

John J. Tobin and Gary Walsh

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Medical Product Regulatory Affairs

Pharmaceuticals, Diagnostics, Medical Devices



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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?

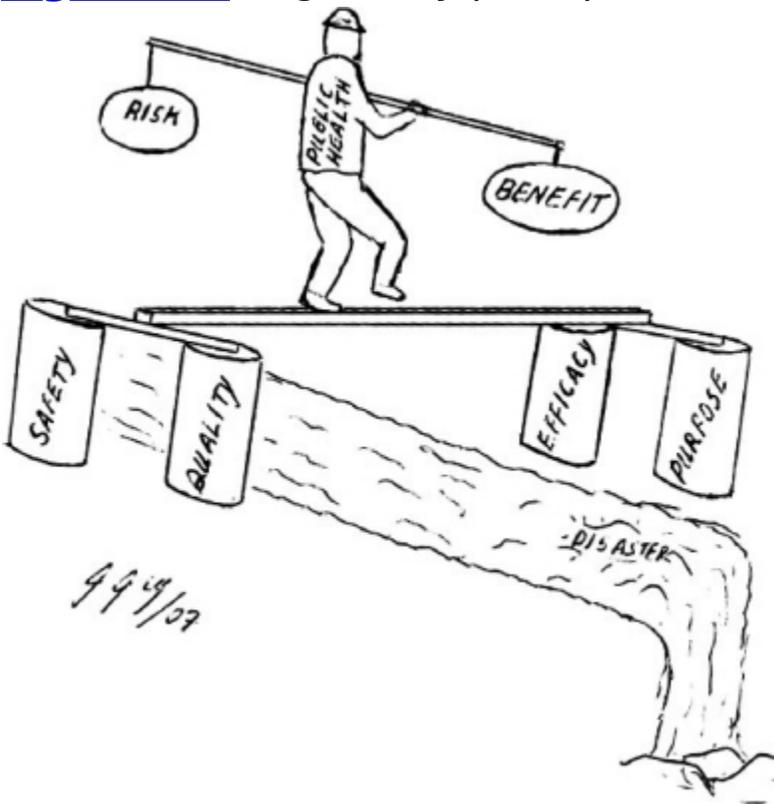
Consideration of the following examples of existing drug products may help you to understand this point. Chemotherapy drugs used to fight cancer are known to have significant side effects, including severe nausea and hair loss, while they are rarely effective in all cancer patients. However, despite 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, 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](#).

Figure 1.1 Regulatory principles.



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.

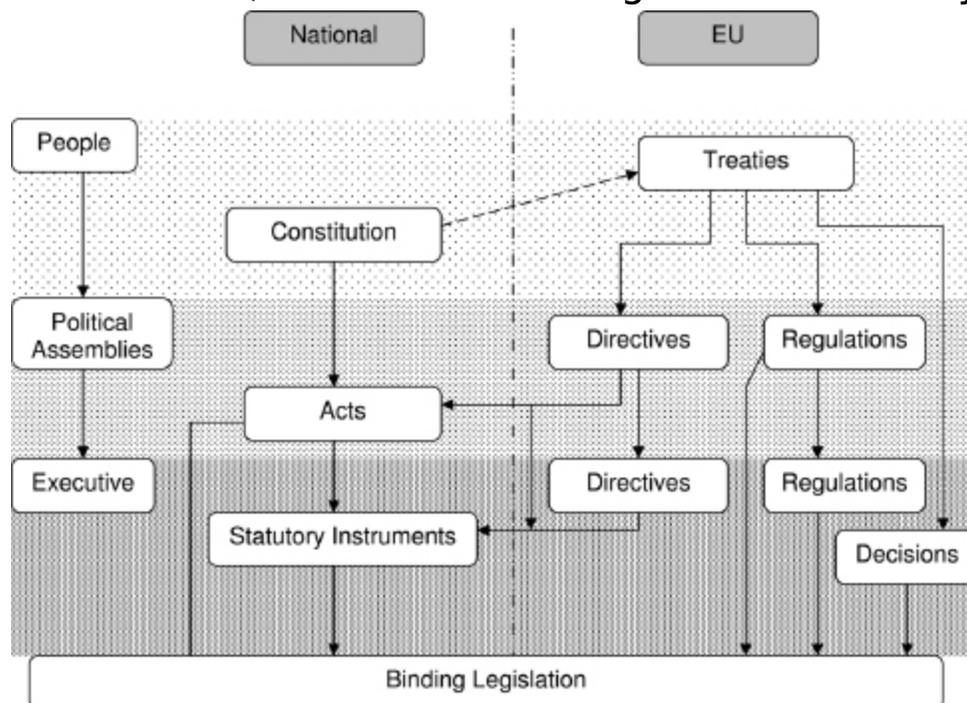
- You will start by reading statements citing the legal basis for the document and the reasoning behind its creation (“whereas” statements).
- Then, you will find the fundamental legal requirements set out in a series of articles.
- Finally, where applicable, you will find detailed technical requirements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

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



1.3.3 Working with Legal Texts

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

- You get both the principal legal requirements (The Articles) and the technical detail (The Annexes) in one document. As mentioned above, national legislation may just transpose the Articles, and you may have to refer back to the directive for the technical Annexes.
- National legislation is moulded by Directives, and new national legislation is invariably a response to EU initiatives.

- Most products are targeted at international rather than just national markets. Once you comply with the requirements of the directive, national legislation may not impose additional requirements other than as provided for in the directive (language requirements, etc.).

However, when working with Directives, 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 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 1.1](#) 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:

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	Amended by Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of

Human blood products	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 process. A summary of the main topics contained in the regulation is shown in [Table 1.3](#).

[Table 1.3](#) Content headings of Regulation (EC) 726/2004.

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

Community-wide regulation of medical devices commenced with the introduction of Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices. Two further “base” directives followed that 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,

[Table 1.4](#) Updates of the Device Directives.

Directive	Scope
2000/70/EC	Amends Council Directive 93/42/EEC as regards medical devices in 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 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;
- 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](#).

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