

Chapter 12

Regulatory Strategy

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OBJECTIVES

- ❑ Learn how to define regulatory strategy
- ❑ Understand how to develop and implement a regulatory strategy
- ❑ Get to know the information available to help develop a regulatory strategy
- ❑ Understand which key considerations need to be addressed during development and lifecycle management

DIRECTIVES, REGULATIONS AND GUIDELINES COVERED IN THIS CHAPTER

- ❑ Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No. 178/2002 and Regulation (EC) No. 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC
- ❑ Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU
- ❑ *Rules governing medicinal products in the Europe Union: Medicinal Products for Human and Veterinary Use list both pharmaceutical legislation (Volumes 1 and 5) and various guidance documents (Volume 2–4 and 6–10)*

Introduction

In the definitive *Harvard Business Review* article on strategy, Michael E. Porter defines strategy as the creation of a unique and valuable position involving a specific set of activities.¹ It involves not only creating a high-level plan to achieve one or more goals under conditions of uncertainty but also creating “fit” and alignment among a company’s activities. Strategy is important because the resources available to achieve the necessary competitive advantage are usually limited.

Regulatory Strategy

Regulatory strategy specifically aligns the regulatory activities required with the business strategy, to bring a new or modified product to market in the desired regions within the desired timeframes. It also provides overall direction to the project team by defining the key regulatory components and proactively identifies the challenges as well as alternative approaches to the chosen development pathway.

In addition, regulatory strategy anticipates issues and concerns with regulatory authorities and stakeholders. It defines key programme milestones, often considered business catalysts driving both investor interest and financing.

Regulatory Strategy—Market Considerations

Regulatory professionals need to understand what the company wants to achieve before developing the regulatory strategy. Questions such as the following should be asked:

- What is the business objective?
- What business problem will the product solve?
- What are the competitor products?

- Upon which regulatory pathways have competitor products embarked?

This regulatory intelligence data will help key stakeholders and decision-makers identify the product features and attributes on which they want to focus in the project scope.

Another key aspect of the regulatory strategy is the assessment of the marketplace opportunities.

- What are the specific needs in each of the 27 EU Member States?
- How big is the market in the remaining European Economic Area (EEA), such as Iceland, Liechtenstein or Norway?
- What are the specific considerations in Switzerland, which is neither an EU nor an EEA member?²
- What are the implications of Brexit on the UK? The Medicines and Healthcare products Regulatory Agency (MHRA) provides current guidance and publications³ on the situation and indicates the new transition rules will take effect on 1 January 2021.⁴

The *EU MDR (2017/745)* refers to national law and provisions in multiple places, including the role of national competent authorities.

- What national requirements will impact product development (e.g., requiring instructions for use or software interfaces in specific languages)?
- What are the regulatory application fees?
- Have translation costs been factored in?
- What are the reimbursement strategies for each country and/or region?
- Do any of the countries require another country's prior approval, which could impact approval staging or timing?
- Is the potential revenue in a target market significant enough to justify the costs of pursuing regulatory approval for that country/region?

Developing and Implementing a Regulatory Strategy

As the old adage says, "If you fail to plan, you can plan to fail." Implementing a strategy allows a company to map its path forward and examine the potential pitfalls and mitigate any risks, challenges or issues the new or revised product might face.

Small companies tend to plan to fail by not recognising the value of strategic planning. They may claim to be "too busy" to put together an overall strategic plan. For example, a company may prepare the general safety

and performance requirements checklist at the end of the medical device development process only to find that additional nonclinical or clinical studies need to be conducted to support the product claims; the company should plan early and consider all its options before proceeding with the programme.

In the long run, developing a strategy and implementing it will save time and money and focus the development or project team.

Good regulatory strategy cannot not be created in a vacuum and often requires balancing competing priorities; a cross-functional project team should be assembled, representing regulatory, marketing, medical/clinical, engineering, usability, reimbursement, manufacturing, quality and/or other functions within the company. Outside experts may be needed from partner companies, key suppliers or consultants.

Table 12-1 depicts key questions from a product development perspective. Additional operational, compliance and promotional considerations are detailed below.

- Major regulations and directives
 - What are the key regulations that apply?
 - Does the product meet the definition of a medical device, medicinal product, combination product or another type of product?
 - Are there timelines that may differ depending on the product functionality? For medical devices, for example, a four-year exemption in the application of the *EU MDR (2017/745)* may apply even though the *EU MDR (2017/745)* entered into force on 26 May 2020.⁵
- Conformity assessment
 - Is a notified body required to be involved?
 - Has the notified body been designated under the required legislation? A list of the bodies designated under the *EU MDR (2017/745)*, for example, can be found on the New Approach Notified and Designated Organisations (NANDO) Information Systems website.⁶
 - Is the desired notified body accepting new clients?
 - Does the notified body have auditors available to approve technical documentation and assess the quality management system within the desired time to market timelines?
- Economic operators
 - Have manufacturers, authorised representatives, importers and distributors been identified?
 - Have formal agreements been put in place?

Table 12-1. Regulatory Key Questions During Development

Key Area	Considerations for EU Development Program
Intended Use	<ul style="list-style-type: none"> • What are the proposed indications for use? • What is the target patient population(s) and/or anatomical site(s)? • What is the use environment (e.g., ICU, surgical suite, office setting, home)? • Is it intended for prescription or over-the-counter use? • Could the product qualify for expedited review or humanitarian use designation?
Description	<ul style="list-style-type: none"> • What features are proposed for marketing? • Which characteristics could be significant from a regulatory perspective? • Are there any device accessories, and will they require approval/clearance?
Claims	<ul style="list-style-type: none"> • Are there unique claims for which regulatory approval is required (or desirable)? • It often is possible to secure a competitive advantage by carefully planning and obtaining the data necessary to support desired claims.
Lifecycle Issues	<ul style="list-style-type: none"> • What short- and long-term changes are anticipated? • How might these changes impact the regulatory strategy, e.g., require a staged approach, with approval of one generation of device building off another? • Will older generations of the device be removed from the marketplace?
Device Classification	<ul style="list-style-type: none"> • How does the device meet the definition of a medical device? • Is the device invasive? • Is the device an active device? • Is the device software? • Will the device be supplied sterile? • Are there special classification rules for specific types of products? • Is the product for prescription use only?
Harmonized Standards and Common Specifications	<ul style="list-style-type: none"> • What are the harmonized standards and common specifications applicable to the product? • Are there other ways to demonstrate compliance with the applicable legal obligations?
Clinical Evaluation and Clinical Investigations	<ul style="list-style-type: none"> • For medical devices, consider: <ul style="list-style-type: none"> ◦ What are requirements for literature review and analysis? ◦ Will equivalence be demonstrated for existing CE-marked devices? ◦ Is clinical investigation required? ◦ What are the requirements for informed consent? • For drugs, consider: <ul style="list-style-type: none"> ◦ What are the requirements for informed consent? ◦ What are the roles of the ethics committees? ◦ What is required for regulatory approval and notification for trial initiation, trial conduct, and trial suspension? ◦ Have clinical supply manufacturing been considered? ◦ What are the requirements for adverse event reporting and serious adverse reaction notification?
Packaging and Labelling	<ul style="list-style-type: none"> • Device labelling on the outer package and instructions for use must meet certain requirements. Also, all medical devices must contain a statement about any time limitations on their safe use. • For drugs, labelling requirements are controlled at the national level.
Technical Documentation	<ul style="list-style-type: none"> • Have the general safety and performance requirements been considered? • Have the clinical evaluation requirements been considered? • Have substantially equivalent devices been identified? • Have the clinical investigation requirements been considered?
Technical Documentation—Postmarket Surveillance	<ul style="list-style-type: none"> • Have the postmarket surveillance plan requirements been considered? • Have the Periodic Safety Update Report (PSUR) requirements been considered? • Have the postmarket clinical follow-up (PMCF) requirements been considered?

- Quality management system
 - Has a person responsible for regulatory compliance been identified?
 - Has a quality plan been established for both premarket activities and postmarket activities?
 - Have standard operating procedures been defined?
 - How will economic operators communicate required information to EU Member States? Consideration should be given to device registration, clinical investigations and postmarket surveillance requirements for medical devices, in light of the news that the European database on medical devices (Eudamed) will not be launched until May 2022.⁷
- Marketing Authorisation procedure
 - For medical devices, CE marking is the only prerequisite to placing products on the market. It is necessary to communicate with the national authorities when placing medical devices on the market, as additional requirements like local language requirement, etc., might be applicable. Please see **Chapter 14 The EU Medical Devices Legal System** for more information.
 - For medicinal products, there are four marketing authorisation routes: the National, Mutual Recognition, Decentralised and Centralised Procedures. For more details on these procedures, please refer to **Chapter 3 Overview of Drug and Biologic Regulatory Pathways**.
- Promotion and advertising
 - Most regulated countries do not allow advertising until products are registered.
 - Marketing claims must match those in the clinical trial and technical documentation.
 - For drugs, this is controlled at the national level. International Federation of Pharmaceutical Manufacturers Association and European Federation of Pharmaceutical Industries and Association codes cover advertising and promotion to healthcare professionals, behavior of sales representatives, supply of samples, sponsorship of meetings and participation by healthcare professionals including travel expenses. For more details, please refer to **Chapter 9 Advertising and Promotion**.

Once the basics are established, the team should “peel the onion” to make sure it understands any subtleties that may have regulatory impact.

Information Available to Help Regulatory Strategy Development

The European Commission provides a range of guidance documents adopted by the Medical Device Coordination Group (MDCG) to assist stakeholders implementing the *EU MDR* (2017/745).⁸ These legally non-binding guidance documents have the objective of ensuring uniform application of the relevant provisions of the regulations within the EU. The guidance documents include documents pertaining to Unique Device Identifiers (UDI), qualification and classification of software, cybersecurity and summary of safety and clinical performance.

While the MDCG continues to work on new guidance documents, the MEDDEVs can be considered for their background information on the most recent consensus reached on various matters. The MEDDEVs were developed for the now repealed Council Directives 90/385/EEC and 93/42/EEC. Details can be found on the European Commission website.⁹

While the European Committee for Standardisation (CEN) and the European Committee for Electrotechnical Standardization (Cenelec) draft revisions to their existing standards, adapt others and issue newly harmonised standards in support of *EU MDR* (2017/745) and *EU IVDR* (2017/746),¹⁰ the current list of harmonised standards published in the *Official Journal of the European Union* can be found on the European Commission website.¹¹ These harmonised standards provide insight into the current thinking on the matter and the state-of-the-art.

The European Medicines Agency’s (EMA) website¹² provides information on the regulation of medicines for human and veterinary use in the EU to help applicants prepare marketing authorisation applications. The legal framework governing medicinal products for human use in the EU¹³ is based on the principle that the placing on the market of medicinal products is subject to a competent authority granting a marketing authorisation.

Documenting Regulatory Strategy

“If it isn’t documented, it doesn’t exist.” There are many reasons to document a strategy in a sort of “playbook” for the team. The team is being asked to think critically about all the factors that go into medical device or medicinal product development, not just their small segments of the process. By seeing the whole picture, people understand how their portions affect the strategy.

Constructing a formal written analysis of the regulatory strategy provides a reference to why a decision was made at a particular juncture in the development timeline, so new team members understand the whole picture. In addition, it can serve as the foundation document for any future updates.

Thus, the process of putting together a regulatory strategy does not need to take months or a year to complete. Regulatory can provide the research, information and intelligence, and come to the table with a reasonable working draft for team discussion (which might take a month or two), but once the initial draft is done, the team can sit down and focus on the task at hand and leave competing interests outside the room to develop the first team draft strategy. Participating in strategy development also requires the team to act and agree, so everyone can stand behind the decisions made.

Confirming the Strategy

It is almost always prudent to confirm the proposed strategy is sound (likely to be effective), practical (reasonable and efficient) and addresses company objectives. The draft strategy should be circulated for cross-functional team review. Despite care taken up front to fully understand the programme, it is possible a key point was missed or perhaps more likely, a change has emerged since the initial meetings. Feedback from others in the company, trusted colleagues or advisors can further vet the strategy.

Finally, for many programmes, particularly if the product is novel or the data required are expected to be extensive, it is wise to contact the notified body or the regulatory authority to refine and/or redirect the strategy as appropriate. In general, contact is desirable as soon as there is enough information available for a meaningful discussion but before the company moves too far ahead or commits significant resources.

Be Prepared for Changes

Even the most diligently developed strategy is almost certain to change in at least some respect during the course of product and regulatory development. A schedule should be established to review and update the strategy periodically with the team. If the product development cycle is short but intense, weekly checks might be needed; but for most products, a quarterly review probably will suffice. A keen eye should be kept for new information that may influence the regulatory strategy. This may include:

- internally driven changes, such as company plans for new or revised indications or claims, device modifications or new markets

- externally driven changes, such as new regulatory requirements or guidance or competent authority action on similar products

Conclusion

A solid regulatory strategy is one of the foundations upon which successful medical product development is based. The company should start by asking a broad range of questions to ensure it has a solid understanding of the product and marketing plans, especially any subtleties that may have regulatory impact. Regulatory intelligence should be used to obtain as much information as possible about the regulation of similar or related products.¹⁴

Being practical and realistic when developing the strategy helps attain the “must haves,” but strategies to stretch for the “nice to haves,” too, is important. The strategy should be validated by internal and external stakeholders, and where appropriate, notified body and regulatory authority personnel. Finally, it is critical to watch product development and the regulatory environment closely and be ready to revise the strategy as necessary.

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Recommended Reading

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- Fan K and Falcone R. Chapter 10 Regulatory Strategy. *Fundamentals of US Regulatory Affairs, 11th Edition*. Regulatory Affairs Professionals Society. 2019.

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