1

The Aims and Structure of Regulations

1.1 Introduction

Drugs and medical devices are among the most stringently regulated products in the developed world. This chapter introduces you to the basic principles and concepts behind the regulations so that you can fully appreciate the importance of compliance. The chapter then looks at the general legislative framework that is used to create regulations and identifies the core legal texts that are used to regulate such products in the European Union (EU) and the United States of America (US). Finally, the chapter examines the legal definitions of drugs and medical devices, which are central to determining the scope of the regulations.

1.2 Purpose and Principles of Regulation

The fundamental purpose of regulation is the protection of public health.

Although this appears a very simple goal, its attainment has required the development of extensive and complex regulations. As a newcomer to the subject, you may find some of the regulations cumbersome and almost overbearing. However, as you study this chapter, you will see that many of the landmark advances in regulatory development were triggered by adverse incidents. Thus, you should accept the current regulations as representing the distilled wisdom of past experience.

To achieve their goal, the regulations rely on a number of core principles and concepts.

- Safety
- Efficacy
- Purpose
- Risk/benefit
- Quality

Product safety is an underlying principle for all products. Ideally, the product should do no harm. Thus, the regulations require that the developer or manufacturer must take appropriate steps to demonstrate and ensure the safety of the product under development.

Medical Product Regulatory Affairs: Pharmaceuticals, Diagnostics, Medical Devices,
Second Edition. John J. Tobin and Gary Walsh.

Obviously, for it to be worthwhile, the product must also do some good. Hence, the principle of **efficacy** or effectiveness has become another cornerstone in achieving the goal of regulation. To evaluate effectiveness, you must also consider the purpose of the product as expressed in either an *indications for use* statement in the case of drugs or *intended use* statement in the case of medical devices. As discussed in Section 1.6, and later in Sections 9.3 and 9.4, intended use statements are also vital in determining how some products are regulated in the first place, which in turn dictates the level of scrutiny to which they may be subjected.

In the case of most simple medical devices (a hospital bed for example) it will be relatively straightforward for you to conclude that the product is safe and effective in achieving its intended purpose. However, for more complicated medical devices and many drugs, the situation may not be so clear-cut. Most drugs have some side effects. These can range from mild to quite severe. Additionally, many drugs show considerable variation in effectiveness within the patient population that the drug is intended to treat. Thus, you will have to apply the concept of **Risk to Benefit** when making a judgement as to whether a product should be marketed and as to what limitations, if any, should apply to its use. Looking at it from a regulatory stance you must ask the questions, do the benefits outweigh the risks, and in the overall balance does the product enhance public health?

Consideration of the following examples of existing drug products may help you to understand this point. Chemotherapy drugs used to fight cancer are known to have significant side effects including severe nausea and hair loss, while they are rarely effective in all cancer patients. However, despite their limitations, they still provide a vital element in the fight against cancer as they can contribute to the cure of what could otherwise be a fatal disease.

Risk to benefit has also been a subject of debate surrounding the administration of vaccines. In recent years, concerns have been raised in the popular press about possible side effects from the MMR vaccine, which is given to infants to guard against Measles, Mumps and Rubella. This led to a drop in the levels of vaccination. However, the advice from health professionals continues to be in favour of vaccination, because even if the claimed side effects were shown to be true, failure to vaccinate would still statistically pose a greater health risk due to the detrimental effects of the diseases themselves. Most recently risk–benefit analysis has guided regulators in providing advice regarding the rollout of vaccines against SARS-COV-2 in efforts to control and mitigate the effects of the COVID-19 pandemic. It was noted that the severity of the disease, which can prove fatal, increased with age while a rare side effect of blood clots, which could also result in death, was observed as some of the vaccines were rolled out. Considering limitations in the availability of vaccines and the urgency to get populations vaccinated, regulators used risk–benefit analysis to guide them in advising which vaccines to use on different population cohorts.

The final element which regulations address is **quality**. Safety and fitness for purpose, as discussed above, are two of the characteristics that you would associate with a quality product. However, these characteristics alone would not describe a quality product. For any product or service to be considered quality you would also expect it to be reliable and consistent. Additionally, in the context of medical products, quality means a requirement to demonstrate conformance to agreed

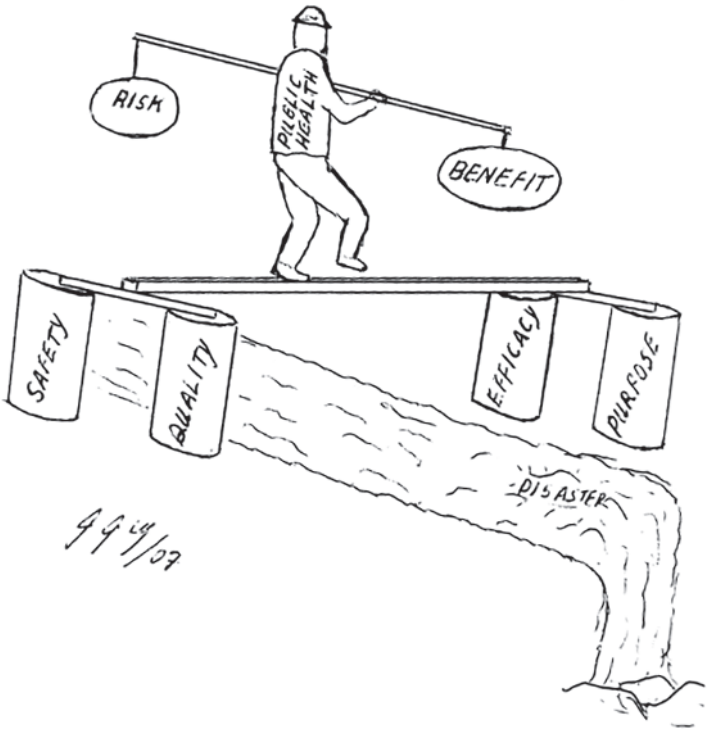

Figure 1.1 Regulatory principles.

specifications or applicable standards for content, purity and stability. Many organisations, from manufacturers to service providers, voluntarily apply quality assurance systems to more effectively meet their customers' needs on a consistent basis. However, this is not a voluntary option for manufacturers of drugs and potential high-risk medical devices. Such enterprises are legally required to apply an appropriate quality assurance system, the specifics of which are, for the most part, defined in regulations. These basic principles are illustrated in Figure 1.1.

1.3 The Legal Framework for Regulation

As you will encounter many different types of legal instruments in the course of this book, it is worthwhile that you take some time to understand the basic principles on which such instruments are constructed. Several are discussed here, with links provided to appropriate websites in the further reading section of this chapter. Many of these legal instruments will be considered in detail in further chapters.

1.3.1 National Legislative Process

In a modern constitutional democracy, laws are created via a hierarchical legislative process. You will find the principal legal principles laid down in a constitution,

which derives its legitimacy directly from the will of the people and can only be amended via referendum. It sets out your basic rights as an individual in the state and establishes a system of governance that provides for legislative, executive and judicial branches of government.

The legislature consists of elected representatives who act on behalf of the people in a legislative assembly (houses of parliament) and have the power to propose new legislation in the form of a Bill. In practice, most legislation is introduced by Government Ministers in their role as the political heads of the executive branch of government. After a number of stages during which it is scrutinised and debated, the Bill, if acceptable, is approved by majority vote in the houses of parliament. It then proceeds to become an Act once it is signed into law by the head of state.

An Act establishes the broad legal requirements pertaining to a particular topic and grants powers of enforcement to the relevant Government Minister. An Act will also usually confer power on the Minister to issue further detailed regulations that enable practical application and enforcement of the Act. Such regulations are issued in the form of Statutory Instruments in Europe or additions to the Code of Federal Regulations (CFR) in the US. The overall legislative process is illustrated in Figure 1.2.

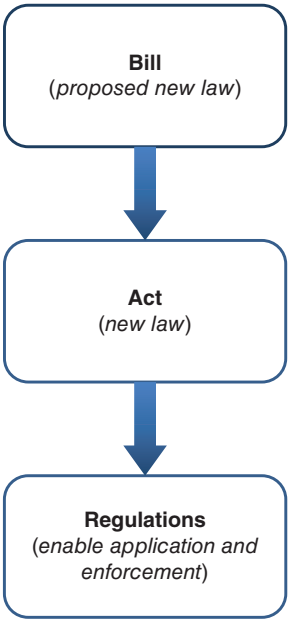

Figure 1.2 National legislative process.

In summary, you will find that Acts contain the broad legal principles whereas you are more likely to find the detailed technical requirements of the law in the regulations.

The executive branch of government is responsible for executing the law. It consists of the ministerial heads of each government department together with the civil service and all other state agencies and authorities empowered to administer and enforce the law. The judicial branch function as independent guardians of your rights and adjudicate on whether the executive have, in applying the law, overstepped the powers granted to them via the constitution, acts or regulations.

1.3.2 EU Legislative Process

A different system applies to the creation of legislation at EU level. The EU is based on a series of treaties between member states, which are comparable to constitutional law at national level. Three institutions are involved in the creation of EU law: The European Commission, The Council of the European Union and The European Parliament. The European Commission acts as the executive body and is headed by Commissioners nominated by the member states. It is primarily

responsible for preparing and presenting legislative proposals. Responsibility for approval of the proposals is shared between the Council, which consists of the government Ministers from each member state, the European Parliament, which contains directly elected representatives, and the Commission. Different mechanisms for distribution of power between the institutions are used, depending on the subject matter of the legislation. Approval of basic legislative measures requires the involvement of the Council and the Parliament, whereas the Commission are empowered to approve provisions of a technical or administrative nature. The issuing authority will always be identified in the title of the document.

Binding EU legislation is issued in the form of Regulations, Directives and Decisions.

An EU Regulation is directly applicable in each member state, without the need for transposition into national legislation. However, you will find that some supplementary national legislation is usually required so as to establish penalties and powers of enforcement at national level.

Directives, on the other hand, are addressed to member states and require that they enact national legislation so as to achieve the objectives of the directives. Thus, a directive allows flexibility in how national legislation is enacted. In practice, national legislation will frequently refer you back to the directive, particularly when a directive contains large amounts of detailed technical requirements.

Note: Because of issues of divergent interpretation of some Directives by Member States, there is a tendency to replace Directives by Regulations in recent legislative updates.

Regulations and Directives use a similar structure.

- You will start by reading statements citing the legal basis for the document and the reasoning behind its creation ('whereas' statements).
- Then you will find the fundamental legal requirements set out in a series of articles.
- Finally, where applicable, you will find detailed technical requirements in one or more Annexes.

In a sense, the articles equate to what you might expect to find in an Act at national level, while the content of Annexes would be more akin to what would be placed in regulations. There is also a parallel in terms of authorisation, in that amendments to the articles usually require the approval of the political institutions, whereas adaption of the Annexes to technical progress is possible via a decision of the Commission, functioning as the executive body. You can see this in practice by just looking at the title of each instrument that you read.

The final legal instrument is a Decision. A decision focuses on an individual measure and is directly binding in its entirety on the specific individuals or entities to whom it is addressed. The Commission uses Decisions to issue marketing authorisations for approval of new drugs granted under a 'centralised' procedure (Chapter 6). Figure 1.3 summarises the relationship between various legal instruments used in Europe.

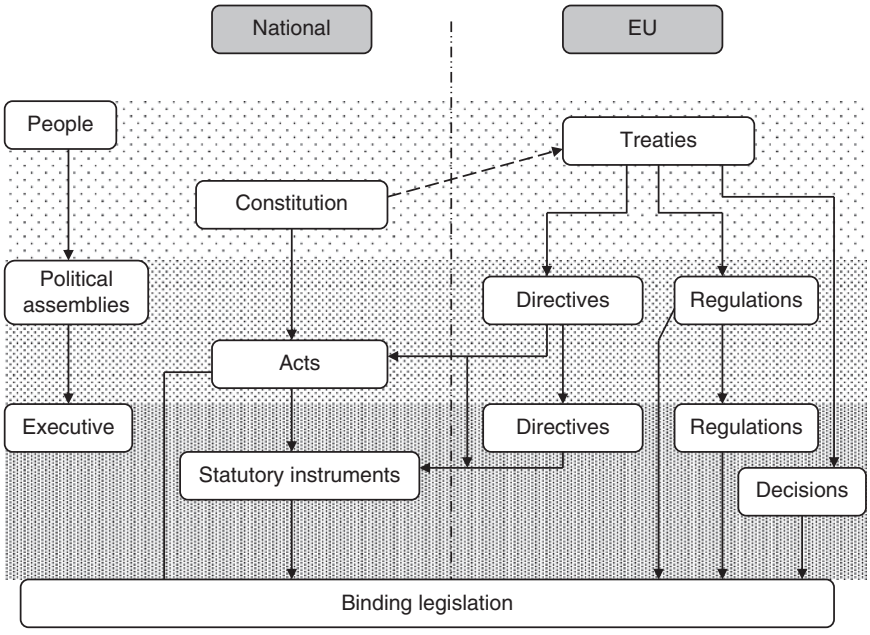

Figure 1.3 The relationship between National and EU legal instruments and the flow of legislative authority.

1.3.3 Working with Legal Texts

It is advisable that for the most part you use the EU documents as your primary source of legislation. There are a number of benefits to doing this:

- You get both the principal legal requirements (The Articles) and the technical detail (The Annexes) in one document. As mentioned above national legislation may just transpose the Articles, and you may have to refer back to the directive for the technical Annexes.
- National legislation is moulded by Directives, and new national legislation is invariably a response to EU initiatives.
- Most products are targeted at international rather than just national markets. Once you comply with the requirements of the directive, national legislation may not impose additional requirements other than as provided for in the directive (language requirements, etc.).

However, when working with Directives or Regulations, you need to be careful about updates. Once a 'base' Directive or Regulation is established, subsequent Directives or Regulations can be issued to amend one or more of the Articles of the 'base' text, or to adapt the Annexes to technical progress. This makes the original section of the base Directive or Regulation no longer applicable. To help you work with the legislation, the EU prepares consolidated texts. However, it is only the Directives or Regulations as published in the *Official Journal of the European Community* that have legal standing. Occasionally, in the interests of clarity, the EU will start afresh and recast a new 'base' Directive or Regulation incorporating all previous amendments.

1.3.4 Guidance Documents

In addition to the legal texts, you will also encounter guidance documents issued by the agencies involved in application and enforcement of legislation and other interested parties.

These are intended to help you understand what the law requires and to provide you with solutions as to what to do to meet the requirements. There is considerable variety in the type of guidance documents available. Some documents are used to describe specific requirements in precise detail, such as the procedures for making regulatory submissions, whereas other documents will tend to be more general in nature and may just raise points to consider or suggested approaches. In practice, they are of great practical value and give a very good insight into what an agency is expecting in terms of application of regulations. Guidance documents, adopted pursuant to specific requirements contained in EU Regulations or Directives, have a derived legal status. However, other guidance does not have formal legal status and may not be taken as an interpretation of what the law requires, as such a determination is the preserve of the judiciary. Irrespective of its status, industry are advised to follow all relevant guidance, so as to facilitate smoother interaction with the regulatory authorities, and avoid having to justify alternative approaches that may otherwise be used.

1.3.5 Pharmacopoeia

Pharmacopoeial publications provide a final important source of information for the pharmaceutical industry, regulatory authorities and the healthcare professions. These are concerned with establishing quality standards. They contain monographs that define specifications for the purity and identity of established pharmaceutical ingredients, both active and non-active, together with recognised analytical methods that may be used to evaluate them. The most relevant are the United States Pharmacopoeia (USP) and the European Pharmacopoeia (Ph.Eur).

1.4 Basic Legislation

1.4.1 EU Legislation

The core legislation governing the regulation of drugs in the EU is contained in three 'base' legal instruments, which provide the framework for regulation of medicines at both national and community level. These are:

Dir. 2001/83/EC	Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use
Reg. EC/726/2004	Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Union procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency
Reg. EU/2019/6	Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC

The human medicines directive replaced an original directive and its amendments that dated back to 1965 (65/65/EEC). This original directive was prompted by a determination to prevent a recurrence of a catastrophe that came to light in the early 1960s, when it was concluded that the birth of thousands of babies with limb deformities was as a result of their mothers having taken a new sedative drug, Thalidomide, during pregnancy. This proved to be a cathartic event as it exposed the limitations in the regulatory measures that existed at the time and prompted new legislative measures in many jurisdictions worldwide. The main purpose of the directive introduced in 1965 was to set standards for drug authorisation that should be applied across all member states. The overall structure of the directive, with articles grouped under various Titles, is shown in Table 1.1. The directive also contains a large Annex that sets out the detailed requirements pertaining to the approval of human medicines in the EU. A number of amending directives and regulations have been issued that update the articles and annex for technical progress. A selection of the more significant updates is shown in Table 1.2.

The first directives regulating veterinary medicines date back to 1981. An equivalent to the human medicines directive, Directive 2001/82/EC provided the basis for regulation of veterinary medicines for almost twenty years, but this has now been replaced by Regulation (EU) 2019/6 with effect from 28 January 2022. One of the purposes of changing from a Directive to a Regulation was to remove the ability of

Table 1.1 Content headings of the Human Medicines Directive.

Title I	Definitions
Title II	Scope
Title III	Placing on the market
	Chapter 1: Marketing authorisation
	Chapter 2: Special provisions applicable to homeopathic medicinal products
	Chapter 3: Procedures relevant to the marketing authorization
	Chapter 4: Mutual recognition procedure and decentralised procedure
Title IV	Manufacture and importation
Title V	Labelling and package leaflet
Title VI	Classification of medicinal products
Title VII	Wholesale distribution of medicinal products
Title VIII	Advertising
Title IX	Pharmacovigilance
Title X	Special provisions on medicinal products derived from human blood and plasma
Title XI	Supervision and sanctions
Title XII	Standing committee
Title XIII	General provisions
Title XIV	Final provisions
Annex I	Analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products

Table 1.2 Selected updates of the Human Medicines Directive.

Dir. 2002/98/EC Human blood products	Amended by Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC
Dir. 2003/63/EC Annex I update	Amended by Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use
Dir. 2004/24/EC Herbal medicines	Amended by Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use
Reg. EC/1901/2006 Paediatric use	Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004
Reg. EC/1394/2007 Advanced therapy	Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004
Dir. 2009/53/EC Marketing variations	Directive 2009/53/EC of the European Parliament and of the Council of 18 June 2009 amending Directive 2001/82/EC and Directive 2001/83/EC, as regards variations to the terms of marketing authorisations for medicinal products
Dir 2011/62/EU Falsified products	Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products
Dir 2012/26/EU Pharmacovigilance	Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance

Member States to interpret the requirements of the Directive, which had led to too much variation in its application. The main headings of the regulation are shown in Table 1.3.

Some categories of medicinal products require direct regulation from EU institutions. Regulation (EC) No. 726/2004 as amended lays down Union procedures for the authorisation, supervision and pharmacovigilance of medicinal products for human and veterinary use, and provides the legal basis for the operation of the European Medicines Agency. This regulation replaces a previous regulation from 1993 (Regulation No. 2309/93) that initiated this process. A summary of the main topics contained in the regulation is shown in Table 1.4.

A number of amending directives and regulations have been issued that update the articles and annexes of the base legislation for technical progress.

Table 1.3 Content headings of the Veterinary Medicines Regulation.

Chapter	Topic
I	SUBJECT MATTER, SCOPE AND DEFINITIONS
II	MARKETING AUTHORISATIONS – GENERAL PROVISIONS AND RULES ON APPLICATIONS
Section 1	General provisions
Section 2	Dossier Requirements
Section 3	Clinical Trials
Section 4	Labelling and package leaflet
Section 5	Specific requirements for generic, hybrid, combination veterinary medical products and for applications based on informed consent and bibliographic data
Section 6	Marketing authorisations for limited market and in exceptional circumstances
Section 7	Examination of applications and basis for granting marketing authorisations
Section 8	Protection of technical documentation
III	PROCEDURES FOR MARKETING AUTHORISATIONS
Section 1	Marketing authorisations valid throughout the Union ('centralised marketing authorisations')
Section 2	Marketing authorisations valid in a single Member State ('national marketing authorisations')
Section 3	Marketing authorisations valid in several Member States ('decentralised marketing authorisations')
Section 4	Mutual recognition of national marketing authorisations
Section 5	Subsequent recognition in the mutual recognition and decentralised marketing authorisation procedures
Section 6	Review procedure
IV	POST-MARKETING AUTHORISATION MEASURES
Section 1	Union product database
Section 2	Collection of data by Member States and responsibilities of marketing authorisation holders
Section 3	Changes to the terms of the marketing authorisations
Section 4	Harmonisation of the summary of product characteristics for nationally authorised products
Section 5	Pharmacovigilance
Section 6	Union interest referral
V	HOMEOPATHIC VETERINARY MEDICINAL PRODUCTS

(Continued)

Table 1.3 (Continued)

Chapter	Topic
VI	MANUFACTURING, IMPORT AND EXPORT
VII	SUPPLY AND USE
Section 1	Wholesale distribution
Section 2	Retail
Section 3	Use
Section 4	Advertising
VIII	INSPECTIONS AND CONTROLS
IX	RESTRICTIONS AND PENALTIES
X	REGULATORY NETWORK
XI	COMMON AND PROCEDURAL PROVISIONS
XII	TRANSITIONAL AND FINAL PROVISIONS
Annex I & II	Technical details on information/dossier to be provided with an application for a marketing authorisation

Table 1.4 Content headings of Regulation (EC) 726/2004.

Title	Topic
I	Definitions & Scope
II	Authorisation and supervision of medicinal products for human use
Chapter 1	Submission and examination of applications — Authorisations
Chapter 2	Supervision and penalties
Chapter 3	Pharmacovigilance
III	Authorisation and supervision of veterinary medicinal products
Chapter 1	Submission and examination of applications — Authorisations
Chapter 2	Supervision and penalties
Chapter 3	Pharmacovigilance
IV	The European Medicines Agency – responsibilities and administrative structures
Chapter 1	Tasks of the agency
Chapter 2	Financial Provisions
Chapter 3	General Provisions governing the Agency
V	General and final provisions

Community-wide regulation of medical devices commenced with the introduction of Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices. Two further 'base' directives followed that covered all other medical devices: The Medical Devices Directive 93/42/EEC and The In Vitro Diagnostics Directive 98/79/EC. Two new Regulations have been published in 2017 to replace these three 'base' directives

MDR 2017/745	Regulation (EU) 2017/745 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No. 178/2002 and Regulation (EC) No. 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC
IVDR 2017/746	Regulation (EU) 2017/746 on in vitro diagnostic (IVD) medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU.

The new regulations fully apply to new devices from 26 May 2021 in the case of medical devices and from 26 May 2022 in the case of IVD products with some transitional provisions relating to existing devices extending up to 26 May 2027. The new regulations incorporate all previous amendments to the base directives and provide for more consistent and tighter regulation of medical devices to counter fraudulent activity that had been encountered with some devices, e.g. use of non-medical grade silicone in breast implants.

There are a number of other regulations/directives that you will need to consult as appropriate. These address topics such as good laboratory practice, good manufacturing practice, the conduct of clinical trials, orphan drugs and the use of genetically modified organisms. A list of the most relevant legislative instruments is shown in Table 1.5

1.4.2 US Legislation

Regulatory authority in the US derives primarily from the Federal Food, Drug, and Cosmetic Act (FDC Act). The act was originally passed into law in 1938, replacing a previous Food and Drugs Act that dated back to 1906. Impetus for approval of the FDC Act came from the drug-related death of 107 people. The victims, mainly children, had taken a sulphanilamide drug preparation that contained poisonous diethylene glycol as a solvent in order that it could be presented in a more palatable, raspberry-flavoured liquid form. The Act required for the first time that manufacturers test new drugs for safety and submit their results to the Food and Drugs Administration (FDA) for marketing approval. In addition, it authorised the FDA to conduct unannounced inspections of manufacturing facilities. Many amendments to the act have been introduced since then, the single most significant being the Kefauver–Harris amendment of 1962, which introduced the requirement that drugs must be shown to be effective as well as safe. This was the main US response to the Thalidomide disaster. The current text of the Act is maintained under Title 21, Chapter 9 of the United States Code (USC) and may be accessed at uscode.house.gov/browse.xhtml. An outline of the most relevant sections of the Act is shown in Figure 1.4.

Table 1.5 Selected other directives and regulations of relevance.

Reg EU 534/2014 (Clinical practice)	Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC
Dir 2005/28/EC (Clinical practice)	Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products
Dir 2003/94/EC (GMP Human)	Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use.
91/412/EEC (GMP Veterinary)	Commission Directive 91/412/EEC of 23 July 1991 laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products
Dir 2004/10/EC (GLP)	Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances
Dir 2001/18/EC (GMO release)	Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC
Dir 2009/41/EC (GMO containment)	Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms
Reg EC/141/2000 (Orphan drug)	Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products
Reg EC/847/2000 (Orphan drug)	Commission Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority'
Reg EC/470/2009 (MRLs)	Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council
Reg EC 469/2009 (Patent protection)	Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products

Chapter I—Short Title
Chapter II—Definitions
Chapter III—Prohibited Acts and Penalties
Chapter IV—Food
Chapter V—Drugs and Devices:
Subchapter A--Drugs and Devices:
SEC. 501. ADULTERATED DRUGS AND DEVICES
SEC. 502. MISBRANDED DRUGS AND DEVICES
SEC. 503. EXEMPTIONS AND CONSIDERATION FOR CERTAIN DRUGS, DEVICES, AND BIOLOGICAL PRODUCTS
SEC. 503A. PHARMACY COMPOUNDING.
SEC. 504. VETERINARY FEED DIRECTIVE DRUGS
SEC. 505. NEW DRUGS
SEC. 505A. PEDIATRIC STUDIES OF DRUGS
SEC. 505B. RESEARCH INTO PEDIATRIC USES FOR DRUGS AND BIOLOGICAL PRODUCTS.
SEC. 506. FAST TRACK PRODUCTS.
SEC. 506A. MANUFACTURING CHANGES.
SEC. 506B. REPORTS OF POSTMARKETING STUDIES.
SEC. 506C. DISCONTINUANCE OF A LIFE-SAVING PRODUCT.
SEC. 508. AUTHORITY TO DESIGNATE OFFICIAL NAMES
SEC. 509 NON-APPLICABILITY TO COSMETICS
SEC. 510. REGISTRATION OF PRODUCERS OF DRUGS AND DEVICES
SEC. 512. NEW ANIMAL DRUGS
SEC. 513. CLASSIFICATION OF DEVICES INTENDED FOR HUMAN USE
SEC. 514. PERFORMANCE STANDARDS
SEC. 515. PREMARKET APPROVAL
SEC. 516. BANNED DEVICES
SEC. 517. JUDICIAL REVIEW
SEC. 518. NOTIFICATION AND OTHER REMEDIES
SEC. 519. RECORDS AND REPORTS ON DEVICES
SEC. 520. GENERAL PROVISIONS RESPECTING CONTROL OF DEVICES INTENDED FOR HUMAN USE
SEC. 521. STATE AND LOCAL REQUIREMENTS RESPECTING DEVICES
SEC. 522. POSTMARKET SURVEILLANCE
SEC. 523. ACCREDITED PERSONS.
Subchapter B--Drugs for Rare Diseases and Conditions
SEC. 525. RECOMMENDATIONS FOR INVESTIGATIONS OF DRUGS FOR RARE DISEASES OR CONDITIONS
SEC. 526. DESIGNATION OF DRUGS FOR RARE DISEASES OR CONDITIONS
SEC. 527. PROTECTION FOR DRUGS FOR RARE DISEASES OR CONDITIONS
SEC. 528. OPEN PROTOCOLS FOR INVESTIGATIONS OF DRUGS FOR RARE DISEASES OR CONDITIONS
Subchapter C--Electronic Product Radiation Control
Subchapter D--Dissemination of Treatment Information
Subchapter E--General Provisions Relating to Drugs and Devices
SEC. 561. EXPANDED ACCESS TO UNAPPROVED THERAPIES AND DIAGNOSTICS.
SEC. 562. DISPUTE RESOLUTION.
SEC. 563. CLASSIFICATION OF PRODUCTS.
SEC. 564. AUTHORIZATION FOR MEDICAL PRODUCTS FOR USE IN EMERGENCIES.

Figure 1.4 Content of the Food, Drug and Cosmetic Act.

Subchapter F—New Animal Drugs for Minor Use and Minor Species
SEC. 571. CONDITIONAL APPROVAL OF NEW ANIMAL DRUGS FOR MINOR USE AND MINOR SPECIES.
SEC. 572. INDEX OF LEGALLY MARKETED UNAPPROVED NEW ANIMAL DRUGS FOR MINOR SPECIES.
SEC. 573. DESIGNATED NEW ANIMAL DRUGS FOR MINOR USE OR MINOR SPECIES.
Chapter VI—Cosmetics
Chapter VII—General Authority:
Subchapter A--General Administrative Provisions
Subchapter B--Colors
Subchapter C--Fees
Subchapter D--Information and Education
Subchapter E--Environmental Impact Review
Subchapter F--National Uniformity for Nonprescription Drugs and Preemption for Labeling or Packaging of Cosmetics
Subchapter G--Safety Reports
Chapter VIII—Imports and Exports
Chapter IX—Miscellaneous

Note: Chapters/subchapters of most relevance are highlighted in bold

Figure 1.4 (*Continued*)

Because of their historical evolution, biologic products are regulated under different acts, section 351 of the Public Health Services (PHS) Act in the case of biologics for human use and sections 151-159 of the Virus-Serum-Toxin Act in the case of veterinary biologics. The current text of the relevant sections of these Acts may be found in USC Title 42, Chapter 6A, Subchapter II, Part F and Title 21, Chapter 5, respectively.

Note: The section numbering differs from what is used in the act as a standalone document when the act is codified in the USC under Title 42. For example, Section 510k of the act which deals with the premarket notification requirements for medical devices appears as Section 360k in the USC See appendix ? for a corelation table.

Detailed regulations supporting the Acts are published principally in Title 21 of the Code of Federal Regulations (21 CFR). An outline of the main sections of the Title is shown in Table 1.6. Regulations in support of veterinary biologics are contained in Title 9 of the CFR, Parts 101-123 – see Table 1.7.

1.5 Scope of the Legislation

The spectrum of drugs and medical devices covered by the legislation is quite diverse. While many products are easily identified as being subject to the regulations, careful application of the legal definitions of drugs and devices is required to establish the status of other ‘borderline’ products. The definitions of drugs and devices taken from the relevant EU and US legislation are shown in Figure 1.5. Note: Drugs are referred to as medicinal products in EU legislation.

Table 1.6 Content of Title 21 of the Code of Federal Regulations.

Volume No	Contents
1	Parts 1 to 99. General regulations for the enforcement of the Federal Food, Drug, and Cosmetic Act and the Fair Packaging and Labeling Act. Color additives. Part 11 Electronic Records; Electronic Signatures Part 50 Protection of Human Subjects Part 54 Financial Disclosure by Clinical Investigators Part 56 Institutional Review Boards Part 58 Good Laboratory Practice
2	Parts 100 to 169. Food standards, good manufacturing practice for foods, low-acid canned foods, acidified foods and food labeling.
3	Parts 170 to 199. Food additives.
4	Parts 200 to 299. General regulations for drugs. Part 201 Labelling Part 207 Registration of Drug Producers & Drug Listings Part 210 cGMP Manufacturing, Processing Packing, Holding Part 211 cGMP Finished Pharmaceuticals Part 225 cGMP Medicated Feeds Part 226 cGMP Medicated Articles
5	Parts 300 to 499. Drugs for human use. Part 312 Investigational New Drug (IND) Part 314 New Drug Marketing Approval Applications (NDA) Part 320 Bioavailability and Bioequivalence Requirements
6	Parts 500 to 599. Animal drugs, feeds and related products. Part 511 New Animal Drugs for Investigational Use Part 514 New Animal Drug Applications (NADA)
7	Parts 600 to 799. Biologics and cosmetics. Part 600 Biologic Products General Part 601 Biologic Licence Applications (BLA) Part 606 cGMP Blood & Blood Products Part 607 Establishment Registration & Product Listing
8	Parts 800 to 1299. Medical devices and radiological health. Regulations under the Federal Import Milk Act, the Federal Tea Importation Act, the Federal Caustic Poison Act and for control of communicable diseases and interstate conveyance sanitation. Part 801 Labelling Part 803 Medical Device Reporting Part 806 Corrections & Removals Part 807 Establishment Registration & Device Listing Part 809 In vitro Diagnostics (IVD's) Part 812 Investigational Device Exemptions (IDE's)

(Continued)

Table 1.6 (Continued)

Volume No	Contents
	Part 814 Pre Market Approval (PMA) Part 820 Quality System Regulation (QSR) Part 822 Market Surveillance Part 860 Medical Device Classification Procedures
9	Parts 1300 through end. Drug Enforcement Administration regulations and requirements.

Table 1.7 Content of Title 9 of the Code of Federal Register dealing with veterinary biologics.

Part	Description
101	Definitions
102	Licenses for biological products
103	Experimental production, distribution and evaluation of biological products prior to licensing
104	Permits for biological products
105	Suspension, revocation, or termination of biological licenses or permits
106	Exemption for biological products used in department programs or under department control or supervision
107	Exemptions from preparation pursuant to an unsuspended and unrevoked license
108	Facility requirements for licensed establishments
109	Sterilization and pasteurization at licensed establishments
112	Packaging and labeling
113	Standard requirements
114	Production requirements for biological products
115	Inspections
116	Records and reports
117	Animals at licensed establishment
118	Detention; seizure and condemnation
121	Possession, use and transfer of biological agents and toxins
122	Organisms and vectors
123	Rules of practice governing proceedings under the Virus-Serum-Toxin Act

To determine the regulatory status of an individual product you need to answer two key questions:

What is it supposed to do?
How does it do it?

Drugs
A medicinal product for human use is defined in the EU as:

(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings
or
(b) Any substance or combination of substances that may be used in or administered to human beings either with a view to restoring, correcting, or modifying physiological functions by exerting a pharmacological, immunological, or metabolic action or to making a medical diagnosis.

A veterinary medicinal product is similarly defined as:
Any substance or combination of substances that fulfils at least one of the following conditions:

(a) it is presented as having properties for treating or preventing disease in animals,
(b) its purpose is to be used in, or administered to, animals with a view to restoring, correcting, or modifying physiological functions by exerting a pharmacological, immunological, or metabolic action
(c) its purpose is to be used in animals with a view to making a medical diagnosis, and
(d) its purpose is to be used for euthanasia of animals;

The relevant elements of the definition of a drug taken from the US FDC Act are as follows:

articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals;
and articles (other than food) intended to affect the structure or any function of the body of man or other animals.

Devices
EU legislation provides the following general definition of a medical device:
"medical device" means any instrument, apparatus, appliance, software, implant, reagent, material, or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- diagnosis, prevention, monitoring, prediction, prognosis, treatment, or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,
- investigation, replacement, or modification of the anatomy or of a physiological or pathological process or state,
- providing information by means of in vitro examination of specimens derived from the human body, including organ, blood, and tissue donations, and which does not achieve its principal intended action by pharmacological, immunological, or metabolic means, in or on the human body, but which may be assisted in its function by such means.

The following products shall also be deemed to be medical devices:

- devices for the control or support of conception;

The subcategories, active device, implantable device, and in vitro medical device are further defined as:
"active device" means any device, the operation of which depends on a source of energy other than that generated by the human body for that purpose, or by gravity, and which acts by changing the density of or converting that energy. Devices "implantable device" means any device, including those that are partially or wholly absorbed, which is intended:

- to be totally introduced into the human body, or
- to replace an epithelial surface or the surface of the eye, by clinical intervention and which is intended to remain in place after the procedure.'

Figure 1.5 Legal definitions of drugs and devices.

"in vitro diagnostic medical device" means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software, or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:

(a) concerning a physiological or pathological process or state,
(b) concerning congenital physical or mental impairments,
(c) concerning the predisposition to a medical condition or a disease,
(d) to determine the safety and compatibility with potential recipients,
(e) to predict treatment response or reactions, and
(f) to define or monitor therapeutic measures.

Specimen receptacles shall also be deemed to be in vitro diagnostic medical devices;

The US FD&C Act just provides the following general definition of a device:

The term "device" means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—

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
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.

Figure 1.5 (*Continued*)

To answer the first question, you need to examine the intended use statement for the product and see if it claims a medical purpose corresponding to any of those contained in the definitions.

The key action verbs to look out for are treat, prevent, diagnose, cure, mitigate, restore, correct, modify, replace, or alleviate a disease or condition.

Once you have established a medical purpose, careful examination of its primary mode of action will allow you to decide whether the product is a drug or device.

To understand the process more clearly we shall look at the following examples, which illustrate some of the distinctions.

Traditional herbal and homeopathic remedies that are supplied as natural treatments for medical conditions or diseases are subject to regulation as drugs, e.g. St John's Wort.

Health foods and other functional foods that may have beneficial health effects are generally not considered drugs, as their primary purpose is nutritional. However, any information on health benefits must not include specific medical claims that are associated with drug products. Recent European legislation (Regulation (EC) No. 1924/2006 on nutrition and health claims made on foods) sets out to define the types of claims that can be made for such products. Examples of such foods include plant-sterol-containing foods that help reduce cholesterol levels, gluten-free foods that prevent the symptoms of coeliac disease and pro-biotic yoghurts that promote healthy gut flora.

Dietary supplements supplied in dosage form can present a grey area. In the US, there is specific legislation dealing with dietary supplements including vitamins, minerals and enzymes. These are excluded from drug regulations, provided that specific drug claims are avoided. In the EU, specific legislation dealing with dietary supplements just covers vitamins and minerals. Enzyme supplements such as lactase, which is used as a digestive aid to treat lactose intolerance, could be viewed as a drug. However, with the advent of authorised health and nutritional claims for functional foods, it is more likely to be viewed as a food.

An asthma inhaler is an example of a product that contains both a drug and a drug delivery device. Such a product would be regulated primarily as a drug since it achieves its medical purpose by pharmaceutical means. The inhaler would additionally have to satisfy the requirements of a device.

Stents used to stabilise damaged arteries are often supplied impregnated with anti-clotting or other drugs. Such products are more likely to be regulated as *devices* as their primary purpose or mode of action is to provide a structural support for the artery. However, the drug could not be used in the device without marketing authorisation under the drug regulations.

A breath test used to determine the presence of *Helicobacter pylori*, associated with stomach ulcers is an example of a diagnostic product involving separate drug and device components. To perform the test, a patient swallows some labelled urea, which is then metabolised by the micro organism, releasing CO_2. A sample of the breath is taken and analysed for the presence of labelled CO_2. The sampling kit consists of the labelled urea, which is a drug; a sampling straw, which is a device; and a sample container, which would be considered an IVD medical device under EU definitions. Other examples of diagnostic drug products used in conjunction with medical devices include dyes administered to visualise blocked veins and arteries.

Ultrasound and X-ray equipment are examples of diagnostic medical devices. In vitro medical devices are distinguished from other diagnostic medical devices, in that a specimen must first of all be removed from the donor. A device worn by a diabetic that continually monitors their glucose via a non-invasive method (near IR energy emissions) would be just regulated as a medical device, whereas a glucose-monitoring device that used a lancet to obtain a blood sample would be an IVD.

Finally, a test kit for analysing specimens without a medical purpose would fall outside the regulations. For example, a test for therapeutic drug monitoring would be regulated as an IVD. However, a test could use the same technology for detecting a drug of abuse but would be outside the scope of the regulations if it is only supplied for forensic testing.

1.6 Chapter Review

In this chapter, you learned that safety, efficacy and quality are key elements in attaining the ultimate goal of regulation, that of protection of public health. The chapter explored the process by which legislation is introduced and identified

the core legal texts that define the requirements for marketing drugs and devices. Finally, the chapter examined the legal definitions of drugs and devices and provided examples of how these can be applied to a selection of products.

1.7 Further Reading

National Legislative Process, Ireland

https://www.oireachtas.ie/en/visit-and-learn/how-parliament-works/how-laws-are-made/

EU Directives and Regulations

https://ec.europa.eu/health/home_en
https://ec.europa.eu/health/documents/eudralex_en
https://ec.europa.eu/health/md_sector/overview_en

Guidance on Demarcation Between Medical Devices and Medicines

MDCG 2022 – 5 Guidance on borderline between medical devices and medicinal products under Regulation (EU) 2017/745 on medical devices
https://health.ec.europa.eu/medical-devices-sector/new-regulations/guidance-mdcg-endorsed-documents-and-other-guidance_en

US Legislation

www.fda.gov
www.aphis.usda.gov
https://uscode.house.gov/browse.xhtml to directly access the current versions of the Acts
www.ecfr.gov to directly access the Code of Federal Register regulations