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# Navigating the Regulatory Landscape for Healthcare Product Development: Key principles and best practices



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**Disclaimer:** The information presented in this guide is intended to outline the general processes, principles and concepts of the healthcare product development lifecycle. Since regulatory requirements are ever-changing, it is **current only as of October 2012** and not intended to provide detailed instructions for product development. Every healthcare product is unique and therefore so is its associated product development program. **Specific advice should be sought from a qualified healthcare or other appropriate professional.**



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# Introduction

Developing an innovative healthcare product (a drug or a biologic, or a medical device) from the proof-of-concept stage to the marketing stage is an expensive and complex process. It involves many years of research and development work.

To save time and money in bringing products to market, product development activities should be conducted in accordance with the related regulatory requirements. Following these requirements can streamline development activities and help you to manufacture a product that meets the regulatory standards of your targeted jurisdiction(s)—that is, a quality product that is safe and effective for its intended use.

Although information on the regulatory requirements (e.g., laws, guidance documents, international standards) for healthcare product development is readily available, navigating the regulatory system is not simple, and it gets even more complex when dealing with multiple jurisdictions.

To help entrepreneurs who are developing healthcare products, MaRS has developed this guide, *Navigating the Regulatory Landscape for Healthcare Product Development: Key principles and best practices*. This collection of short articles surveys regulatory-related issues that may be encountered during healthcare product development. The articles were originally published by MaRS in October 2012 in the Entrepreneur's Toolkit. Written in plain language, the guide aims to facilitate the regulatory understanding that governs product development and ensure regulatory compliance in these activities. It can be used as a starting point to assist you in developing your product.

Rather than serving as a compilation of regulations, the guide discusses the fundamental concepts and principles in regulatory affairs. Through examples and illustrations, it makes clear the interrelated activities involved in product development. It gives entrepreneurs a road map to follow.

Due to the broad variety of healthcare products, the constant advancement of scientific technology and ever-changing regulatory requirements, this guide cannot replace the actual reading of regulatory requirements published by local and international regulatory bodies. Nor does it replace advice from a qualified regulatory professional who can add value that is specific to your product.

If you are not familiar with the healthcare product development lifecycle, we suggest you start with Chapter 1 of this guide, which highlights the 10 key steps of healthcare product development. These steps outline the development and maintenance activities that are generally applicable for innovative healthcare products. Chapters 2 to 9 address activities that support product development. The table of contents will help you see which topics are explored so that you can determine which are most relevant for your stage of product development.

Once you understand the regulatory concepts and principles related to your product, tailor them to your development program. Learn the regulatory requirements and implement them. Keep in mind that regulatory requirements often change, so make sure to monitor them and adapt your program as needed.

# Chapter 1: **Ten steps of healthcare product development**

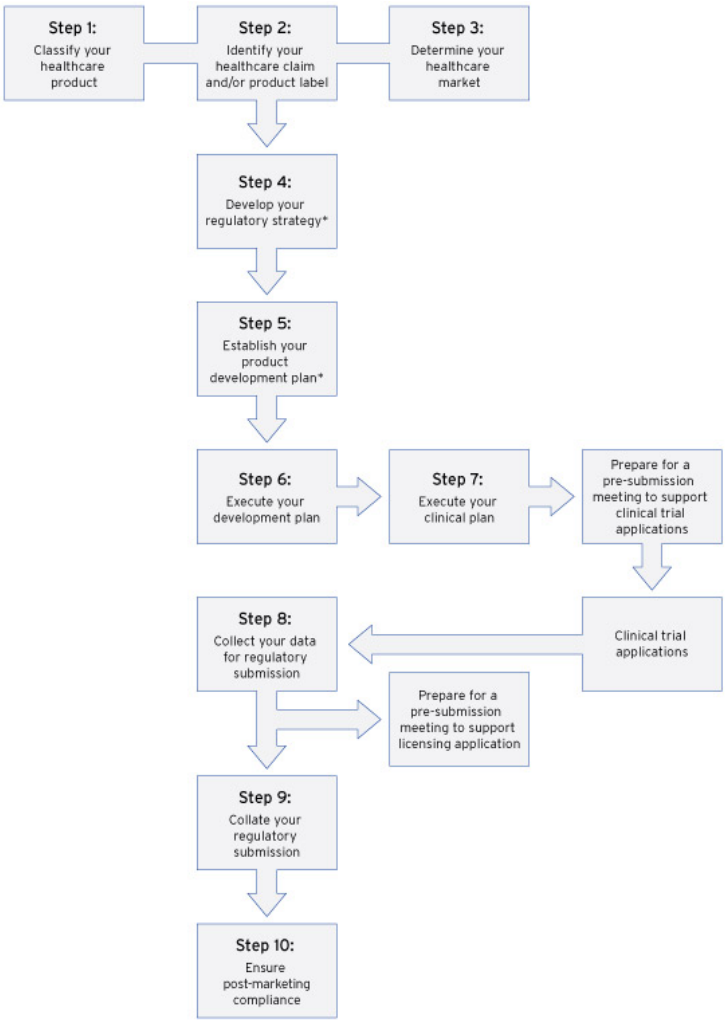
For those not familiar with the healthcare product development lifecycle, this chapter highlights the 10 key steps to help you navigate from proof of concept to maintaining your licence. These steps outline the development and maintenance activities that generally apply to innovative healthcare products.

## 1.1 Overview: The 10 key steps

Healthcare product development (i.e., the development of a drug, biologic or medical device) is a long and complex process. It is critical to know the general product development lifecycle from the proof-of-concept (POC) stage to the licensing stage so that your development process can follow the correct path. Knowing which pitfalls to avoid will speed your time to market.

The healthcare product development process involves 10 key steps, as shown in Figure 1.1-1. Further details related in-depth articles are below.

**Figure 1.1-1: Ten key steps to healthcare product development**




* *The regulatory strategy and the development plan are evolving documents. They should be reviewed and updated on a regular basis during the product development* process.

***Step 1:*** Properly classify your healthcare product (i.e., as a drug, a biologic, a medical device or a combination product) so that you know which regulatory path to take. If in doubt, contact the appropriate regulatory body to confirm the product type and how your product is regulated.

***Step 2:*** Identify the claim of your healthcare product so that you know what types of studies to conduct to support the claim and your product label. For instance, changing your claim may change the medical device classification which can lead to different regulatory oversight requirements (e.g., class II versus class III device – meaning a 510(k) submission versus a Premarket Approval [PMA] submission in the US).

***Step 3:*** Determine your healthcare market. This will guide you to the requirements that are specific to each jurisdiction. It is important to identify jurisdiction-specific requirements upfront so that they can be included early in the product development plan.

***Step 4:*** Develop your regulatory strategy by identifying the specific regulatory requirements as well as the possible pathway(s) to take. A thorough understanding of these requirements will guide the development of your regulatory strategy.

***Step 5:*** Establish a healthcare product development plan so that the product requirements can be translated into actions – i.e., who does what and by when and for how much. Such plan should be established collaboratively with input from different functional groups. It should include key milestones, critical paths and periodic reviews for "go and no-go" decisions and be updated periodically.

***Step 6:*** Execute the product development plan. It is subject-matter experts who possess knowledge of the investigational product who must carry out (and be responsible for) the corresponding manufacturing, quality, regulatory, non-clinical and clinical programs, as well as any coordination with third parties.

***Step 7:*** Execute the clinical plan. If a clinical program is required in support of the licensing application, these studies should be conducted according to good clinical practices (GCP) and country-specific requirements, such as ethics approvals and/or necessary regulatory approvals for conducting the clinical trial(s). Often, it helps to have a pre-submission meeting with the regulatory agency prior to submitting a clinical trial application in order to address specific issues (e.g., the design of the clinical trial and the study end point[s]).

***Step 8:*** Collect your data for regulatory submission. Once the data from the product design and the manufacturing, quality, non-clinical and clinical programs are available, these data and reports should be collected for inclusion in the regulatory submission.

***Step 9:*** Collate your regulatory submission according to applicable regulatory requirements specific to your type of submission. Ensure the completeness of the submission and anticipate the resources needed to address questions from the agency during the submission review. For an innovative healthcare product, it is often recommended to have a pre-submission meeting with your agency prior to submitting the licensing application.

***Step 10:*** Ensure post-marketing compliance. Make sure to fulfill all necessary post-marketing obligations.

For more details on healthcare product development, please refer to Chapters 1.2 to 1.11 for an in-depth look at each of these 10 steps.

## 1.2 Step 1: Classify your healthcare product

When developing a healthcare product, the first question to ask is, "is my product regulated?" If the answer is yes, the next question to address is, "how is my product classified?"

Different types of products are regulated under different regulations. By knowing the correct product classification, you can identify the right path to have your product reach your target market. The four major groups of products are defined[i] below:

- **Drug:** A substance which exerts an action on the structure or function of the body by *chemical action or metabolism*. For example, a drug is defined in the US as "(A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)."[1]
- **Biological product:** Generally, a biological product is of a *substance derived from or made with the aid of living organisms*. It is defined in the US as "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings."[2]
- **Medical device:** A medical device is defined in the US as an "instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any component, part, or accessory, which is—(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is **not dependent upon being metabolized** for the achievement of its primary intended purposes."[3] This may include products such as software designed to aid in the diagnosis of a certain condition.
- **Combination product:**[ii] A combination product is one which has two components in different regulatory categories (e.g., drug/device, biologic/device, drug/biologic, or drug/device/biologic); these two components are physically, chemically or otherwise combined or mixed and produced as a single entity.[4]

### 1.2.1 Combination products

The classification for most healthcare products may be obvious, but this may not be the case for combination products.[5] Thorough evaluation is needed to identify how these products are regulated. Although all components (e.g., both drug and device) are subject to regulatory review to support the quality, safety and efficacy, identifying the classification for a combination product will determine the regulatory pathway for your product – i.e., the submission type required (e.g., a Premarket Approval [PMA]or a New Drug Application [NDA]) and the review division that will lead the review of your application.

***Identify the classification of your healthcare product***

When identifying the classification of your healthcare product, the key questions to address are:

- What is my product intended to do?
- Through what means can the intended use be primarily achieved?

To answer the first question, you need to identify the claim or the intended use. Is it to diagnosis, cure, mitigate, treat or prevent a certain disease or condition? The next step will be to identify the "primary mode of action" (PMOA) for your product to achieve such a result.[5]

The examples in Table 1.2-1 illustrate how the intended use and PMOA can affect product classification. They are based on combination products approved or cleared by the U.S. Food and Drug Administration (FDA).[6]

In example 1, a skin transdermal patch containing a drug [substance X] that activates receptors in the body (i.e., the PMOA) is classified as a drug. Similarly, in example 2, the inhaler is a device designed to deliver a drug [substance Y] to treat [condition 2]. As the PMOA is through [substance Y], it is classified as a drug.

In examples 3 and 4, although antimicrobial/antibiotic agents are used to prevent microbial adhesion on the devices, the PMOA is achieved through the implant or physical covering of a wound that does not exert via a chemical action or by being metabolized. Thus these products are classified as devices.

The decision tree (Figure 1.2-1) outlines the key steps in identifying the classification of a combination product.

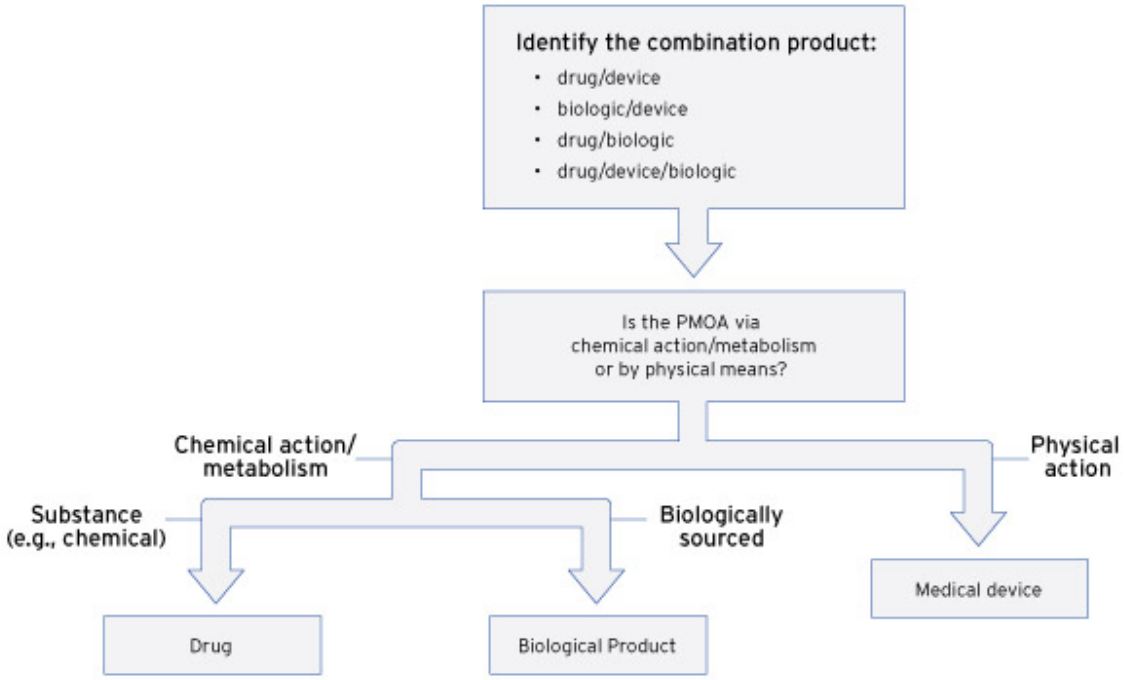
***Table 1.2-1: Combination products: Examples***

| Product example | Design | | Intended use | Primary mode of action (PMOA) | Other mode of action | Classification decision |
|---|---|---|---|---|---|---|
| | Drug | Device | | | | |
| 1. Skin transdermal patch containing a backing, an adhesive drug, [substance X], and a release liner | Substance X | Transdermal patch | Patch works by delivering [substance X] through the skin and into the bloodstream to treat [condition 1]. [Substance X] is an agonist that works by activating receptors in the body | Substance X activates the receptors | Patch as a delivery tool | Drug |
| 2. Inhaler with [substance Y] | Substance Y | Inhaler | Inhaler that delivers [substance Y] to treat [condition 2] | [Substance Y] to treat [condition 2], whereas inhaler is only a delivery tool | Inhaler as a delivery tool | Drug |
| 3. Surgical mesh with antibiotic coating | Antibiotic in coating | Mesh | Implant intended to treat [condition 3] | Implant | Antibiotic acts as an ancillary function | Device |
| 4. Wound dressing containing antimicrobial agent | Anti-microbial agent | Wound dressing | Dressing is intended to absorb exudates and cover a wound | Wound covering | Antimicrobial acts as an ancillary function | Device |

***Confirm the classification with the regulatory agency***

Once the healthcare product classification for a combination product has been identified, the developer should confirm the classification with the relevant regulatory agency (or agencies). This should be done at the start of the product development lifecycle (drugs and medical devices) as this determination will impact the regulatory pathway required and the studies needed to support product approval.

***Figure 1.2-1: Decision tree for classifying combination products***




[i] Definitions based on US regulations. Wording used by different jurisdictions (i.e., Canada, US and EU) may vary, but the general principles remain the same.

[ii] Other types of combination products are listed in 21 CFR 3.2(e).[7]

## References


[1] United States Code. (2011). Title 21, Section 321, *Definitions; generally*. Subsection (g)(1). Retrieved August, 15, 2012, from http://www.gpo.gov/fdsys/pkg/USCODE-2011-title21/html/USCODE-2011-title21-chap9-subchapII-sec321.htm.

[2] United States Code. (2011). Title 42, Section 262, *Regulations of biological products*. Retrieved August 15, 2012, from http://www.gpo.gov/fdsys/pkg/USCODE-2011-title42/html/USCODE-2011-title42-chap6A-subchapII.htm.

[3] United States Code. (2011). Title 21, Section 321, *Definitions; generally*. Subsection (h). Retrieved August 15, 2012, from http://www.gpo.gov/fdsys/pkg/USCODE-2011-title21/html/USCODE-2011-title21-chap9-subchapII-sec321.htm.

[4] U.S. Food and Drug Administration. Combination product definition. Retrieved September 21, 2012, from http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm118332.htm.

[5] Tobin, J.J. & Walsh, G. (2008). Chapter 1. The aims and structure of regulations. Pharmaceuticals, diagnostics, medical devices. Weinheim: Wiley-VCH Verlag GmbH & Co. KGaA.

[6] U.S. Food and Drug Administration (2011, December). Examples of combination product approvals. Retrieved September 21, 2012, from http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101598.htm.

[7] United States Code. (2012). Title 21, Section 3.2(e). *Combination products*. Retrieved September 21, 2012, from http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=3.2.

## 1.3 Step 2: Identify your healthcare claim and product label

A claim or an indication of a healthcare product is a simple and concise statement of the condition(s) under which a drug, biologic or medical device will be used. It normally has the following format:

> **[Product X] is to diagnosis, cure, mitigate, treat or prevent a certain disease or condition.**

Although a simple statement, it is, in fact, the *essence* of all the facts and scientific data collected throughout the many years spent in the product development.[1]

### 1.3.1 Your data and the healthcare product label

How are the collected data used to support this statement?

For most healthcare products,[i] the **scientific data** are compiled in a specific format and submitted in a licence application[ii] for regulatory clearance or approval. The regulatory body then reviews the application and may raise questions for the applicant to address or clarify.

The product label that is cleared or approved typically includes the company details and product information (e.g., a product description) as well as information on the uses for which the healthcare product has been shown to be effective, any associated risks and how to use the product. For example, labelling for a prescription drug in the US represents a summary of all the non-clinical and clinical studies conducted over the period of years from drug discovery through product development to approval by the U.S. Food and Drug Administration (FDA). The essential prescribing information for a prescription drug for use in humans is provided in the package insert, which states the usefulness and the risks associated with the product to ensure safe and effective use. All marketing activities must be consistent with the claim and the information presented on this label.[1,2]

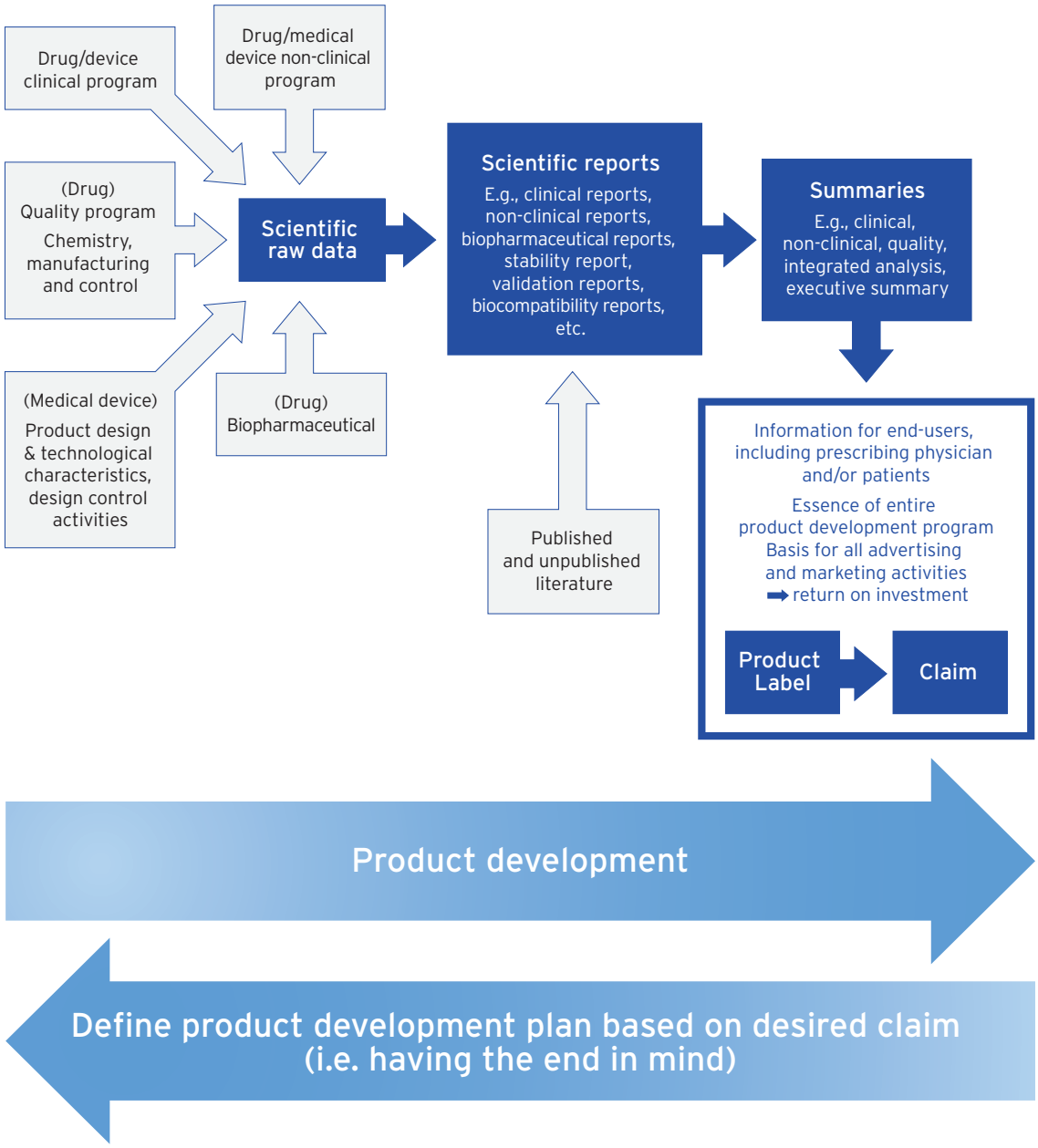
At the end of the review, if the agency concludes that the data supplied in the application substantiates the proposed claim from the standpoints of safety, efficacy (or effectiveness) and quality, then an approval or clearance is issued. A regulatory approval or clearance is for the ***combination*** of the product and its label (including product claim).

### 1.3.2 Keep the end product in mind

To have a successful and effective healthcare product development program, it is critical for a developer to identify the desired end product (i.e., what the intended claim and product label will say) right from the beginning. This way, all information that will need to be collected during product development can be identified and properly procured.

To illustrate this point, Figure 1.3-1 shows how the information collected during product development is organized and presented in a licence application.

***Figure 1.3-1: From raw data to product label (including product claim)***




1. During the product development phase, scientific raw data are collected from clinical, non-clinical, biopharmaceutical and manufacturing or design control activities.
2. Raw data are then organized, analyzed and presented in various scientific reports, which may also be supported by any published and/or unpublished literature.
3. Scientific reports are further summarized into different types of clinical, non-clinical and quality summaries, or integrated analysis or executive summaries, as required by different types of licence applications.
4. Finally, summaries are condensed to the essential information on the drug, biologic or medical device and presented as the product label, which also includes the claim statement.

Since the product label is ultimately *the* document that is presented to the end-users and is the basis for advertising and marketing activities (i.e., the return on investment), careful attention and investment should be paid to it in order to allow it to drive the product development program.

***Did you know?***

Sometimes, the product claim is vital in determining how some healthcare products are regulated, which in turn dictates the level of scrutiny to which they may be subjected.

For example, in the US, a device such as software that analyzes MRI[iii] images is designated as a class II 510(k) product if it only measures the size or volume of anatomical structures. However, if the software detects abnormalities or provides diagnostic information, it would be considered a class III PMA (premarket approval) device.

A medical device developer may choose to "start small" and begin interacting with the FDA with a simpler 510(k) before moving to a more challenging PMA once a revenue stream is established.[3]

[i] In the US, some products (e.g., low-risk class I devices or 510(k) exempt devices, regulatory review is not required prior to the commercialization of the product.

[ii] Licence applications can be made for drugs, biologics or medical devices, such as a Canadian New Drug Submission (NDS), a US New Drug Application (NDA), an EU Marketing Authorization Application (MAA), a US Biological License Application (BLA), a US 510(k) application, a US premarket approval (PMA) or a Canadian medical device licence application.

[iii] MRI = magnetic resonance imaging

**References**


[1] Ansel, H.C., Popovich, N.C. & Allen, L.V. Jr. (1995). Chapter 2. New drug development and approval process. In *Pharmaceutical dosage forms and drug delivery systems* (6th ed.). Baltimore: A Waverly Company.

[2] Tobin, J.J. & Walsh, G. (2008). Chapter 12. Oversight and Vigilance. In *Medical product regulatory affairs. Pharmaceuticals, diagnostics, medical devices*. Weinheim: Wiley-VCH Verlag GmbH & Co. KGaA.

[3] Pisano, D.J. & Mantus, D.S. (Eds.). (2008). *FDA Regulatory Affairs: A Guide for Prescription Drugs, Medical Devices, and Biologics* (2nd ed.). New York, NY: Informa Healthcare.


## 1.4 Step 3: Determine your healthcare market

In order to introduce a new healthcare prouct or technology to a market, many important factors need to be considered and evaluated, including market size, pricing and reimbursement, medical practices and distribution activities. In addition to this, thorough knowledge of the regulatory requirements of the jurisdiction(s) is critical in order to have a successful and efficient product development program. These regulatory requirements should be identified upfront (i.e., early on in the development process) and reviewed periodically to ensure that any changes in the regulatory environment as well as any new scientific technologies are taken into account. This can then be incorporated into the development program so that the necessary scientific data support the licensing review process.

There have been significant improvements in the harmonization of international technical requirements through the work of the International Conference on Harmonisation (ICH), the International Medical Device Regulators Forum (IMDRF),* and standards-development bodies (e.g., ISO, IEC, ASTM). However, many jurisdiction-specific requirements still exist as regulatory systems were developed independently in different countries. It is well recognized that such differences pose a barrier to the introduction of new products in terms of time and money.[1]

### 1.4.1 Know your market

It is critical to know your market! The last thing any company would like to hear from the licensing review process is that additional information is required to demonstrate the quality, safety or efficacy/effectiveness of your healthcare product because the target country's requirements have not been addressed.

For example, a regulatory agency may not accept a clinical trial that was conducted in a "foreign" country that did not address the targeted country's requirements,[2] or it may find that the source material of a biological product was not appropriate because it was sourced from a country that causes concerns regarding transmissible spongiform encephalopathy (TSE) or Creutzfeldt-Jakob disease (vCJD),[3] or it may advise that the standard followed in the testing of a medical device has been withdrawn by the agency.[4] Such outcomes could have a huge impact on the product approval timelines and cause delays in any subsequent launch and marketing activities, which would bring revenue to the company.

### 1.4.2 What to know for different jurisdictions

When reviewing the regulatory requirements for different jurisdictions, make sure to find out the following:

- What are the harmonized technical guidance documents that can be followed?
- Are there any jurisdiction-specific requirements?
- Are there any product-specific or disease-specific guidance documents? If so, are they also applicable to other countries?
- Are there any programs that can facilitate product development and reduce time and cost to market?

### 1.4.3 Programs to facilitate healthcare product development

Other than verifying the data requirements to support licensing activities, check if there are any programs available that can facilitate the product development. Many jurisdictions offer programs to support sponsors in developing healthcare products that are targeted for life-threatening conditions that have unmet medical needs. Examples of these programs may include orphan drug designations; fast-track, priority or accelerated reviews; or scientific advice or protocol assistance. If eligible, companies should take advantage of these programs and work with the regulatory bodies to bring these products to market in a timely fashion. In addition, fee reductions and waivers are also available for businesses that qualify as small- and medium-sized enterprises (SMEs).[5]

### 1.4.4 Summary: Think globally, act locally

To support your product development program, identify and review regulatory requirements from international groups (e.g., ICH, IMDRF) as well as the jurisdiction-specific requirements related to your healthcare product.

* The documents that were previously developed by the Global Harmonization Task Force (GHTF) are now posted on the website of the International Medical Device Regulators Forum (IMDRF).

**References**

[1] Tobin, J.J. & Walsh, G. (2008). Chapter 2. Regulatory strategy. In *Medical product regulatory affairs. Pharmaceuticals, diagnostics, medical devices*. Weinheim: Wiley-VCH Verlag GmbH & Co. KGaA.

[2] U.S. Food and Drug Administration. (2001, March). Guidance for Industry - Acceptance of Foreign Clinical Studies. Retrieved September 26, 2012, from http://www.fda.gov/RegulatoryInformation/Guidances/ucm124932.htm.

[3] European Commission. (2011). Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev. 3). Retrieved September 26, 2012, from http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003700.pdf

[4] U.S. Food and Drug Administration. (2007, September 17). Frequently Asked Questions on Recognition of Consensus Standards. Retrieved September 26, 2012, from http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm074973.htm

[5] Tobin, J.J. & Walsh, G. (2008). Chapter 8. Variations in drug authorization process. In *Medical product regulatory affairs. Pharmaceuticals, diagnostics, medical devices*. Weinheim: Wiley-VCH Verlag GmbH & Co. KGaA.

## 1.5 Step 4: Develop your regulatory strategy

Once the product classification, claim and healthcare market(s) for a drug, biologic or medical device are identified, it is time to collect all relevant information associated with your product. Information on drug, biologic and medical device development can be easily obtained from websites (such as the MaRS one), professional organizations, books, journals and conferences, and, of course, formal academic training. Direction is readily available, ranging from legislation to regulations to guidance documents to the latest information on science, technology and approved therapies.

### 1.5.1 Customize strategy[1]

Gathering information is an important step in preparing a regulatory strategy document. The knowledge you compile on regulations, competing products, therapeutic markets or clinical practices must be filtered, interpreted, connected and adapted to your healthcare product and to your organization. Knowing the regulations and content of relevant guidance documents, the disease or conditions being investigated and the approved therapies and their basis of approvals provides the foundation for your regulatory strategy.

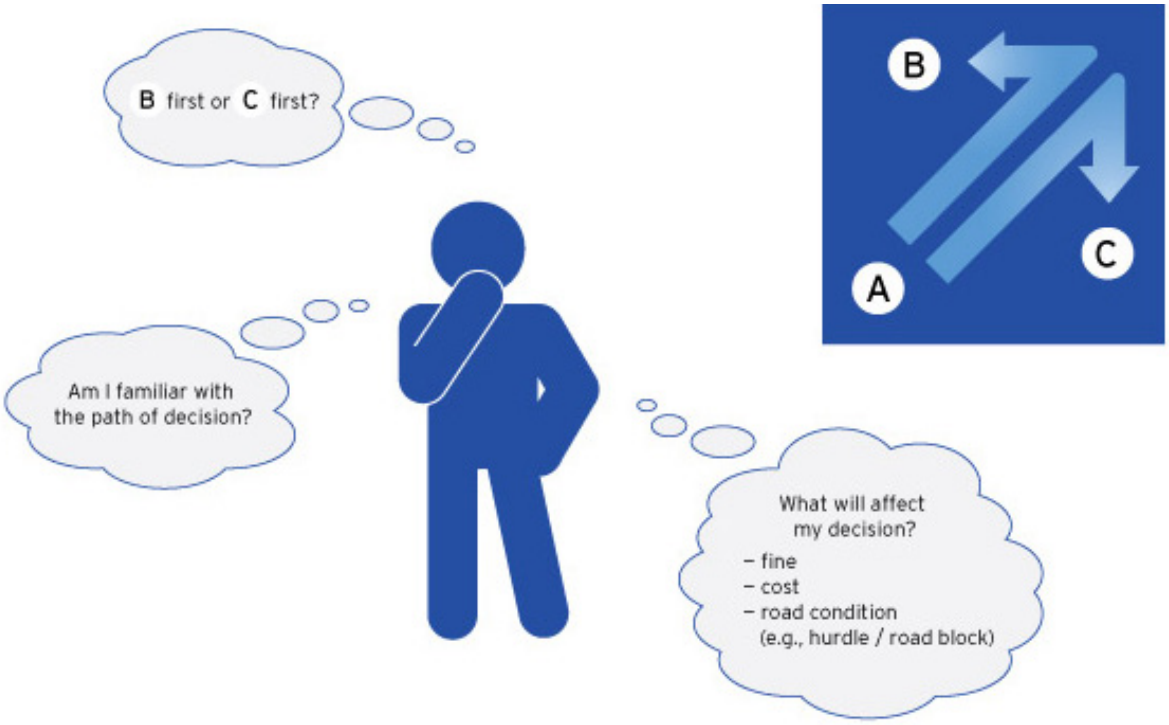
Additionally, to successfully navigate the complex regulatory system, recognize and respect factors such as development timelines, budgets, resources and available expertise.

**A well-planned regulatory strategy document should be balanced, realistic and achievable to support the organization's mission and vision.** The document should not only outline which path to take, but also include the rationale of why a specific path is selected or recommended. It should be user-friendly as it will need to be communicated to the team (e.g., company executives, investors, scientists, engineers, the project manager, and investigators) who provide the financing or carry out the development activities.

### 1.5.2 Analogy

Consider a road trip as an analogy, with your plan being to travel from point A to points B and C (but not necessarily in that order). You have options such as avoiding tolls or choosing highway driving. Depending on traffic and road conditions, it may be better to go to point C before point B. You would be wise to base these decisions on costs, time, traffic situations and the conditions at the final destinations.

***Figure 1.5-1: Strategic planning analogy: Mental roadmap***




Similarly, if you are planning to bring a product to countries X and Y, factors such as budget, timelines, regulatory requirements in different jurisdictions (e.g., device classification or registration requirements, especially if a clinical study is required) and market conditions (e.g., established distribution channels, support of key opinion leaders, competitors) may affect your decision.

The same principles apply to a product that can be developed for multiple indications. A device classification may change due to any risk associated with different intended uses. For example, in the US, a human chronic gonadotropin (HCG) test system used for the detection of early pregnancy is categorized as class II, but it changes to class III if the product is intended to aid in the diagnosis, prognosis, management or treatment of tumours or carcinomas.[2] And a medicinal product may be targeted for a general or an orphan population, which can lead to different regulatory pathways.

All these options should be reviewed against the organization's circumstances before finalizing the strategy. A company may wish to start with a simpler pathway, e.g., a 510(k), and gain regulatory experience prior to pursuing a more challenging but more desired indication (e.g., a premarket approval [PMA]).

Lastly, make sure to periodically review and update the regulatory strategy document to address any changes in regulations, markets, and study results that arise from product development.

### 1.5.3 Key elements of a regulatory strategy document

A strategy document is a concise summary and analysis of data collected. The key elements include the following:

- Date and version number
- Product/project code and product name
- Product information (e.g., background information, product type, product design, marketing history)
- Proposed claim or indication
- Identification of different submission phases (e.g., pre-submission meeting, clinical trial applications, other types of applications [such as an orphan drug designation], licensing applications, post-marketing requirements) and their corresponding submission types and agency review timeframes.
- Specific requirements to develop the healthcare product and support each of the submission phases, including the data requirements to support the safety, efficacy/effectiveness and quality of your healthcare product and its intended use, which may include links to relevant guidance documents and standards
- Summary
- Conclusion, options or recommendations (e.g., if multiple pathways are identified, explain the pros and cons of each so that management can make an informed decision).

**References**

[1] Manuts, D.S. (2008). Chapter 11. The practice of regulatory affairs. In Pisano, D.J. & Mantus, D.S. (Eds.), *FDA regulatory affairs: A guide for prescription drugs, medical devices, and biologics* (2nd ed., pp.109-23). New York: Informa Healthcare.

[2] United States Code. (2012, April 1). Title 21, Section 862.1155, *Human chorionic gonadotropin (HCG) test system*. Retrieved August 16, 2012, from http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=862.1155.

## 1.6 Step 5: Establish your healthcare product development plan

Before placing a drug, biologic or medical device on the market, a multi-phase procedure must be followed.

A typical drug or biologics product development lifecycle begins with a number of non-clinical studies, which are normally followed by three phases of clinical trials prior to applying for licensing approval. The U.S. Food and Drug Administration (FDA) offers an excellent graphical representation of a typical drug development process, entitled, "*The New Drug Development Process: Steps from Test Tube to New Drug Application Review.*"[1]

The product development pathway for a medical device is similar; however, the non-clinical and clinical programs are often less extensive than those of drugs and biologics, as these products are not intended to elicit a biological response (i.e., a chemical or metabolic action).[2] The FDA offers an excellent graphical presentation of a typical medical device development process. Entitled "Figure 2," it depicts "the medical device development pathway from discovery and ideation to product launch and post market monitoring" and notes that "the

regulatory process affects a significant portion of the device development pathway and should accommodate the iterative, cyclical nature of device design and development."[3]

Once a healthcare product has reached regulatory approval, a company may also conduct post-marketing studies (i.e., Phase IV studies), such as market surveillance studies and/or post-approval studies, if desired by the company or requested by the regulatory agency.

### 1.6.1 Product development plan

Generally speaking, different healthcare products will follow a similar product development approach; however, the activities and requirements, as well as necessary time, costs and resources can vary considerably depending on the type and complexity of each product. This is particularly true for medical devices if comparing the submission requirements for a lower-risk device (e.g., US 510(k) or Canadian class II medical device licence application) versus a higher-risk device (e.g., US PMA [premarket approval] or Canadian class IV medical device licence application).

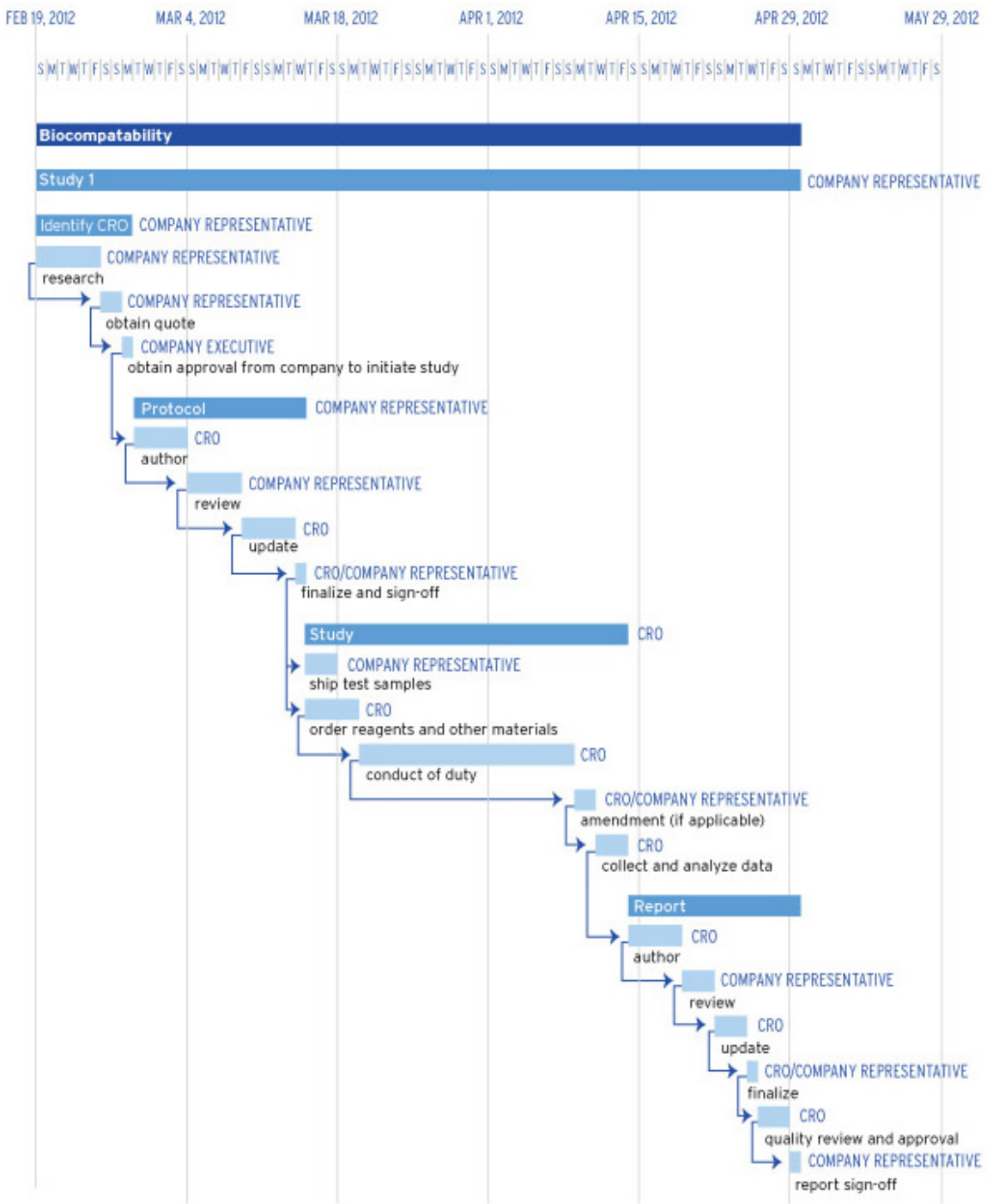
When establishing a product development plan, any design activities, studies required to demonstrate product quality, safety and efficacy/effectiveness, and other needs (e.g., meeting with the agency, orphan drug designation application) as identified in the regulatory strategy document should be carefully mapped to each phase of the development lifecycle.

Once all the tasks are identified, the responsibilities for the completion of each task should be clearly defined, i.e., "who" does "what" and by "when" and for "how much." **A development plan should be realistic and achievable**.

If a company is working with third parties (e.g., contract manufacturing organizations or contract research organizations), to complete each milestone, a dedicated individual should be designated as the contact person in order to identify, qualify and follow up on information such as protocol development, the conduct of the study, the generation of the study report and any amendments required during different phases of the tasks. Each major task (e.g., the conduct of a biocompatibility study) should be broken down into subtasks (e.g., protocol development, study conduct, report generation) to allow the creation of a realistic plan. Each subtask should then be further divided with regard to the authoring, review, updating, finalization and sign-off for each document.

Figure 1.6-1 is a simplified example of the tasks and subtasks required for conducting a biocompatibility study that forms part of the development plan.

*Figure 1.6-1: Example: Project plan for biocompatibility study by a third party (Gantt Chart Format)*



Such a development plan should be established collaboratively with input from different functional groups, which generally include marketing, manufacturing, quality, non-clinical, data management, clinical, biostatistics, medical, research and development, legal and regulatory. Key milestones, critical paths and periodic reviews for "go and no-go" decisions should also be included in this plan. Revisit and update the plan periodically to monitor the progress of the product development, and ensure that management reviews and approves this document.

***Did you know?***

Gantt charts are commonly used for projects as they display the tasks, schedule, progress, responsibilities and milestones in one visual representation. A Gantt chart also allows you to spot any possible problems during your project timeline (by showing dependencies between tasks), which in turns allows you to correct the problem (e.g., by allocating needed resources) before it occurs. More information, as well as chart templates, can be found at http://www.ganttchart.com.

**References**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[3] U.S. Food and Drug Administration. (2011, February). Medical Device Innovation Initiative White Paper. Retrieved August 15, 2012, from http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHInnovation/ucm242067.htm.


## 1.7 Step 6: Execute your healthcare product development plan

After your healthcare product development plan is established and approved by senior management, it is ready for execution. By this stage, specific regulatory requirements should have been identified in the regulatory strategy document. Such requirements may concern quality, safety and efficacy, or may be specific to a particular product or disease. Subject-matter experts who possess knowledge of the investigational product are responsible for carrying out the corresponding manufacturing, non-clinical and clinical programs, including any coordination of activities with third parties.

Many factors, including **regulatory requirements, product characteristics, the proposed claim and/or product label and the study duration** should be incorporated into the study design so that appropriate data can be generated to support product approval or clearance.

### 1.7.1 Execution of manufacturing, non-clinical and clinical programs

The execution of each manufacturing, non-clinical or clinical program should be in accordance with applicable regional Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) to ensure the integrity of the data being collected. Although the details of the development plan vary from product to product, the general activities will include the following:

- Identification of requirements for each manufacturing, quality, non-clinical or clinical program
- Information gathering
- Study design (e.g., study plan or protocol, statistical analysis plan)
- Implementation of the study according to the plan and recording of changes to the plan (e.g., notes to file, deviations, protocol amendments)
- Study completion
- Data analysis
- Report generation

Product development plan for drugs and biologics as well as for medical devices are presented below.

***Drugs and biologics***

*Manufacturing program*
Manufacturing programs are carried out to ensure and demonstrate the quality of a product and to establish controls for both drug substance(s) and drug product(s). Information on the following is normally required in support of product registration:[1]

- Manufacturing activities (i.e., who does what and how), so as to safeguard the consistent production of quality drug substance(s) and drug product(s). This information should cover areas such as the identification of in-process control steps, critical processes and parameters; contamination minimization; and validation activities. Each facility involved (e.g., fabrication, testing, packaging, storage) should comply with regional Good Manufacturing Practice (GMP) requirements
- Product characterization and formulation development
- Control activities for drug substance(s), drug product(s) and excipients, including details for defining the appropriate release specifications, identifying related substances or impurities and establishing validated analytical procedures
- Reference standards
- Container closure systems, which are appropriate to protect the drug substance and drug product from environmental conditions involving factors such as humidity, light, temperature and shipping. Materials used in packaging should be compatible with the product and should not interact with the drug substance and drug product or leach materials into the product
- The stability program, which establishes the shelf-life, storage conditions and any in-use shelf-life for the drug substance and drug product

*Non-clinical program*[2]
In a non-clinical program, safety and preliminary efficacy are obtained to demonstrate product safety. These studies may include:

- Pharmacology
- Toxicological kinetic and pharmacokinetics
- Pharmaceutical safety
- Toxicity
- Genotoxicity
- Carcinogenicity[i]
- Reproductive toxicity
- Immunotoxicity
- Photosafety
- Any other studies specific to your product

*Clinical program*
Information on clinical programs **for drug and biologics as well as medical devices** is provided in a separate article. For more details, please see Chapter 1.8 Step 7: Execute your clinical plan.

***Medical devices***
Manufacturers should establish and maintain product development plans that describe the design and development activities and that define the responsibilities for the completion of the design (i.e., what must be done and by whom). Although the activities can vary considerably depending on the type and complexity of the medical device being tested, one of the general approaches is to follow the design controls requirements. The design control elements of ISO 13485 and of Title 21, Section 820.30 of the US Code of Federal Regulations (CFR) are quite similar and are presented below:[3,4,5]

| **ISO 13485**<br>**7.3 Design and development**[ii] | **21 CFR**<br>**820.30 Design Controls** |
|---|---|
| 7.3.1 Design and development planning | b) Design and development planning |
| 7.3.2 Design and development inputs | c) Design input |
| 7.3.3 Design and development outputs | d) Design output |
| 7.3.4 Design and development review | e) Design review |
| 7.3.5 Design and development verification | f) Design verification |
| 7.3.6 Design and development validation | g) Design validation |
| 7.3.7 Control of design and development changes | h) Design transfer |
| | i) Design changes |
| | j) Design history file |

For more information, please see the article Medical device regulations, classification and submissions.

[i] This may not be required if the drug or biologic is intended for short-term use.

[ii] The requirements for design transfer and design history files in the US Code of Federal Regulations, Title 21, 820.30 are addressed under ISO 13485 in sections 4.2.4 Records and 7.3.1 Design & development.

**References**

[1] International Conference on Harmonisation. (2002, September 12.) ICH M4Q(R1). *The Common Technical Document For The Registration Of Pharmaceuticals For Human Use: Quality – M4Q(R1): Quality Overall Summary Of Module 2 Module 3: Quality*. Retrieved August 16, 2012, from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R1_Quality/M4Q__R1_.pdf.

[2] International Conference on Harmonisation. *Safety guidelines*. Retrieved August 16, 2012, from http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html.

[3] United States Code. (2012, April 1.) Title 21, Section 820.30, *Design Controls*. Retrieved August 16, 2012, from http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=820.30.

[4] ISO 13485:2003. Medical devices – Quality management systems – Requirements for regulatory purposes.

[5] Tobin, J.J. & Walsh, G. (2008). Chapter 9. Medical devices. In *Medical product regulatory affairs. Pharmaceuticals, diagnostics, medical devices*. Weinheim: Wiley-VCH Verlag GmbH & Co. KGaA.

## 1.8 Step 7: Execute your clinical plan

For a healthcare product that requires a clinical trial (or trials) to support product licensing or regulatory clearance,[i] the execution of the clinical plan is probably the most critical stage in the development process. The results gathered on safety and efficacy/effectiveness will ultimately determine whether a successful licensing/clearance application can be made. If the application is successful, this will determine the final claim that can be listed on the product label. This in turn drives the marketing and advertising activities and produces the return on investment.[1]

**The purpose of the clinical trial program is to collect *objective evidence* that the product is safe and effective/efficacious in human use under a specific condition (i.e., per the claim) to the extent that the *risk-benefit relationship is acceptable.***[2]

The extent of clinical information required for a drug, biologic, or medical device may vary; however, the general principles outlined below apply to all product types.

### 1.8.1 Before initiating the clinical trial

Certain activities are required before a clinical trial can be initiated. These include:

- Collecting the results from non-clinical studies
- Finalizing the product design or formulation
- Establishing the product manufacturing process and related quality activities
- Designing the clinical trial and identifying the countries for testing
- Meeting with the regulatory agency as need be
- Submitting clinical trial applications to the ethical review board(s) and/or regulatory agencies[i]

***Non-clinical studies*[3]**

Non-clinical studies are used to demonstrate that the risks to human subjects from the proposed clinical trial are outweighed by the anticipated benefits and that there is reason to believe that the product as proposed for use will be effective. These studies should be conducted using Good Laboratory Practice (GLP) and may include toxicology, pharmacology and pharmacokinetics for drugs and biologics, and bench (non-clinical), animal and biocompatibility studies for medical devices.

***Investigational products***[3]
Any product that is to be tested in a clinical setting should be manufactured under Good Manufacturing Practice (GMP) conditions or recognized standards (e.g., for sterilization). Extensive investigations should take place to establish product quality. For drugs and biologics, these may include collecting information on the composition, chemistry, manufacture, control and stability of the drug substance and drug product. For medical devices, these may include gathering data on the methods, facilities and controls used for the manufacturing, processing, packaging, storage and installation of the product.

It is critical to ensure that product tested in clinical trials is the version that is "finalized" (e.g., the formulation and dosage form of a drug or biologic should not change, nor should the prototype of a device). Any subsequent changes in the final product may affect the conclusion that can be drawn at the licensing stage to support the quality, safety and/or efficacy and may lead to the need for an additional study (e.g., a bridging study).

***Clinical trial design***[4]
Clinical trials should be designed, conducted and analyzed according to sound scientific principles to achieve their objectives. Each part should be defined in a written protocol before study starts. This study plan, or protocol, should describe the objective(s), design, methodology, inclusion/exclusion criteria, statistical considerations, safety/efficacy end point, and organization of the trial.

***Pre-submission meeting and clinical trial applications (CTAs)***[ii,5]
The purpose of the pre-submission meeting is to discuss and resolve any issues relating to the clinical trial and to obtain feedback or agreement from the regulatory agency on the clinical plan/protocol design as well as the statistical analysis plan prior to submitting the corresponding clinical trial applications (CTAs) to the regulatory agency(ies) for approval. This is to ensure that the plan developed (if successfully conducted) is able to support the proposed claim in the licensing or clearance application.

CTAs should be submitted to the relevant countries[iii] where the study will be conducted as well as to the appropriate institutional review boards (IRBs)[iv] for approvals.

***Executing the clinical trial***[6]
Once the clinical trial application is approved, the clinical study should be initiated according to the approved protocol. The clinical trial must be conducted in accordance with applicable Good Clinical Practice (GCP) standards. A clinical research organization (CRO) is normally involved in the conduct of study; however, the ultimate responsibility lies with the study sponsor.

The conduct of a clinical trial has many activities, which may be specific to your product. Some of the key principles are highlighted below:

- The investigator(s) responsible for the conduct of the clinical trial must have adequate education, training and experience *appropriate to the study*. They are responsible for managing the recruitment of study subjects, executing the study product(s), monitoring subjects and recording responses. They should also be involved in preparing the study protocol and report.
- A principal investigator must be identified for a multi-centre clinical trial.
- The study must be conducted in compliance with the study protocol. If an amendment is required and is deemed to be significant or substantial (e.g., it affects the safety of the trial subject or the quality of the investigational product), a CTA amendment must be submitted to relevant IRBs and/or regulatory agencies for approval.

- Procedures to obtain informed consent from subjects involved in the study must be properly followed according to applicable regulatory requirements.
- Proper record keeping of essential documentation is required, such as documenting any deviations and administration related to the clinical trial and any concomitant medication, adverse events, trial results and other information as identified in the case report forms.
- Safety reporting (e.g., spontaneous and/or periodic reports) must be submitted as per regulatory requirements.
- Study subjects, regulatory bodies and IRBs must be promptly notified of any premature termination or suspension of the clinical trial.
- The clinical trial should be properly monitored (for example, with regard to the overall conduct of trial, data handling and data verification).
- The final study report should be prepared according to applicable standards.

***Did you know?***

Many documents are associated with the conduct of a clinical trial. These may include but are not limited to:

- Protocol, amendment and case report forms
- Informed-consent form and other information given to study subjects
- Advertisement to recruit subjects
- Insurance statement (where required)
- Signed agreements (e.g., between the investigator/institution and the sponsor, or between the sponsor and the contract research organization [CRO])
- Regulatory and/or ethics board approvals
- Curriculum vitae (résumés) of investigators
- Investigational product labels
- Randomization scheme
- Clinical study reports

[i] Some products may not require clinical studies as part of the licensing application – e.g., low-risk class I medical devices and a majority of medical devices subject to 510(k) submission in the US. Make sure to check the regulations related to your product to confirm the clinical requirements.

[ii] Pre-submission meetings may cover pre-IND, pre-CTA, pre-IDE and pre-ITA.
IND = Investigational New Drug
CTA = Clinical trial application
IDE = Investigational Device Exemption
ITA = Investigational Testing Application

[iii] Under some circumstances, a clinical trial application may not need to be submitted to a regulatory agency for approval (e.g., a class I medical device in Canada or non-significant risk device in the US).

[iv] In Canada, this ethics board is referred to as an ethics review board; in the US, as an institutional review board (IRB); and in the EU, as an ethical committee.

**References**

[1] Ansel, H.C., Popovich, N.C. & Allen, L.V. Jr. (1995). Chapter 2. New drug development and approval process. **In** *Pharmaceutical dosage forms and drug delivery systems* **(6th ed.). Baltimore: A Waverly Company.**

[2] Tobin, J.J. & Walsh, G. (2008). Chapter 5. Clinical trial. In *Medical product regulatory affairs. Pharmaceuticals, diagnostics, medical devices*. Weinheim: Wiley-VCH Verlag GmbH & Co. KGaA.

[3] Tobin, J.J. & Walsh, G. (2008). Chapter 4. Non-clinical studies. In *Medical product regulatory affairs. Pharmaceuticals, diagnostics, medical devices*. Weinheim: Wiley-VCH Verlag GmbH & Co. KGaA.

[4] International Conference on Harmonisation. (1997, July). *E8: General considerations for clinical trials*. Retrieved September 18, 2012, from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/Step4/E8_Guideline.pdf.

[5] Grignolo, A. (2008). Meeting with the FDA. In Pisano, D.J. & Mantus, D.S. (Eds.), *FDA regulatory affairs: A guide for prescription drugs, medical devices, and biologics* (2nd ed., pp.109-23). New York: Informa Healthcare.

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## 1.9 Step 8: Collect your data for regulatory submission

When developing a healthcare product, you will collect scientific data from various sources, which may include chemistry, manufacturing and control (CMC) and design activities, as well as necessary biopharmaceutical, non-clinical and clinical studies. All these data should be organized, summarized and analyzed so that the licence or clearance application is complete, transparent and unambiguous and will facilitate regulatory review and approval or clearance of the healthcare product. Although the data will be obtained only after the execution of each study, it is at the planning stage for each study that the data presentation should be defined (i.e., what to collect, and how to present it). Note that planning ahead will help you achieve the results you want.[1]

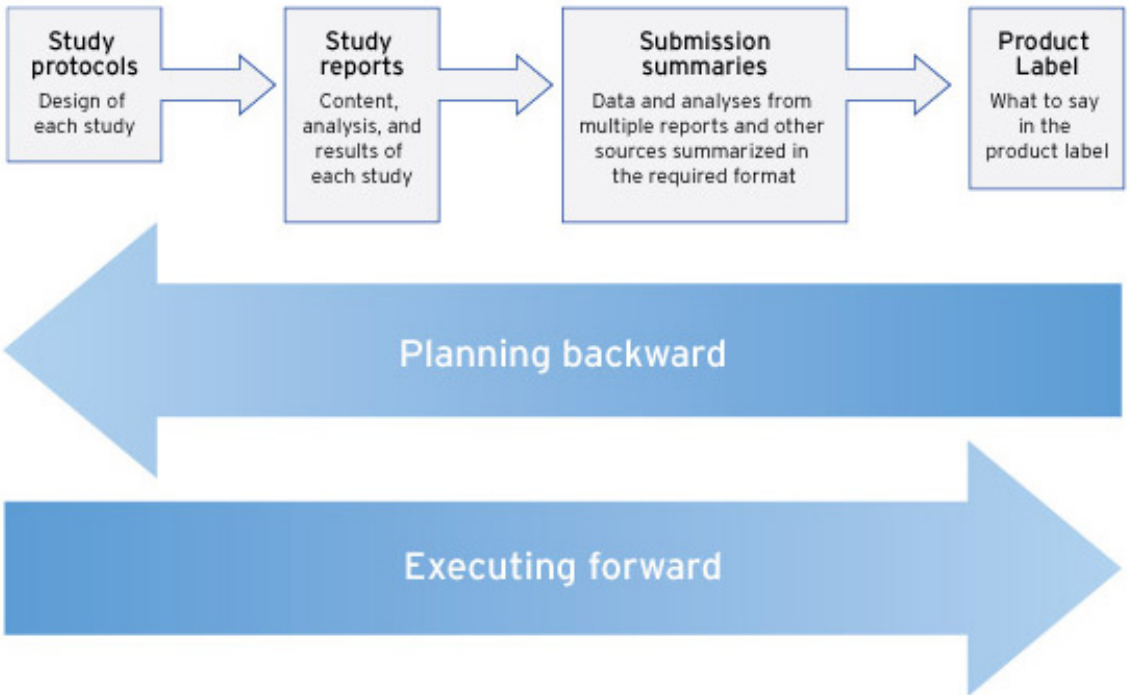
### 1.9.1 Healthcare product development: What data to collect? [1,2]

The type of data and information collected will be summarized in your product label. To ensure the *completeness* of the data being collected, plan for the content of the study reports and submission summaries* while you are at the stage of the study design or protocol planning. A careful review of applicable guidelines that discuss the format and content of submission documents is thus extremely important. This information can be gathered by reviewing documents published by the International Conference on Harmonisation (ICH), different regulatory agencies (such as Health Canada, the U.S. Food and Drug Administration [FDA] and the European Medicines Agency [EMA]), as well as other recognized standards.

Examples of these documents may include clinical study reports, clinical protocols/plans, Quality Overall Summaries, Non-Clinical Summaries, Clinical Summaries, and integrated summaries of safety and effectiveness. As well, many product-specific guidance documents (e.g., for anti-cancer medicinal products, antiviral drugs) are available that address different types or phases of product development.

Figure 1.9-1 illustrates the relationship between the different regulatory documents, including study protocols, study reports, submission summaries and the product label.

*Figure 1.9-1: Product development: Planning backward while executing forward*




## 1.9.2 Using templates

Information in a regulatory submission should be presented in a logical and consistent manner that will facilitate regulatory review. A high-quality and professional submission helps assure regulatory reviewers that the submission has been carefully prepared and that any concerns have been appropriately addressed.

One way to achieve a well-organized submission is through the use of templates. These templates should be created and they should:

- Be user-friendly (e.g., with suggested wordings or examples of how to present tables and figures)
- Provide references to the applicable guidance documents so that the author(s) can understand the basis for the data requirements and presentation format
- Include a built-in style for how each document should be presented (e.g., headings, headers, footers, pagination, table of contents)

The use of templates is particularly useful to help generate summaries (e.g., an integrated summary of safety) using data from multiple study reports.

## 1.9.3 Conclusion

The process of establishing the specific content and format of each regulatory document included in a clearance or licensing application can be lengthy and difficult. Nevertheless, this process allows the developer to ensure the completeness of the data being collected and it facilitates the preparation of the regulatory submission. "Doing it right" at the beginning also helps expedite the regulatory review and approval process.

* Examples of regulatory summaries include the executive summary for medical devices, and the Quality Overall Summary, Non-Clinical Summary and Clinical Summary for drugs or biologics.

**References**

[1] McPhatter, K., Walch, K., Miller L. & Kneifel, A. (1999). Chapter 27. Assembling and filing the NDA/BLA. In S.E. Linberg (Ed.) *Expediting drug and biologics development: A strategic approach*. (n.d.) Watham, MA: PAREXEL International.

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## 1.10 Step 9: Collate your regulatory submission

In the development of a healthcare product, the regulatory submission is intended to "tell a story" about your product[1]. Depending on your product and the submission type, it may include information on the following:

- The raw materials or active substance used
- The formulation of the drug or biologic, or the design of the medical device
- The manufacturing process and packaging
- The results of non-clinical tests (e.g., bench, *in vitro* or *in vivo* animal studies) and/or clinical trials
- How the product behaves for its intended use under the appropriate conditions of use

These data should support the product's label, which is designed for use by medical professionals as well as the general public. The product label forms the basis for marketing and advertising activities.

A regulatory submission is thus a complex document and it contains input from multiple technical areas. Often, data that supports the quality, safety and efficacy/effectiveness of an innovative product are collected throughout many years of product development. Thorough planning and management of these data are required to present them logically in terms of continuity and connectivity while at the same time **speaking in a single voice** about your product.[2]

### 1.10.1 Typical stages of the regulatory submission process

The following outlines the typical stages of the regulatory submission process:

1. **Pre-submission meeting**
   Although not mandatory, a pre-submission meeting is a key step in achieving a successful submission. To arrange a meeting, submit a meeting request and a pre-submission package to the relevant regulatory bodies. For more information on pre-submission meetings, please see Chapter 2.2 Pre-submission regulatory meetings: Preparation.

2. **Submission planning and compilation[3]**
   Assembling a regulatory submission is a lengthy process. Although such a document will be submitted at the end of the product development process, the compilation of the submission should begin and continue throughout the product development program. Consider implementing the following as part of your compilation procedures:
   - Develop a detailed regulatory submission plan identifying the individual tasks (e.g., generation of study reports, submission summaries), timelines and the individuals responsible for authoring, reviewing and approving the various sections of the application.
   - Have each section authored, reviewed and approved by the relevant technical functions – i.e., quality, medical, non-clinical, clinical, manufacturing, engineering and regulatory. Ensure discussions on the product quality, safety and efficacy/effectiveness focus on supporting the proposed indication.

- Generate submission sections in accordance with regulatory requirements, and tie different sections together through the use of summaries and navigational features (e.g., tables of content, cross-referencing statements).
- Ensure the completeness of the submission content by using the regulatory submission's table of content as your checklist.

For more information, please see Chapter 3.3 Regulatory submissions: A primer.

3. **Publication**[3]
   Ensure all regulatory submissions adhere to the stipulated format, and publish the required number of submission copies. Review all information carefully to ensure nothing is missing or misplaced. All specifications for a regulatory submission (particularly for an electronic submission) should be met to ensure it is acceptable to the regulatory agency.

4. **Submission of documentation**

5. **Post-submission activities**[4]
   After the submission is filed, be prepared to respond to the agency's questions or requests for additional information (this may occur at the submission screening and/or at review stages). Ensure that your responses are submitted within the timeframe indicated to avoid the risk of your submission being withdrawn. Pre-approval inspections (re: Good Manufacturing Practices [GMP] or biomonitoring, for example) for some products (such as drugs, biologics or premarket-approval [PMA] devices) may also take place prior to an approval being issued.

6. **Product approval/clearance**
   If the review is satisfactory, the regulatory authorities will grant a marketing authorization or clearance to enable commercial sales to commence.

**References**


[1] U.S. Food and Drug Administration. (2012, May 18). *New Drug Application*. Retrieved September 18,2012, from http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm

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## 1.11 Step 10: Ensure post-marketing compliance

Once you have received regulatory clearance or approval for your healthcare product, what's next? Beyond marketing, advertising, pricing and reimbursement, distribution, and other activities to start selling your healthcare product, it is critical to meet the manufacturer's regulatory obligations to ensure ongoing compliance. Some obligations exist for administrative purposes; others are specifically designed for continual monitoring of the safety, quality and efficacy/effectiveness of your product in the marketplace throughout the product lifecycle.

### 1.11.1 Post-marketing obligations

There are many different post-marketing obligations for the manufacturer of a healthcare product. The ones discussed below are **not** an exhaustive list, as requirements are specific to different products in different jurisdictions. Manufacturers should identify these requirements at the point of market approval or clearance in the relevant jurisdiction(s).

- **Post-market surveillance, post-approval studies or post-marketing commitments:** These are studies and/or clinical trials which, at the time the licence is issued, the manufacturer commits to conduct. The intention of these studies is to gather additional information about a product's safety, efficacy or optimal use. The product label may be amended depending on the results collected from these studies.[1]
- **Safety reporting for drugs, biologics and medical devices:** Reports on reportable adverse events (e.g., death, life-threatening events) must be submitted to the appropriate regulatory agencies, in compliance with the mandatory timeline, for the ongoing evaluation of product safety. Sometimes the new safety information collected may lead to changes in product labelling or even the withdrawal of the product from the market. Other reporting requirements may include the submission of periodic reports on safety (e.g., Periodic Safety Update Reports for drugs & biologics).[2,3]
- **Establishment registration and product listing:** Depending on the jurisdiction issuing the approval, local and foreign-based companies ("establishments") that are involved in the manufacturing, packaging, labelling and testing of the drug, drug components or medical devices may be required to register their names and addresses with the local regulatory agency. Registrants may also be required to list their products.[4]
- **Licensing requirements — environmental protection:** Sites that handle chemicals or engage in operations that are potentially dangerous to the environment must register with the relevant environmental protection agencies. These sites are subject to inspection to ensure that adequate controls, containment measures and emergency response procedures are in place to prevent damage to the environment.[5]
- **Inspections:** On-site inspections will be carried out by the regulatory authorities or third parties to ensure continued compliance with the relevant Good Manufacturing Practice (GMP) or ISO 13485 standards. These may be scheduled or unannounced. Manufacturers must ensure continuing compliance with appropriate quality standards.

  For manufacturers who have products registered in foreign countries, note that the frequency of inspections by foreign regulatory authorities has been greatly reduced by the establishment of mutual recognition agreements wherein the parties accept the validity of their respective GMP inspection regimes.[5]
- **Product licence renewal**: Different products may be subject to a licence renewal process and this varies across jurisdictions. For instance, in Canada, a manufacturer holding a class II, III or IV medical device licence is required to confirm annually their intention to renew their licence by submitting a renewal form to Health Canada.[5] In the EU, a marketing authorization for a medicinal product is valid for five years and it can be renewed by submitting a renewal application. Once renewed, the EU marketing authorization will be valid for an unlimited period, unless the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal period.[6]

- **Changes to approved products**: Changes to approved products should be evaluated to assess their impact on product quality, safety and efficacy/effectiveness. These changes should be documented properly (e.g., through the company's change-control process). Depending on the degree of impact, some changes may simply need the company to document the change being evaluated, some can be initiated after notifying the appropriate regulatory agencies, and some will require regulatory approval prior to implementation. Different mechanisms exist in different jurisdictions for reporting these changes and these can vary from an annual report to an amendment/variation application to a new licence application.[7] Manufacturers should consult the guidance documents specific to the jurisdiction in order to follow the proper compliance procedures.

***Did you know?***

In the US, establishment registration for a drug or medical device is an administrative exercise resulting in the issuance of an Establishment Registration Number and a product listing code. However, such registration means that the site is included in the FDA database and that your establishment is subject to FDA inspection.[8]

## References


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# Chapter 2: **Interacting with regulatory agencies**

During the development of an innovative healthcare product, it is important not only to seek input from the regulatory agency (or agencies) on your product development program, but also to discuss and resolve any critical issues that may arise. Such early and effective communication with your regulatory agency is essential to achieve a complete and robust submission that meets the agency's expectation. Ultimately, this streamlines the review process. Chapter 2 discusses the best practices for communicating with your regulatory agency and how to prepare for and make the most of a pre-submission meeting.

## 2.1 Communicating with your regulatory agency

During the development of an innovative healthcare product, early and effective communication with your regulatory agency is essential to achieve a complete and robust regulatory submission and streamline the review process. Generally, a company should consider interacting with the agency at critical stages of product development to exchange ideas on program status and planning (e.g., before the initiation of a clinical trial or the submission of a marketing application*).[1]

Omissions of significant data in a regulatory submission may lead to the agency's refusal to file the application, additional data being requested (i.e., not achieving first-cycle approval), the submission not being approved or cleared by regulatory agency or the application being voluntarily withdrawn by the company.[1]

### 2.1.1 A collaborative effort to streamline product development

Product development should be a collaborative effort on the part of both the healthcare industry and the regulatory agency. Although the primary responsibility for product development (especially its identification, design and execution) lies with the healthcare industry, it is important to communicate the development plan to the regulatory agency and discuss any specific issues early on in the development phase. Such interactions allow critical issues to be discussed and resolved, bringing clarity to the agency's expectations on submission requirements. Not facing these issues during the development phase may eventually lead to questions or the identification of deficiencies during the regulatory review process. Both these situations can entail significant remedial work and increase your time to market.[1,2]

Through early and open communication, regulatory agencies may help to:

- **Clarify the regulatory pathway for product development.** This could include the classification of a medical device, the designation of a product type, the identification of eligibility for programs such as orphan drug designation or priority review, and so on.
- **Identify and interpret relevant acts, regulations, directives and other applicable statutes, guidance documents and recognized standards applicable and specific to your product.** This helps to clarify the regulatory expectations in support of the regulatory application for your product.
- **Provide scientific and regulatory advice during product development that results in a more efficient and robust development program.** This can ensure that the necessary types of studies and information are included in the regulatory submission, which helps to prevent deficiencies that could cause the agency to refuse to file the application or cause additional review cycles.

- **Provide advice regarding the study design that may affect the regulatory decision about submission approval.** This advice may include helping you define adequate evidence of effectiveness (e.g., end points, study design, patient populations), safety (e.g., sample size, dose response, assessment of drug-drug interactions, demographic differences) and quality (e.g., manufacturing procedures).
- **Discuss with the applicant any deficiencies that may occur at critical points of product development.** This could include identifying potential filing and review issues that could be addressed before the application is submitted for review.[3]

Communications may occur via informal or formal means. Informal means may include telephone calls or e-mails for clarification of regulation requirements. Formal means may include pre-submission meetings.

***Did you know?***

In the US, the Food and Drug Administration (FDA) has instituted a number of activities to provide technical and regulatory assistance to small manufacturers with the aim to help them to comply with FDA requirements. These activities include:

- Holding meetings to hear the views and perspectives of small businesses
- Conducting educational workshops (e.g., FDA Small Business Regulatory Education for Industry [REdI])
- Developing informational materials (e.g., *FDA/CDER Small Business Chronicles*)
- Providing channels through which small businesses can acquire information from the FDA[3]

* *Types of clinical trial applications may include:*
- IND = Investigational New Drug
- CTA = Clinical trial application
- IDE = Investigational Device Exemption

*Types of marketing applications may include:*
- NDS = New Drug Submission
- NDA = New Drug Application
- BLA = Biologics License Application
- MAA = Marketing Authorization Application
- PMA = Premarket Approval

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[1] U.S. Food and Drug Administration. (2005, April). *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products.* Retrieved June 6, 2012, from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079748.pdf.

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## 2.2 Pre-submission regulatory meetings: Preparation

When developing a healthcare product, effective communication with your regulatory agency is critical. This holds especially true at key milestones, which may include (but are not limited to) pre-submission meetings for clinical trial and marketing applications* and end-of-phase 1 or end-of-phase 2 meetings. Pre-submission meetings provide both you and the agency a forum for sharing essential information about your healthcare product.[1]

Regulatory agencies from different jurisdictions have specific procedures or requirements to successfully prepare for a pre-submission meeting, and applicants should adhere to these.

Product approval is ultimately determined by the scientific data that demonstrate a positive benefit-risk ratio related to product safety, efficacy and quality for use in a specific indication. Nevertheless, appropriately preparing for milestone meetings with your regulatory agency, particularly around issues that need resolution, can mean the difference between a timely product approval and costly delays with multiple review cycles or even a refusal of the application.[2]

### 2.2.1 Characteristics of a pre-submission meeting

Typically, a pre-submission meeting should have the following characteristics. It should:[2]

- Establish clear objectives and a specific agenda, and be scientifically-based and data-driven. Identify what you aim to accomplish and develop a meeting agenda to facilitate the agency's answer or feedback to the questions that are critical to product development and submission approval.
- Focus on discussing the plans and status of product development, presenting scientific data and proposals, and facilitating reaching a consensus on key scientific and technical issues that have arisen during various stages of product development. The outcome of the meeting should be used to evaluate "go" or "no-go" decisions for the next phase of product development.
- Focus on scientific or medical issues that directly relate to the product under development or to regulatory requirements and guidance documents.

It is important to remember that a regulatory agency differs from a regulatory consultant. Keep questions focused and specific (e.g., "Is it acceptable to take this approach due to rationale xyz?") and not open-ended (e.g., "How should I develop this product?").

Various guidance documents are available that detail the meeting process as well as the format and content of different types of pre-submission meetings. Although factors such as jurisdiction, different review divisions (e.g., drug vs. medical devices), and the type of meeting may affect certain procedures, the following general principles apply.

### 2.2.2 Requesting a pre-submission meeting[2,3]

All meeting requests should be in writing. Ensure that you include adequate information for the agency to assess the potential utility of the meeting and to identify staff necessary to discuss the proposed agenda items. Ensure also that you follow the specific regulatory guidance related to the type of meeting that you are requesting.

For instance, in the US, a formal request to meet with concerning a drugs or a biologic should include:

- The product name and application number (if applicable)
- Product information (e.g., chemical name and structure)
- The proposed indication
- The type of meeting requested (type A, B or C)
- A brief statement of the purpose and objective of meeting
- A proposed agenda, and the estimated time needed for each agenda item and designated speakers.
- A list of specific questions grouped by discipline (the agency may grant or decline the meeting primarily on the basis of the detailed nature and specificity of the questions)
- A list of preliminary proposed attendees representing your company
- A list of agency staff or representatives of a particular discipline that you would like to have attend (if applicable).
- Suggested dates and times for the meeting
- Suggested meeting format (e.g., face-to-face, teleconference, videoconference)
- An approximation of what and when supporting documentation will be sent to the agency.

Once a meeting is scheduled (e.g., a formal meeting with the FDA, or a pre-CTA meeting with Health Canada for drug and biologics), adhere to the specified timelines, format and content when preparing and submitting the required meeting package. This package should provide information relevant to the discussion topics (e.g., a summary of non-clinical, clinical, and chemistry and manufacturing data) and enable the agency to prepare adequately for the meeting.[3,4]

### 2.2.3 Before the meeting[2]

In advance of the meeting, consider whether the following are applicable to your meeting and prepare accordingly:

- Appoint a team leader to coordinate the company's responses during the meeting.
- Identify the role of each member who will attend.
- Conduct a "dry run" to practice who will say what.
- Identify potential questions that the agency may raise and discuss how these questions will be addressed.
- If the agency has provided a "preliminary" response to questions submitted, review your approach of remaining issues so as to keep the focus on key items (e.g., where clarification is required or disagreement exists).

### 2.2.4 During the meeting[2]

During the meeting, strive to:

- Seek consensus and resolve all issues professionally and scientifically so that product development can proceed.
- Keep the meeting focused and run it according to the proposed agenda.
- At the end of meeting, ensure both parties have a clear understanding about any actions that need to be taken – and by whom.

### 2.2.5 After the meeting

After the meeting, remember the following:

- It is a good practice to submit your meeting minutes (official or not) to the agency.
- If issues are identified which need to be addressed, follow up on these promptly.

* *Types of clinical trial applications may include:*
- IND = Investigational New Drug
- CTA = Clinical trial application
- IDE = Investigational Device Exemption

*Types of marketing applications may include:*
- NDS = New Drug Submission
- NDA = New Drug Application
- BLA = Biologics License Application
- MAA = Marketing Authorization Application
- PMA = Premarket Approval

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# Chapter 3: **Regulatory documentation and submissions**

When preparing for eventual regulatory review, getting the documentation and the submissions right is critical. It can mean the difference between a successful, cost-effective review process or rounds of clarifications. Chapter 3, therefore, starts with the fundamentals of Good Documentation Practices (GDP). It outlines key principles in managing study protocols, reports, amendments and submission applications. It then reviews the different processes and requirements for drug and medical device submissions. For eligible products developed for use by a special population or by those with unmet medical needs, Chapter 3 also highlights the fast-track programs that regulatory authorities may offer.

## 3.1 Good Documentation Practices (GDP)

Documentation is one of the most valuable assets in the regulated healthcare industry. Information generated during the many years of healthcare product development must be properly documented so that correct, complete and consistent information can be provided to your regulatory agency in support of regulatory submissions and inspections.

As different individuals have their own ideas or methods for documenting information, simply tracking everything does not equate to implementing Good Documentation Practices (GDP). Without standardized documentation rules (e.g., the requirement of document review and approval, and criteria for presentation formats), documents generated may contain various different formats and content from which it is difficult to generate an integrated analysis and present it in a regulatory submission. **Inconsistency across documents can also lead to an inadequate level of data being recorded, inaccurate data being collected, or incorrect interpretations being produced.** GDP is therefore an *expected* practice in the regulated healthcare industry.[1-3]

### 3.1.1 Use of Good Documentation Practices is expected[1-3]

The use of GDP allows companies to comply with regulatory requirements such as Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP) or the applicable quality management system (e.g., ISO 13485, 21 CFR 820), or Good Clinical Practices (GCP) in Canada, the US and the EU. Documentation that is used in support of manufacturing, laboratory and clinical practices should adhere to GDP.

In addition to this regulatory expectation, it is essential to keep in mind that **any and all** records generated may be used by any member of the sponsoring company (i.e., the applicant) or their business partners, contract research organizations (CROs) and contract manufacturing organizations (CMOs) in support of development, testing and m anufacturing, as well as the conduct of laboratory, animal and clinical studies. End-users can also include potential investors, lawyers, patent reviewers, regulators (reviewers and inspectors), or the general public. Thus it is critical for sponsors to standardize their documentation activities (i.e., GDP) so that records will be consistent and clear.

Documentation that should follow GDP includes but is not limited to:

- Laboratory notebooks
- Logbooks
- Master batch records

- Specifications
- Product release certificates
- Analytical methods
- Protocols and reports (e.g., validation, sterilization, stability, laboratory, animal and clinical studies)
- Purchase orders
- Contracts
- Training records
- Medical-device history files and records

### 3.1.2 Key qualities of regulated documents[1]

What key qualities are needed in your records? Generate documents that are:

- **Concise:** Present information clearly so it can be easily understood with no room for misinterpretation. For example, the date format "05/06/12" can cause confusion. Use one that is unambiguous, such as "05 Jun 2012."
- **Legible:** Information should be readable and leave no room for error (e.g., hand-written data that are not legible may cloud data analysis or result in "missing data").
- **Accurate:** Documentation should be error-free – properly reviewed, verified and approved. Information should be recorded as an event happens and not after the fact, so as to avoid recording "what you remember" rather than "what actually happened."
- **Traceable:** Documentation should be traceable. Make it clear who logged the information, what it was, and when and why it was documented.[1]

***Do's and don'ts[1,2]***

Depending on the needs of your organization, GDP can include many different activities. Evaluate what applies for you. Some basic GDP "do's and don'ts" are listed below.

| Do's | Don'ts |
|---|---|
| • Use black or blue permanent, indelible ink.<br>• Make clear, complete and legible entries.<br>• Make an entry when an event happens (not later).<br>• Make corrections that are legible and traceable. E.g., when a correction is required, put a line through the error, make the correction next to the error, include an explanation (if it is not self-explanatory), and initial and date the correction.<br>• If it is not appropriate to fill in a space in a document (e.g., an empty page), enter "N/A," your initials and the date so that no further information can be added later.<br>• Follow established standard operating procedures (SOPs) – e.g., document review and approval processes, version control, and date and time formats, as well as record retention, change control, electronic signature (if applicable) and so on.<br>• Provide training to everyone in company. | • Do not use pencils or erasable ink.<br>• Do not use "write-out" or any masking devices.<br>• Do not make corrections that are not traceable (e.g., overwriting entries with no date, initial or explanation).<br>• Do not use "sticky" notes.<br>• Do not back-date or post-date.<br>• Do not use ditto marks.<br>• Do not use asterisks that may cause confusion (such as using the same asterisk for different footnotes).<br>• Do not transcribe data.<br>• Do not use unbound laboratory notebooks without page numbers (i.e., avoid any doubt concerning missing pages). |

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## 3.2 Study protocols, reports and amendments

In a regulated environment, regardless of the type of healthcare product development pursued (e.g., of a drug, biologic or medical device), studies need to be conducted to demonstrate the healthcare product's quality, safety and effectiveness/efficacy with respect to the proposed indication.

Although the exact data requirements may vary depending on the product design, the proposed indication and/or the targeted jurisdiction, studies that support submission applications must be carefully designed, conducted, analyzed and recorded in compliance with relevant regulatory requirements and good industry practices (e.g., Good Laboratory Practice [GLP], Good Manufacturing Practice [GMP], Good Clinical Practice [GCP], and Good Documentation Practices [GDP]).

### 3.2.1 Clinical studies and the regulatory submission

Studies to be included in regulatory submissions should follow a written protocol that outlines the purpose and details of how the study will be conducted and the justification for the approach taken. Record the study results and data analysis in a study report. These documents should be appropriately reviewed and approved by relevant personnel prior to finalization of the document. Any amendments introduced after the document sign-off should be properly evaluated, documented and approved.[1]

The types of studies to be included in a regulatory submission may include the following:

- Validation studies (e.g., process validation, sterilization validation)
- Stability studies
- Bench testing (e.g., mechanical, physical or chemical testing)
- Biocompatibility studies
- Non-clinical studies (e.g., acute toxicity, chronic toxicity, reproductive toxicity, genotoxicity, carcinogenicity)
- Pharmacokinetic and pharmacodynamic studies
- Biopharmaceutical studies (e.g., bioequivalence studies)
- Clinical studies (e.g., feasibility, safety or efficacy studies)

### 3.2.2 Study protocol and study report: Companion documents[2]

Consider developing the template of your study report while building the study protocol. *By having the end in mind,* you can plan and design the study (e.g., the duration, patient population, sample size, statistical analysis plan) so that specific data and results (e.g., the meaningful clinical end point) that answer particular questions (e.g., whether healthcare product A effectively prevents disease X) can be collected, anaylzed and reported. By clearly defining all of these elements in the protocol, the study can be properly conducted and the results will avoid censure related to bias or data manipulation. **The study protocol is crucial to establishing the foundation for the results and conclusions of individual trials—and ultimately, those reached in the licensing application.**

Should the study protocol or the finalized study report need to be changed, generate an amendment that includes:

- A description of the change
- The rationale to support the change
- An impact analysis (if relevant)
- Identification of the affected documents and their sections
- Signature(s) of the individual(s) who give approval
- Date of the approval of the change
- Date of when the change takes effect

In the case of a clinical study, if a study application has been approved under Investigational New Drug (IND), Investigational Device Exemption (IDE), Clinical Trial Application (CTA), or Investigational Testing Application (ITA), make sure to comply with local post-approval requirements. For instance, any significant amendment (i.e., changes that significantly affect the safety of the trial subjects, or quality of the investigational product) should be submitted to the corresponding ethics board(s) and regulatory agency(ies) for approval prior to its implementation.[3] The sponsor may also need to notify the agency for minor changes. Make sure to review all the submission requirements for amendments relating to the conduct of clinical trials in all relevant jurisdictions.

**Tips:** The use of protocol and report templates allows upfront research to be conducted and recorded in compliance with regulatory requirements and guidance documents. When compiling information, organize it into sections and subsections, with logical groupings of related data clearly identified through the use of headings.[1]

#### References


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## 3.3 Regulatory submissions: A primer

A regulatory submission for a healthcare product includes any documentation or information submitted to a regulatory agency for review, for notification or in response to a request for additional information related to a healthcare product. The format can be paper or electronic, or both. The amount of information involved and its required complexity can vary significantly. A licensing application for a drug or biological product may contain hundreds of paper volumes whereas a response to an agency's question for a clarification may involve a single page.[1,2]

Due to the enormous amount of information presented in a marketing application, agencies are encouraging applicants to submit applications electronically in required formats that will reduce the paper burden and facilitate their regulatory review.[1,2] In fact, filing an application in an electronic format is mandatory for some submission types. In the US, the FDA will only place a premarket submission of a medical device under review if it has an "eCopy" (i.e., a duplicate of the paper submission) that has been validated by the agency.[3] In Canada, all premarket review documents for class III and class IV medical device licence applications and licence amendment applications are expected to be submitted in both paper and electronic formats, and the applicant must structure the format of the electronic submission to meet the agency's specifications.[2,4] As the specifications vary and are subject to change, it is critical that you check format requirements before filing a submission.

### 3.3.1 Types of regulatory submissions

Types of regulatory submissions can include:

- Licensing applications for drug, biologics or devices
- Clinical trial applications
- Requests for orphan drug or fast-track designations
- Requests for protocol assistance
- Responses to agency questions that arise during the review; e.g. clarifaxes, deficiency letter, requests for additional information
- Post-approval studies or commitments
- Amendment/variation applications or notification submissions

### 3.3.2 Planning for and preparing your regulatory submission

Before preparing any regulatory submission, identify the relevant regulatory requirements so that you can ensure your submission will comply. Note that the requirements for drug and medical device submissions are quite different.

Consider the following:

- Who is the regulatory agency and what is the review division for my product?
- What are the regulatory requirements that govern my submission?
- What kind of information should be included? Is there a guidance document available that details the format and content requirements of the submission?
- Where do I send the submission?
- How many copies should I submit?

- Should I submit the submission in an electronic format? Is that mandatory?
- For hard-copy submissions, are there requirements regarding binding?
- For electronic submissions, what is the acceptable data format, file size and means for submission (e.g., CD-ROM, secure gateway)?

Develop a standard format or style guide for managing submissions. Submission templates should have built-in styles for headers and footers, headings, table and figure titles, and so forth. Such templates should also identify the paper size as well as the margins (both portrait and landscape) for printing and binding purposes. This is particularly important if you plan to generate global submissions, as the information can then be printed on both letter size and A4 paper and permit proper binding.

As the submission should facilitate the regulatory review, organize the information so that it is easy to read and properly sectioned. Have it support navigation so the reviewer can quickly find what they need. Where applicable, consider using these elements:

- Cover letter
- Table of contents
- Volume and page numbers
- Clear headings and subheadings
- Table and figure numbers, with accurate references to them from within the text
- Tabs that aid quick finding of the submission sections
- Reader-friendly font sizes, types and colours

Ensure that content is clearly legible and that submissions are properly bound using binders acceptable to the regulatory agency. Lastly, if any source document is in another language, make sure you provide an appropriate translation.

Generate electronic submissions in accordance with regulatory requirements.

Once you have prepared your regulatory submission, **examine it thoroughly.** It must be accurate and complete (e.g., no missing pages within a hard copy, no broken links within an electronic submission) before you submit it to the regulatory agency.

***Remember:***
Your submission should make it easy for the reviewer to understand the objective of your application and how your data contribute to it. As different regulatory reviewers have different backgrounds, experience and training and may be handling multiple submissions at once, it is useful to always provide a concise summary at the start to "set the stage" for the submission. Such information may highlight a very brief product description, the proposed indication, the intended patient population, the purpose of the submission (e.g., a modification to an existing device design) or any key information that could assist the reviewer's understanding prior to the review.[5]

[i] eCTD = electronic Common Technical Document

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## 3.4 Drug development: Drug submissions and the harmonized process

In the process of drug development (i.e., bringing a drug or biologic to market), obtaining a marketing authorization is the final step before placing it on the market. To reach this stage, the data generated during product development must be presented in a drug submission dossier that is specific to each jurisdiction. The drug submission must contain extensive technical data on the quality, safety and efficacy of the product, as well as regional-specific information and documents such as application forms, declarations, patents, labels and leaflets.

When it receives the drug submission, the regulatory authority will review it thoroughly to ensure the evidence for quality, safety and efficacy is satisfactory before it grants a marketing authorization. Only after marketing authorization is issued can the company who owns the product licence commercialize it, and start recouping the money invested in the drug development program.[1]

### 3.4.1. International Conference on Harmonisation: Drug submissions and the Common Technical Document[2]

Before the Common Technical Document guideline was developed by the International Conference on Harmonisation (ICH), each regulatory authority required technical data to be presented in a jurisdiction-specific format. For companies who were pursuing global drug development, this involved a great deal of administrative work to reorganize information for each drug submission. The introduction of the CTD provided a more unified approach in presenting regulatory submissions for drugs and biologics. Today, the CTD format has been widely adopted by Canada, the US, the EU, Japan and other jurisdictions.

The CTD structure covers five modules (the schematic presentation of the CTD structure and hierarchy can be found on the ICH website).[2] Module 1 is *jurisdiction-specific* and thus not a part of the CTD. Modules 2 to 5 are part of the CTD and are intended to be common across jurisdictions.

- **Module 1** contains information that is specific for each jurisdiction. It includes submission documents such as application forms, the fee form, declarations, proposed labels, the patent(s) and other administrative information. This section is jurisdiction-specific and cannot be harmonized; therefore, it is not a part of the CTD.

- **Module 2** contains critical overview assessments of the quality, non-clinical and clinical data, together with summaries of non-clinical and clinical data. These summary documents should be cross-referenced to Modules 3, 4 and 5 to facilitate regulatory review.
- **Module 3** contains information on quality, such as the identity, characteristics, manufacturing methods, control, packaging and stability of the drug substance (DS) and drug product (DP).
- **Module 4** contains reports of the non-clinical studies that investigated the pharmacological and toxicological properties of the DS and DP.
- **Module 5** contains clinical study reports and raw data (where applicable) to demonstrate the safety and efficacy of the drug in humans.

### 3.4.2 Drug submissions: Harmonized, but with specific regional information

The ICH M4 CTD guidance document has significantly streamlined the preparation process for global drug submissions. It offers a harmonized way to present the technical data. Nevertheless, the company pursuing the drug development and compiling these modules needs to be aware that specific regional differences and requirements may exist. For instance:

- Health Canada has developed a template for *Module 2.3 Quality Overall Summary (QOS) – Chemical Entities (New Drug Submissions/Abbreviated New Drug Submissions)*. This document outlines the suggested format specific to Canada.[3] Also, there are guidance documents for the preparation of QOS for other products (e.g., blood products, biotech products) that include product-specific considerations to be addressed in a Canadian New Drug Submission (NDS).[4] In your NDS, make sure to include executed production documents, master production documents and information on the medical devices used to deliver the dosage form (if applicable).[3]
- In the US, *Module 3 Quality* should contain samples of executed batch records, the method validation package and comparability protocols.[1,5]
- In the EU, *Module 3 Quality* should contain:
  - A process validation scheme for the drug product
  - Specific forms relating to the prevention of transmissible spongiform encephalopathy (TSE) from animal-derived materials or other infections from materials of human origin
  - Medical device information if a device is used as part of the drug-delivery system[1,5,6]

These differences exist because the CTD only provides a harmonized way of organizing the technical information—it does not change the drug submission requirements legislated in each jurisdiction.

For example, the required content of a US New Drug Application (NDA) is outlined in the *Food, Drug, and Cosmetic Act* and 21 Code of Federal Regulations, Part 314. Using the CTD format, a drug-development company can "map" the specific requirements of an NDA to the relevant section of a CTD to address the US drug submission requirement. Information presented in Modules 2 to 5 can be "recycled" for other jurisdictions. Ensure you also include any regional-specific information.

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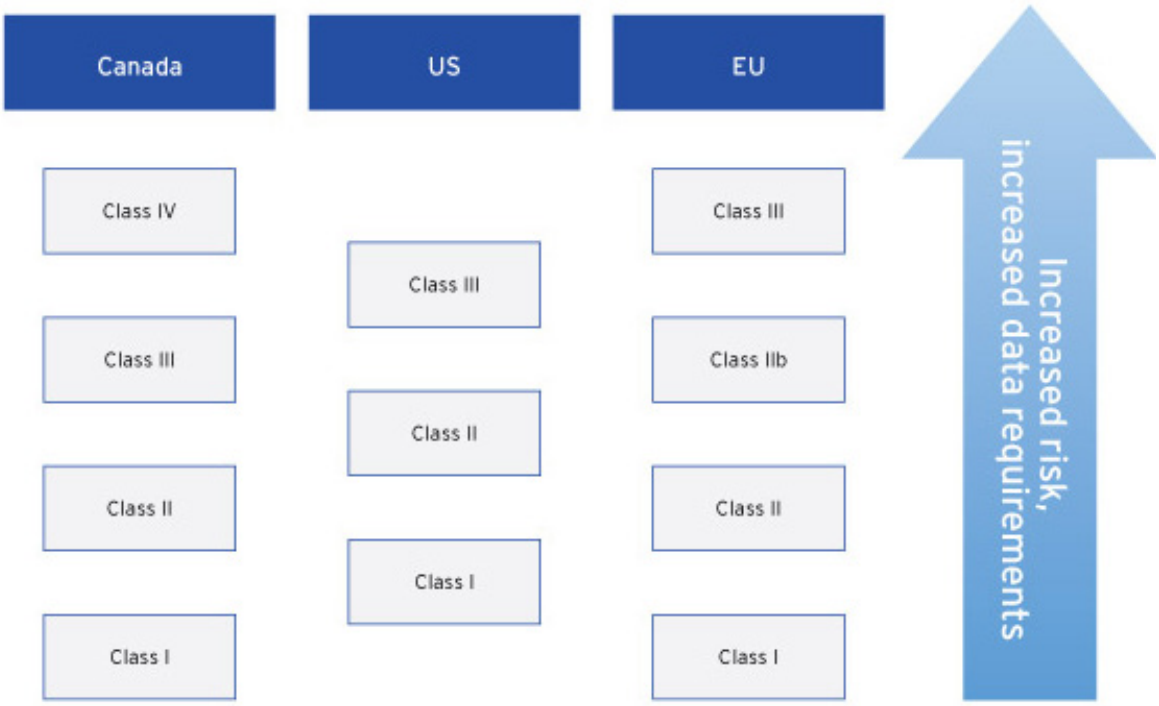
## 3.5 Medical device regulations, classification and submissions

Medical devices play a crucial role in the diagnosis, prevention, monitoring and treatment of diseases. Unlike drugs or biologics, a medical device can vary from the simple, which poses little or no risk to the user (e.g., a tongue depressor), to the life-sustaining (e.g., a pacemaker). The technology and design can rely on any combination of mechanical, electronic, software or chemical/biochemical action to achieve their purpose.[1,2] Registration processes (i.e., to reach regulatory clearance or approval) for medical devices vary greatly across jurisdictions.

### 3.5.1 Classification and data requirements

Due to the wide variety of medical devices, these products are regulated on a risk-based classification system. In Canada and the EU, devices are grouped into four different classes. In the US, they are divided into three groups. Generally, the higher the risk of the medical device, the higher the medical device classification. And with a higher classification come more stringent data requirements to demonstrate the device's safety, effectiveness and performance (Figure 3.5-1).

***Figure 3.5-1: Relationship between medical device classification and data requirements***




## 3.5.2 Procedures to classify medical devices[2-5]

The classification procedures in Canada and the EU are quite similar—manufacturers must classify their medical devices according to the rules and criteria set out in the relevant medical device regulations (Canada) and directives (EU), as indicated in Table 3.5-1.

In the US, the classifications and ancillary information relating to medical device regulations are published in US Code of Federal Regulations (CFR), Title 21, Parts 862–892. These were introduced in 1976 when the U.S. Food & Drug Administration (FDA) mandated expert advisory panels (classification panels) to consider the different types of medical devices on the market based on the intended user, intended use, the risk-to-benefit ratio and the reliability of the device.

In the US, manufacturers of a new medical device can determine its classification by comparing its intended use and technological features to those that have already been classified. However, if the device is technologically innovative with no existing predicate device, it will automatically be classified as class III. Manufacturers of class III medical devices may petition the FDA for a lower classification via a "*de novo*" process, based on supporting objective scientific evidence as to the device's safety and effectiveness.

***Table 3.5-1: Regulations or directives related to medical device classification***[3,4,6,7]

| Jurisdiction | Applicable medical device regulations/directives |
|---|---|
| Canada[i] | **Medical Devices Regulations (SOR/98-282).**<br>Schedule 1. Classification rules for medical devices.<br>• Part 1 – Medical devices other than *in vitro* diagnostic devices<br>• Part 2 – *In vitro* diagnostic devices |
| US | **Code of Federal Regulations (CFR), Title 21, Parts 862–892** |
| EU[i] | • **Medical Device Directive 93/42/EEC** regulates most devices. Classification rules are listed in Annex IX of the directive.[1]<br>• **Active Implantable Medical Devices (AIMDs) Directive 90/385/EEC**. AIMDs are regulated as high-risk devices.<br>• ***In Vitro* Diagnostics (IVDs) Directive 98/79/EC**. Most IVDs are regulated as low-risk devices, except for tests that underpin the safety of blood and blood products (blood group, HIV and hepatitis tests), where additional specific requirements equating to a high-risk category apply.<br>• **Subsequent directives:** A number of additional directives amending the original directives have been introduced:<br>• Directive 2007/47/EC amends Directive 90/385/EEC and Directive 93/42/EEC<br>• Directive 2001/104/EC brings medical devices incorporating stable blood derivatives within the scope of the general directive<br>• Directive 2003/12/EC reclassifies breast implants into class III<br>• Directive 2003/32/EC relates to medical devices that are manufactured utilizing tissues of animal origin<br>• Directive 2005/50/EC reclassifies total hip, knee and shoulder joints into class III |

## 3.5.3 Going to market: Medical device licences and registration[5,8,9]

***Canada***

Manufacturers, distributors and importers who wish to sell a medical device must obtain an establishment licence for class I devices. For class II, III or IV medical devices, the company must obtain a medical device licence issued by Health Canada. To do so, they must submit a device licence application and include a certificate demonstrating compliance to ISO 13485:2003. The application for class II devices is administrative in nature. Applications for class III devices are based on the submission of summary documents, and those for class IV devices are based on extensive data, including all study reports, quality plan, risk assessments and so on.

***US***

Most class I (and also a few class II) medical devices are exempt from registration requirements as specified in the CFR Parts 862–892. If registration is exempted, the manufacturer must register their establishment with the FDA and comply with the applicable Quality System Regulation (QSR), labelling and medical device reporting requirements. For other class I and II devices that are subject to Premarket Notification, a 510(k) application must be submitted for FDA clearance. If the device is classified as a class III device, the manufacturer must go through the Premarket Approval (PMA) procedure, or the *de novo* procedure to reclassify the product in a lower-risk category before placing it on the market.

***EU***

For low-risk medical devices (most class I and certain class IIa devices), the manufacturer may make a declaration of conformity with the essential requirements, based on a self-assessment without the involvement of a Notified Body.[ii] For other medical devices, a Notified Body's involvement is required.

*Technical documentation in the EU*

Technical documentation that provides evidence of conformity with the Essential Requirements as specified in the directives is fundamental to the conformity assessment procedures. The Essential Requirements are listed in Annex I of the Medical Device Directive 93/42/EEC and its corresponding amendments (Table 5.3-1). The technical documentation should include relevant performance data, procedures, standards, labelling, certifications by a Notified Body and/or the manufacturer's declaration of conformity. The technical documentation must be maintained at the disposal of the Competent Authorities (i.e., national authorities in the EU Member States) for a period of five years after manufacture of the last product. Requests from Competent Authorities to view the technical documentation will usually be triggered by problems in the market.

*Changes proposed in 2012*[11-13]

On September 26, 2012, the European Commission proposed two regulations that would overhaul the medical device regulatory framework in the EU—one proposal for general medical devices, including active implantables,[14] and another for *in vitro* devices.[15] These proposals significantly tighten the controls for assessing safety and monitoring the use of medical devices and implants.

Some of the key elements of the 2012 proposals include:

- A wider and clearer scope to the EU legislation – it is extended to include, for example, implants for aesthetic purposes and clarifications with regards to medical software
- Stronger supervision of independent assessment bodies by national authorities
- More powers and obligations for assessment bodies, to ensure thorough testing and regular checks on manufacturers, including unannounced inspections and sample testing
- Clearer rights and responsibilities for manufacturers, importers and distributors, which also apply to diagnostic services and internet sales
- An extended database on medical devices available in the EU
- Better traceability of devices throughout the supply chain (e.g., a unique device identification system to enhance post-market safety)
- Stricter requirements for clinical evidence
- Adaptation of the rules in line with technological and scientific progress, to cover, for example, new software or nanomaterials
- Better coordination between national surveillance authorities
- Improved alignment with international guidelines to facilitate international trade

The proposed legislation must be jointly approved by EU governments and lawmakers; this could take up to two years. Once adopted by the European Parliament and by the Council, these regulations will replace the existing three medical devices directives (see Table 3.5-1). If you are developing a medical device for the EU market, make sure to follow these developments.

[i] If more than one rule applies, a medical device must be assigned the **highest** class that applies under the various rules.

[ii] A Notified Body is a certification organization that the national authority (the Competent Authority) of an EU Member State designates to carry out one or more of the conformity assessment procedures described in the annex(es) of the EU Directives. It must be qualified to perform all the functions set out in any annex for which it is designated.[10]

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## 3.6 Regulatory programs: Expediting product development for special populations and unmet medical needs

Some drugs or medical devices are developed to help treat rare and life-threatening conditions with unmet medical needs, and some are developed for use by a special population (e.g., a pediatric population). Different regulatory agencies have designated programs that offer incentives to companies that develop these products to help them go to market. These regulatory programs can include features such as a faster review process, scientific advice, conditional approval, marketing protection, or reduced or waived submission fees.[1]

### 3.6.1 Drugs

***Orphan drugs*[1-3]**

Products intended to treat rare diseases or conditions (affecting fewer than 200,000 persons in the US, or not more than 5 in 10,000 persons in the EU) may be categorized as **orphan drugs**. The criteria for this designation vary slightly in the US and the EU (Table 3.6-1). Although not currently available, Health Canada is developing a modern framework for the designation, authorization and monitoring of orphan drugs for rare diseases.[4]

***Table 3.6-1: Orphan-drug designation criteria: US and EU***

| US | EU |
|---|---|
| A rare disease or condition is any disease or condition which:<br>a) Affects less than 200,000 persons in the US<br>OR<br>b) Affects more than 200,000 persons in the US and for which there is no reasonable expectation that the cost of development and making available in the US a drug for such a disease or condition will be recovered from sales of such a drug in the US | A medicinal product shall be designated as an orphan medicinal product if the sponsor can establish that:<br>a) It is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition<br>– that affects not more than 5 in 10,000 persons in the community when the application is made<br>OR<br>– that without incentives is unlikely to generate sufficient return to justify the necessary investment<br>AND<br>b) No satisfactory method for the diagnosis, prevention or treatment of the condition has been authorized in the EU; **or,** if such a method does exist, the new medicinal product will be of significant benefit to those affected by the condition. |

To have a product designated as an orphan drug, the company developing it must submit an *Application for Orphan Medicinal Product Designation* to the EU Committee for Orphan Medicinal Products (COMP) and/or a request for orphan drug designation to the US Office of Orphan Products Development (OOPD).

Incentives are offered for orphan-drug products in the following areas:

- Market exclusivity (e.g., seven years in the US and 10 years in the EU)
- Financial assistance (e.g., up to a 50% tax credit in the US against expenses incurred during clinical trials, or grant aid in the US and the EU to support orphan-drug research)
- Scientific assistance (e.g., assistance in developing clinical trial protocols)
- Reduced application fees (e.g., exemption from prescription drug user fees for NDA[i] review in the US, or reduced fees for protocol assistance in the EU[ii])

***Pediatric applications[1]***

In Canada, an additional six-month extension to the eight-year data protection period will be applied if a company includes in their new drug submission, or in its supplement (filed within the first five years of the eight-year data protection period), the results of clinical trials designed and conducted to increase knowledge regarding pediatric use of a drug which would lead to a health benefit for children.[6]

In the US, unless a waiver is granted, a company must assess the safety and efficacy of a drug for use by pediatric patients in a marketing application. An application with pediatric indications is granted six months of extra market exclusivity.[7]

In the EU, companies who undertake an agreed-upon pediatric investigation plan for new or existing drugs may gain an additional market-protection period that ranges from six months to two years, if the product is considered an orphan drug. Financial aid is also available for conducting research and development of pediatric drugs.[8]

***Expedited review[1,9-12]***

Drugs that are intended to treat or diagnose serious, life-threatening or severely debilitating diseases or conditions may qualify for a faster review process in Canada, the US and the EU (Table 3.6-2).

***Table 3.6-2: Expedited review programs in Canada, the US and the EU: Summary***

| Jurisdiction | Programs and their highlights | |
|---|---|---|
| Canada | Priority review | A shortened regulatory review target of 180 days instead of 300 days |
| | Conditional approval (NOC/c) | The company must agree to carry out additional clinical trials to verify the clinical benefit(s) of the drug. In addition, the conditional approval includes:<br>• A requirement to undertake increased monitoring of the drug and reporting to Health Canada<br>• A requirement to provide educational material, including the nature of the conditions of use, to healthcare practitioners and patients<br>• Restrictions on advertising and labelling<br>Such conditions will be removed once the company submits satisfactory evidence of the drug's clinical effectiveness and all the agreed-upon conditions have been met |
| US | Fast track designation | Frequent interactions with the U.S. Food & Drug Administration (FDA) and the possibility of a "rolling submission" (i.e., the FDA will review the completed sections of an NDA [e.g. quality, non-clinical] rather than waiting until every section of the application is completed – usually the clinical section is the last component) |
| | Accelerated approval (21 CFR 314 Subpart H) | An approval based on a surrogate end point with the Phase IV confirmation clinical trial to be conducted post-marketing |
| | Priority review | A review period of six months instead of 10 months |
| | Breakthrough therapy[iii] | Once the sponsor receives this designation, the FDA offers the following to the sponsor to expedite the development and application review of the breakthrough therapy:<br>• Meets with sponsor and review team throughout the drug development<br>• Provides timely advice to, and interactive communication with, the sponsor regarding drug development to ensure that the development program gathers the non-clinical and clinical data necessary for approval as efficiently as is practicable (e.g., minimizing the number of patients exposed to a potentially less efficacious treatment)<br>• Involves senior managers and experienced review staff in a collaborative, cross-disciplinary review<br>• Assigns a cross-disciplinary project lead for the FDA review team for an efficient review of the development program and to serve as a scientific liaison between the review team and the sponsor |
| EU | Accelerated assessment | A review of an application can be conducted within 150 days instead of 210 days |

### 3.6.2 Medical devices

***Canada***

In Canada, a priority review is granted to a class III or class IV medical-device licence application in cases where:

- the medical device is intended for the diagnosis or treatment of a serious, life-threatening or severely debilitating disease or condition

AND

- substantial clinical evidence exists supporting the device

A written request for a priority review must be submitted at least 21 calendar days prior to the filing of the licence application. The targets for screening and review for class III and IV of the original application are 15 days and 60 days, respectively. For any required screening and review of additional information, the targets are 15 days and 30 days, respectively. Applications granted priority review status will be assigned an interim performance target of 45 days from time of receipt, including both screening and review time.[13]

***US***

In the US, an application for a humanitarian device exemption (HDE) may be submitted if a device is intended to benefit patients by diagnosing or treating a disease or condition that affects fewer than 4,000 individuals annually. An HDE is similar to a PMA[iv] but is exempt from the effectiveness requirements. It must, however, contain sufficient information to show that:

- the device does not pose an unreasonable or significant risk of illness or injury

AND

- the probable health benefit outweighs the risk of injury or illness from its use, considering the existing available medical devices or alternative treatment

AND

- no comparable device exists to diagnose or treat the disease or condition

An approved HDE authorizes the marketing of a "Humanitarian Use Device" (HUD). However, the authorization is limited and an HUD may only be used in facilities that have a local institutional review board (IRB) to supervise the clinical testing of devices with an IRB approval for such use. It must bear a label stating that "although the device is authorized by Federal Law, the effectiveness of the device for the specific indication has not been demonstrated."[14]

[i] NDA = New Drug Application

[ii] In the EU, micro-, small- and medium-sized enterprises are entitled to a 100% fee reduction for protocol assistance, scientific services, pre-authorization inspections and marketing authorization applications. In the first year of post-authorization activities, they are also entitled to a 100% reduction in fees, including the annual fees. The post-authorization inspection is subject to a 90% reduction in the total applicable fee.[6]

[iii] The FDA defines a breakthrough therapy as a drug that is "intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and *preliminary* clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant end points, such as substantial treatment effects observed early in clinical development."[12]

[iv] PMA = Premarket approval application

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# Chapter 4: **Product development and lifecycle**

To successfully position innovative healthcare products in the marketplace, product development must proceed with market, commercial and regulatory issues in mind. In other words, visualize the finish line as you develop the product. Chapter 4 looks at elements that should be included in your product development program. It also explains the typical activities included in the product development lifecycle for a new drug or medical device.

## 4.1 Positioning new healthcare products in the marketplace

New healthcare products often begin with a technological innovation or biological insight that aims to address a need or improve current technology in the medical arena. To successfully position these products in the market, product development must proceed with market, commercial and regulatory issues in mind.

### 4.1.1 Market research and analysis[1]

Good market research and an analysis of the needs and economics of your target market are imperative to define the market potential of your innovation and develop your business plan.

Market research and analysis enables you to:

- Identify and segment markets for your technology.
- Define the product characteristics required to address market needs.
- Understand the pros and cons of other market players (which will help you define your competitive edge).
- Project sales revenues and profits.
- Determine appropriate pricing.

### 4.1.2 Product development and the regulatory environment

On top of market research, the regulatory issues related to healthcare product development cannot be overlooked. In the KPMG Pharmaceutical Outlook Survey conducted in May 2012, 60% of executives said that regulatory and legislative pressures are the most significant barrier to their company's growth over the next year.[2]

In addition to being aware of all the relevant industry regulations and guidance documents, it is important to identify the regulatory status or classification of other marketed healthcare products. This will guide you in positioning your product in the marketplace. The following sources offer information relating to marketed healthcare products:

- Websites of competitors and regulatory agencies
- Product labels
- Marketing literature
- Tradeshows
- Published literature
- Patient groups
- Public databases

### 4.1.3 Pricing and reimbursement affect positioning and product development[1]

Pricing and reimbursement are other factors that greatly affect the positioning of healthcare products as well as their product development. Start planning your pricing and reimbursement strategy early in the product development process. Do not wait until after a product is approved as these issues are complex due to the different systems employed in different jurisdictions.

When structuring pricing and reimbursement for new healthcare products, it is important to know for each country:

- Who are the payers – is it the government, the hospital or a third party (e.g., an insurance company)? Is it the consumer (e.g., over-the-counter products)?
- What are the data requirements for these payers?
- What are the pricing and reimbursement procedures?

Reimbursement planning should typically begin before clinical development of the product. It can help to:

- Determine if the product can deliver appropriate returns
- Develop specific clinical data on performance and benefit, to differentiate the product for payers and hospital and clinical customers
- Identify possible strategic business relationships for product launch
- Assist in the pharmacoeconomic evaluation necessary to support the reimbursement procedure

### 4.1.4 Product development: Good science alone does not lead to good healthcare products

Development of healthcare products is highly regulated. It is a long and expensive undertaking. In addition to the good science in support of the quality, safety and effectiveness of the product, factors such as market research, regulatory issues, and reimbursement and pricing strategies need to be evaluated. Such an overall appraisal will provide important feedback for the product development program. It can yield important insights to steer the positioning as well as decisions related to product design, its intended use, and the clinical trial design or types of studies that need to be conducted.[1]

In short, good science alone does not necessarily lead to a good product. Scientific expertise needs to be leveraged within the context of market forces in order to achieve a successful and profitable product.

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## 4.2 New drug development

The development of a new therapeutic product (i.e., a new drug or biologic) is a long, complex and expensive process which typically takes 10 to 12 years (and sometimes more) from product identification to commercialization.[1] This lifecycle usually involves the following stages:

1. **Discovery and research:** Identification of a target therapy for the diagnosis, cure, mitigation, treatment or prevention of a disease or condition.
2. **Development:** This includes the necessary non-clinical research, clinical studies and chemistry, manufacturing and controls (CMC) development to support clinical trials (e.g., IND, IDE, CTA, IDE) and licensing applications (e.g., NDA, NDS, MAA).*
3. **Regulatory review and approval:** Submission of data for regulatory review to demonstrate product safety, efficacy and quality for its proposed indication.
4. **Commercialization and marketing:** Ongoing regulatory compliance through safety reports and other required submissions (e.g., product renewal).

This article focuses on the development stage (#2) outlined above.

### 4.2.1 New therapeutic product development

Development of a new therapeutic product normally begins with non-clinical testing followed by different phases of human clinical trials in support of the licensing application. Chemistry, Manufacturing and Controls (CMC) activities are conducted concurrently to support these studies.[1]

### 4.2.2 Preclinical/non-clinical studies[2,3]

Non-clinical testing (laboratory experimentation and animal investigation) assesses the potential therapeutic effects of a drug substance and demonstrates the reasonable safety of a substance before it can move to human studies. It may also include long-term studies (e.g., reproductive and carcinogenicity studies) that are conducted after the clinical trial is initiated. Non-clinical studies must be conducted following Good Laboratory Practices (GLP). This phase of testing may include *in vitro* and *in vivo* studies to research metabolism (pharmacodynamics [PD] and pharmacokinetics [PK]), safety, toxicity, dosage and efficacy. When designing these studies, ensure you review all related regulatory materials, such as guidance documents from your regulatory agency and safety topics from the International Conference on Harmonization [ICH].

### 4.2.3 Clinical trials[2]

The objective of clinical trials is to evaluate the safety and efficacy of a product in humans. A clinical program typically involves four phases and must comply with regional requirements as well as Good Clinical Practices (GCP). Phases I to III are conducted to collect safety and efficacy information in support of the licensing application. Phase IV is conducted post-marketing (i.e., once the product reaches the market).

***Phase I – Human pharmacology***
Phase I starts with the initial administration of an investigational product into humans (healthy volunteers, or in patients if for the use of cytotoxic drugs). **These studies usually have non-therapeutic objectives.** The study design can be open and baseline-controlled, or may use randomization and blinding to improve the validity of observations in the study. Phase I clinical trials may include:

- An estimation of the initial safety and tolerability, including both single- and multiple-dose administration
- A PK study
- PD studies, and studies relating drug blood levels to response (PK/PD studies)
- Early measures of product activity

***Phase II – Therapeutic exploratory***
Phase II **explores the therapeutic efficacy** in patients, with the designs including concurrent controls and comparisons with the baseline status. The patient population is normally selected with narrow criteria. A major objective is to determine the dose(s) and regimen to support Phase III trials. Other objectives may include potential study end point evaluations, therapeutic regimens and target populations (e.g., mild versus severe disease) via exploratory analyses, examining data subsets and using multiple end points in clinical trials.

***Phase III – Therapeutic confirmatory***
Phase III clinical trials are intended to **confirm the therapeutic benefit** – that is, the safety and efficacy of an intended indication in specific patient population. These are pivotal studies intended to provide an adequate basis for marketing approval.

***Phase IV – Therapeutic use (post-marketing)***
Phase IV begins after the product is approved. It may include a post-approval study that is designed to answer specific issue(s) identified during the regulatory review process. Commonly conducted studies include additional drug-drug interaction, dose-response or safety studies, and studies designed to support the use under the approved indication (e.g., mortality/morbidity studies, epidemiological studies).

## 4.2.4 Product quality: CMC activities[4,5]

Extensive CMC activities must take place to establish the quality of the therapeutic substance (i.e., the drug substance) and product (i.e., the drug product in its final dosage form). Initial substance characterization allows a complete understanding of structure, stereochemistry, impurities, and chemical and physical characteristics. These products may be produced initially at a laboratory scale, but production should be scaled up in pilot and commercial scales during product development with corresponding validation activities. Analytical methods and specifications must be established and validated to control the quality and purity of the drug substance, intermediates and the finished product. Data to demonstrate the substance and product stability must be collected. All activities should adhere to Good Manufacturing Practices (GMP) and must be carefully designed and planned to support the different studies that will take place in the non-clinical and clinical phases.

* IND = Investigational New Drug
IDE = Investigational Device Exemption
CTA = Clinical trial application
NDS = New Drug Submission
MAA = Marketing Authorization Application
NDA = New Drug Application
BLA = Biologics License Application

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## 4.3 Medical device design and development

After conceptualizing a new medical device, the next step in its development is the product design. This is the most important stage in the development of a medical device since a flawed design may lead to it being ineffective or unsafe (i.e., not approved or cleared by the regulatory agency).[1] At the design stage, a design control process needs to be initiated and implemented as part of the quality system requirement.* In essence, design controls are simple and logical steps to ensure that what you develop is what you *meant* to develop, and that the final product meets your customer's needs and expectations.[2,3]

### 4.3.1 The design control process

The design control process includes a set of interrelated practices and procedures that are documented and incorporated during the medical device design and development. Through design control activities, a company can:

- Identify the customers' needs and understand the competitor's product.
- Meet essential requirements necessary to achieve a high-quality product, from inception through to production.
- Identify early inconsistencies or discrepancies by comparing what is currently made to the initial concept (thereby reducing redesign and rework and improving product design and quality – i.e., getting it right the first time).
- Establish a consistent process.
- Be reasonably sure that the end product works and meets customer needs.[2,3]

The US 21 CFR 820.30 design control requirements are outlined below:[1-5]

***Design and development planning***

Establish and maintain a plan that describes the design and development activities and allocates the individual responsibilities for each activity. Ensure you review, update and approve the plan until the device design is completed, verified and validated.

***Design input***
Use performance, safety, business economics, outputs of risk management and regulatory requirements as a basis to design the device so that its purpose and the intended use are clear. Input may also come from surveying your customers (e.g., clinicians, nurses, patients). Review and address information gathered as you develop the product specifications.

***Design output***
Design output procedures or specifications need to stipulate or refer to the design input document developed by the team and need to identify the critical measures/outputs for the proper function of the device. These include the tests and procedures that may have been developed, adapted or used to show conformance with the defined design inputs. Examples of design outputs may include:

- The device itself
- The user manual
- Specifications
- A risk analysis
- Study results (e.g., validation and biocompatibility studies, storage and shipping tests)
- Technical files

**Design review**
Confirm the design, or detect early on and correct any deficiencies identified at other design and development phases. Two common types of review are hazard analysis, and failure mode and effect analysis (FMEA). Ensure the design is reviewed by personnel from all areas involved with this stage as well as by someone who does not have direct responsibility for this design stage. Document the design review results (e.g., the design identification, date and individual[s] performing the review) in the design history file (DHF).

**Design verification**
Confirm the device design via examination and objective evidence, verify that *the design outputs meet the design inputs*. Design verification activities must be planned and routinely examined and the results must be documented. Most design verification activities become DHF records that support the effectiveness of design outputs (e.g., risk analysis and management results, test method validations, software verification, biocompatibility results, transit test, and third-party certifications).

**Design validation**
Validate the device design via examination and objective evidence, confirm that the final design output *consistently meets the specific intended use.* Design validation should follow successful design verification. Because design verification is conducted while the design work is being performed, design validation confirms that the medical device meets its intended use. Usually this is established through *in vitro* performance, functional testing, animal testing and/or *in vivo* clinical evaluations and trials.

**Design changes**
Ensure that all design changes are identified, documented, validated, verified, reviewed and approved prior to implementation.

**Design transfer**
Ensure that the design of the medical device can be correctly translated into production specifications (i.e., advancing successfully from product development to manufacturing).

**Design history file**
The design history file (DHF) compiles evidence (i.e., the history of the design) that shows that the design was developed in accordance with design controls – specifically, the design and development plan, or the design-change plan.

* This article discusses the design control process based on the requirements outlined in Title 21, Section 820.30 of US Code of Federal Regulations. This is very similar to the design control elements of ISO 13485. A table comparing the two approaches is presented in Chapter 1.7 Step 6: Execute your healthcare product development plan. Additionally, please refer to Table 5.2-1 in Chapter 5.2 Quality system: Medical device product development for information on whether it is mandatory for you to meet design control requirements as part of your quality system requirements.

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# Chapter 5: **Product-related quality**

Chapter 5 focuses on quality. It discusses Good Manufacturing Practices (GMP) for drugs, biologics and active pharmaceutical ingredients (APIs) along with examples of related activities. It also looks at the responsibilities and requirements of a quality system in the manufacture of medical devices, and at the critical nature of controlling the quality of raw materials used in developing a healthcare product. Additionally, this chapter highlights the key areas of validation, sterilization and stability.

## 5.1 Good Manufacturing Practices (GMP): Drugs and biologics

In the development and manufacture of a therapeutic product (a drug or a biologic), Good Manufacturing Practices (GMP)* activities help ensure that a manufacturer can consistently control and produce these products to meet the identity, strength, purity and quality appropriate to their intended use.[1-9]

In the US the cGMP* are based on the fundamental principles of quality assurance:[9]

1. Quality, safety and effectiveness must be designed and built into the product.
2. Quality cannot be inspected or tested into the product.
3. Each step of the manufacturing process must be controlled to maximize the likelihood that the product will be acceptable.

Sponsors (companies) that develop therapeutic products are ultimately responsible for ensuring that their products comply with relevant GMP regulations at all stages of the product lifecycle. This holds true even if part or all of the manufacturing activities are outsourced to a third party (e.g., a contract manufacturing organization).

### 5.1.1 Safeguarding product quality

Regulatory authorities safeguard product quality via routine inspections of manufacturers to verify their compliance with relevant GMP regulations.[1-8] These regulations contain the minimum requirements for the methods, facilities, equipment, personnel and control activities used in the manufacturing, processing and packaging of a therapeutic product.[2] Aside from the finished product, GMP also applies to the active pharmaceutical ingredients (APIs). The development and manufacture of the API should follow the principles described in the Q7A and Q11 guidance documents of ICH (International Conference on Harmonisation).[10,11]

The ICH guidelines Q8, Q9 and Q10[12-14] relate to the development of quality systems in the pharmaceutical industry. These guidelines describe principles such as "quality by design," quality risk management and quality systems. In addition to these general requirements, it is recommended to adhere to any other specific GMP guidance documents that may apply to the development of your product (e.g., those governing sterile products produced by aseptic processes).[15]

### 5.1.2 GMP throughout the product lifecycle[9]

GMP should be applied throughout the product lifecycle. As the product moves through the product development phases, the GMP stringency increases with progression from clinical trials through to commercialization. For instance, the chemistry, manufacturing and control (CMC) information that is included with the early-stage clinical trials may be less detailed than with

the licensing application and post-approval amendment applications. Data requirements (e.g., process validation) for GMP increase as knowledge about product accumulates. Such information is submitted in the Quality section of the clinical trial and licensing applications. The Quality section contains detailed information on the quality aspects, characteristics and manufacture of the drug substance and drug products.

### 5.1.3 Examples: GMP activities

GMP regulations address all areas that affect process performance and product quality, including personnel, materials, procedures, equipment, facilities and records. The following are some brief, general examples of GMP activities:[1,9]

- Personnel must be qualified and trained to perform their function.
- Materials used in the process must meet specified quality attributes and be controlled in a manner to prevent mix-ups.
- Procedures must be established and followed for the manufacture, testing, cleaning, validation and stability activities associated with the product (from raw materials and the drug substance to the finished product to packaging materials).
- Equipment must be properly identified, cleaned and maintained to prevent cross-contamination.
- Facilities must be suitable for their intended purpose with proper lighting, air handling, plumbing and sanitation.
- Records to demonstrate GMP compliance must be properly maintained.

* In the US, it is referred to as Current Good Manufacturing Practices, or cGMP.

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## 5.2 Quality system: Medical device product development

The primary goal in the design and manufacture of a medical device is to produce a quality product that meets the applicable requirements and specifications for its intended use. Such a product provides assurance that the medical device can be consistently manufactured and will perform as planned, safely and effectively. This can be achieved through the implementation of a quality system.[1]

### 5.2.1 What do quality system requirements cover?

Medical device manufacturers who plan to take their product to the global marketplace should carefully review the ISO 13485 Medical Devices *Quality management systems requirements for regulatory purposes* and the US Code of Federal Regulations (CFR) Title 21, Part 820 Quality System Regulations (QSR).[2,3] These requirements define the quality system standards for medical device design and manufacturing – i.e., good manufacturing practices for medical devices.

These quality system requirements (as per QSR) cover a wide range of topics such as:[1,2]

- Management and organization
- Design
- Document controls
- Purchasing controls
- Identification and traceability
- Production and process controls
- Acceptance activity (in relation to inspections, tests and verification activities)
- Non-conforming products
- Corrective and preventive actions
- Labelling and packaging control

- Handling, storage, distribution and installation
- Records
- Servicing
- Statistical techniques
- Inspections

Due to the broad variety of current and conceivable medical devices, the ISO 13485 standard and the US QSR do not stipulate how a manufacturer must produce a specific device. Rather, they ensure product quality by providing a framework that requires manufacturers to develop and follow written procedures specific to their medical devices.[4] In other words, the manufacturer should establish methods and procedures to address the applicable quality system requirements related to the design, manufacture and distribution of their devices. Depending on the type of medical device or your organization, these requirements and standards may represent only a minimum baseline for designing and producing your medical device. Manufacturers may implement additional requirements or more sophisticated quality programs to meet the needs of their operations and the needs of their customers.

It is critical to understand that the *ultimate responsibility* for meeting these requirements resides with the manufacturer, even if some of the activities are delegated to a third party (e.g., a contract manufacturing organization).[4]

### 5.2.2 Quality system requirements: Canada, the US and the EU

The specific quality system requirements for Canada, the US and the EU are summarized in Table 5.2-1.

***Table 5.2-1: Quality system requirements for Canada, the US and the EU***

| Country | Requirements |
|---|---|
| Canada | • Mandatory for class II, III and IV medical devices to be manufactured (class II) or designed and manufactured (class III & IV) under ISO 13485:2003.*<br>• No regulatory quality system requirements apply for class I medical devices.[5] |
| US | • Mandatory for class II, III, and select class I devices (e.g., class I devices automated by software).<br>• Devices exempt from Good Manufacturing Practices (GMP) are codified in 21 CFR 862 to 892.<br>• Exemption from GMP requirements does not exempt manufacturers of finished devices from keeping complaint files (21 CFR 820.198) or from general requirements concerning records (21 CFR 820.180).[4] |
| EU | • Device manufacturers have several options in obtaining CE marking via different conformity assessment routes (e.g., having their devices tested or having a quality system).<br>• With the quality system route, compliance with ISO 13485 is voluntary and a company can choose to use other systems that are equivalent. However, it is important to keep in mind that Notified Bodies** prefer to have a well-understood system when auditing.[6] |

* Standards are updated periodically. It is important to ensure that the version followed is recognized by corresponding markets.

** A Notified Body is certification organization that the national authority of an EU Member State designates to carry out one or more of the conformity assessment procedures described in the annex(es) of the EU Directives. It must be qualified to perform all the functions set out in any annex for which it is designated.[7]

### 5.2.3 Assuring medical devices are of the highest quality

There are many way in which a manufacturer can provide greater assurance that their medical device is of the highest quality. These include:[1]

- Developing an effective design control plan
- Conducting risk analyses
- Following adequate and appropriate standard operating procedures and protocols for testing
- Using validated methods and procedures
- Monitoring and auditing clinical trials
- Establishing and implementing a company quality policy
- Ensuring adequate staff training
- Conducting quality audits
- Implementing a quality control program
- Maintaining, analyzing and following up on complaint files
- Adopting and implementing appropriate corrective and preventive action plans

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## 5.3 Importance of quality: Raw materials of healthcare products

When manufacturing a healthcare product, controlling the quality of the raw materials used (e.g., the excipients or the components that make up your product) is as important as controlling the quality of your active pharmaceutical ingredients and your finished product. Managing your raw materials as part of your quality system will help to ensure that your finished healthcare product meets its quality attributes. It is wise to initiate such a system at the outset of product development and build it into the product design.[1] Having this in place will help steer appropriate selection of the raw materials used.

### 5.3.1 Selecting the right raw materials[2,3]

Key considerations when selecting the raw materials include:

- **Is there enough information to support the safety of the material selected (as well as its by-product[s])?** For example, is the raw material commonly used in the regulated industry (i.e., is it "generally recognized as safe" [GRAS] material)? Is it known to have toxicological concerns (e.g., carcinogenetic potential)?
- **Would the raw material lead to any pharmaceutical response or is it considered an inert substance?** For pharmaceutical products, does it raise questions about interaction with your drug substance? For medical devices, does it change your product from a medical device to a combination product (which would lead to different regulatory requirements and pathways)? If yes, is there a different agent that could help you avoid a more difficult pathway?
- **Is the supply of this material limited?** If so, can it be replaced with another raw material? If not, it is critical to ensure the supply of this material (have a contract with the supplier or identify an alternate supplier) so that no shortages affect the manufacture of your healthcare product during clinical or commercialization phases.
- **Is the material compatible with your finished product?** For instance, in pharmaceutical products, the excipients can comprise more than 90% of a product's weight. Therefore, evaluate the compatibility of the ingredients that may contribute to the quality (e.g., hardness, dissolution rate) of the dosage form.
- **Is the ingredient available as a pharmacopeial grade or medical grade?** If it is, does it meet the requirements in the targeted jurisdiction? If not, can it be substituted by another ingredient?

In summary, the quality, safety and efficacy of the healthcare product should be scientifically evaluated to ensure the right materials are selected.

### 5.3.2 Ensuring the right quality of raw materials[2]

Once the product design is finalized, implement a robust supplier management program to assure and control the quality of the raw ingredients. In general, base this program on general Good Manufacturing Practices (GMP). Some aspects may include:

- Reviewing the supplier history, including any relevant information on their manufacturing reliability
- Determining the reliability of results reported on Certificates of Analysis (a document issued by a supplier to certify the quality and purity of each product lot)
- Assessing the quality of raw materials through routine testing
- Performing a supplier audit, if required
- Considering information obtained via ongoing communication with suppliers

**In summary, know the supply chain of the raw material for your product.** Identify and mitigate risks throughout the supply chain and document the measures you take to secure it.[2]

***Consider cooking as an analogy***

One of the fundamental principles of good cuisine is the use of high-quality ingredients. Even if you have a great recipe with the steps, ingredients, and cooking methods and conditions (i.e., your formulation and the manufacturing process) clearly stated, the dish will not turn out quite right, or even safely, if the ingredients used are not what they purport to be, and if they are not fresh (that is, not expired) and clean (that is, not contaminated with chemicals or microbes). The span of ingredients can include the main ingredient (say, chicken) as well as all the spices. Sometimes just changing the brand (i.e., changing the supplier) of an ingredient may be enough to affect the "quality," or taste, of the food. Similarly, the quality of the raw materials selected to manufacture your healthcare product could significantly affect the quality, safety and efficacy of your product; hence the need for tight controls.

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## 5.4 Validation

When manufacturing a healthcare product, be it a drug, a biologic, or a medical device, validation activities (including that of the active pharmaceutical ingredient) are an essential component of Good Manufacturing Practice (GMP) requirements.

Validation is the documented act of demonstrating that any procedure, process or activity will consistently lead to the expected results. It includes the qualification of systems and equipment. A careful design and validation of systems and process controls can establish a high degree of confidence that all lots or batches of the healthcare product manufactured will meet their intended specifications.[1]

The proof of validation is obtained through experimental design and through evaluating data that is collected throughout the product and process development. Routine end-product testing *alone* is not considered sufficient. Quality cannot be "tested" into the finished healthcare product, but rather it should be built into the manufacturing processes – with controls established so that the end product meets all the pre-defined quality specifications.[1,2]

### 5.4.1 Typical validation activities[1,3]

Typical validation activities include validating the process, the analytical methods, the equipment, the computer system and software, and the cleaning methods.

***Process validation***

Process validation involves documenting evidence to provide a high degree of assurance that a specific process will consistently produce a product that meets its predetermined specifications and quality.

Process validation includes identifying, monitoring and controlling any sources of variation that can contribute to changes in the healthcare product. This is achieved after satisfactory product and process development, scale-up studies, equipment and system qualification, and the successful completion of initial validation batches (also known as conformance batches). Validation batches are prepared in order to demonstrate that, under normal conditions and defined ranges of operating parameters, the commercial-scale process appears to make an acceptable product based on its predetermined specifications and quality attributes. Process validation typically includes evaluating three consecutive commercial-scale batches to demonstrate their consistency and quality.

***Analytical method validation***
Analytical methods are required to measure the healthcare product characteristics (e.g., identity, purity, potency and safety) that support product quality, safety and effectiveness. Once developed, these analytical methods should be evaluated for the following to ensure that they are capable of producing consistent and correct results without error:

- Accuracy
- Precision
- Range
- Selectivity
- Recovery
- Calibration (detection and quantitation limits)
- Assay sampling
- Robustness
- Stability

Once a method is validated, different analyzers should be able to follow the same procedure and generate consistent results.

***Equipment validation***
This is established to ensure that the processing equipment and any ancillary systems are capable of consistently operating within the established limits and tolerances. Studies include equipment specifications, installation qualification (IQ)[i] and operational qualification (OQ)[ii] of all major equipment to be used in the manufacture of commercial-scale batches. Equipment qualification should simulate actual production conditions, including "worst-case" or stressed conditions.

***Computer system and software validation***
Any computer system or software that is used to automate any part of the manufacturing process and its related activities should be validated for its intended use. For instance, any software used to automate any aspect of the quality system (e.g., medical device design, manufacturing, testing or packaging) should be validated accordingly.[4] Compliance with Code of Federal Regulations (CFR), Title 21, Part 11, regarding electronic records and electronic signatures, is expected.[5]

***Cleaning validation***
This demonstrates that the procedures for cleaning processing components and equipment are capable of reducing all residues (e.g., from products or cleaning agents) to an acceptable level. This is particularly important in multi-use plants that manufacture more than one

product in order to avoid any batch-to-batch carryover. Cleaning validation is also used to demonstrate that routine cleaning and storage of equipment does not allow microbial proliferation. If cleaning validation cannot be demonstrated, consider using dedicated equipment or disposable processing components instead.

### 5.4.2 Key aspects of validation

It is important to know that regulatory agencies conduct inspections to ensure manufacturing companies comply with validation activities. When implementing and conducting validation, key concerns include:[1]

- Make sure to follow relevant regulatory requirements and guidance documents – validation is a GMP requirement. Examples of such documents and their issuing authorities are:
  - Health Canada: *Validation guidelines for pharmaceutical dosage form (GUI-0029)*
  - International Conference on Harmonisation: CH Q2(R1), *Validation of analytical procedures*
  - U.S. Food and Drug Administration (FDA): *General principles of software validation*
  - US FDA: CPG Sec. 490.100, *Process validation requirements for drug products and active pharmaceutical ingredients subject to pre-market approval*
  - U.S. FDA: *Process validation: general principles and practices*
- Establish a "Validation master plan" to provide an overview of the entire validation operation, its organizational structure, and its content and planning. The main elements of the plan would be a list of the items to be validated and the planning schedule. Make sure to include all validation activities concerning critical technical operations related to product and process controls.
- Validate all critical production processes.
- Conduct validation studies in accordance with pre-defined protocols. Prepare, evaluate, approve and maintain written reports that summarize the recorded results and conclusions.
- Prior to implementation, validate any changes to production processes, operating parameters, equipment or materials that may affect the product quality or the reproducibility of the process.

[i] IQ: Documented evidence that process equipment and ancillary systems are properly selected and correctly installed.

[ii] OQ: Documented evidence demonstrating that process equipment and ancillary systems work correctly and operate consistently in accordance with established specifications.

#### References


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## 5.5 Sterilization

According to the US Centers for Disease Control and Prevention, sterilization means "the use of physical or chemical procedure to destroy all microbial life, including highly resistant bacterial endospores."[1]

The objective of sterilization is to completely destroy or remove all microorganisms (including spore-forming and non-spore-forming bacteria, viruses, fungi and protozoa) that could contaminate a healthcare product (e.g., those introduced in the manufacturing process via raw materials, process, equipment, facilities or personnel).

Although Good Manufacturing Practices (GMP) are applied throughout the manufacture of healthcare products to minimize preventable microbial contamination, products that are labelled "sterile" and can be sterilized in their final containers normally undergo a sterilization process. For products that cannot be sterilized in their final containers, aseptic processing is needed.[2]

### 5.5.1 Sterilization methods

The sterilization method used and the efficacy of the process depends on factors such as the costs, the characteristics of product and packaging materials, the extent and type of contamination(s), and the conditions under which the final product has been prepared. Traditional sterilization methods are described below.[2,3]

***Dry heat sterilization***
Dry heat sterilization achieves sterilization via the oxidation of cell constituents. It requires a higher temperature than moist heat and a longer exposure time. It is most suitable for heat-stable, non-aqueous materials that cannot be sterilized by steam due to its deleterious effects (e.g., the product is moisture-sensitive) or its failure to penetrate (e.g., the product is packaged in glassware container).

***Moist heat sterilization***
Moist heat sterilization exposes microorganisms to saturated steam under pressure which achieves the irreversible denaturation of enzymes and structural proteins. It is commonly used in aqueous preparations, surgical dressings and medical devices. A steam autoclave, for example, uses this method.

***Ethylene oxide – in a fixed chamber***
Ethylene oxide (EO) is used to sterilize items that are heat- or moisture-sensitive. The disadvantages are that the EO gas can leave toxic residues on sterilized items, and it presents several physical and health hazards to personnel and patients. Thus, the maximum levels of EO residual gas and ethylene chlorohydrin that remain on the product should be evaluated as required by *ISO 10993-7. Biological Evaluation of Medical Devices – Part 7: Ethylene Oxide sterilization residuals.*

***Radiation (gamma and electron beam)***
Radiation affects the ionization of molecules in organisms. Mutations are thus formed in the DNA and these reactions alter replication of the microbes. This method can be used for certain active ingredients, drug products and medical devices.

***Liquid chemical sterilants***
Liquid chemical sterilants are used to sterilize single-use medical devices that contain material(s) of animal origin which are not compatible with commonly applied sterilization methods. Examples of such devices include biological heart valves and tissue patches.[4]

### 5.5.2 Regulatory submissions and sterilization data

In regulatory submissions, information on the sterilization method used and its validation as well as a description of the packaging to maintain product sterility are normally included.* This is to ensure that the proper sterility assurance level (e.g., $10^{-6}$ for all medical devices, except $10^{-3}$ for devices that only contact intact skin) can be consistently achieved before a healthcare product can be labelled as "sterile."[3]

If the characteristics, quality, safety and effectiveness of the healthcare product after sterilization may be affected, consider doing testing (e.g., biocompatibility, bench, animal and clinical studies) on the finished sterilized healthcare product for inclusion in the regulatory submission.

When conducting sterilization activies, follow the applicable, recognized standards (e.g., ISO 11137, ISO 11737, ISO 11135). For medical devices that are shipped non-sterile and are intended to be sterilized by users, or those that are reusable and meant to be re-sterilized by users, the product labelling should provide adequate information regarding at least one suitable method of sterilization and any needed precautions or safeguards that need to be followed. The labelling should also include information such as special cleaning methods, any changes in the physical characteristics of the device that may result from reprocessing which can affect its safety, effectiveness or performance, and any limit on the number of times for resterilization and reuse.[5]

***Did you know?***

In the US, if a company decides to use a sterilization method that is considered non-traditional, an inspection of the sterilization facility may be considered a priority in the post-market period. Such non-traditional methods could include EO not being used in a fixed chamber, or the use of high-intensity light, chlorine dioxide, ultraviolet light, combined vapour and gas plasma, filtration methods, a vapour system such as peroxide or peracetic acid, or a limited use of liquid peracetic acid system in endoscopy with a metal instrument.[3]

* For drugs that are sterilized via aseptic processing, information on the aseptic fill manufacturing processes should also be submitted.[6]

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## 5.6 Stability

For healthcare products that have a shelf life, stability studies play a central role in their development. These stability assessments of the active substance (e.g., the active pharmaceutical ingredient) and the finished healthcare product are mandated by international regulatory agencies. Before a healthcare product can be studied in a clinical trial or be placed on the market, the appropriate shelf life (i.e., storage condition and duration) and expiry limits must be established. These stability data must be submitted for regulatory evaluation to ensure that over its proposed shelf life and storage conditions, the product in its packaging will continue to meet the required identity, strength, quality, purity and impurities that support the safety and efficacy claims of the product.[1,2]

### 5.6.1 Stability studies: What the data yield[1,2]

In general, stability studies are conducted to:

- **Establish shelf-life and storage condition(s):** This identifies the storage period under a set of specified conditions within which the healthcare product will meet its established end-of-shelf-life specifications.
- **Permit understanding of product and formulation development:** This includes understanding the chemical characteristics of the active substance (e.g., the degradation pathway that may yield toxic by-products over time). It also includes understanding the chemical stability, which is important to evaluate as the product may become less effective as it undergoes degradation over time (e.g., its antimicrobial activities may decrease).
- **Assist in formulation development**: Studies can, for example, evaluate if there is any change in the physical properties, such as hardness, phase separation and change in dissolution rate, in the developed formulation.
- **Aid in the development of analytical methods**: Sometimes, the physical and chemical properties of the product may change over time (e.g., a gel used in a matrix may harden) and the analytical methods will need to be modified accordingly.
- **Identify appropriate packaging**: Data from stability studies can confirm the right packaging for the active substance as well as the final product (e.g., the packaging must protect the product from environmental factors such as light, moisture and shipping conditions). Having an appropriate container closure system (i.e., packaging) is particularly critical for sterile products, and it should be designed and evaluated over time to ensure no penetration of microbes can be made into the product.

### 5.6.2 Designing and conducting stability studies[3-7]

Key considerations in designing and conducting a stability program in accordance with regulatory requirements include:

- Identify and follow the relevant regulatory guidance documents in designing your stability program. In addition to general stability requirements, consult product-specific guidance documents to ensure you evaluate and capture the required parameters in the stability program. Examples of these documents may include:
  - International Conference on Harmonisation (ICH): Topic Q1
  - U.S. Food and Drug Administration (FDA): *Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products*
  - ASTM F1980 - 07: *Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices*
  - U.S. FDA: *Shelf Life of Medical Devices*

- Submit stability protocols and data together with the stability commitment statement (if relevant) for both accelerated and long-term studies.
- In general, conduct studies using three different batches of both the active substance and finished product for each formulation in their respective containers or packaging.
- Provide a justification if bracketing and matrixing designs are used in the stability program.
- Collect long-term data under temperature and relative-humidity conditions in line with the storage recommendations.
- For products intended for the global market, consider the environmental conditions in different climate zones (e.g., zones III and IV).
- Support long-term data with accelerated and intermediate stress testing at a higher temperature and relative humidity. Verify the photostability using a single batch.
- Remember that an accelerated stability study alone does not suffice to support the product shelf life.
- Beyond considering reasonable analytical and manufacturing variability, justify your acceptance criteria with development data, pharmacopoeial standards, test data for the active substance and finished products used in the toxicology and clinical studies, as well as stability results.

***Did you know?***

It is common to have a stability program for an investigational healthcare product run in parallel with the clinical trial. Depending on the amount of stability data submitted in the initial clinical trial application (CTA), manufacturers who wish to extend a product shelf life need to evaluate the relevant requirements and determine whether a submission is required to the regulatory agency prior to extending the shelf life of the investigational product.

In Canada, for example, if the CTA-approved shelf life for a biological product is *less* than 18 months, a CTA-amendment approval would be required before the company can extend its product shelf life. If the product is approved with *more* than 18 months of shelf life, then a CTA-notification must be submitted to Health Canada within 15 days of implementing the extended shelf life; no prior approval from Health Canada is required.[8]

## References


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# Chapter 6: **Product-related safety**

Chapter 6 examines healthcare product-related safety issues. It looks at the non-clinical and clinical information needed to support the drug safety profile of an investigational product, and why it is required. It highlights key guidance documents. The chapter also looks at safety requirements for the development of a medical device. It explains that the amount and type of required product safety information will depend on factors such as the nature of the device and its classification, intended use and targeted jurisdictions.

## 6.1 Product safety: Drug development

Product safety is a major question to address during the drug development process. When undertaking drug development, the product safety profile of the investigational product must be properly evaluated to support the conduct of clinical studies and product licensing. This is because every single drug that affects the human body has some side effects. A drug can receive regulatory approval when its benefits (efficacy) outweigh its known risks (safety) for its intended use.[1]

### 6.1.1 Product safety: Non-clinical and clinical information

The product safety information presented in a submission dossier (for regulatory review) is generally comprised of non-clinical and clinical information. To understand the safety assessment of a drug, one needs to understanding the drug itself and its intended use. In addition to the drug itself, factors such as the dosing regimen, treatment duration and route of administration can affect the data required to establish product safety.[2]

The cost of new drug development is high, with only about 3% to 5% of products that enter initial clinical evaluation becoming marketed drugs. It is estimated that just getting to the point of opening a clinical trial (e.g., an Investigational New Drug Application [IND]) costs a minimum of $2.2 million, plus the cost of drug synthesis. Biological therapeutics are more expensive yet, with the estimated cost to reach IND at $4.5 million.[2] Because of these financial implications, **minimizing the drug development time and cost is essential.** To this end, design and perform clinical studies according to regulatory standards.

***Non-clinical evaluation***[2,3]

Non-clinical safety assessments (such as all supportive toxicokinetic and metabolism activities and studies) are conducted to support:

1. **Clinical trial application filing for first-in-human studies:** These non-clinical studies normally include acute and repeated dose systemic toxicity studies in rodent and non-rodent species, genetic toxicity and safety pharmacology studies to support repeat dose clinical studies up to at most four weeks in duration.
2. **Continual clinical evaluation and drug development, up to and through Phase III studies:** For Phase III clinical trials that are often longer than four weeks of dosing, longer-term non-clinical toxicity studies must be conducted in both selected rodent and non-rodent species. Additionally, developmental and reproductive toxicity studies are usually required to include a broader range of patients in clinical trials.
3. **Marketing approval application (i.e., a New Drug Submission or its equivalent):** This includes long-term non-clinical studies such as carcinogenicity studies and the final part of reproductive toxicity studies.

The International Conference on Harmonisation (ICH) has published guidance documents* that include the following safety topics.[3]

- Carcinogenicity studies
- Genotoxicity studies
- Toxicokinetics and pharmacokinetics
- Toxicity testing
- Reproductive toxicity
- Biotechnological products
- Pharmacology studies
- Immunotoxicology studies
- Non-clinical evaluation for anticancer pharmaceuticals
- Photosafety evaluation

In addition, the following joint safety/efficacy (multidisciplinary) guidance documents should be evaluated in support of the product safety information required for clinical studies:[3]

- ICH M3(R2) and its Q&A documents*: Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*
- ICH M7*: Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk* (Step 2)*
- ICH Topic E8: *General Considerations for Clinical Trials*

For drug products administered by routes other than oral, additional studies that address local tissue response to the administered clinical dosage are expected. These tests include studies such as:

- Hemolysis (for intravenous products)
- Pyrogenicity (for parenteral products)
- Sensitization (for dermal products)
- Route-specific irritation assays (e.g., eye, skin, muscle, mucosal, nasal)[2]

As well, determine whether any local guidance documents apply to your product.

***Drug development: Clinical safety assessment***
As with all drug products, adequate and well-controlled clinical studies are conducted to evaluate the product safety in human use. It is critical to include such information in your submission to support regulatory approval.

## 6.1.2 Drug development: Product safety evaluations do not end

Drug safety evaluation is an ongoing activity as the premarket testing of drugs cannot detect all the problems that can occur with a drug, especially rare events (e.g., those occurring in 1 in 10,000 people). Other problems such as medication errors and mix-ups with similar-sounding products are hard to foresee prior to regulatory approval. Thus, a vigorous program is needed after drugs are marketed to detect product safety problems and correct them as soon as possible.[4]

Compliance with any regional-specific requirements is critical to maintain your product licence and to protect public health. Such activities may include safety reporting, annual safety reports, post-approval studies, post-market surveillance studies and more. If the risk-benefit ratio changes, the product label may need to change, or the product may even need to be withdrawn to protect patient safety.

* *Note:* Guidance documents must reach Step 4 of the ICH process before they are ready for adoption by regulatory agencies. For more information about the harmonization steps, see ICH's FAQs page (click on "ICH Harmonisation Process").

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## 6.2 Product safety: Medical devices

The product safety of a medical device is one of the primary questions to address in healthcare product development. Regulatory agencies worldwide are responsible to safeguard public health. No matter how effective a healthcare product is, if the company developing it cannot prove that its benefits (effectiveness) outweigh the risks (safety), the medical device will not receive regulatory clearance or regulatory approval. Product-related safety is also one of the major reasons for product recalls, label changes (e.g., increased warnings) and licence withdrawals or suspensions for marketed medical devices.[1]

### 6.2.1 Scientific evidence needs to be submitted to support product safety

During the regulatory review of a medical device, scientific evidence is submitted to support the product safety. Depending on its classification, evidence may come from non-clinical data (e.g., bench studies, animal studies) and/or clinical studies. Ultimately, the probable benefits should outweigh the risk of injury or illness from product use. Obviously, the safety of the medical device plays a major role in such benefit-risk assessment.[1]

When developing a medical device, the amount and type of product safety information required will vary depending on factors such as what the device is as well as its classification, intended use and targeted jurisdictions. The information to support device safety may include, but is not limited to, the areas outlined below.

***Risk management of medical device***

Throughout the medical device lifecycle, establish, document and maintain an ongoing process for:

- Identifying hazards associated with your medical device
- Estimating and evaluating the associated risks
- Controlling these risks
- Monitoring the effectiveness of these controls

This process shall include risk analysis, risk evaluation, risk control as well as production and post-production information.[2]

Identify possible hazards with the device design under both normal and fault conditions, including those resulting from user/human error. **Unacceptable risks should be reduced to acceptable levels** via mitigations such as redesigning the medical device (e.g., adding an alarm or changing the material), changing the manufacturing process, or including warnings or precautions in the product label.[1,2]

***Non-clinical testing***[1,3]
Non-clinical tests may include:

- ***Chemical testing*** on the medical device composition and its components. Materials such as metallic alloys, plastics, natural or synthetic biomaterials, or composite materials should be of acceptable quality (e.g., medical grade instead of industrial grade) with no safety concerns. If applicable, the degradation profile and degradation mechanisms should be identified and their corresponding impact evaluated.
- ***Biocompatibility*** **testing**, which should be conducted in accordance with *ISO 10993 Biological Evaluation of Medical Devices* if the device or any part of it will come into contact with the human body. Biocompatibility testing is intended to reveal any potential for adverse events or allergic reactions and may be used to establish preliminary levels of toxicity. The number of tests (e.g., cytotoxicity, sensitization, irritation, different types of toxicities) is selected based on the patient exposure to the device.* The biocompatibility of the material used in the medical device is a particular issue for polymeric ingredients, degradable components, animal-sourced substances and novel materials. Additionally, the manufacturing process (e.g., sterilization) may affect the biocompatibility of the device and thus testing should be conducted on the finished sterilized device unless you can provide a justification not to do so.
- ***Sterility & stability*** – for details, please see Chapter 5.5 Sterilization: Healthcare products and Chapter 5.6 Stability: Healthcare products.
- ***Animal tissue safety*** – if the device incorporates material of animal origin (e.g., collagen), provide information regarding the inactivation or removal of infectious/transmissible agents and the absence of infectious agents such as bacteria, fungi, yeast, mycoplasma and viruses. Provide also information (e.g., a Certificate of Suitability) related to transmissible spongiform encephalopathies (TSEs).
- ***Medical equipment safety*** testing, which demonstrates your compliance with safety standards (e.g., IEC 60601 series), helps show that your medical device poses no risk of:
  - Fire
  - Electrical shock
  - Burns or tissue damage due to contact with high-energy sources
  - Exposure to ionizing radiation
  - Physical injury due to mechanical hazards
  - Malfunction due to electromagnetic interference or electrostatic discharge
- ***Mechanical safety*** testing, which ensures the medical device (e.g., an orthopedic device) is sufficiently strong to retain its integrity under conditions of normal wear and tear for its intended use.

***Animal studies***
If required, animal studies should be conducted in accordance with Good Laboratory Practices (GLP) using an appropriate study design. For instance, for an absorbable hemostatic device, animal testing may be required to evaluate and monitor complications such as infection, hematoma, coagulopathy or increased wound-healing time.[4]

***Clinical data***
Depending on the medical device classification, your product and the targeted jurisdictions, clinical evaluation and/or clinical trials may be required to evaluate the safety of the device in human use.

## 6.2.2 Medical devices: Product safety evaluations do not end

The safety evaluation of a medical device is an ongoing process and does not end with regulatory approval to market the healthcare product, or its clearance. Post-marketing activities related to monitoring the safety of the medical device may include:

- Medical-device reporting
- Post-approval studies
- Post-market surveillance studies
- Medical-device tracking
- Voluntary or mandatory recalls
- Handling of complaints
- Any necessary notifications, repairs, replacements or refunds[1]

If the risk-benefit ratio changes with new safety evidence from post-marketing activities, the medical device label or design may need to change, or the product may even need to be withdrawn to protect user safety.

*The U.S. Food and Drug Administration (FDA) has issued a guidance document called *Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing."* It replaces #G87-1 #8294 [blue book memo]). In addition to the tests recommended in the ISO standard, the FDA has identified additional tests that may be applicable for your medical device. Consider these as you design studies for products that are intended for the US market.

### References


[1] DeMarco, C.T. (2011). *Medical Device Design and Regulation*. WI: Quality Press.

[2] International Organization for Standardization. ISO 14971:2007. *Medical devices – Application of riskmanagement to medical devices.*

[3] Prutchi, D. & Norris, M. (2005). *Design and Development of Medical Electronic Instrumentation: A Practical Perspective of the Design, Construction and Test of Medical Devices.* NJ: Wiley-Interscience.

[4] U.S. Food and Drug Administration. (2006, October 31). *Draft Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Absorbable Hemostatic Device*. Retrieved July 11, 2012, from http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071424.htm.

# Chapter 7: **Product-related efficacy**

This chapter concentrates on clinical trials. Chapter 7 discusses Good Clinical Practice (GCP) – what it is, the main principles and where to find further reading on these standards. Chapter 7 looks at how clinical trials are fundamental to the development of innovative, investigational drugs and certain medical devices. Chapter 7.3 highlights the roles and responsibilities of sponsors and sponsor-investigators, and the difference between the two.

## 7.1 Clinical trials and Good Clinical Practice (GCP)

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects.[1]

Regardless of whether a clinical trial is a large, multi-centre study in patients or a small clinical pharmacological study in healthy subjects, the relevant GCP standard should be followed by the sponsoring company of the healthcare product, the investigators, the ethics committees and any clinical research organizations.

### 7.1.1 Companies undertaking a clinical trial must follow certain procedures and practices

Companies undertaking a clinical trial should develop written procedures for implementing GCP.[2] Such procedures may include, but are not limited to, the following:

- Investigator site selection
- Regulatory document collection, review and submission
- Financial disclosure
- Investigator site initiation
- Investigational product distribution and tracking
- Clinical monitoring of investigator site
- Investigator site close-out
- Safety reporting
- Quality assurance audits
- Required documents for study master file and document retention
- Vendor qualification and oversight (e.g., contract research organization)
- Indemnity, compensation and insurance

### 7.1.2 GCP and the International Conference on Harmonisation[3,4]

Prior to the GCP guidance document developed by the International Conference on Harmonisation (ICH), different jurisdictions had different guidelines relating to the conduct of clinical trials. With the introduction of ICH GCP, the conduct of clinical trials globally has become more uniform and practicable. Today, the implementation of ICH good clinical practice in most jurisdictions is reasonably similar and the vast majority of the regulations are the same.

Despite the effort of ICH, there still exists some local differences. For example, the US no longer adheres to the Declaration of Helsinki in its entirety, because the declaration considers placebo-controlled trials unethical in cases where an active drug is available. New privacy regulations in the EU and the financial disclosure requirements in the US are also making the clinical trial landscape more complicated.

**Healthcare product developers should therefore work to ICH in the context of local regulations.**

### 7.1.3 GCP principles for clinical trials[5-7]

The regulations, guidance and industry standards that make up Good Clinical Practice are intended to provide assurance that the rights, safety and well-being of clinical trial subjects are protected. GCP is also intended to assure that the research yields quality scientific data. Fundamentally, Good Clinical Practice requires:

- Oversight of the local ethics committee(s)
- Verification of the investigator's qualifications
- A study protocol, investigator's brochure,[i] informed consent, and the documentation that is essential for undertaking a clinical trial
- Monitoring of the clinical trial
- Submission of reports and maintenance of records

The ICH GCP lays out the responsibilities of the ethics committees, sponsors and investigators.

The core principles of ICH Good Clinical Practice are presented in Table 7.1-1.

***Table 7.1-1: Thirteen core principles of GCP[1,5]***

| | |
|---|---|
| Ethical principles: Declaration of Helsinki | Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and applicable regulatory requirement(s). |
| Favourable benefit(s) vs. risk(s) | Before a clinical trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A clinical trial should be initiated and continued only if the anticipated benefits justify the risks. |
| Subject's rights | The rights, safety and well-being of the trial subjects override the interests of science and society. |
| Adequate supporting data | The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial. |
| Scientifically sound protocol | Clinical trials should be scientifically sound and described in a clear, detailed protocol. |
| Independent ethics committee oversight | A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval or favourable opinion. |

| | |
|---|---|
| Medical care by qualified investigator | The medical care given to subjects, and the medical decisions made on their behalf, should always be the responsibility of a qualified physician or, when appropriate, a qualified dentist. |
| Qualified personnel | Each individual involved in conducting a clinical trial should be qualified by education, training and experience to do their respective task(s). |
| Informed consent | Freely-given informed consent should be obtained from every subject prior to participation in the clinical trial. |
| Record-keeping | All clinical trial information should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification. |
| Subject confidentiality | The confidentiality of records that could identify subjects should be protected – respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s). |
| GMP manufacturing of the investigational product | Investigational products should be manufactured, handled and stored in accordance with applicable Good Manufacturing Practice (GMP). They should be used in accordance with the approved protocol. |
| Quality assurance & monitoring | Systems with procedures that assure the quality of every aspect of the clinical trial should be implemented. |

### 7.1.4 GCP: Related regulations and guidance documents

For further reading, key documents related to GCP are listed below.

- International Conference on Harmonisation (ICH). *ICH E6(R1) Notice for Guidance on Good Clinical Practice: Consolidated Guideline*
- US Code of Federal Regulations, Title 21:
  - Part 50, *Protection of Human Subjects*
  - Part 54, *Financial disclosure by clinical investigators*
  - Part 56, *Institutional review board*
- US Code of Federal Regulations, Title 45, Part 46, subtitle A, *Protection of Human subjects*
- US *Health Insurance Portability & Accountability Act* (HIPAA): US Code of Federal Regulations, Title 45 Part 160, and Subparts A and E of Part 164.
- EU Clinical Trials Directive (2001/20/EC)
- EU GCP Directive (2005/28/EC)
- Health Canada. Regulations amending the *Food and Drug Regulations* (Schedule No. 1024 – Clinical Trials). Division 5. Drugs for Clinical Trials Involving Human Subjects.
- Department of Justice Canada. *Personal Information Protection and Electronic Documents Act*
- ISO 14155. *Clinical investigation of medical devices for human subjects – Good clinical practice*

### 7.1.5 Importance of GCP: An example from the US[8]

On February 25, 2013, the U.S. Food and Drug Administration (FDA) issued a *draft* guidance document entitled *Human Subject Protection: Acceptance of Data from Clinical Studies for Medical Devices*. Once finalized, this will require that clinical studies conducted *outside* the US and used to support medical device applications[ii] comply with GCP. This compliance would include obtaining and documenting the review and approval of the study by an independent ethics committee (IEC), and obtaining and documenting freely given informed consent from study subjects. Applicants would need to ensure that the quality and integrity of the data was in line with US requirements. The proposed amendment intends to make consistent the FDA requirements for accepting clinical data, whatever the application or submission type, drug or device. The amendment also expands the FDA's authority to not accept any non-compliant foreign clinical data that supports a medical device application.

[i] A product information brochure, package leaflet or labelling may be an appropriate alternative as permitted by regulatory agencies.

[ii] For example, investigational device exemption (IDE) applications, premarket notification (510[k]) submissions, premarket approval (PMA) applications, humanitarian device exemption (HDE) applications, or product development protocol (PDP) applications

#### References


1 Tobin, J.J. & Walsh, G. (2008). Chapter 5. Clinical trial. In *Medical product regulatory affairs. Pharmaceuticals, diagnostics, medical devices*. Weinheim: Wiley-VCH Verlag GmbH & Co. KGaA.

2 Buckley, B. & Blanks, R. (2008). Chapter 8. Overview of the GxPs for the regulatory professional. In Pisano, D.J., Mantus, D.S. (Eds.), *FDA regulatory affairs. A guide for prescription drugs, medical devices and biologics*. (2nd ed.). New York: Informa Healthcare.

3 Darwin, K.L.R. (2009). Chapter 7. Conduct of clinical trials: Good Clinical Practice. In Griffin, J.P. (Ed) *The textbook of pharmaceutical medicine*. (6th ed.). West Sussex: John Wiley & Sons Ltd.

4 Kolman, J., Meng, P. & Scott, G. (1998). Introduction. In *Good clinical practice: Standard operating procedures for clinical researchers*. West Sussex: John Wiley & Sons Ltd.

5 International Conference on Harmonisation. (1996, June). *E6(R1): Good clinical practice.* Retrieved July 12, 2012, from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf.

6 Becker, K.M. & Whyte, J.J. (2006). *Clinical evaluation of medical devices. Principles and case studies.* (2nd ed.). Totowa: Humana Press.

7 Brody, T. (2012). *Clinical Trials: Study Design, Endpoints and Biomarkers, Drug Safety, and FDA and ICH Guidelines.* London: Academic Press.

8 U.S. Food and Drug Administration. (2013, February 25). Human Subject Protection: Acceptance of Data from Clinical Studies for Medical Devices. *Federal Register*, 78(37), p.12664. Retrieved March 15, 2013, from http://www.gpo.gov/fdsys/pkg/FR-2013-02-25/pdf/2013-04201.pdf.


## 7.2 Clinical trials: Medical device and drug development

Clinical trials are fundamental to the development of innovative, investigational products such as drugs or high-risk (and some medium-risk) medical devices.* Many products are found to be safe and effective in bench testing, *in vitro* testing or animal studies, but fail to demonstrate the same effect in humans.[1,2] These investigational products must be proven safe and effective in a human clinical study before use in the general population.

### 7.2.1 Clinical trials: Drug development

Drug development is often complex, time-consuming and resource-intensive. It requires particular attention to ensure the appropriateness of the clinical trial being conducted for the drug or biologic.

***Adequate and well-controlled clinical studies***

Clinical studies that support regulatory submissions are expected to be **adequate and well-controlled.** The clinical study reports should provide sufficient details of the study design, conduct and analysis to determine whether there is substantial evidence to support the claims of effectiveness of the investigational product.

The US Code of Federal Regulations, Title 21, Part 314.126 describes the characteristics of such a study:[3]

1. **Study objective and analysis method**: Document this in the clinical study protocol and report.
2. **Study design:** Design with a valid comparison to a control (e.g., placebo, dose-comparison, active, no treatment, or historical controls) to provide a quantitative assessment of the product's effect. The clinical study design, including treatment duration, whether treatments are parallel, sequential or crossover, and whether the sample size is predetermined or based upon interim analysis should be included in the protocol and the report.
3. **Subject selection method:** Use a method that provides adequate assurance that the subjects have the disease or condition being studied, or evidence of susceptibility and exposure to the condition against which prophylaxis is directed.
4. **Patient assignment method:** Use a method to assign patients to treatment and control groups that minimizes bias and assures group comparability regarding pertinent variables such as age, sex, severity of disease, duration of disease, and use of therapy other than the investigational product. Assignment is normally by randomization, with or without stratification, in a concurrently controlled clinical study.
5. **Minimize bias:** Take adequate measures (e.g., blinding) to minimize bias on or by subjects, observers and data analysts.
6. **Assessment method of subject's response:** Use a method that is well-defined and reliable. In the clinical trial protocol and report, include the variables measured, the observation methods and the criteria used to assess response.
7. **Product effect analysis:** In the clinical trial protocol and report, include the results and analytic methods, as well as any statistical methods. The analysis should include information such as the comparability of test and control groups regarding pertinent variables and the effects of any interim data analyses performed.

***Uncontrolled or partially controlled clinical studies[3]***

Uncontrolled or partially controlled clinical studies are generally not acceptable as the **sole** basis for approval of claims of effectiveness. Such studies that are carefully conducted and documented **may provide corroborative support** of well-controlled studies regarding efficacy, and may yield valuable data regarding the safety of the test product. Isolated case reports, random experience and reports lacking the details that permit scientific evaluation are not generally considered.

### 7.2.2 Clinical trials: Medical devices[4]

For medical devices, frequent innovations in the design and use (e.g., minor modifications that enhance safety, reliability, patient comfort, or ease of use) are common and often do not require prior regulatory approval. Bench and/or animal testing is often sufficient to validate the suitability of a design change.

In cases when a clinical trial is required (e.g., for high-risk or some medium-risk devices), evidence can come from sources other than well-controlled clinical studies, when justified. Such sources may include:

- Partially controlled clinical studies
- Clinical studies and objective trials without matched controls
- Well-documented case histories conducted by qualified experts
- Reports of significant human experience with a marketed device

The reason for these varied sources of evidence is that the design of medical-device clinical trials may present some special challenges that do not arise with drug trials. These are outlined below.

***Challenges in designing clinical trials for medical devices***

- **Devices are primarily used by healthcare professionals:** The clinical outcomes of a medical device's safety and effectiveness are a function of the user's skill paired with the device-patient interaction. Having training in the use of the medical device is a key part of its clinical performance.
- **Inability to blind the user/patient:** Medical devices are often designed differently and this can introduce bias into the assessment of the clinical performance if the clinical investigator is jointly responsible for treatment and assessment of performance. Thus, whenever possible, blinded evaluators are preferred to clinical investigators for the assessment of efficacy.
- **Limitation in comparative trial design (e.g., an implanted device):** Comparative clinical trials may be precluded due to ethical considerations. The use of historical controls in the trial or patients as their own controls (pre- and post-surgery) may be required to evaluate outcomes.

***Often, the process for regulatory clearance or approval for medical devices is more flexible than it is for drug development.***

In drug development, the replication of clinical findings (i.e., more than one clinical trial) is required. However, for medical devices, sometimes a single pivotal clinical trial can suffice because the mechanism of action is a result of product design and can be substantially verified by *in vitro* performance testing.[5] Nevertheless, due to the challenges highlighted above, it is recommended that you consult with the relevant regulatory body (or bodies) at your product development stage. This will help ensure that the design of your clinical program is adequate to support your medical device application.

* Certain lower-risk medical devices (e.g., class I or most 510[k] devices) do not require a clinical study.

**References**

[1] Canada trials. (2008, April 26.) *What is clinical research?* Retrieved July 13, 2012, from http://www.canadatrials.com/AboutClinicalResearch.php.

[2] People for the Ethical Treatment of Animals. (n.d.). *Animal Experiments: Overview*. Retrieved September 24, 2012, from http://www.peta.org/issues/animals-used-for-experimentation/animal-experiments-overview.aspx.

[3] United States Code. Title 21, Part 314.126, *Adequate and well-controlled studies.*

[4] Becker, K.M. (2006). Clinical trials in development and marketing of medical devices. In Becker, K.M., Whyte, J.J. (Eds.) *Clinical evaluation of medical devices. Principles and case studies*. (2nd ed.). Totowa: Humana Press.

[5] U.S. Department of Health and Human Services. (1995, August 1). *Statement Regarding the Demonstrations of Effectiveness of Human Drug Products and Devices*. Docket No. 95N-0230. Retrieved September 26, 2012, from US Federal Register Online via the Government Printing Office: http://www.gpo.gov/fdsys/pkg/FR-1995-08-01/html/95-18877.htm.

## 7.3 Clinical trials: Sponsors and sponsor-investigators

In the conduct of a clinical trial, a **sponsor** is an individual, institution, company or organization (e.g., a contract research organization) that takes the responsibility to initiate, manage or finance the clinical trial,[1] but does not actually conduct the investigation.

A **sponsor-investigator**, on the other hand, takes on the responsibility as a clinical study sponsor and *also* conducts or oversees the clinical trial. Thus, a sponsor-investigator must comply with the applicable regulatory requirements that pertain to both the sponsor and the investigator.[2,3]

### 7.3.1 Study sponsor responsibilities

The specific regional requirements for a clinical study sponsor can vary. Generally, a sponsor is responsible for:[3,4]

- Selecting the investigator(s)
- Providing investigator(s) with the necessary information to conduct the clinical trial
- Ensuring proper monitoring of the clinical study
- Ensuring all the necessary ethic review(s) and approval(s) are obtained
- Preparing and submitting clinical trial application(s) and amendment(s) to the appropriate regulatory agencies
- Ensuring that any reviewing ethics board and regulatory agencies are promptly informed of any significant new information (e.g., important findings that affect product safety) in a clinical study
- Ensuring compliance with labelling, reporting and record-keeping requirements
- Refraining from engaging in promotional activities and other prohibited activities such as commercializing an investigational medical device
- Ensuring that the clinical study is conducted in accordance with Good Clinical Practice (GCP)

### 7.3.2 Study investigator responsibilities

In a clinical trial, the responsibilities of an investigator generally include:

- Protecting the rights, safety and welfare of subjects in the clinical study
- Ensuring that informed consent is properly obtained from clinical trial subjects
- Conducting the clinical study (i.e., directly overseeing the administration of the test products to the subject). In situations where there is a team of researchers, the investigator will act as the team leader
- Ensuring that the clinical trial is conducted in accordance with the signed agreement and the investigational plan
- Controlling the products under investigation (e.g., supervising medical-device use and disposal)
- Ensuring proper record-keeping and reporting requirements are met (e.g., mandatory safety reporting)[3,4]

***Sponsor-investigators: Additional considerations***[1]

Sponsor-investigators also generally need to manage the following:

- Securing funding for the clinical trial
- Applying for the appropriate insurance
- Generating the appropriate clinical trial documentation (e.g., informed consent, protocols) and submissions (e.g., ethics and/or regulatory submissions)
- Ensuring adequate resources are available for the duration of the trial (e.g., experienced staff, investigational and control products, clinical and medical supplies, an analytical laboratory)
- Creating appropriate written procedures (e.g., standard operating procedures related to GCP)
- Meeting all the applicable regulatory requirements such as obtaining and maintaining necessary approvals from the relevant ethics review boards and regulatory agencies

### 7.3.3 Sponsor-investigators: Getting started with a clinical trial application

While the completion of a clinical trial application involves many tasks and may seem daunting, there are many resources to help. The following approach can assist you:

1. Research the regulatory requirements pertaining to the applicable submissions. Make good use of regulatory agency websites and professional organizations as well as related publications, seminars and training.
2. Contact the relevant regulatory agency via formal or informal means. Formal means may take the form of a request for a pre-submission meeting with the agency. Informal means may include contacting them with general questions.
3. Prepare and submit the application based on the format and content relevant to the specific submission. Make sure that any comments or feedback received at the pre-submission meeting are incorporated in the submission dossier.
4. After a submission is approved, ensure that all the post-approval requirements are fulfilled, such as any required safety reporting, annual reporting and amendment submissions relating to significant changes to the products or study plan.
5. Make certain that you fulfill your responsibilities as a sponsor as well as an investigator according to applicable regulatory requirements.

## References


[1] International Conference on Harmonisation. (1996, June). *E6(R1): Good clinical practice.* Retrieved September 25, 2012, from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf.

[2] European Community. (2001, April 4). Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. *Official Journal of the European Communities.* Retrieved July 13, 2012, from http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF.

[3] Kracov, D.A. & Dwyer, L.M. (2006). Regulatory requirements for clinical studies of medical devices and diagnostics. In Becker, K.M., Whyte, J.J. (Eds.) *Clinical evaluation of medical devices. Principles and case studies*. (2nd ed.). Totowa: Humana Press.

[4] United States Code. (2012, April 1). Title 21, Part 812, *Investigational device exemption.* Retrieved August 17, 2012, from http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=812&showFR=1.

# Chapter 8: **Regulatory submission processes: Canada, US and the EU**

The procedures and timelines needed to reach regulatory approval vary across jurisdictions and depend on the type of product involved. Chapter 8 surveys the regulations that govern submissions in Canada, the US and the EU.

## 8.1 Drug submissions: Procedures to reach regulatory approval

Before a new drug or biologic can go to market, a submission must be compiled and filed with all relevant regulatory agencies to seek a review and, ultimately, regulatory approval.

Canada, the US and the EU each require different types of submissions (Table 8.1-1).

***Table 8.1-1: Drug/biologic submission types: Canada, the US and the EU[1-4]***

| Jurisdiction | Submission type |
|---|---|
| Canada | *New Drug Submission* (NDS) – for both drugs and biologics |
| US | *New Drug Application* (NDA) – for drugs<br>*Biologic License Application* (BLA) – for biologics |
| EU | *Marketing Authorization Application* (MAA) – via the centralized procedure for eligible products (Table 8.1-2).<br>For other products, routes such as the decentralized procedure, the mutual recognition procedure or national authorization apply. |

***Table 8.1-2: EU: Products eligible for the centralized procedure[4]***

| Mandatory | Optional |
|---|---|
| • Human medicines for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, autoimmune and other immune dysfunctions, and viral diseases<br>• Medicines derived from biotechnology processes, such as genetic engineering<br>• Advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines<br>• Officially-designated "orphan medicines"(medicines used for rare human diseases) | • Other new active substances not authorized in the European Community before May 20, 2004<br>• Medicinal products that contribute significant therapeutic, scientific or technical innovation or are in the interests of patient health<br>• A generic copy of a centrally authorized product |

### 8.1.1 Review and approval procedures[1-4]

Each jurisdiction has its own procedures to review drug submissions filed to their regulatory agency. These procedures can vary substantially with respect to how the drug submission will be handled, the composition of the review team, review timelines and so on.

Despite the differences, the procedures to reach regulatory approval generally follow these stages:

**Pre-submission meeting**[5]
Although optional, a pre-submission meeting is often useful, especially for innovative products, so that any scientific or submission issues can be discussed and resolved prior to the actual submission. This meeting also provides the agency insight into your drug or biologic submission and allows them to organize their internal resources accordingly.

*Tip:* Ensure the issues discussed at the pre-submission meeting are addressed in the submission dossier, with additional data or a sound scientific justification provided.

**Pre-submission activities**
Review what communication is required prior to submitting your marketing application. In Canada, sponsors (i.e., applicants) are requested to send advance requests for Priority Review status and for Requests for Advance Consideration under the NOC/c.[6] In the EU, an applicant should notify the European Medicines Agency (EMA) of its intention to submit via the centralized procedure at least seven months before the drug submission.[7] Any orphan drug designation should also be requested and approved before your drug submission will be reviewed as an orphan product.

**Administrative review**
Once a drug submission is filed, it goes through an administrative review to ensure its acceptability (e.g., completeness). A submission number (e.g., NDS Control Number, NDA number) is assigned and this number must be used in all subsequent communication with the regulatory agency.

If the drug submission is found to be acceptable at this stage, it will be accepted for review. If minor deficiencies are identified (e.g., missing forms), the agency will normally allow the sponsor time to respond. If the response is satisfactory, then the submission will proceed to review. If the sponsor fails to provide the requested information within the set timeframe, or if that the response is unsatisfactory, the agency can reject (refuse to file) the submission.

*Tip:* Adhere to the response timeline indicated. Should you need more time, contact the agency and request an extension, providing a justification. The agency will determine if an extension can be granted.

**Agency review and sponsor response**
Once a drug submission is accepted, it is evaluated by reviewers with the necessary expertise. In the US, for example, a review team may include clinicians, pharmacokineticists, pharmacologists, toxicologists, statisticians, microbiologists and chemists, as well as a regulatory project manager (RPM). The objective of the review is to confirm and validate the sponsor's conclusion that the drug is safe and effective for its proposed use.

Once the technical review is complete, an evaluation report will be generated. If the submission is deemed acceptable, then the technical review of the submission is complete. If deficiencies are identified, then the agency will issue a list of questions for the sponsor to address within a set timeline.

This review also evaluates the text in the proposed labelling, which needs to be justified by the data submitted in the submission. If the reviewers question the proposed labelling, they will discuss revised wording with the sponsor.

*Tip:* Assemble a response team that can address agency questions and requests for additional information. A quick response by the sponsor facilitates the review process.

**Activities prior to the agency's decision**
These may include any necessary pre-approval inspections (e.g., of drug manufacturing sites or clinical trial sites). In the US, for example, the Food and Drug Administration (FDA) may decide to convene an advisory committee (AC) meeting and seek input. Based on the discussions at the AC meeting and its recommendations, the FDA may ask for additional data or analyses to review.

**Decision**
The decision made at the end of the review process normally results in regulatory approval, an approval with conditions, or a rejection.

* NOC/c = Notice of Compliance with conditions

## References


[1] Health Canada. (2011, March 29). *Guidance for industry: Management of drug submissions*. Retrieved July 18, 2012, from http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/mgmt-gest/mands_gespd-eng.php#a5.2.

[2] U.S. Food and Drug Administration. (2005, April). *Guidance for Review Staff and Industry. Good Review Management Principles and Practices for PDUFA Products*. Retrieved July 18, 2012, from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079748.pdf.

[3] European Commission. (2007, February). *Notice to applicants. Volume 2A. Procedures for marketing authorisation. Chapter 2 Mutual Recognition*. Retrieved July 18, 2012, from http://ec.europa.eu/health/files/eudralex/vol-2/a/vol2a_chap2_2007-02_en.pdf.

[4] European Commission. (2006, April). *Notice to applicants. Volume 2A. Procedures for marketing authorisation. Chapter 4 Centralized Procedure*. Retrieved July 18, 2012, from http://ec.europa.eu/health/files/eudralex/vol-2/a/chap4rev200604_en.pdf.

[5] Grignolo, A. (2008). Meeting with the FDA. In Pisano, D.J. & Mantus, D.S. (Eds.) *FDA regulatory affairs: A guide for prescription drugs, medical devices, and biologics* (2nd ed., pp.109-23). New York: Informa Healthcare.

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[7] European Medicines Agency. (2012, April). *European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure*. Retrieved September 26, 2012, from http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004069.pdf.

## 8.2 Medical device submissions: Procedures to legally place a medical device on the market

The procedures required to legally place a medical device on the market vary in Canada, the US and the EU. Different regulatory bodies are involved, requiring different types of submissions (Table 8.2-1) and review timelines depending on the classification of the device.

***Table 8.2-1: Medical device submissions: Canada, the US and the EU[1-7]***

| Jurisdiction | Submission | Device classification | Regulatory body |
|---|---|---|---|
| Canada | Establishment registration | Class I | Health Canada |
| | Medical Device Licence Application | Classes II, III & IV | |
| US | Establishment registration | Classes I, II & III | U.S. Food and Drug Administration (FDA) |
| | Traditional, abbreviated or special 510(k)s | Class II, and some class I | FDA<br>**OR**<br>Accredited party + FDA (for products eligible for third-party review) |
| | *De novo* | Low- to moderate-risk devices that have been classified as class III because they were found not substantially equivalent to existing devices | FDA |
| | PMA/PDP* | Class III | FDA |
| EU | Technical documentation | Class I, and certain class IIa | Self-certification by manufacturer |
| | Technical file | Class IIa & IIb | Notified Body |
| | Design dossier | Class III | Notified Body |
| | Consultation dossier (only for the medicinal ingredient used in the device) | Class III (a device with a medicinal ingredient) | Competent Authority (coordinate via the Notified Body) |

* PMA = Premarket authorization application
PDP = Product development protocol

### 8.2.1 Canada: Registration process for medical devices

The regulatory review process in Canada is straightforward. The sponsor (applicant) deals with a single regulatory agency, Health Canada. For class I medical devices, the manufacturer needs to apply for an establishment licence unless he or she imports or distributes it solely through someone who already holds an establishment licence. For medical devices that are classified as class II, III or IV, a Medical Device Licence Application must be submitted.

The higher the risk of the medical device, the more information is required in the licence application and the more the time is required to reach regulatory approval (e.g., in the first screening and review cycle, the agency's performance goals are 15 days for class II and 90 days for class IV).

The submission typically goes through an administrative screening, an application validation and a review. At each stage, the submission is checked to see if it meets Health Canada's standards of acceptability and regulatory safety and effectiveness requirements. A medical device submission can be deemed unacceptable at any point in the review process. If this occurs, the sponsor will have to provide additional information or a clarification before the submission can advance. Otherwise, a refusal letter may be issued by Health Canada.[1]

When a submission reaches the end of the review process, a decision whether or not to provide regulatory approval will be made.

### 8.2.2 US: Registration process for medical devices

The type of review required by the FDA depends on the medical device classification. Devices that are exempt from the premarket notification or authorization requirements are subject to general controls, including the establishment registration and device listing and labelling, record-keeping and reporting requirements. For medical devices that are subject to the 510(k) notification process, the target review timeline is 90 days. The target review timeline for a Special 510(k) is 30 days. For PMA applications for class III devices, the target review timeline is 180 days.[2]

**De novo *process***

For lower-risk medical devices that do not have a predicate device (which results in an automatic class III designation), a sponsor may request a *de novo* classification of the product in order to reclassify it as class I or II. The request must be in writing and sent within 30 days from the receipt of the Non-Substantial Equivalence (NSE) determination. The request should include all of the following:

- A description of the medical device
- Labelling information
- Reasons for the recommended classification (as class I or II)
- Information to support the recommendation

The *de novo* process has a 60-day review period. If the FDA classifies the medical device as class I or II, the sponsor will then receive regulatory approval to market the medical device. This device can then be used as a predicate device for other firms to submit a 510(k).[3]

***Third-party review***

For eligible medical devices, a sponsor may choose an FDA-accredited third party (i.e., an "Accredited Person") to conduct the primary review of 510(k). After the primary review of the 510(k), the Accredited Person forwards their review, recommendation and the 510(k) to the FDA. The FDA then issues a final determination within 30 days.[4]

### 8.2.3 EU: Legally placing medical devices on the market[5,6]

Before a medical device can be legally placed on the market in Europe, it must go through an appropriate "conformity assessment process" to establish that it meets all the essential requirements of the applicable EU Directives. This process ensures that the device as it is designed and subsequently manufactured will meet the essential requirements. This enables the manufacturer to make a formal declaration of conformity and apply the CE mark of conformity[i] to the device.

For low-risk medical devices (class I and some class IIa), such as a tongue depressor or a colostomy bag, the manufacturer can make a declaration of conformity with the essential requirements based solely on a self-assessment, without needing the involvement of a Notified Body.[ii]

For medium- to high-risk medical devices (Classes IIa, IIb and III), the manufacturer must call on a Notified Body to assess the conformity. The Notified Body may perform one or more tasks as listed in Table 8.2-2. To some degree, the manufacturer may choose their method for the conformity assessment of the device and/or manufacturing system, depending on the type of device and the level of associated risk (Tables 8.2-2 and 8.2-3). The end result is a certificate of conformity that enables the manufacturer to apply CE marking to the product.

***Table 8.2-2: Certification activities of Notified Bodies[6,7]***

| Quality system certification | Device certification |
|---|---|
| • *Full QA system certification:* Certification based on auditing against a quality system standard for design, production and final inspection (e.g., ISO 13485)<br>• *Production QA system certification:* Certification based on auditing against a quality system standard for production and final inspection (e.g., ISO 13485 – design control)<br>• *Product QA system certification:* Certification based on auditing against a quality system standard for final inspection (e.g., EN 46003) | • *EC Design-examination certification:* Certification based on the examination of the design dossier versus standards/essential requirements (paperwork review)<br>• *EC type-examination certification:* Certification of the design based on testing of physical samples versus standards/essential requirements<br>• *EC verification certification:* Certification of individual production batches based on the testing of the whole batch or of batch samples versus standards/acceptance criteria |

***Table 8.2-3: Conformity assessment options available to manufacturers, based on device classifications per the Medical Device Directive 93/42/EEC[6,7]***

| Device classification | Conformity assessment options available to manufacturers |
|---|---|
| I | EC Self Declaration (Annex VII) |
| IIa | Full QA (Annex II) ***minus*** EC Design-examination<br>**OR**<br>EC Declaration of conformity (Annex VII)<br>***plus***<br>EC Verification (Annex IV)<br>*or*<br>Production QA (Annex V)<br>*or*<br>Product QA (Annex VI) |
| IIb | Full QA (Annex II) ***minus*** EC Design-examination<br>**OR**<br>EC Type-examination (Annex III)<br>***plus***<br>EC Verification (Annex IV)<br>*or*<br>Production QA (Annex V)<br>*or*<br>Product QA (Annex VI) |
| III | Full QA (Annex II)<br>**OR**<br>EC Type-examination (Annex III)<br>***plus***<br>EC Verification (Annex IV)<br>*or*<br>Production QA (Annex V) |

The majority of Notified Bodies are independent commercial organizations that are designated, monitored and audited by the relevant Member States (of the EU) via their national Competent Authorities. A company is free to choose any Notified Body to cover the particular class of medical device under review. After approval, post-market surveillance is the responsibility of a Member State via the Competent Authority.

Manufacturers not located in the EU must appoint an authorized representative within the EU. After a product obtains the CE marking, its manufacturers must comply with any additional local registration requirements in each relevant Member State (such as informing the Competent Authority of their registered place of business or of any device description being placed on the market).

Finally, as discussed in Chapter 3.5 Medical device regulations, classification and submissions, make sure to monitor the changes in the EU regulatory environment with respect to the implementation of the two regulations proposed in 2012. Evaluate any impact they may have on the development of your medical device.

[i] A designation that indicates a product meets EU safety, health and environmental protection requirements.

[ii] A Notified Body is certification organization that the national authority (the Competent Authority) of an EU Member State designates to carry out one or more of the conformity assessment procedures described in the annex(es) of the EU Directives. It must be qualified to perform all the functions set out in any annex for which it is designated.[8]

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# Chapter 9: **Unlicensed and licensed products: Advertising and promotion**

Around the world, regulations govern the advertising of licensed healthcare products. Similarly, regulations prohibit the advertising or promotion of unlicensed healthcare products. Chapter 9 looks at what you need to know to stay in compliance.

## 9.1 Unlicensed healthcare products: No advertising or promotion allowed

Internationally, regulations exist to prohibit the advertising or promotion of unlicensed healthcare products. In Canada, Section 9(1) of the *Food and Drugs Act* states that, "*no person shall label, package, treat, process, sell or advertise any drug in a manner that is false, misleading or deceptive or is likely to create an erroneous impression regarding its composition, merit or safety.*" Since the terms and any proposed indication of unlicensed healthcare products have not been established, advertising such products is not permitted.[1]

Similar provisions are laid out in the US Code of Federal Regulations (CFR), Title 21, section 312.7(a) and 812.7(a) – the promotion of any investigational drug or medical device (including a new use under investigation for an existing device) is expressly prohibited.[2,3]

### 9.1.1 Why the promotion or advertising of unlicensed healthcare products is prohibited

The primary concern about the promotion or advertising of unlicensed healthcare products or off-label uses is that a healthcare provider may form an opinion about a product's use on the basis of the claims made by its company before it receives regulatory approval, and that opinion may be incorrect relative to the pending regulatory approval. Such an erroneous opinion on the part of the healthcare provider could lead to incorrect use of the licensed product, thus using the product off-label.[4]

### 9.1.2 When disseminating information on unlicensed healthcare products *may* be deemed acceptable

Although companies that develop healthcare products are not allowed to promote unlicensed products or off-label uses, disseminating information about an investigational product may be acceptable under certain circumstances, as outlined below.

***Scientific information: Medical conferences and continuing medical education*[4,5]**
The US 21 CFR section 213.7(a) recognizes that the prohibition of promoting investigational healthcare products is not intended to restrict the full exchange of scientific information concerning such a product, including presenting scientific findings in scientific or lay media. Additionally, it is recognized by the EU Advertising Directives that without industry sponsorship of scientific meetings and attendance by doctors at such meetings, the medical community would be less well informed.

Companies that develop healthcare products commonly sponsor medical conferences, continuing medical education (CME) or events for the exchange of scientific information (e.g., a poster

presentation of a disease state at a medical conference). All sponsorships should be developed in line with the following:

- Distinguish the critical difference between the provision of information, and promotional material (advertising). Evaluate whether the material is informational or promotional. Do not distribute information if it is promotional in nature.
- Avoid "unduly influencing" speakers to disseminate off-label information.
- Clearly label the marketing status of the product so that you do not mislead your audience. (E.g., you may encounter a situation where a product is approved in some jurisdictions but not in the country of a conference, or that in that particular country is has a different approved indication of use).

To ensure compliance, companies may establish internal programs, procedures and policies that follow industry guidelines regarding CME events and the exchange of scientific information. For instance, the Accreditation Council for Continuing Medical Education (ACCME) has strict accreditation requirements to which CME providers must adhere when holding an event and providing related educational materials.

***Clinical investigation***[4]

When a new drug or medical device, or a new use of a licensed product, is under investigation, any claims of safety and effectiveness about such healthcare products are prohibited unless the company is seeking to recruit clinical investigators or enroll patients in a study. Permissible activities may include:

- "Institutional ads" in which a company states that it is conducting research in a certain therapeutic area to develop a new product, but does not mention the proprietary or established name of the product
- "Coming soon" advertisements, which state the name of the product, but make no representation about the new product's safety, efficacy or intended use

***Unsolicited requests for information***[4]

Often, physicians request scientific information from a company regarding certain healthcare products, and the company's response can contain off-label information. For example, a physician may inquire whether a drug prescribed at X mg/kg for a certain indication can be given at a different dose for another indication for which the drug is not approved. Responses that are non-promotional with balanced scientific information are not considered advertising as long as the company documents the nature of the requests and does not show a pattern of repeatedly disseminating any off-label information.

## References


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## 9.2 Advertising licensed healthcare products

### 9.2.1 What counts as promotion or advertising?

According to the Section 2 of Canada's *Food and Drugs Act*, an advertisement includes "any representation by any means whatever for the purpose of promoting directly or indirectly the sale or disposal of any food, drug, cosmetic or device."[1]

Promotion can take on many forms, including:[2]

- Advertisements
- Internet sites
- Brochures
- Exhibition panels
- Gifts
- Samples
- Reprints
- Product monographs
- A sales representative's activities
- Training materials or briefings
- Press releases
- Meetings or symposia

### 9.2.2 Different regulatory bodies have different views on advertising healthcare products[3,4]

Regulatory systems are in place to safeguard the public from false and misleading advertising of healthcare products. However, among jurisdictions, these systems differ on what constitutes advertising and promotional activities, and thus their regulations and enforcement vary as well.[3] To ensure you comply with industry regulations, **understand the local requirements**.

In Canada, advertising is primarily self-regulated and materials are submitted for preclearance on a voluntary basis. Health Canada is ultimately responsible for enforcement (e.g., in cases when advertising may present a significant health hazard such as when a prescription drug is illegally advertised to the general public or an unauthorized health product is promoted). However, many preclearance activities are delegated to associations such as Rx&D (for review by their *Code of Marketing Practices* committee), Advertising Standards Canada (ASC) and the Pharmaceutical Advertising Advisory Board (PAAB).

South of the border, the U.S. Food and Drug Administration (FDA) regulates the promotional labelling and advertising of prescription drugs directed at healthcare professionals and consumers via the Office of Prescription Drug Promotion (OPDP). It regulates the promotion of "restricted" medical devices* via the Center for Devices and Radiological Health (CDRH). Other devices and over-the-counter drugs are regulated by the Federal Trade Commission (FTC). In most cases, the submission of advertising materials to the FDA is voluntary, with the exception of products that are approved via the accelerated approval process, and "restricted" medical devices. Other than New Zealand, the US is the only country that allows direct-to-consumer advertising of prescription products.

In the EU, advertising regulations vary per country. In the UK, for example, advertising is controlled by both statutory measures (with both criminal and civil sanctions) enforced by the Medicines and Healthcare products Regulatory Agency (MHRA), and self-regulatory measures (through voluntary codes of practices) administered by trade associations.

### 9.2.3 Voluntary practices for advertising

Further to legislation and to guidance documents published by regulatory agencies, pharmaceutical and medical device associations also publish voluntary practices related to the advertising of healthcare products. These associations and their publications include:

- International Federation of Pharmaceutical Manufacturers & Associations (IFPMA): *Code of Pharmaceutical Marketing Practices*
- European Federation of Pharmaceutical Industries and Associations (EFPIA): *Code of Practice on the promotion of prescription-only medicines to, and interactions with, health professionals*
- EFPIA: *Code of Practice on Relationships between the Pharmaceutical Industry and Patient Organisations*
- World Health Organization: *Ethical criteria for medicinal drug promotion*
- International Pharmaceutical Congress Advisory Association (IPCAA): *Healthcare Congress Guidelines*
- Association of the British Pharmaceutical Industry (ABPI): *Code of Practice for the Pharmaceutical Industry*
- Pharmaceutical Advertising Advisory Board (PAAB) [Canada]: *Code of Advertising Acceptance*
- Pharmaceutical Research and Manufacturers of America (PhRMA):
  - *Code on Interactions with Healthcare Professionals*
  - Guiding Principles – Direct to Consumer Advertisements About Prescription Medicines
- AdvaMed: *Code of Ethics on Interactions with Health Care Professionals*

### 9.2.4 SOPs to keep your advertising in compliance with regulations[5-10]

If your company develops healthcare products, establish standard operating procedures (SOPs) that relate to your advertising and promotional activities. These SOPs will help ensure the proper training of your employees. The SOPs adhere to relevant regulations and applicable voluntary industry standards. Having these will help you stay in compliance and thus avoid any enforcement action from the regulatory bodies. Such enforcement can include warning letters, the publication of a corrective advertisement, or even legal proceedings, including criminal charges.

Keep in mind the following key points when developing advertising and promotional materials:

1. Promotional activities should be consistent with the product labelling that has been cleared or approved.
2. Promotional claims should be reliable, accurate, truthful, informative, fair, balanced and up-to-date, and you must be able to substantiate them.

3. The information should not contain misleading or unverifiable statements or omissions likely to induce medically unjustifiable product use or to give rise to undue risks.
4. Any comparison of products should be factual and fair, and you must be able to substantiate it.

* In the US, most class III Premarket Approval medical devices have been restricted as a condition of approval, in accordance with section 515(d)(1)(B)(ii) of the US *Federal Food, Drug, and Cosmetic Act*. A few class I and II devices (e.g., hearing aids) are restricted by regulations in accordance with section 520(e) of the same act.[6]

## References


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