
THE LIFE SCIENCES LAW REVIEW

FIFTH EDITION

EDITOR
RICHARD KINGHAM

LAW BUSINESS RESEARCH

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EDITOR'S PREFACE

The fifth edition of *The Life Sciences Law Review* covers a total of 37 jurisdictions, providing an overview of legal requirements of interest to pharmaceutical, biotechnology and medical device companies. The chapters are arranged to describe requirements throughout the life cycle of a regulated product, from discovery to clinical trials, the marketing authorisation process and post-approval controls. Certain other legal matters of special interest to manufacturers of medical products – including administrative remedies, pricing and reimbursement, competition law, special liability regimes and commercial transactions – are also covered. Finally, there is a special chapter on international harmonisation, which is of increasing importance in many of the regulatory systems that are described in the national chapters.

Now, more than ever, it is important for leaders in the pharmaceutical and medical device industries and their advisers to be knowledgeable about the laws and regulations in major jurisdictions around the world. In the past year, there have been significant developments in the regulation of drugs and medical devices, especially in the United States, where a new law – the 21st Century Cures Act – was passed at the end of 2016. There are prospects for further developments in the coming year. The new president and the Republican-controlled Congress will consider legislative measures affecting the pharmaceutical and medical device sectors, including proposed repeal of the Affordable Care Act, continuing inquiries into pricing of medical products and reauthorisation of user fee laws that fund a substantial part of the drug and device approval processes. The United Kingdom will initiate formal proceedings to begin the process of withdrawing from the European Union, with potential consequences for the medical products sectors. Other jurisdictions, including China and India, are considering reforms to their regulatory systems for medicinal products.

Each of the chapters has been written by leading experts within the relevant jurisdiction. They are an impressive group, and it is a pleasure to be associated with them in the preparation of this annual publication.

Richard Kingham
Covington & Burling LLP
Washington, DC
March 2017

Chapter 1

INTERNATIONAL HARMONISATION

*Richard Kingham*¹

I INTRODUCTION

Over the past 25 years, major efforts have been made to harmonise the technical requirements relating to the drug regulatory process and – to a lesser extent – that for medical devices. By far the most successful such initiative has been the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH guidelines have now been incorporated into the drug regulatory systems in the European Union, the United States, Japan and many other jurisdictions, and the ICH Common Technical Document (CTD) and its electronic version (eCTD) have become the standard format for the submission of data in support of marketing authorisation applications in most major developed countries. In addition to the ICH, there are a number of other harmonisation initiatives, including the International Medical Device Regulators Forum (IMDRF) and a variety of regional harmonisation programmes.

II ICH

i History

For many years, certain major drug regulatory agencies maintained informal arrangements for cooperation and communication, but there was no formal mechanism to agree on the harmonisation of technical requirements for the drug development and approval process. Experience with successful harmonisation initiatives in the European Community during the 1980s led to the establishment of the ICH, following a meeting of regulators and industry representatives in Brussels in 1990 that was hosted by the European Federation of Pharmaceutical Industries and Associations. The original parties to the ICH were the European Community (now the EU), the US Food and Drug Administration (FDA) and the

¹ Richard Kingham is a partner at Covington & Burling LLP.

Japanese Ministry of Health, Labour and Welfare, along with the national trade associations of the pharmaceutical industry in the EU, US and Japan.² The World Health Organization (WHO), European Free Trade Association and Canada were given observer status.³

Initial efforts focused on well-defined technical issues, such as the design of stability studies and standard toxicology studies, about which there was no serious disagreement on general principles and objectives. There was no effort made to establish requirements for the mutual recognition of approval decisions or to address other potentially controversial topics.

Over the years, the ICH has broadened the base of organisations that contribute to its processes. For example, in 1996, generic industry experts and manufacturers of non-prescription medicines were invited to participate in technical discussions of issues of special interest to them. More recently, several regional harmonisation initiatives have participated in meetings of the ICH,⁴ as have the drug regulatory agencies and ministries of health of countries outside the EU, the US and Japan.⁵

ii Organisation and procedures

The ICH is governed by a steering committee, composed of members from the regulatory authorities and industry groups from the EU, US and Japan, which determines policies and procedures, selects topics for harmonisation, monitors and facilitates the progress of expert working groups and signs off ICH documents. There is also a secretariat, based in Switzerland and supported by the International Federation of Pharmaceutical Manufacturers Associations. A separate managing board within the ICH supervises the Medical Dictionary for Regulatory Activities (MeDRA), which establishes standardised terminology for communicating regulatory information concerning pharmaceuticals, including information in drug safety reports.

The main work of the ICH is done by expert working groups, which are organised into four broad categories: safety, efficacy, quality and multidisciplinary topics. These groups, which include experts from regulatory agencies and the pharmaceutical industry, draft guidelines and other documents and propose them for adoption through the ICH process. That process consists of five steps, which involve: (1) development of the scientific consensus for a guideline; (2) agreeing on the draft text of a guideline; (3) consulting with regional regulatory agencies; (4) adoption of harmonised guidelines; and (5) implementation of guidelines in the ICH regions. Although participants in the ICH process undertake to

2 These included the European Federation of Pharmaceutical Industries and Associations, the Pharmaceutical Research and Manufacturers of America and the Japan Pharmaceutical Manufacturers Association.

3 Detailed information on the ICH and its programmes is contained on the website, www.ich.org.

4 These are the Association of Southeast Asian Nations, the Asia-Pacific Economic Cooperation countries, the Cooperation Council for the Arab States of the Gulf, the Pan-American Network for Drug Regulatory Harmonization, the Southeastern African Development Community and the East African Community.

5 These are Australia, Brazil, China, Chinese Taipei, India, Korea, Russia and Singapore.

adopt harmonised guidelines as part of their national or regional regulatory requirements, full implementation may not be automatic if changes are required in local legislation or regulations.⁶ Final guidance may be supplemented by Q&As or other explanatory documents.

iii Principal ICH guidelines

Quality

One of the first topics identified for harmonisation by the ICH relates to drug quality – specifically, stability studies of drug products. Since then, the ICH has pursued harmonisation efforts in connection with analytical validation,⁷ impurities,⁸ pharmaceutical development,⁹ pharmaceutical quality systems¹⁰ and development and manufacture of drug substances,¹¹ *inter alia*. Of particular significance are workstreams relating to pharmacopoeias, which support efforts to harmonise compendial requirements in the EU, the US and Japan;¹² quality of biotechnology products,¹³ including important issues such as viral safety and comparability of biological products following manufacturing changes; good manufacturing practice (GMP);¹⁴ and quality risk management.¹⁵

Safety

Harmonisation of the major categories of non-clinical safety studies has been a major accomplishment of the ICH. Until the ICH process began, the FDA actually maintained few formal guidelines for non-clinical safety studies of drug products, and requirements were based largely on custom and informal compilations of documents written by agency staff. Today, there are agreed standards for studies of carcinogenicity,¹⁶ genotoxicity,¹⁷ toxicokinetics

6 When the CTD was adopted, the EU issued secondary legislation to make its use a legally binding requirement for applicants, whereas the FDA chose not to amend its regulations governing the content and format of a new drug application, on the theory that the same information was required to be submitted and only the organisation of the information was changed.

7 ICH Q1A-Q1F.

8 ICH Q3A-Q3D.

9 ICH Q8.

10 ICH Q10.

11 ICH Q11.

12 ICH Q4-Q4B.

13 ICH Q5A-Q5E.

14 ICH Q7.

15 ICH Q9.

16 ICH S1A-S1C.

17 ICH S2.

and pharmacokinetics,¹⁸ toxicity generally,¹⁹ reproductive toxicity²⁰ and immunotoxicity,²¹ as well as procedures for studies of biotechnology products,²² pharmacology,²³ non-clinical evaluation of anti-cancer pharmaceuticals²⁴ and photosafety.²⁵

Efficacy

The 'efficacy' category actually includes topics relating to human safety studies and pharmacovigilance as well as studies to determine the effectiveness of drug products. One of the most significant guidelines, relating to good clinical practice and originally adopted in 1996,²⁶ has become the internationally recognised standard for conducting clinical trials. It deals with the full range of topics, including study design, protection of human subjects, assurance of quality and reliability of data in clinical trials, the roles of sponsors, investigators and institutions, and many other issues. Of similar importance is the guideline on the format and content of clinical study reports,²⁷ which also serves as the model for all major developed jurisdictions. Other topics are clinical safety (including pharmacovigilance),²⁸ dose-response studies,²⁹ ethnic factors,³⁰ clinical trials generally (including statistical principles),³¹ clinical evaluation,³² clinical evaluation by therapeutic category³³ and pharmacogenomics.³⁴

The Common Technical Document

One of the most important accomplishments of the ICH process has been adoption of the CTD, which is now the generally accepted format for submission of data and analyses in support of marketing authorisation applications in major developed countries.³⁵ Use of the CTD became mandatory in the EU and Japan in 2003, and its use was also strongly recommended – and in practice required – by the FDA. It has greatly reduced duplication of effort in the preparation of dossiers for submission in major markets around the world.

The CTD comprises five modules: Module 1 consists of regional administrative information, which varies by jurisdiction; Module 2 contains summaries and overview

18 ICH S3A-S3B.

19 ICH S4.

20 ICH S5.

21 ICH S8.

22 ICH S6.

23 ICH S7A-S7B.

24 ICH S9.

25 ICH S10.

26 ICH E6.

27 ICH E3.

28 ICH E1-E2F.

29 ICH E4.

30 ICH E5.

31 ICH E7-E11.

32 ICH E14.

33 ICH E12A.

34 ICH E15-E16.

35 The CTD was adopted as a multidisciplinary topic (ICH M4), as was the electronic version, or eCTD (ICH M8).

documents; Module 3 contains information on the quality of the drug product, including components, manufacturing procedures, facilities and similar matters (what the FDA calls chemistry, manufacturing and controls); Module 4 contains reports of non-clinical studies (safety); and Module 5 contains reports of clinical studies (efficacy).

MeDRA

MeDRA establishes common terminology for use in individual case safety reports, periodic safety update reports and similar documents used for monitoring and evaluating safety signals related to drug products. It is supervised by the MeDRA Oversight Board, which contracts with the Maintenance and Support Services Organisation to ensure that the dictionary is kept up to date. The MeDRA system is coordinated with an earlier international dictionary developed by the WHO (the WHO Adverse Reaction Terminology).

III OTHER HARMONISATION INITIATIVES

i PIC/S

The Pharmaceutical Inspection Convention (PIC), originally agreed among several European nations in 1970, established procedures for common standards for drug manufacturing quality, mutual recognition of inspections and other matters. It was supplemented in 1995 by the Pharmaceutical Inspection Co-operation Scheme, and today the two entities are commonly referred to as PIC/S. Members include 44 regulatory authorities and international organisations. PIC/S seeks to establish common standards for GMP, training of inspectors, conduct of inspections, information sharing (including a rapid alert system) and other multinational initiatives relating to drug quality. Some member state authorities will accept GMP certificates from other PIC/S members, and membership in the PIC/S programme can facilitate bilateral mutual recognition agreements for GMP inspections.³⁶

ii IMDRF and other medical device initiatives

The IMDRF is a voluntary group of medical device regulators that seeks to advance harmonisation of regulatory requirements for medical devices. Established in 2011, it is the successor to the Global Harmonisation Task Force on Medical Devices. Current members are Argentina, Brazil, Canada, the EU, Japan and the United States, with the WHO as an observer; China and Russia are currently under consideration for membership. Guidelines have been issued concerning requirements and training for auditing organisations and regulatory assessors for medical devices, unique device identification and software medical devices.³⁷

The International Organisation for Standardisation (ISO) and the International Electrotechnical Commission have issued numerous standards that have important practical effects on regulation of medical devices. Perhaps most important has been the ISO 9000 series of standards, relating to quality-management systems, which was adopted as one of the key

36 Further details are set out in the PIC/S website, www.picscheme.org.

37 Details can be found at www.imdrf.org.

standards for the implementation of the EU medical device legislation.³⁸ Concepts derived from ISO 9000 have also been incorporated into device quality system regulations in the United States.³⁹

38 See, e.g., Council Directive 90/385/EEC on approximation of the laws of the Member States relating to active implantable medical devices; Council Directive 93/42/EEC concerning medical devices.

39 21 CFR, Part 820.

Appendix 1

ABOUT THE AUTHORS

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