

John J. Tobin and Gary Walsh

Medical Product Regulatory Affairs

Pharmaceuticals, Diagnostics, Medical Devices



**WILEY-
BLACKWELL**

WILEY-VCH Verlag GmbH & Co. KGaA

John J. Tobin and Gary Walsh
**Medical Product Regulatory
Affairs**

Related Titles

Walsh, G.

Pharmaceutical Biotechnology

Concepts and Applications

2007

ISBN: 978-0-470-01245-1

Walsh, G.

Biopharmaceuticals

Biochemistry and Biotechnology

2003

ISBN: 978-0-470-84327-7

Barnfield, P.

Research and Development in the Chemical and Pharmaceutical Industry

2006

ISBN: 978-3-527-31775-2

Webster, J. G. (ed.)

Encyclopedia of Medical Devices and Instrumentation

6 Volume Set

2006

ISBN: 978-0-471-26358-6

Zatz, J. L., Teixeira, M. G.

Pharmaceutical Calculations

2004

ISBN: 978-0-471-43353-8

John J. Tobin and Gary Walsh

Medical Product Regulatory Affairs

Pharmaceuticals, Diagnostics, Medical Devices



**WILEY-
BLACKWELL**

WILEY-VCH Verlag GmbH & Co. KGaA

The Authors

Dr. John J. Tobin

ChemHaz Solutions Ltd.
Laccaroe, Feakle
County Clare
Ireland

Prof. Dr. Gary Walsh

Chemical and Environmental Sciences
Department
University of Limerick
Castletroy, Limerick City
Ireland

All books published by Wiley-VCH are carefully produced. Nevertheless, authors, editors, and publisher do not warrant the information contained in these books, including this book, to be free of errors. Readers are advised to keep in mind that statements, data, illustrations, procedural details or other items may inadvertently be inaccurate.

Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek

Die Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available in the Internet at <http://dnb.d-nb.de>.

© 2008 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

All rights reserved (including those of translation into other languages). No part of this book may be reproduced in any form – by photoprinting, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Registered names, trademarks, etc. used in this book, even when not specifically marked as such, are not to be considered unprotected by law.

Typesetting Thomson Digital, Noida, India

Printing betz-druck GmbH, Darmstadt

Binding Litges & Dopf Buchbinderei GmbH, Heppenheim

Cover design Adam-Design, Weinheim

Printed in the Federal Republic of Germany
Printed on acid-free paper

ISBN: 978-3-527-31877-3

Contents

Preface *XIII*

1	The Aims and Structure of Regulations	1
1.1	Introduction	1
1.2	Purpose and Principles of Regulation	1
1.3	The Legal Framework for Regulation	3
1.3.1	National Legislative Process	3
1.3.2	EU Legislative Process	4
1.3.3	Working with Legal Texts	5
1.3.4	Guidance Documents	6
1.3.5	Pharmacopoeia	7
1.4	Basic Legislation	7
1.4.1	EU Legislation	7
1.4.2	US Legislation	11
1.5	Scope of the Legislation	16
1.6	Chapter Review	19
1.7	Further Reading	19
2	Regulatory Strategy	21
2.1	Chapter Introduction	21
2.2	Basic Regulatory Strategy	21
2.2.1	Product Development	21
2.2.2	Product Manufacture	21
2.2.3	Market Vigilance	22
2.3	Quality Assurance Systems	22
2.3.1	Personnel	23
2.3.2	Documentation	24
2.3.3	Facilities and Equipment	25

2.3.4	Corrective and Preventive Action	25
2.4	Validation	26
2.5	Regulatory Bodies	27
2.5.1	European Commission	27
2.5.2	The EMEA	29
2.5.3	National Competent Authorities	30
2.5.4	Notified Bodies	32
2.5.5	The FDA	32
2.5.6	US Department of Agriculture	35
2.5.7	Pharmacopoeia Authorities	36
2.6	International Harmonisation Bodies	36
2.7	International Conference on Harmonisation	36
2.7.1	VICH	39
2.7.2	The Global Harmonisation Task Force	39
2.8	Pharmaceutical Inspection Cooperation Scheme	40
2.9	The World Health Organization (WHO)	42
2.10	Chapter Review	42
2.11	Further Reading	42
3	Drug Discovery and Development	43
3.1	Chapter Introduction	43
3.2	Drug Categorisation	43
3.2.1	Prescription Status	43
3.2.2	Physical Properties	44
3.2.3	Mode of Action	44
3.2.4	Therapeutic Use	45
3.3	Drug Discovery	45
3.4	Drug Development	50
3.5	Drug Delivery	52
3.5.1	Location	52
3.5.2	Drug Characteristics	52
3.5.3	Speed and Duration of Therapeutic Effect	53
3.5.4	Stability	55
3.6	Chapter Review	55
3.7	Suggested Reading	55
4	Non-Clinical Studies	57
4.1	Chapter Introduction	57
4.2	Non-Clinical Study Objectives and Timing	57
4.3	Pharmacological Studies	58
4.3.1	Pharmacodynamic Studies	59
4.3.2	Pharmacokinetic/Toxicokinetic Studies	62
4.4	Bioavailability and Bioequivalence	64
4.5	Toxicology Studies	65

4.5.1	Toxicity Studies	65
4.5.2	Genotoxicity Studies	66
4.5.3	Carcinogenicity Studies	67
4.5.4	Reproductive Toxicology Studies	67
4.6	Chemistry, Manufacturing and Control Development (CMC)	67
4.7	Quality of Biotech Products	68
4.7.1	Stability Studies	68
4.8	Good Laboratory Practice (GLP)	69
4.9	Chapter Review	69
4.10	Further Reading	71
5	Clinical Trials	73
5.1	Chapter Introduction	73
5.2	Clinical Trials	73
5.2.1	Phase I Trials	74
5.2.2	Phase II Trials	74
5.2.3	Phase III Trials	75
5.3	Clinical Trial Design	76
5.4	Good Clinical Practice	78
5.5	Clinical Trials in the EU	78
5.5.1	The Sponsor	80
5.5.2	The Investigator's Brochure	80
5.5.3	The Investigator	81
5.5.4	The Trial Protocol	81
5.5.5	The Investigational Medicinal Product Dossier	82
5.5.6	Informed Consent	82
5.5.7	Manufacture of Investigational Medicinal Product	82
5.5.8	Competent Authority Clinical Trial Application	84
5.5.9	Independent Ethics Committee CTA	85
5.5.10	Amendments to Clinical Trials	87
5.5.11	Case Report Forms	87
5.5.12	Adverse Event Reporting	87
5.5.13	Annual Safety Report	88
5.5.14	Monitoring of Trials	88
5.5.15	End of Trial	88
5.5.16	Trial Master File	88
5.6	Clinical Trials in The US	89
5.6.1	Investigational New Drug Application (IND)	89
5.6.2	Institutional Review Board	91
5.6.3	Communication with the FDA	94
5.6.4	Labelling of Investigational Drugs	95
5.7	Chapter Review	95
5.8	Further Reading	95

6	Marketing Authorisation	97
6.1	Chapter Introduction	97
6.2	The Application Dossier	97
6.3	CTD	98
6.3.1	Module Structure	101
6.3.2	Module 3: Quality	101
6.3.3	Drug Master Files	104
6.3.4	Module 4: Non-Clinical Study Reports	105
6.3.5	Module 5: Clinical Study Reports	105
6.3.6	Module 2: Summaries	107
6.3.7	Module I: Region-Specific	110
6.3.8	Module 1: EU	110
6.3.9	Module 1: US	113
6.4	Submission and Review Process in the EU	114
6.4.1	Community Authorisation	114
6.4.2	Scientific Evaluation Process	119
6.4.3	Decision-Making Process	120
6.4.4	National Authorisations	121
6.4.5	Decentralised Procedure	121
6.4.6	Mutual Recognition Procedure	123
6.4.7	Plasma Master Files and Vaccine Antigen Master Files	124
6.5	Submission and Review Process in the US	124
6.6	Chapter Review	127
6.7	Further Reading	127
7	Authorisation of Veterinary Medicines	129
7.1	Chapter Introduction	129
7.2	Overview of Development Process for Veterinary Medicines	129
7.2.1	Pre-Clinical Studies	130
7.2.2	Clinical Trials	131
7.2.3	Good Clinical Practices	131
7.3	Authorisation of Clinical Trials in the EU	134
7.4	Authorisation of Clinical Trials in the US	135
7.5	Maximum Residue Limits	136
7.6	Authorisation of Veterinary Medicines in the EU	138
7.6.1	Applications to Establish MRLs	138
7.6.2	Review of Applications and Establishment of MRLs	138
7.6.3	Marketing Authorisations	142
7.6.4	Presentation of the Dossier	143
7.7	Approval of Veterinary Medicines in the US	144
7.7.1	New Animal Drug Application	144
7.7.2	Approval of Veterinary Biological Products	147
7.8	Chapter Review	148
7.9	Further Reading	148

8	Variations to the Drug Authorisation Process	149
8.1	Chapter Introduction	149
8.2	Provisions in Support of Special Drug Applications	149
8.2.1	Orphan Drugs	149
8.3	Accelerated Access to New Drug Therapies	151
8.3.1	EMA Accelerated Review	151
8.3.2	Compassionate Use	151
8.3.3	Fast-Track Products	152
8.3.4	Treatment INDs	152
8.3.5	Paediatric Applications	152
8.4	Approval of New Drugs when Human Efficacy Studies are not Ethical or Feasible	153
8.5	Animal Drugs for Minor Use and Minor Species	153
8.5.1	Conditional Approval	153
8.5.2	Indexing	154
8.5.3	Designation	154
8.6	Use of Non-Authorised Drugs for Animal Treatment in the EU	154
8.7	Changes to an Authorised Drug	154
8.8	EU System for Processing Changes	154
8.8.1	Extension Applications	155
8.8.2	Major Variation (Type II)	155
8.8.3	Minor Variation (Type IA or IB)	156
8.9	Processing Changes in the US	156
8.9.1	Manufacturing Change Supplements	156
8.9.2	Major Changes	157
8.9.3	Moderate Changes	157
8.9.4	Minor Changes	157
8.10	Authorisation of Generic Drugs	158
8.10.1	EU Regulations	158
8.10.2	US Regulations	159
8.11	Reference Drug Exclusivity	159
8.12	Other Authorisation Procedures	161
8.12.1	Well-Established Medical Use Products	161
8.12.2	Combination Products	161
8.12.3	Homeopathic Medicines	161
8.12.4	Traditional Herbal Medicines	162
8.12.5	US Regulation of OTC Drugs	162
8.13	Chapter Review	164
8.14	Further Reading	164
9	Medical Devices	167
9.1	Chapter Introduction	167
9.2	Regulatory Strategy for Medical Devices in the EU	167
9.2.1	Use of Standards to Establish Conformity	168
9.2.2	Classification of Devices	170

9.3	Regulatory Strategy for Medical Devices in the US	173
9.3.1	Classification of Devices	173
9.3.1.1	Class I Devices	176
9.3.1.2	Class II Devices	177
9.3.1.3	Class III Devices	178
9.3.2	Classification of New Devices	178
9.4	Development of Devices	178
9.4.1	Design Controls	180
9.4.2	Design and Development Planning	180
9.4.3	Design Input	182
9.4.4	Design Output	182
9.4.5	Design Verification and Design Validation	183
9.4.6	Design Review	183
9.4.7	Risk Analysis	184
9.4.8	Design Changes	185
9.5	Chapter Review	185
9.6	Further Reading	185
10	Authorisation of Medical Devices	187
10.1	Chapter Introduction	187
10.2	Evaluation of Medical Devices in Europe	187
10.2.1	Clinical Investigations	188
10.2.2	Performance Evaluations	190
10.3	Evaluation of Medical Devices in the US	191
10.3.1	IDE-Exempted Investigations	191
10.3.2	Abbreviated Requirement Investigations	192
10.3.3	IDE Investigations	192
10.3.4	Labelling of Devices for Investigational Use	193
10.4	Placing of Devices on the Market in the EU	194
10.4.1	Conformity Assessment Procedures	195
10.4.2	Full Quality Assurance	197
10.4.3	EC Type-Examination	197
10.4.4	Production Quality Assurance	199
10.4.5	EC Verification	199
10.4.6	Product QA	199
10.4.7	EC (Self) Declaration of Conformity	199
10.4.8	Technical Documentation	199
10.4.9	Labelling Requirements	200
10.4.10	Competent Authority Notifications and the European Databank	201
10.5	Placing of Devices on the Market in the US	202
10.5.1	510(k) Pre-market Notification	202
10.5.1.1	Traditional 510(k)	202
10.5.1.2	Abbreviated 510(k)	203
10.5.1.3	Special 510(k)	203
10.5.1.4	De Novo 510(k)	203

10.5.2	Notification and Review Procedures	203
10.5.3	Pre-market Approval (PMA)	203
10.5.4	Changes to a PMA-Approved Device	205
10.5.5	Humanitarian Use Devices	206
10.5.6	Labelling of Devices	206
10.6	Chapter Review	206
10.7	Further Reading	208
11	Good Manufacturing Practice (GMP)	209
11.1	Chapter Introduction	209
11.2	Drug GMP Regulations and Guidance	209
11.3	Essential GMP Requirements	212
11.3.1	Quality Assurance System	212
11.3.2	Personnel	212
11.3.3	Premises and Equipment	213
11.3.4	Documentation	221
11.3.5	Production	222
11.3.6	Quality Control	222
11.3.7	Work Contracted Out	222
11.3.8	Complaints, Product Recall and Emergency Un-Blinding	223
11.3.9	Self-Inspection	223
11.4	Validation	223
11.4.1	Facilities and Equipment Validation	225
11.4.2	Process Validation	225
11.4.3	Computer Systems Validation	226
11.4.4	Methods Validation	227
11.4.5	Cleaning Validation	229
11.4.6	Validation of Sterilisation Procedures	230
11.4.7	Water Purification System Validation	230
11.5	GMP Requirements for Devices	231
11.6	Chapter Review	234
11.7	Further Reading	235
12	Oversight and Vigilance	237
12.1	Chapter Introduction	237
12.2	Registration of Manufacturers and Other Entities	237
12.3	Manufacturing Authorisation of Medicinal Products in the EU	237
12.3.1	Wholesale Distribution of Medicinal Products	238
12.3.2	Registration of Persons Responsible for Placing Medical Devices on the EU Market	240
12.4	Registration of Producers of Drugs and Devices in the US	241
12.4.1	Additional Licensing Requirements	242
12.5	Inspections	242
12.5.1	Inspection Techniques	245
12.5.2	Audit Findings and Consequences	248

12.6	Market Vigilance and Oversight of Drugs	253
12.6.1	Pharmacovigilance in the EU	254
12.6.2	Qualified Person	254
12.6.3	Reporting Requirements	254
12.6.4	Expedited Reports	255
12.6.5	Periodic Safety Update Reports	256
12.6.6	Safety Study Reports	256
12.6.7	Response to Issues	256
12.6.8	Renewal of Marketing Authorisations	258
12.6.9	Reporting Requirements in the US	258
12.6.10	Expedited Reports	258
12.6.11	Periodic Reports	262
12.7	Advertising and Promotion	262
12.8	Market Vigilance and Oversight of Devices	262
12.8.1	Market Vigilance in the EU	263
12.8.2	Medical Device Vigilance in the US	271
12.8.3	Medical Device Reporting	272
12.8.4	Reports of Corrections and Removals	273
12.8.5	Post-Market Surveillance	273
12.9	Chapter Review	274
12.10	Further Reading	274

Index	277
--------------	-----

Preface

Medical Product Regulatory Affairs aims to introduce and overview the regulatory affairs framework governing the development, approval, manufacturing and surveillance of both pharmaceuticals and medical devices, including *in-vitro* diagnostic products. The book focuses upon the regulatory framework and practice within the European Union and the United States of America, while also outlining global regulatory harmonization measures driven by the International Conference on Harmonization initiative. It should also serve as a reference source for those wishing to work in regulatory affairs, as well as for non-regulatory pharmaceutical/healthcare industry scientists and managers. The scope of this book should also render it a useful reference source for third-level students undertaking healthcare-related programmes of study (e.g. undergraduate or taught postgraduate programs in pharmacy, pharmaceutical science, (bio)materials science, biotechnology or applied biology).

Likewise, it should serve as a useful reference for academic and industry researchers whose research interests relate to the pharmaceutical, diagnostic, or medical device sector.

We would like to gratefully acknowledge EMEA, ISO, EDQM, PIC/S, IMB, ISPE and Health Canada that granted us permission to reproduce selected copyrighted material. We reserve a special acknowledgement and thanks to the European Commission, the FDA and the ICH secretariat, the VICH and the GHTF, who have placed their regulatory documentation in the public domain, and we have reproduced several documents from these sources herein.

Finally we dedicate this book to our parents.

December 2007.

J.J. Tobin
G. Walsh

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

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 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.

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,

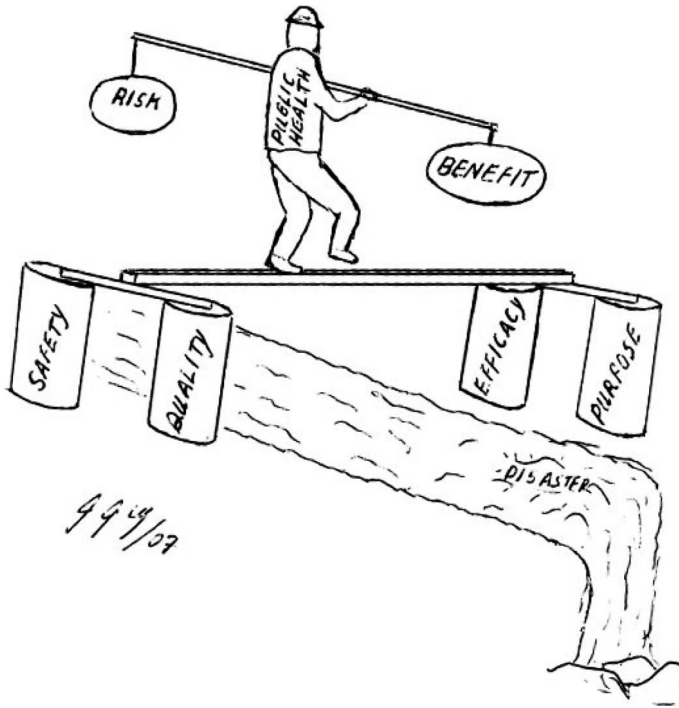


Figure 1.1 Regulatory principles.

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.

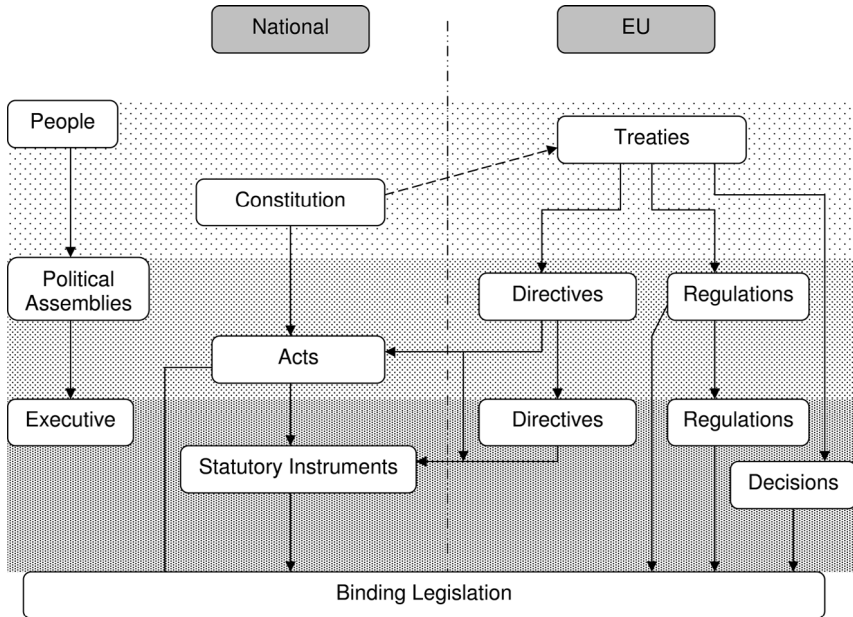


Figure 1.2 The relationship between National and EU legal instruments, and the flow of legislative authority.

- 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 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. 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 derivatives 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.