on the same page concerning the scope of the device to be designed. Therefore, before starting any activities, it is crucial that an interdisciplinary team involving, among others, design and process engineers, marketing specialists, quality engineers, and regulatory specialists, agrees on the medical device's:

- Intended use,
- Intended purpose,
- Indications for use,
- Classification (depends on the market that will be targeted), and
- Performance claims.

The defined intended use, intended purpose, indications for use, and classification are the basis for product development, risk management, verification and validation

activities, clinical evaluation, and clinical investigation strategy. The scope will determine the overall business and regulatory strategy.

Besides defining the scope, potential markets should be investigated on their unique regulatory requirements, reimbursement policies, potential product acceptance, and more. The regulatory strategy plan is useful for internal and external communication and centralizing all relevant information about the medical device and the associated implications of certain choices and considerations.

> *Investors manage the funding and will have their own and often ambitious expectations, so it is important that they are kept informed about the timelines.*

Regulatory intelligence

Many start-ups are struggling to stay current with the latest regulatory requirements for medical devices, especially those that may differ significantly between countries and regions. A powerful way to keep up with these changes and updates and ensure continued compliance is to have a regulatory intelligence process within your quality management system (QMS) for gathering global regulatory information. Within this process, several sources such as the International Organization for Standardization, the International Electrotechnical Commission, the European Commission, and the FDA could be tracked for intelligence. In addition, subscribing to newsletters from consultants or regulatory agencies might also help track and gather information about regulations, standards, or guidelines.

Stakeholder management

In addition to having residual regulatory knowledge, it is important to have experience and skills in managing start-up stakeholders. Clear, timely communication is crucial for effectively managing the expectations of both internal and external decision makers and keeping teams on track to ensure regulatory compliance throughout the lifecycle and ultimately, successful approval.

Investors

Start-ups are typically funded by venture capital firms and/or angel investors. A regulatory specialist or consultant does not always have access to the investors – that contact is usually limited to top management, which should be considered the "gateway" to the investors. Because investors manage the funding and have their own and often ambitious expectations, it is important they are kept informed about the timelines. Early-phase investors may have different regulatory knowledge levels compared with investors who join at a later phase, and this needs to be factored into how top management engages with them.

Top management

Regulatory staff must ensure that top management is involved as early as possible in discussions about the expectations around regulatory compliance and the associated approval timelines to ensure. In turn, top management must keep investors apprised of developments so that everyone will have a realistic view of the different approval timelines of different target markets and the implications of nonfulfillment of applicable regulatory requirements.

Top management may be under pressure from investors to push back on the development and approval timelines. However, it is important to remember that all companies have to follow the same path and timelines, and it is hard to game the regulatory system to advance more quickly (unless one is approved for priority review, for example). Having a regulatory strategy plan early in the development process that reflects the scope of the product, applicable regulatory requirements, clinical evaluation strategy, and associated development and approval timelines may help the "bottom-up" management of top management and investors.

Engineering and operations

The product development path is highly dependent

on a specific regulatory framework, and regulatory staff should therefore work closely with the internal and external stakeholders responsible for design and process engineering. Engineers tend to be creative, curious, and willing to think and act outside of the box. Operating within a strict framework of regulatory requirements and documentation obligations typically leads to friction between regulatory affairs and the engineering teams. Therefore, it is important to be upfront in communicating and managing regulatory expectations or boundaries that might affect product development. Regulator testing is crucial to advance development, ensure compliance, and keep operations on track.

> *Sales and marketing personnel should be involved when exploring potential markets and included in planning and regulatory strategy discussions.*

Clinical operations

The clinical operations team is an important stakeholder for regulatory affairs as the approval process is highly dependent on the quantity and quality of the clinical data. The clinical operations team must be involved in the regulatory strategy from the very beginning to ensure the clinical evaluation and potential investigations yield sufficient data and evidence to demonstrate device safety, performance, and effectiveness as part of the regulatory approval process.

Sales and marketing

Another internal stakeholder to consider is sales and marketing. These personnel tend to be passionate and persuasive. However, there are specific and exacting limitations within the regulatory framework. In particular, product claims and associated labeling must be aligned between regulatory and the marketing team. Sales and marketing personnel should also be involved when exploring potential markets and be included in planning and regulatory strategy discussions.

Regulatory consultants

It is not unusual that start-ups might initially use regulatory consultants for certain requirements such as regulatory intelligence, clinical evaluation, and technical documentation. A potential pitfall, however, is the decentralization of crucial regulatory information because of the involvement of several consultants. Therefore, start-ups will benefit from one dedicated and central person or team responsible for regulatory affairs and managing all associated feedback and input from several regulatory consultants.

Regulatory authorities

Communication and maintaining relationships with regulatory bodies, such as the FDA in the US or a notified body in the EU, is crucial to ensure the most appropriate pathway for successful approval and sound product development strategy. In contrast to established medical device companies with historical relationships with regulatory authorities, start-ups must consider allocating time and resources to start new relationships with relevant regulatory stakeholders. Here again, there should be a single person responsible for managing communication with regulatory authorities and disseminating the information internally.

Taken together, regulatory affairs management is a crucial part of a medical device start-up's success, ranging from identifying the most fitting and efficient regulatory pathway to approval, to implementing or changing practice based on regulatory intelligence findings, and managing internal and external stakeholders. Consequently, the regulatory professional responsible in a start-up environment should be proactive, flexible, persistent, and have sufficient experience to know where to find essential information.

Experiences from working with multiple start-ups

There are key considerations and strategic lessons to keep in mind to succeed in medical innovation as a start-up. Unlike established companies, start-ups often lack deep experience in regulatory, quality, and clinical areas. A significant part of a project will involve

training, explaining regulatory nuances, and guiding the start-up through unfamiliar territory.

> *Invest time upfront for detailed strategic planning. A few weeks of planning could save months of work subsequently.*

Before beginning, it is important to recognize that one will likely be working with external consultants or field experts rather than directly with the start-up's core team. This can introduce communication challenges, so a focus on clear, consistent communication with all stakeholders is essential. It is also important to have regular checks to ensure that everyone is aligned on tasks and in meeting key milestones along the way. The start-up's appointed regulatory and quality assurance contacts may not have chosen these roles, and their motivation may be low, given that these responsibilities are often viewed as obligations rather than interests.

In regard to communication, it is important to remember that regulatory terminology can be quite specific. Start-ups often have different definitions for key terms derived from the residual scientific knowledge and experience of the majority of employees. It is therefore advisable to compile a glossary of terms to avoid confusion and ensure that everyone is using the same language.

Strategic planning: The essential first steps

A key priority should be investing time upfront for detailed strategic planning. A few weeks of planning could save months of work subsequently. Begin by developing a clear regulatory and clinical strategy, as already outlined in this article. This foundation will serve as a guiding framework for the project and affect the start-up's ability to secure investment.

Investors look for a realistic timeline; an overly optimistic estimate (e.g., "market-ready 7 months") can damage credibility. Instead, provide a feasible timeline that aligns with regulatory requirements, and ensure the budget projections are accurate to account for potential delays. This cuts both ways, as there is a bigger chance of meeting goals and attracting investors.

This planning should also include a strategy for the launch of the device, including which version will be marketed first and which features will be included and excluded.

The time to market can be accelerated by starting with a simpler version of the product. For example, if the concept includes a device that measures a physiological process, software for processing that data, and AI-driven analytics, then consider launching first with just the measurement function. Once revenue has been generated, subsequent versions can introduce software processing and AI, which are more complex and take more time to market. This approach reduces initial time to market, lowers risk, and allows early revenue to fund further development.

The same principle is also true for the product claims because the market access route and clinical study design depend on them. If the plan is to make broad claims, then ensure there is sufficient data to support them. Otherwise, one should consider starting with more specific claims that will result in a lower number of patient data, which will simplify the regulatory process.

Lean SOPs for start-ups

Start-ups often start implementing a full QMS based on their reading of ISO 13485[5] or QMSR. This is counterproductive because it forces the young company into unnecessary bureaucracy – for example, a complaint procedure is not necessary if the start-up does not have devices on the market. Therefore, stick to the most important procedures in the early phase, then build the QMS from the core standard operating procedures:

- Document and records control
- Design and development
- Risk management
- Supplier control

Tailor these processes thoughtfully, ensuring compliance without overwhelming the team.

Finally, plan the "design freeze" carefully. This milestone locks in product specifications, after which all previous tests may no longer be valid. The timing of this design freeze is, therefore, of the utmost importance.

> *Focus early on regulatory and clinical intelligence and strategy because focusing on a single goal might result in project failure and financial losses for the investor.*

Key takeaway: Think first, act later

Success in guiding a medical device start-up requires thoughtful planning and strategic foresight. Prioritize a solid regulatory and clinical strategy from the outset, make realistic decisions on product complexity, and set up essential procedures without overloading the team. Thinking ahead and sticking to a well-crafted plan ensures a smoother path to market and a stronger foundation for long-term success.

Experience has shown that many investors push start-ups to go to the US because the regulatory framework is stable and predictable and the costs for most regulatory pathways for start-ups are significantly lower than in Europe. However, although this might be the case for the majority of cases, there will still be cases in which the European regulatory framework is easier to go through based on the classification system. That being said, focus early on regulatory and clinical intelligence and strategy because running blindly toward a single goal because an investor wants it might result in project failure and financial losses for the investor.

Abbreviations

CE [mark], conformité européenne; **EU,** European Union; **EU MDR,** EU Medical Devices Regulation; **FDA,** US Food and Drug Administration; **GSPR,** general safety and performance requirements; **PMA,** premarket approval; **QMS,** quality management system; **US,** United States.

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