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 regulation cumbersome and 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

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ISBN: 978-3-527-31877-3

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.

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 adverse side effects which may 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 serve 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.

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. Although this has led to a drop in the levels of vaccination, 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 the greater health risk due to the detrimental effects of the diseases themselves.

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 specifications or applicable standards for content, purity and stability. Many organisations, from manufacturers to service providers, voluntarily apply quality assurance systems in order to more effectively meet their customers' needs on a consistent basis. However,

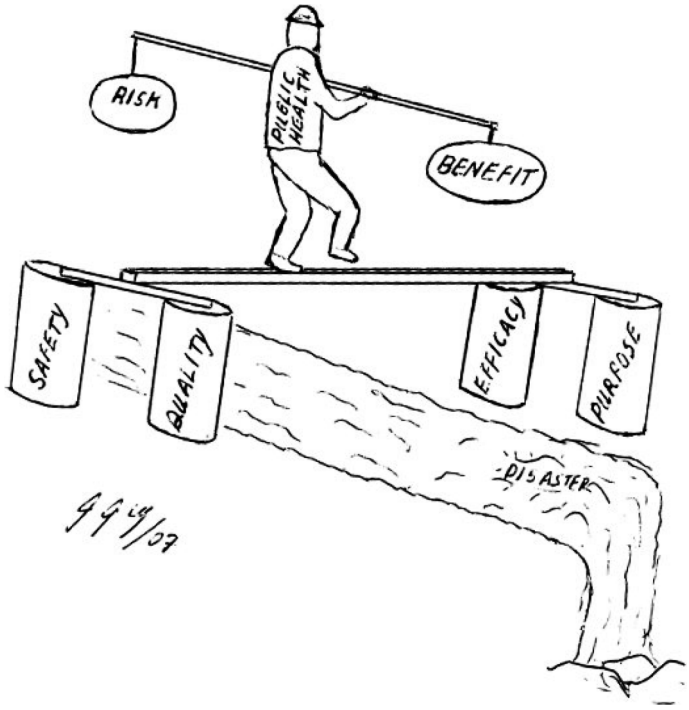

Figure 1.1 Regulatory principles.

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 during the course of this book, it is worthwhile that you take some time to understand the basic principles on which such instruments are constructed.

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. The constitution 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.

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: (i) The European Commission; (ii) The Council of the European Union; and (iii) 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 the 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.

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 adaptation 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 (see Chapter 6). Figure 1.2 summarises the relationship between various legal instruments used in Europe.

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.

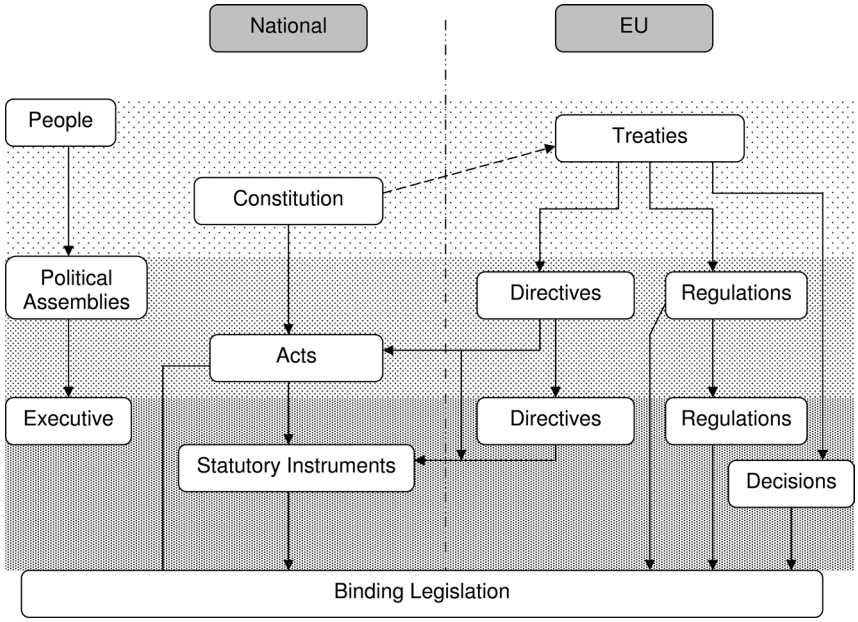

Figure 1.2 The relationship between National and EU legal instruments, and the flow of legislative authority.

- 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, you need to be careful about updates. Once a "base" Directive is established, subsequent Directives can be issued to amend one or more of the Articles of the "base" Directive, or to adapt the Annexes to technical progress. This makes the original section of the base directive no longer applicable. To help you work with the legislation, the EU prepares consolidated texts. However, it is only the Directives 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 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 it 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. These publications include 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 two "base" Directives, which provide the framework for regulation of medicines at national level. These are:

- 2001/82/EC: Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products.
- 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.

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

Table 1.1 Comparison of the content headings of the Human and Veterinary Medicines Directives.

Veterinary Medicines Directive 2001/82/EC (96 Articles)	Human Medicines Directive 2001/83/EC (130 Articles)
Title I: Definitions	Title I: Definitions
Title II: Scope	Title II: Scope
Title III: Marketing	Title III: Placing on the market
Chapter 1: Marketing authorisation	Chapter 1: Marketing authorisation
Chapter 2: Particular provisions applicable to homeopathic veterinary medicinal products	Chapter 2: Special provisions applicable to homeopathic medicinal products
Chapter 3: Procedure for marketing authorization	Chapter 3: Procedures relevant to the marketing authorization
Chapter 4: Mutual recognition procedure and decentralised procedure	Chapter 4: Mutual recognition procedure and decentralised procedure
Title IV: Manufacture and imports	Title IV: Manufacture and importation
Title V: Labelling and package insert	Title V: Labelling and package leaflet
	Title VI: Classification of medicinal products
Title VI: Possession, distribution and dispensing of veterinary medicinal products	Title VII: Wholesale distribution of medicinal products
	Title VIII: Advertising
Title VII: Pharmacovigilance	Title IX: Pharmacovigilance
	Title X: Special provisions on medicinal products derived from human blood and plasma
Title VIII: Supervision and sanctions	Title XI: Supervision and sanctions
Title IX: Standing committee	Title XII: Standing committee
Title X: General provisions	Title XIII: General provisions
Title XI: Final provisions	Title XIV: Final provisions
Annex I:	Annex I:

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 Veterinary Medicines Directive replaced a similar set of directives dating back to 1981. Both directives are similar in structure, with articles grouped under various titles, as shown in Table 1.1. The directives also contain large Annexes that set out the detailed requirements pertaining to the approval of drugs in the EU. A number of amending directives and regulations have already been issued that update the articles and annexes for technical progress (see Table 1.2).

Table 1.2 Updates of the Medicines Directives.

Veterinary Medicines Directive 2001/82/EC Updates	
Dir. 2004/28/EC	Amended by Directive 2004/28/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/82/EC on the Community code relating to veterinary medicinal products
Human Medicines Directive 2001/83/EC Updates	
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
Dir. 2004/27/EC	Amended by Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending 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/1902/2006 (Paediatric use)	Regulation (EC) No. 1902/2006 of the European Parliament and of the Council of 20 December 2006 amending Regulation 1901/2006 on medicinal products for paediatric use
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

Some categories of medicinal products require direct regulation from EU institutions. Regulation (EC) No. 726/2004 lays down Community procedures for the authorisation, supervision and pharmacovigilance of medicinal products for human and veterinary use, and establishes a European Medicines Agency. This regulation replaces a previous regulation from 1993 (Regulation No. 2309/93) that initiated this

Table 1.3 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

process. A summary of the main topics contained in the regulation is shown in Table 1.3.

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 cover all other medical devices: The Medical Devices Directive 93/42/EEC and The In Vitro Diagnostics Directive 98/79/EC. All three "base" directives are similar in content and structure. However, it should be noted that, in addition to dealing with the particular subject matter, the Medical Devices Directive and the In Vitro Diagnostics Directive also contained amendments to the previous device directives. The Medical Devices Directive amended articles in the Active Implantable Medical Devices Directive, while the In Vitro Diagnostics Directive amended articles in the Medical Devices Directive.

There have been a number of amending directives since the base directives were issued; these are summarised in Table 1.4. Directive 2007/47/EC is the most important as it contains significant amendments to all three base directives. It builds on the practical experience gained in implementing the directives, and sets out to simplify and harmonise the language of the directives so as to ensure consistent interpretation and application of the requirements in all Member States. Among other items addressed,

- it amends the definition of a medical device so that software can be regarded as a medical device in its own right;
- it enhances the requirements for clinical investigations in line with international developments;
- it updates some of the classification rules for medical devices to achieve greater clarity;

Table 1.4 Updates of the Device Directives.

Directive	Scope
2000/70/EC	Amends Council Directive 93/42/EEC as regards medical devices incorporating stable derivates of human blood or human plasma
2001/104/EC	Contains further clarification on the regulation of human blood or plasma products
2003/12/EC	Reclassifies breast implants as Class III devices by way of derogation from the general classification rules
2003/32/EC	Introduces detailed specifications as regards the requirements laid down in Council Directive 93/42/EEC with respect to medical devices manufactured utilizing tissues of animal origin
2005/50/EC	Reclassifies hip, knee and shoulder joint replacements as Class III devices by way of derogation from the general classification rules
2007/47/EC	Contains a general update and overhaul of all three base directives

- it recognises the advances in information technology that facilitate the distribution of instructions for use by electronic means; and
- and it clarifies that the post-market vigilance reporting system should apply to custom made devices.

There are a number of other regulations/directives that you will need to consult, as appropriate. These address topics such as Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP), the conduct of clinical trials, variations to authorised drugs, and the use of genetically modified organisms. A list of the most relevant directives 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. An outline of the content of the Act is shown in Figure 1.3. Because of their historical evolution, biologic products are regulated under different

Table 1.5 Selected other directives and regulations of relevance.

2001/20/EC (Clinical practice)	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.
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
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
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
EC/1084/2003 (Variations)	Commission Regulation (EC) No. 1084/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State
EC/1085/2003 (Variations)	Commission Regulation (EC) No. 1085/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No. 2309/93
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
98/81/EC (GMO containment)	Council Directive 98/81/EC of 26 October 1998 amending Directive 90/219/EEC on the contained use of genetically modified micro-organisms
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
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'
EEC/2377/90 (MRLs)	Council Regulation (EEC) No. 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits for veterinary medicinal products in foodstuffs of animal origin.
EC/1308/1999 (MRLs)	Council Regulation (EC) No. 1308/1999 of 15 June 1999 amending Regulation (EC) No. 2377/90 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin
EEC/1768/92 (Patent protection)	Council Regulation (EEC) No. 1768/92 of 18 June 1992 concerning the creation of a 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	NONAPPLICABILITY 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.

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

Figure 1.3 Content of the Food, Drug and Cosmetic (FDC) Act.

Chapter VIII – Imports and Exports

Chapter IX—Miscellaneous

Note: Chapters/sub-chapters of most relevance are highlighted in bold.

Figure 1.3 (*Continued*)

acts, section 351 of the Public Health Services (PHS) Act in the case of biologics for human use and section 151–159 of the Virus-Serum-Toxin Act in the case of veterinary biologics.

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 Code of Federal Regulations, Parts 101–123 (see Table 1.7).

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

(*Continued*)

Table 1.6 (*Continued*)

Volume No	Contents
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 (IVDs) Part 812 Investigational Device Exemptions (IDEs) 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.

Note: Parts of most relevance for the current book are individually listed

Table 1.7 Contents 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

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 1.4. (Note: Drugs are referred to as medicinal products in EU legislation.)

In order 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?

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 to *treat*, *prevent*, *diagnose*, *cure*, *mitigate*, *restore*, *correct*, *modify*, *replace* or *alleviate* a disease or condition.

Once you have established a medical purpose, a 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, for example 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 covers only 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.

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 which 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:

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

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, material or other article, whether used alone or in combination, together with any accessories, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

Figure 1.4 Legal definitions of drugs and devices.

The subcategories, active implantable medical devices and in vitro medical devices are further defined as:

'active implantable medical device' means any active medical device which is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure

'in vitro diagnostic medical device' means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, 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:
— concerning a physiological or pathological state, or
— concerning a congenital abnormality, or
— to determine the safety and compatibility with potential recipients, or
— to monitor therapeutic measures.

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 metabolised for the achievement of its primary intended purposes.

Figure 1.4 (*Continued*)

- 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 as 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 isotopically (e.g. ^{13}C or ^{14}C) labelled urea, which is then metabolised by the 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 *in-vitro* diagnostic (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-infra-red 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 were 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 the 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

- Legislative process
  http://www.fsai.ie/legislation/irish_and_eu/index.aspIrish and EU Legislation
- EU Directives and Regulations
  http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm
  http://ec.europa.eu/enterprise/medical_devices/legislation_en.htm
- EU Pharmaceutical legislation on CD
  http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homecd.htm

- Guidance on demarcation between medical devices and medicines
  MEDDEV Guide 2.1/3
  MEDDEV Guide 2.14/1
  http://ec.europa.eu/enterprise/medical_devices/meddev/index.htm
- US Legislation
  www.access.gpo.gov
  www.fda.gov
  www.aphis.usda.gov