about the book…

With 45 chapters that cover all of the major technical and clinical topics in a Common Technical Document registration, including summaries, quality of the drug substance and dosage form, nonclinical studies and clinical trials, this Second Edition provides a roadmap for International Conference on Harmonisation (ICH) and other technical and regulatory requirements for global filings in the US, EU, Japan and elsewhere.

This book provides a comprehensive overview of all of the scientific areas involved in the development and registration of new drug and other pharmaceutical products intended for registration internationally.

The book provides an essential practical toolkit for:

• regulatory affairs staff involved with writing, assembling, compiling, publishing and submitting registration files

• the professional staff in the ‘data provider’ teams who design the studies and provide the technical and scientific reports and documentation—the pharmaceutical R&D staff, chemical manufacturing, pharmaceutical manufacturing, analytical development, packaging development, QC, clinical trials staff, medical and scientific affairs, medical affairs, and project management.

• reviewers in the regulatory agencies

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Preface

THE OBJECTIVES AND SCOPE OF THE NEW EDITION
The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Common Technical Document (CTD) provides for a harmonized structure and format for new pharmaceutical product registration applications. The CTD format has been adopted in the three ICH regions of the United States, the European Union, and Japan and is increasingly used elsewhere in the world. The chapters in the new second edition of this book cover all the major technical and clinical topics that are included under the main headings in the Common Technical Document—the Module 2 summaries and overviews, Module 3 Quality, Module 4 Nonclinical Safety, and Module 5 Clinical Efficacy. One chapter deals with the particular national and region specific administrative and prescribing information in Module 1 in terms of application forms, health professional, and patient information, etc.; other chapters deal with the electronic CTD and environmental risk assessment.

This book, therefore, provides a comprehensive overview of all the scientific areas involved in the development and registration of new drug and other pharmaceutical products intended for registration internationally. The book is written to meet the needs of both regulatory affairs staff involved in writing, assembling, compiling, publishing, and submitting registration files, and the professional staffs in the “data provider” teams who design the studies and provide the technical and scientific reports and documentation—the pharmaceutical R&D staff, chemical manufacturing, pharmaceutical manufacturing, analytical development, packaging development, QC, clinical trials staff, medical and scientific affairs, medical affairs, and project management.

We have also included one or two chapters dealing with “cutting edge” issues where the regulatory policy is not yet fully agreed. Thus, we have included chapters on “Modeling and Medicinal Product R&D,” and a copy of an Agence française de sécurité sanitaire des produits de santé (Afssaps) Working Group on Nonclinical Innovation document entitled “Recommendations for Toxicological Evaluation of Nanoparticle Medicinal Products.”

Medicinal products cover such an enormous range—from in vivo diagnostic agents to radiopharmaceuticals to specialist biological and biotechnological products—so that to cover in detail the needs of all types of product would have required writing an encyclopedia rather than a single book. Inevitably, the editors have had to omit some aspects in relation to these specialist products.

PROGRESS IN INTERNATIONAL HARMONIZATION
Since the first edition of this book, there have been enormous changes in the technical and scientific requirements for the dossier, as the work of the ICH has continued to devise and approve new guidelines in the categories of Quality, Safety, Efficacy, and Multidisciplinary. The CTD harmonized structure and modular format for new medicinal product registration files that were adopted in San Diego, is now the obligatory format in the European Union (EU), Japan, Canada, Switzerland, and Australia. It is the recommended format in the United States. As mentioned in Chapter 1 of this book, derivatives of the CTD are becoming widely accepted in other regions of the world.

THE CTD—A COMMON FORMAT, NOT A HARMONIZED CONTENT FOR SUBMISSIONS
Enormous efforts have been expended by the staffs of the regulatory agencies and the pharmaceutical industry in the work of the ICH, and this has achieved a remarkable degree of
harmonization in many scientific and technical areas of the dossier. Despite this there are still national differences in the content of submissions not only in Module 1, the administrative and prescribing information, but also in other areas of the dossier. These arise from differences in regulatory practice and procedures, different practices of medicine and pharmacy, and differences in access to diagnostic and therapeutic procedures. We are, however, still far from a genuinely global single registration dossier. The chapter authors have tried to capture some of these differences wherever feasible to help those planning to market their products in different regions of the world.

INCREASED COOPERATION BETWEEN AGENCIES BASED ON ICH

Mutual Recognition Agreements between agencies in relation to Good Manufacturing Practice (GMP) are in operation between the EU and Canada, Australia, New Zealand, Switzerland, and Japan. Arrangements exist between many countries (including the ICH members) for exchange of pharmacovigilance and defect information.

The confidentiality arrangements between the EU and the FDA now allow for exchange of information on legal and regulatory issues, scientific advice, orphan drug designation, inspection reports, marketing authorization procedures, and postmarketing surveillance. In September 2004, the European Medicines Agency (EMEA) and the Food and Drugs Administration (FDA) instituted a pilot program of parallel scientific advice meetings for sponsors to obtain advice on scientific issues during the development phase of new medicinal products. Orphan indication products and pediatric products have been targeted in particular.

Under the aegis of the Transatlantic Economic Council, the EU and FDA have reviewed ways in which cooperation can reduce administration and enable them to share best regulatory practices. This has been followed by an EMEA announcement of proposals for a EU–US–Australian pilot program to make more efficient use of global GMP inspection resources.

Bilateral and trilateral collaboration has increased in 2008. Health Canada has agreed to exchange information with the European Commission and EMEA about the authorization and safety of drugs. Canada and Australia have started their parallel review project for biologicals (originally launched in 2006).

All of this has only been possible based on the prior work that has been done in harmonization of regulatory requirements and in the development of the CTD format of the dossier in ICH, which are discussed in this book.

SPREADING THE ICH MESSAGE—THE ICH GLOBAL COOPERATION GROUP

The ICH-affiliated and other developed countries, which have adopted the CTD format (the United States, EU, Japan, Canada, Switzerland, and Australia), comprise in total approximately 15% of the current (2008) world population of 6650 million people. The ICH Global Cooperation Group (GCG) was formed on March 11, 1999 as a subcommittee of the ICH Steering Committee. Its purpose is to make information available on ICH, ICH activities, and any ICH guideline to a wider group of countries.

Regional Harmonization Initiatives

A number of regional harmonization initiatives (RHIs) have been set up where a geographic grouping of countries harmonizes technical and scientific requirements and in some cases the format of submissions for member countries. These groups have been invited to designate permanent representatives to the GCG. They currently comprise:

- **Asia-Pacific Economic Cooperation** (APEC): 21 countries in the Asia-Pacific region.
- **Association of Southeast Asian Nations** (ASEAN): Brunei Darussalam, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand and Vietnam.
- **Gulf Cooperation Countries** (GCC): Saudi Arabia, Kuwait, United Arab Emirates, Oman, Bahrain, Qatar and Yemen.
- **Pan American Network on Drug Regulatory Harmonisation** (PANDRH): Argentina, Barbados, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Guatemala, Jamaica, Mexico, Panama, Trinidad and Tobago and Venezuela.
• **South African Development Community (SADC):** Angola, Botswana, Democratic Republic of Congo, Lesotho, Malawi, Mauritius, Madagascar, Namibia, Seychelles, South Africa, Swaziland, Tanzania, Zambia and Zimbabwe.

The regional groups review the applicability of the ICH guidelines in their own specific countries. Particular topics of interest include the ICH stability guideline, GMP guidances, requirements for bioavailability and bioequivalence studies, clinical trials, export/import of medicines, traditional medicines, and market surveillance. Many of these topics are covered in this book.

**DRUG SAFETY AND RISK MANAGEMENT**

In 2008, both the EMEA and the FDA placed an increasing emphasis on drug safety and risk management. The FDA launched its Safety First initiative to strengthen its internal policies to improve drug safety review.

In Europe, the EMEA consulted on proposals to strengthen its pharmacovigilance system, and in December 2008, brought forward a new “pharma package” of draft legislation for consideration. This includes adding a new legal requirement for a risk management system for each new medicinal product. Adverse drug reporting and periodic safety update reports (PSURs) would be made more proportionate to the risks, and all data would be added to the Eudravigilance database. A new Pharmacovigilance Risk Assessment Advisory Committee would be set up to assess pharmacovigilance data.

Current requirements for pharmacovigilance and postmarketing are summarized in chapters in this book.

**OUTSOURCING OF R&D, CLINICAL TRIALS, ETC.**

There are currently single-digit percentage increases in drug sales in the United States and Europe, as the rate of new drug approval (particularly in the United States) slows down and there is increasing competition from generics. Companies are shedding staff and outsourcing R&D, manufacture, etc., increasingly to Asia and China. Again, the existence of internationally accepted guidelines (such as those discussed in this book) enables work to be outsourced and carried out to acceptable agreed standards.

In addition, many pharma companies are integrating clinical trials outside the ICH regions into global clinical development programs. These trials conducted according to ICH Good Clinical Practice and reported in accordance with ICH guidelines (as discussed in this book) will have access to well-trained physicians and a large number of treatment-naïve patients at significantly lower cost. Such global trials will enable clinical data to be obtained on patients with different ethnic backgrounds and will help facilitate a coordinated registration and reduce the “drug lag” in delayed registration outside the ICH regions.

**New Chemical Entity or New Biotechnological Products**

It is evident that a huge effort has been put into the harmonization discussions and negotiations between the major regulatory agencies and the pharmaceutical trade associations in the United States, Japan, and Europe. This book reviews the key international requirements for registering a New Active Substance product containing a New Chemical Entity (NCE) or new biological/biotechnological entity and to try to explain how these requirements could be met by defined programs of work. The book is intended to cover all the major scientific and technical topics in such a registration file.

Where harmonization has already taken place (either under the auspices of ICH or elsewhere), the authors of the individual chapters of this book have reviewed progress and have suggested the main directions that this is likely to take. Programs of drug discovery and development for new drug products usually take place over a 10- to 12-year period, and thus studies started now will often not be the subject of a submission to the authorities for some years. An astute research laboratory or a development manager is one who identifies and anticipates the trends in development of scientific and technical thinking and how these may eventually be translated into legal rules and guidelines for registration of medicinal products so that the company’s
submission can be seen to be “state of the art.” We feel that this book will be of some assistance in this process.

Where harmonization has not taken place, there are often either no clearly defined requirements or even divergent requirements. In these cases, the authors have been asked to address the following questions in their chapters:

- What is the current state of science and technology in this area?
- In which direction is scientific development taking in terms of determining practical test requirements?
- How can the current scientific and technical regulatory requirements for a product intended for all major markets (and particularly the EU, the United States, and Japan) be best satisfied by a program of experimental work?

**Generic Products, Biosimilars, etc.**

The CTD format is applicable to all types of medicinal products, not just New Chemical Entities and biotechnological products. Many of the technical requirements in Modules 1, 2, 3, and 5 will also apply to generic chemical and biotechnological products (“biosimilars”) and even Over-the-Counter (OTC) products. Thus, many of the relevant chapters also cover these technical requirements.

**CHOICE OF AUTHORS**

The editors have chosen authors based on their wide expertise and knowledge of the scientific and technical requirements involved in drug regulation. They have been chosen mainly from experts from the national authorities involved in the harmonization process, from international companies whose daily task is to provide the data for filing world-wide submissions, and from the consultants who advise such companies. The editors would like to express their gratitude to all the authors who have given so generously of their time and expertise to provide this text as well as to the organizations, for which they work, which have graciously allowed them to do so.

**DISCLAIMER**

The contents of this book represent the views of its authors. They do not necessarily reflect the policies or opinions of the national competent authorities (regulatory agencies), the health departments, advisory or regulatory committees, the pharmaceutical companies, the Contact Research Organizations, consultancy companies, academic institutions, hospitals, etc., for whom the authors work.

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Anthony C. Cartwright  
Brian J. Matthews
Acknowledgements

The recruitment of suitable authors for the large number of individual chapters in this second edition of the book relied heavily on the friends and colleagues of the editors. However, the range of subjects covered in the book is very wide and the editors wish in particular to thank Dr. David Snodin for his help in recruiting nonclinical authors and Professor Jean-Marc Husson for his help in recommending clinical authors. The willingness of the authors to take time out of their busy professional lives for writing chapters of this book is gratefully acknowledged.

Many of the authors work for official national competent authorities or as experts associated with these authorities. Others work for pharmaceutical companies, contract companies, academic institutions, and consultancies. The permission of these authorities, companies, and consultancies for their approval for individual authors to write and publish the texts of their chapters is acknowledged.

In some chapters the authors have used registered and other trademarks when mentioning particular products. The rights of the owners of those trademarks are hereby acknowledged. The mention of a particular product or service is not intended to represent an endorsement for the product or to necessarily imply fitness for a particular use.

The editors wish to thank Carolyn Honour, Sherri Niziolek, and the staff at Informa Healthcare USA, Inc. for their support, encouragement, and forbearance during production of this book.
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INTERNATIONAL HARMONIZATION
Harmonization of regulatory requirements for registering new medicinal products began in the 1970s as the European Community (now the European Union, EU) moved toward developing a single market for pharmaceutical products. European guidelines were developed by the Committee for Proprietary Medicinal Products (CPMP) and its scientific working parties. At the same time, there were bilateral discussions between Europe and the United States (U.S.A.) on the one hand and Europe and Japan on the other on the possibilities of harmonizing data requirements for registration files for pharmaceutical medicinal products. In 1989, the pharmaceutical industry proposed that a joint industry-regulatory authority initiative be set up to harmonize requirements for safety, quality, and efficacy. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was set up in 1990. Its objective is to ensure that good quality, safe and effective medicines are developed and registered in the most cost-effective and efficient way.

The “players” in ICH are the regulatory agencies and the research-based industry in the three ICH regions of Europe, Japan, and the United States. They comprise the Food and Drug Administration (FDA) and the Pharmaceutical Research and Manufacturers of America (PhRMA) for the United States, the European Commission/European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA) for Europe, and the Ministry of Health, Labour and Welfare (MHLW) and the Japan Pharmaceutical Manufacturers Association (JPMA) for Japan. There are observers at meetings of the ICH from the World Health Organization (WHO), the European Free Trade Area (EFTA) (currently represented by Swissmedic), and Health Canada.

The ICH is managed by its Steering Committee, which meets twice yearly. Topics for harmonization agreed by the Steering Committee are considered by Expert Working Groups (EWGs), which meet in parallel with the Steering Committee to discuss scientific and technical aspects. The EWGs recommend texts of guidelines to the Steering Committee for issue for consultation and then for adoption.

WORK ON THE COMMON TECHNICAL DOCUMENT
The first topics considered for harmonization are related to safety, quality, and efficacy. The topics chosen were those where there were significant regional differences between the regulatory requirements, which added to the costs for developing of new drug products. After this first period of harmonization of key regulatory requirements, the ICH turned its attention to the format for documentation in a registration file. The objective was to remove redundancy and duplication so that as far as possible a single set of data could be provided to demonstrate safety, quality, and efficacy. The aim was also to reduce the delays and costs involved in converting registration files between the different national formats.

Adoption and Implementation of the CTD
The final text of the CTD was issued in November 2000 by the ICH Steering Committee and this has now been revised and updated (1–4). The CTD was implemented as an optional format in the European Union, the United States, Japan, Canada, and Switzerland. It became mandatory from July 2003 in the European Union, Japan, Canada, and Switzerland. It is the recommended format in the United States as ICH documents have always been considered as guidance by the
FDA, and the September 2000 Good Guidances Practice Final Rule requires that the CTD not be mandatory.

The CTD format has also been adopted in Australia by the Therapeutic Goods Administration (TGA) and it became the mandatory format after June 30, 2004. The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) announced that the CTD format became mandatory for all intermediate-risk and high-risk new medicine applications from September 1, 2006.

MODULAR STRUCTURE OF THE ICH CTD (1)
The CTD has a highly modular structure
- Module 1: Administrative Information (different for each ICH region or country)
- Module 2: Summaries
- Module 3: Quality
- Module 4: Nonclinical Study Reports
- Module 5: Clinical Study Reports

The organizational structure is shown diagrammatically (Fig. 1), and the high-level structure is summarized below.

Module 2: Summaries
Module 2 contains seven high-level summaries of quality, nonclinical safety, and clinical safety and efficacy. It comprises the following:

Module 2.1: CTD Table of Contents
Module 2.2: CTD Introduction

Figure 1  Organization of the CTD.
Module 2.3: Quality Overall Summary
Module 2.4: Nonclinical Overview
Module 2.5: Clinical Overview
Module 2.6: Nonclinical Summaries
Module 2.7: Clinical Summaries

Module 3: Quality
3.1 Table of Contents of Module 3
3.2 Body of Data
   3.2.S Drug Substance
   3.2.P Drug Product
   3.2.R Regional Information
3.3 Literature References

Module 4: Nonclinical Study Reports
4.1 Table of Contents of Module 4
4.2 Study Reports
4.3 Literature References

Module 5: Clinical Study Reports
5.1 Table of Contents of Module 5
5.2 Tabular Listing of all Clinical Studies
5.3 Clinical Study Reports
5.4 Literature References

DETAILED MODULAR STRUCTURE OF THE CTD

Module 2: CTD Summaries
2.1 Table of Contents
2.2 CTD Introduction
2.3 Quality Overall Summary
   2.3.S Drug Substance
      2.3.S.1 General Information
      2.3.S.2 Manufacture
      2.3.S.3 Characterization
      2.3.S.4 Control of Drug Substance
      2.3.S.5 Reference Standards or Materials
      2.3.S.6 Container Closure System
      2.3.S.7 Stability
   2.3.P Drug Product
      2.3.P.1 Description and Composition of the Drug Product
      2.3.P.2 Pharmaceutical Development
      2.3.P.3 Manufacture
      2.3.P.4 Control of Excipients
      2.3.P.5 Control of Drug Product
      2.3.P.6 Reference Standards or Materials
      2.3.P.7 Container Closure System
      2.3.P.8 Stability
   2.3.A. Appendices
      2.3.A.1 Facilities and Equipment
      2.3.A.2 Adventitious Agents Safety Evaluation
      2.3.A.1.3 Excipients
   2.3.R Regional Information
2.4 Nonclinical Overview
   2.4.1 Overview of the Nonclinical Testing Strategy
   2.4.2 Pharmacology

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