BIOHEALTHCARE PUBLISHING SERIES ON
PHARMA, BIOTECH AND BIOSCIENCES: SCIENCE, TECHNOLOGY AND BUSINESS

The stated aim of authors of this book is that "it will be a 'consultant-in-a-book' for managers and leaders in biotech companies. It will support what you already know, it will encourage you to keep going through difficult times, it will challenge you to take a different view on matters, and it will make you think about how what you are doing will impact on you, your company and those around you, not just now but in the future. It is our hope that this book will also annoy you, disturb some of your cherished views and challenge some of your most ingrained behaviours – exactly what we would do if we were acting as consultants, but without us drinking your coffee."

Readership: people working in management in biotech; would be entrepreneurs; people working in biotech away from major US and European clusters (Australasia, India and China) where mentoring and experience is not always available.

Key features include:

- No other 'how to' manual exists for this sector.
- Written by a range of expert professionals in each area, all in one book.
- Is the only 'bench to bedside' book covering the whole spectrum of development.
- Covers key business and managerial skills.

Dr Michael O'Neill is an innovation advisor who founded his own company, Eolas Biosciences Ltd, to help companies by providing strategic advice and detailed practical know-how across a range of disciplines and therapeutic areas. His work includes writing business and commercialisation plans, project management, product development to marketing strategy and regulatory advice on drug development. He has worked in a number of research and managerial roles in Merck, Laboratorios Almirall and Eli Lilly.

Michael Hopkins is a Senior Lecturer at SPRU – Science and Technology Policy Research, at the University of Sussex, UK. He has spent more than 15 years studying and researching how biotechnology innovation works in practice. Michael has consulted for the UK's Department of Trade and Industry, Human Genetics Commission, OECD and European Commission, as well as providing executive training for biotech and pharmaceutical firms in the UK and beyond.

Biohealthcare Publishing is an international publisher of books in the following areas:

PHARMACEUTICALS • BIOPHARMACEUTICALS • LIFE SCIENCE
BIOTECHNOLOGY • MEDICAL SCIENCE AND TECHNOLOGY

ISBN 978-1-907568-14-5
9 781907 568145

For a full listing of Biohealthcare Publishing's titles, please contact us or visit our website:
Biohealthcare Publishing (Oxford) Limited, Hexagon House, Avenue 4,
Station Lane, Witney, Oxford OX28 4BN, United Kingdom
Tel: +44 (0) 1993 848726 Fax: +44 (0) 1865 884448
Email: info@biohealthcarepublishing.com Website: www.biohealthcarepublishing.com

VOL 4

A BIOTECH MANAGER'S HANDBOOK
A PRACTICAL GUIDE

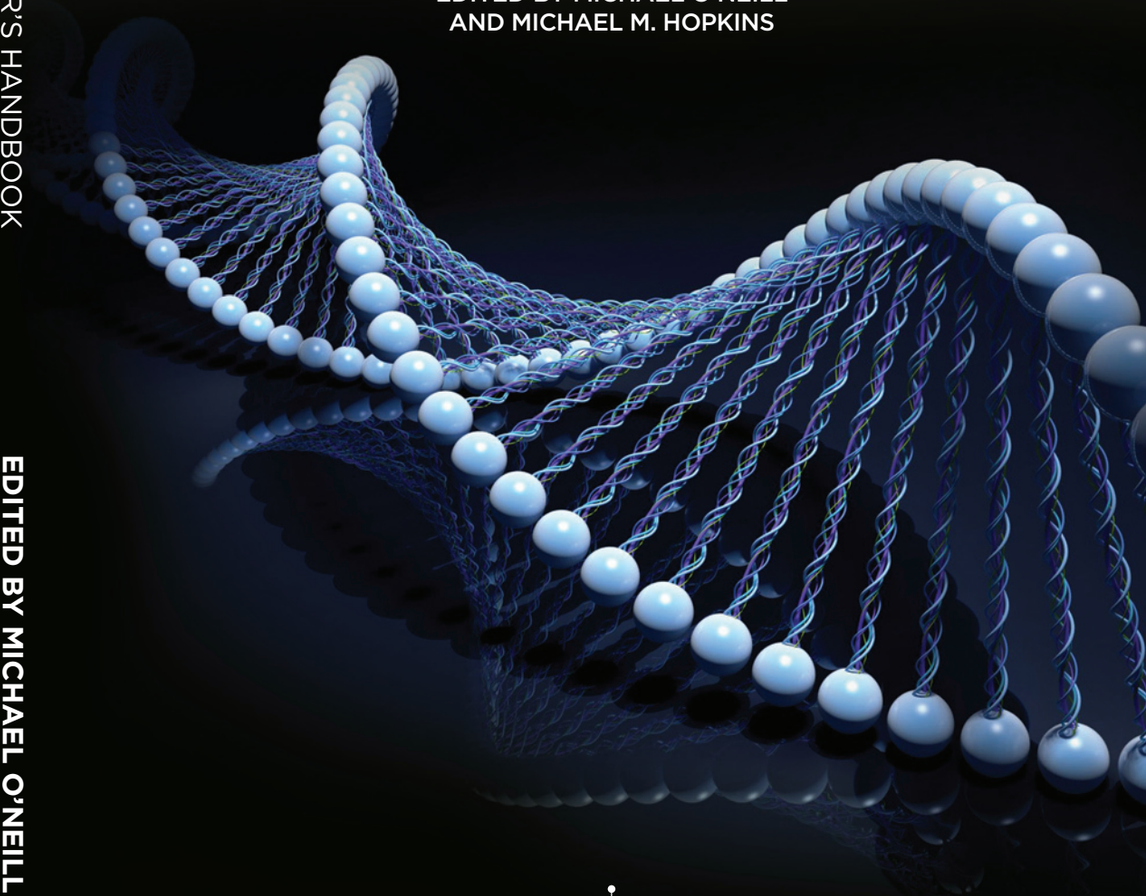
EDITED BY MICHAEL O'NEILL AND MICHAEL M. HOPKINS

BIOHEALTHCARE PUBLISHING SERIES ON
PHARMA, BIOTECH AND BIOSCIENCES: SCIENCE, TECHNOLOGY AND BUSINESS

A BIOTECH MANAGER'S HANDBOOK

A PRACTICAL GUIDE

EDITED BY MICHAEL O'NEILL
AND MICHAEL M. HOPKINS



Biohealthcare
PUBLISHING (OXFORD) LIMITED
Oxford • New York

A Biotech Manager's Handbook

Biohealthcare Publishing Series on Pharma, Biotech and Biosciences: Science, Technology and Business

Volumes in the Series

1. *Clinical Research in Asia*. U. Sahoo (ISBN 9781907568008).
2. *Outsourcing Biopharma R&D to India*. P.R. Chowdhury (ISBN 9781907568084).
3. *Practical Leadership for Biopharmaceutical Executives*. J. Chin (ISBN 9781907568060)
4. *A Biotech Manager's Handbook*. M. O'Neill and M.M. Hopkins (eds.) (ISBN 9781907568145).
5. *RNA Interference*. T. Novobrantseva et al. (ISBN 9781907568169).
6. *Therapeutic Protein Formulation*. B. Meyer (ed.) (ISBN 9781907568183).
7. *Patent Litigation in the Pharmaceutical and Biotechnology Industries*. G. Morgan (ISBN 9781907568206).
8. *Matlab® in Bioscience and Biotechnology*. L. Burstein (ISBN 9781907568046).
9. *Clinical Research in Paediatric Psychopharmacology*. P. Auby (ISBN 9781907568244).
10. *Concepts and Techniques in Genomics and Proteomics*. N. Saraswathy and P. Ramalingam (ISBN 9781907568107).
11. *An Introduction to Biotechnology*. W.T. Godbey (ISBN 9781907568282).
12. *The Application of SPC in the Pharmaceutical and Biotechnology Industries*. T. Cochrane (ISBN 9781907568336).
13. *Patently Innovative: How Pharmaceutical Firms Use Emerging Patent Law to Extend Monopolies on Blockbuster Drugs*. R. Bouchard (ISBN 9781907568121).
14. *Therapeutic Antibody Engineering*. W.R. Strohl and L.M. Strohl (ISBN 9781907568374).
15. *Ultrafiltration for Bioprocessing*. H. Lutz (ISBN 9781907568466).
16. *Therapeutic Risk Management of Medicines*. A.K. Banerjee (ISBN 9781907568480).
17. *21st Century Quality Management and Good Management Practices: Value Added Compliance for the Pharmaceutical and Biotechnology Industry*. S. Williams (ISBN 9781907568503).
18. *An Introduction to Pharmaceutical Sciences*. J. Roy (ISBN 9781907568527).
19. *Pharmaceutical Licenses: Valuation and Execution*. S. Mayhew and I. Walker (ISBN 9781907568565).
20. *CAPA in the Pharmaceutical and Biotech Industries*. J. Rodriguez (ISBN 9781907568589).
21. *Commercialising the Stem Cell Sciences*. O. Harvey (ISBN 9781907568602).
22. *Process Validation for the Production of Biopharmaceuticals: Principles*

and Best Practice. Applied Strategies for Bioprocess Development and Manufacture. A. Newcombe et al. (ISBN 9781907568640).

23. *Clinical Trial Management. An Overview*. A.U. Sahoo et al. (ISBN 9781907568664).
24. *Annotating New Genes: From In Silico to Validations by Experiments*. S. Uchida (ISBN 9781907568688).
25. *Impact of Regulation on Drug Development*. H. Guenter Hennings (ISBN 9781907568701).
26. *The Design and Manufacture of Medical Devices*. J. Paulo Davim (ISBN 9781907568725).
27. *Human Papillomavirus Infections. From the Laboratory to Clinical Practice*. F. Cobo (ISBN 9781907568749).
28. *Developments in Tissue Engineered and Regenerative Medicine Products. A Practical Approach*. J. Basu and J.W. Ludlow (ISBN 9781907568763).
29. *Lean Biomanufacturing*. N.J. Smart (ISBN 9781907568787).
30. *Marine Enzymes for Biocatalysis*. A. Trincone (ISBN 9781907568800).
31. *Recombinant Vaccines*. S. Pincus et al (ISBN 9781907568824).
32. *Ocular Transporters and Receptors in the Eye: Their Role in Drug Delivery*. A.K. Mitra (ISBN 9781907568862).
33. *Stem Cell Bioprocessing: For Cellular Therapy, Diagnostics and Drug Development*. T.P.G. Fernandes et al (ISBN 9781907568886).
34. *The Quality by Design Handbook: A Systems View on Pharmaceutical and Biopharmaceutical Development and Manufacturing*. C. Herwig and J.C. Menezes (ISBN 9781907568909).
35. *Fed-Batch Fermentation: A Practical Guide to Scalable Recombinant Protein Production in Escherichia coli*. G.G. Moulton and T. Vedvick (ISBN 9781907568923).
36. *The Funding of Biopharmaceutical Research and Development*. D.R. Williams (ISBN 9781907568947).
37. *The Parathyroid Hormone Receptor*. J-P. Vilardaga (ISBN 9781907568961).
38. *Free and Open Software in Applied Life Science and Industry*. L. Harland and M. Foster (ISBN 9781907568978).
39. *Nanoparticulate Drug Delivery*. Patravale V., Dandekar P. and Jain R. (ISBN 9781907568985).
40. *Formulation Tools for Pharmaceutical Development*. Diaz, J.E. Aguilar (ISBN 9781907568992).
41. *Bacterial Cellular Metabolic Systems*. Shimuzu K. (ISBN 9781907568015).
42. *Drug-Biomembrane Interaction Studies*. Pignatello R. (ISBN 9781907568053).

Biohealthcare Publishing Series on Medical and Health Science, Technology and Policy

Volumes in the Series

1. *Medical Education, Training and Care Delivery in a Virtual World*. K. Kahol (ISBN 9781907568039).
2. *Allergens and Respiratory Pollutants*. M. Williams (ed.) (ISBN 9781907568541).
3. *NMR Metabolomics in Cancer Research*. M. Williams (ed.) (ISBN 9781907568848).

Biohealthcare Publishing Series on Bioinformatics

Volumes in the Series

1. *In Silico Protein Design*. C.M. Frenz (ISBN 9781907568268).
2. *Bioinformatics for Computer Science*. K. Revett (ISBN 9781907568329).
3. *Gene Expression Analysis in the RNA World*. J.Q. Clement (ISBN 9781907568305).
4. *Computational Methods for Finding Inferential Bases in Molecular Genetics*. Q.-N. Tran (ISBN 9781907568398).
5. *Computer-Aided Vaccine Design*. T.J. Chuan and S. Ranganathan (ISBN 9781907568411).
6. *Bioinformatics for Biomedical Science and Clinical Applications*. K.-H. Liang (ISBN 9781907568442).
7. *Deterministic Versus Stochastic Modelling in Biochemistry and Systems Biology*. P. Lecca et al. (ISBN 9781907568626).

A Biotech Manager's Handbook

A practical guide

Edited by
Michael O'Neill
and
Michael M. Hopkins

Biohealthcare
PUBLISHING (OXFORD) LIMITED
Oxford · New York

Biohealthcare Publishing (Oxford) Limited

Hexagon House
Avenue 4
Station Lane
Witney
Oxford OX28 4BN, UK
Tel: +44 (0) 1865 598888; Fax: +44 (0) 1865 884448
Email: info@biohealthcarepublishing.com
Website: www.biohealthcarepublishing.com

First published in 2012 by Biohealthcare Publishing (Oxford) Limited
ISBNs: 978 1 907568 14 5 (print) and 978 1 908818 15 7 (e-book)

© The editor, contributors and the Publishers, 2012

The right of M. O'Neill and the contributors to be identified as author of the editiorial material in this Work has been asserted by them in accordance with sections 77 and 78 of the Copyright, Designs and Patents Act 1988.

British Library Cataloguing-in-Publication Data: a catalogue record for this book is available from the British Library.

All rights reserved. No part of this publication may be reproduced, stored in or introduced into a retrieval system, or transmitted, in any form, or by any means (electronic, mechanical, photocopying, recording or otherwise) without the prior written permission of the Publishers. This publication may not be lent, resold, hired out or otherwise disposed of by way of trade in any form of binding or cover other than that in which it is published without the prior consent of the Publishers. Any person who does any unauthorised act in relation to this publication may be liable to criminal prosecution and civil claims for damages.

Permissions may be sought directly from the Publishers, at the above address.

The use in this publication of trade names, trademarks, service marks, and similar terms, even if they are not identified as such, is not to be taken as an expression of opinion as to whether or not they are subject to proprietary rights. The Publishers are not associated with any product or vendor mentioned in this publication.

The authors, editors, contributors and Publishers have attempted to trace the copyright holders of all material reproduced in this publication and apologise to any copyright holders if permission to publish in this form has not been obtained. If any copyright material has not been acknowledged, please write and let us know so we may rectify in any future reprint. Any screenshots in this publication are the copyright of the website owner(s), unless indicated otherwise.

Limit of Liability/Disclaimer of Warranty
The Publishers, author(s), editor(s) and contributor(s) make no representations or warranties with respect to the accuracy or completeness of the contents of this publication and specifically disclaim all warranties, including without limitation warranties of fitness for a particular purpose. No warranty may be created or extended by sales or promotional materials. The advice and strategies contained herein may not be suitable for every situation. This publication is sold with the understanding that the Publishers are not rendering legal, accounting or other professional services. If professional assistance is required, the services of a competent professional person should be sought. No responsibility is assumed by the Publishers, author(s), editor(s) or contributor(s) for any loss of profit or any other commercial damages, injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions or ideas contained in the material herein. The fact that an organisation or website is referred to in this publication as a citation and/or potential source of further information does not mean that the Publishers nor the author(s), editor(s) and contributor(s) endorses the information the organisation or website may provide or recommendations it may make. Further, readers should be aware that internet websites listed in this work may have changed or disappeared between when this publication was written and when it is read. Because of rapid advances in medical sciences, in particular, independent verifi cation of diagnoses and drug dosages should be made.

Typeset by Domex, India
Printed in the UK and USA
Cover design by Hutchins Creative

Contents

10

Successful registration of new therapies in the EU and USA

Gerard McGettigan and Michael O'Neill

Abstract. This chapter summarises the main regulatory frameworks operating in the major pharmaceutical markets as operated by the Regulatory Authorities in the EU, the USA and with a brief reference to Japan. There is a high degree of convergence in the requirements for a marketing authorisation under the International Convention on Harmonisation but there are still important differences in the content and procedures that need to be taken into account. A huge amount of detailed information is now available on-line from the regulatory agencies. Considerable time and care is still required to navigate through the different regulatory processes. Regulatory requirements are constantly evolving in the light of evolving science, experience with novel treatments and as new insights into assessment techniques for quality, safety or efficacy emerge. Clinical trial design is also in the process of constant evolution. It is vital that sponsoring companies discuss their development programmes with the relevant regulatory authorities prior to embarking on them. Likewise, regulators are constantly looking for ways to facilitate the path to the clinic for new treatments, while bearing in mind that their primary duty is to protect the public from unproven or unsafe treatments. Taking a lead from the USA and other countries, the EU has introduced the orphan legislation that incentivises companies to develop drugs for rare diseases. On occasion, normally due to scarcity of patients, these medicines can be approved with a reduced data package although the

same regulations and guidelines on product development apply to orphan drugs as to conventional products. The EU has taken the lead on biosimilars and has comprehensive legislation on 'Advanced Therapies'. Other major changes recently in the EU include those relating to centralised procedures and pharmacovigilance. The Food and Drug Administration has been going through a rather turbulent period but there has been an increasingly closer relationship with the European Medicines Agency, sometimes resulting in companies having their global development programmes agreed with both agencies almost simultaneously. The FDA is still seen as providing better options for fast track approval in some cases. Engagement with regulatory authorities is best seen as an ongoing dialogue in which development plans are discussed rather than as an end-of-term examination where a submission is either passed or rejected. In summary, regulatory affairs is a wide-ranging discipline and companies are well advised to take early and ongoing advice from either their internal regulatory advisors or external experts.

Keywords: centralised procedure, European Medicines Agency, Food and Drug Administration, investigational new drug, new drug application, orphan drug status.

10.1 Introduction

Companies wishing to market a new medicine must satisfy the requirements of the regulatory authorities responsible for the country or region (such as Europe) in which they wish the marketing authorisation to apply. The primary function of this licence is to guarantee that the drug meets basic standards for quality, safety and efficacy, the three pillars of drug development and registration (which we return to below). It is a common mistake in biotech companies, especially those intending to license out their products before registration, to think that regulatory matters only apply at registration. They don't, and your pharma partners will evaluate your data to regulatory standards during any licensing deal. For biotechs aiming for registration and the market themselves, it is financially calamitous to have to repeat non-compliant studies at the end of development to meet regulatory requirements. So, getting to

grips with regulatory affairs as they apply to your products is essential from the start.

Pharmacoeconomic and Health Technology Assessments (HTAs) are also becoming more of a requirement than a desire for some products. Agencies such as the UK's National Institute for Health and Clinical Excellence increasingly give advice on what health insurers should or should not reimburse. However, these components sit outside of the strictly regulatory issues and are only briefly discussed in this chapter.

Any new product for the diagnosis, prevention or treatment of a medical condition must undergo a programme of CMC (Chemistry, Manufacturing and Control), preclinical and clinical development before it can be evaluated and approved for marketing. The components of this development programme and the programme itself are subject to stringent regulatory legislation and guidance. Once on the market the product is also subject to high levels of legislation in terms of safety monitoring and marketing. This chapter provides a brief description and analysis of the regulatory process in the EU and USA and how this influences drug development. It reviews the relevant regulatory agencies in the EU and USA, and the key elements of CMC, preclinical and clinical development. We will also look in more detail at the process of monitoring a drug's safety and efficacy once it is on the market and in the clinic. Finally, we consider certain specific aspects of drug development that have been directly impacted by fairly recent regulatory changes.

It is a theme of almost every chapter in this book so we might as well mention it here as well: the earlier a company starts to think about the regulatory requirements for a product in the development process, the more likely it is to succeed in getting that product approved. Regulation is a constantly moving set of goalposts, an evolving discipline, and one that drug developers and marketers need to keep abreast of to ensure legal compliance and develop products to current scientific standards. For this reason, in large pharmaceutical companies the practice has evolved of having regulatory requirements as a principal guide to what is done in the development process. There are some dangers inherent to this strictly 'by the book' approach, namely that drug development can become a simple box-ticking exercise. But most smart companies are aware of this and treat regulatory guidelines as such, i.e. guidance rather than diktats,

notwithstanding the fact that some fundamental principles are effectively written into law. In the EU, the latter includes the so-called 'community code' Directive 2001/83/EC, and the various Regulations such as 76/2004/EC that are implemented into national law of EU member countries. This approach is far more effective than merely following the guidelines blindly without interpretation or, on the other hand, developing a product up to the later stages of clinical development and then starting to ask what regulatory requirements apply to your drug. In terms of the evolving nature of drug regulation, even in the highly complex system that currently exists, it is enlightening to note that as this book goes to print, several proposed major changes have been implemented or are under discussion. In Europe, these include the Heads of Agencies [i.e. national regulatory agencies as opposed to the European Medicines Agency (EMA)] Strategy Paper published in October 2010, what is referred to as the 'EMA Road Map to 2015', and the so-called 'Pharmaceutical Package'. The Road Map has three strategic areas, namely:

- addressing public health needs
- facilitating access to medicines
- optimising the safe and rational use of medicines.

The Pharmaceutical Package deals with three major areas:

- pharmacovigilance (changes to Regulation 726/2004 and Directive 2001/83/EC)
- falsified medicines (changes to Directive 2001/83/EC)
- information for patients (changes to Regulation 726/2004 and Directive 2001/83/EC).

The ground-breaking EU legislative framework for biosimilars (i.e. new versions of off-patent biologics) and product-specific guidance is also a genuine regulatory innovation, and one not likely to be mirrored in the USA until late 2011. As with every other stage in the process we have discussed thus far, it is important to plan your way through the regulatory process. A little bit of thinking ahead and planning can save a huge amount of work later on.

10.2 Regulatory institutions and processes in the EU

Almost every country in the world has a body responsible for checking the quality, safety and efficacy of medicines used in that country. Most people will have heard of the Food and Drug Administration (FDA), the responsible regulatory authority for the United States. In Japan the Pharmaceuticals and Medical Device Agency reviews all applications for marketing approvals and grants licences to successful applicants although final authority to issue approvals rests with the Ministry of Health, Labour and Welfare (MHLW). In Europe, each of the member states of the EU has its own national regulatory agency, for example the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK (www.mhra.gov.uk), Afssaps in France (www.afssaps.fr), the BfArM in Germany (www.bfarm.de) or AEMPS in Spain (www.aemps.es). The European Medicines Agency (www.ema.europa.eu), formerly known as the European Medicines Evaluation Agency (EMEA), centralises an increasingly greater amount of regulatory activity in the EU and collaborates with the national agencies.

It used to be an enormously slow process to have a medicine reviewed independently in some European countries. Throughout the 1980s and 1990s there was considerable convergence in the requirements for medicines in each country and, simultaneously, much political pressure to harmonise regulations and new drug evaluations across the EU. For this reason there is now a single regulatory body that can approve many drugs for use in the entire EU – the EMA. We will look at some of these regulatory bodies in more detail below.

A large ongoing effort to harmonise regulation across all the major regulatory agencies (USA, EU and Japan) has led to a substantial degree of harmonisation by the International Conference on Harmonisation (ICH). The core of this harmonised system is the Common Technical Document (CDT), which lays out in considerable detail the requirements, common to all of the major regulatory bodies, for sponsors requesting a marketing authorisation for a new product. See http://www.fda.gov/RegulatoryInformation/Guidances/ucm129901.htm for details of the expected layout and core content

of a regulatory submission. Thus, although the application requirements and procedures can differ in details, the overall form and scientific content of the applications across national regulatory domains are broadly similar. There are, however, important differences in the details at every stage of the regulatory process and care should be taken to seek appropriate guidance through the system appropriate for each agency (Simmons and Bernstein, 2006).

10.2.1 The European Medicines Evaluation Agency

The EMA (or EMEA as it was initially named) was established in 1995. It is responsible for protecting and promoting health in the EU by evaluating, approving and monitoring medicines for human and veterinary use. Six committees exist within the EMEA:

- Committee for Medicinal Products for Human Use (CHMP)
- Committee for Medicinal Products for Veterinary Use (CVMP)
- Committee for Orphan Medicinal Products (COMP)
- Committee on Herbal Medicinal Products (HMPC)
- Paediatric Committee (PDCO)
- Committee for Advanced Therapies (CAT).

We focus here on the activities surrounding medicines for human use. In this sense we make reference to all of these committees, except the CVMP, and especially the CHMP, which is the ultimate arbitrator of marketing authorisation applications by companies and of many other important issues. The CHMP is composed of one member from each of the national regulatory agencies of the member states of the EU plus their stand-ins and a chairman. In addition to the expertise of its members, the CHMP calls on a panel of over 3000 experts to advise on any aspect of drug safety or efficacy as and when needed. In some cases patient groups will also have a member on these committees.

Although it is still possible to apply on a country-by-country basis for registration (see below), certain classes of new drugs must be registered through the EMA Centralised Procedure rather than by national agencies (e.g. oncology, neurodegenerative and diabetes

drugs, as well as all biotechnology-derived products). The fairly recently legislated advanced therapies (formally known as Advanced Therapy Medicinal Products, or ATMPs – e.g. gene therapies, combination drug-devices, cell therapies – also regulated by the CAT) and products to diagnose, prevent or treat orphan diseases (those with a prevalence of fewer than five in 10,000 of the population) are also evaluated through the centralised procedure. This, therefore, is the most relevant procedure for most biotechnology companies going by the strictest definition of biotechnology, i.e. those involved in recombinant DNA technology of some kind. However, when one refers to biotechnology companies in the broader sense (i.e. emerging, innovative organisations), this is not necessarily the case. For other new drugs, companies have a choice to use the centralised procedure or one of the procedures administered by the national agencies [mutual recognition (MRP) and decentralised procedure (DCP)]. These are discussed below. Since the 1990s, and as a result of the policies designed to create greater harmonisation, it has not been possible to register a new drug simultaneously at each of the national agencies. Applications to national agencies are for that national market only. Until recently, generic drugs could not be registered through the EMA but had to go through MRP or DCP.

10.2.1.1 Centralised procedure

The clearest advantage of the centralised procedure is that the marketing authorisation, once attained, applies instantly in all member states of the EU. A company wishing to obtain a licence for a drug via this procedure submits a single marketing authorisation application to the EMA, nowadays in electronic format. This is allocated by CHMP to two of its members (Rapporteur and co-Rapporteur) and is typically evaluated by the national regulatory agency staff of each on behalf of the CHMP. They produce an independent report that is combined into one by Day 120 of the procedure. The CHMP reviews the combined evaluation by the rapporteurs and almost always presents questions to the Applicant (company) that must be answered to secure an approval. A positive opinion is adopted if the CHMP is satisfied as to the quality, safety and efficacy of the drug and the product has a favourable

benefit/risk profile. This positive opinion is subsequently converted into a marketing authorisation by the European Commission. A marketing authorisation permits the pharmaceutical company to market the drug in all member states of the EU plus Norway, Iceland and Leichtenstein.

10.2.2 Mutual recognition procedure (MRP)

A pharmaceutical company wishing to license a drug via this procedure submits a marketing authorisation application to one or more member states rather than directly submitting its application to the EMA. The application is evaluated by the national regulatory agency of one of the members states – the reference member state (RMS).

As with the centralised procedure, the RMS adopts a positive opinion if it is satisfied as to the drug's quality, safety and efficacy and if it is also convinced that it has a favourable benefit/risk profile. The Applicant then submits the same data package to the concerned member states (CMS) in which it also wants to market the product. This opinion can be accepted or rejected by the other member states to whom the application has been submitted (the CMS). A proposed rejection by a CMS leads to further discussion both between the CMS and the RMS, and between the RMS and the pharmaceutical company, which may be required to undertake further analyses or to perform new studies. If the RMS and the CMS cannot reach an agreement, the applicant may withdraw a CMS or the product may be referred to the CHMP, depending on the nature of the CMS objection. A marketing authorisation approved through the mutual recognition procedure permits the pharmaceutical company to market the drug in the RMS and CMSs. This procedure is similar to the decentralised procedure (see below).

10.2.3 Decentralised procedure (DCP)

This procedure was essentially born out of the feedback from industry on the performance of the MRP, mostly in terms of the lack

of harmonisation of evaluation of drug dossiers. It is not dissimilar to the MRP, unless you happen to be a regulatory affairs expert! It requires the Applicant to submit the registration dossier to all member states in which it wishes to market the product at a given time. One of these member states will take up the evaluation process on behalf of all member states. In certain cases this procedure may be faster than the MRP. Again, it can be used for new chemical entities not required to go through the CP and for generics.

Irrespective of the route of registration, companies should carefully consider all relevant legislation and guidelines. The EMA's core and drug and/or disease-specific requirements are documented in the myriad Notes for Guidance which they publish for many diseases.[1]

There are also many notes for guidance on quality and safety topics and a range of multidisciplinary guidance notes, in addition to the wealth of ICH guidance. Larger companies will have a regulatory affairs department with people whose job it is to keep to date with all of these regulations. Smaller companies will often rely on outside experts such as specific regulatory consultancies to help them through these processes. Discussions with regulatory experts now commonly take place even before treatments enter the later stages of product development. It is sensible to have regulatory input even before a candidate enters preclinical safety evaluation. Emerging companies typically rely on consultants until they get to clinical phase 1, or even phase 2, although some more visionary and ambitious organisations will employ regulatory staff during the non-clinical safety and CMC optimisation phase.

When companies with products that could be registered through more than one of these procedures discuss which one to select, the discussion inevitably turns to respective timings. In principle, the CP can be done in 210 days plus the time to translate labelling (30 days) plus the time (about 2 months) for the European Commission to ratify the decision, but the time to respond to questions has to be added. The DCP in theory can be done in about 240 days, while MRP is closer to 400 days but again this depends on agency questions and on how smoothly the negotiations with the agencies go, time to update certain documents, etc. Most people involved in regulation agree that the CP is a more robust and predictable

procedure but it is also highly resource-intensive. However, the possibility of an approval that simultaneously covers 30 countries is a huge advantage, so if your product is eligible, having checked either with the website or regulatory expert, the CP may be the best option. Eligibility criteria are set out in the legislation covering the CP, and for products that do not fall easily into a particular category of eligibility an enquiry can be made to the EMA.

10.2.4 First contact with EU regulatory agencies

The first contact that a company will have with an agency is likely to be a request for scientific advice or, perhaps, a clinical trial application. These processes are discussed below.

10.2.5 Scientific advice from regulatory agencies

In a more product-specific approach, a sponsoring company (applicant) can obtain Scientific Advice (also called Protocol Assistance when referred to orphan drugs at the EMA) from the EMA and/or national authorities following the submission of briefing documents that outline their proposed CMC, non-clinical and/or clinical development programme of a drug. This is an invaluable aid to the design and planning of a preclinical or clinical development programme and every company should consider this very seriously before embarking on such a programme. In this process the applicant company prepares a Briefing Document that outlines the basic information on the product and the development programme to date. This is submitted to the agency along with the questions that the company would like to have answered. There is usually a meeting to discuss the data and in most cases the agency issues a letter explaining its advice. Most agencies, including the EMA, charge for this service, but it is currently free for orphan drugs at the EMA (and FDA). In the case of the EMA, the advice is not legally binding but for practical purposes should normally be considered as such. If you ask their opinion, you are highly advised to act on the advice given. Within the various national bodies advice might not come with such a heavy tie in, but it is still

sensible to review any issues at this stage before the enormously costly clinical trials take place. It would be damaging to find yourself sitting in front of a regulatory panel at some stage in the future answering questions about your failure to power the statistics according to the guidelines or explaining why you chose a particular drug as a positive control that the panel feels to be irrelevant. It does happen!

10.2.6 Clinical trial applications

Once a promising drug candidate has completed sufficient non-clinical safety testing and can be manufactured in sufficient quantities at an acceptable quality level, it may be the subject of a clinical trial application (CTA). Normally, these first human trials are done in healthy volunteers, although in certain cases such as oncology first trials can be carried out in patients. This is not the place for a detailed examination of the process and content of a CTA. However, some key points should be made:

- There is a harmonised procedure in the EU for CTA submissions (see Clinical Trial Directive 2001/20/EC and the 2005 Note for Guidance on Applications) but applications are made to individual national agencies that conduct the assessments and approve or reject the applications.
- Sponsors must summarise all studies completed to date, preferably in no more than 80–100 pages, although there is no mandated volume size.
- The evaluations focus primarily on safety and therefore consider the key quality and toxicology/exposure data.
- Assessments should be completed in 30 days although some agencies complete them in less time, especially if you have sent a concise document fulfilling the exact requirements. If questions are asked the agency has further time to review the responses and make a decision.
- Each clinical protocol requires a separate CTA.
- Companies must file basic drug and trial data with the EMA via the EudraCT system.

There are product and/or disease-specific requirements that must be fulfilled, and there are minimum core requirements that all drugs must meet, irrespective of the geographical location of the company or intended market. This is discussed below, but first it is important to review the corresponding institutions and processes in the USA, as companies need to be sure of meeting both EU and US requirements. In terms of the third major regulatory region, it should be noted that most Japanese requirements are similar to those in the EU and USA (and are covered by the ICH), but still differ sufficiently for companies to address the Japanese market separately. This is also because of differences in medical practice and marketing of drugs in this country compared with the USA and EU.

10.3 Regulation in the USA: the FDA

10.3.1 Investigational new drug (IND)

The IND application is, to a great extent, analogous to the EU CTA. It also has the specific purpose of allowing transport of a clinical candidate substance across state lines. As most clinical investigation programmes will involve multiple testing centres across several states this is the minimal information required to initiate a clinical development programme. For some reason the IND application seems to induce something close to awe and wonder in companies although it is, in fact, a fairly simple procedure in theory. Regulators need to know that the drug has been manufactured to an acceptable quality standard and appears to be safe to test in humans (this is the same tenet that drives clinical trial assessment at EU national authorities too). The requirements are clearly laid out on the FDA website.[2] An application must contain information relating to the preclinical efficacy and safety testing in animals (Pharmacology and Toxicology studies). It must contain all relevant information relating to the chemical characteristics of the product, its manufacturing process, stability and all of the controls used in the manufacture (Chemical and Manufacturing Information). Finally, the IND will contain the Clinical Protocols and Investigator information. This allows the

regulators to assess if the clinical plan will adequately test the efficacy and safety of the compound. The format for presenting the data is also provided. Of course, the devil is in the detail and it only takes a few issues over inconsistent technical matters (comparative purity of the drug in preclinical and clinical studies, insufficient stability data, etc.) to result in a delay, a rejection or in the USA a 'clinical hold', effectively a suspension until sufficient data can be provided.

The benefit to the sponsoring company of having regulatory feedback from Scientific Advice or a similar US procedure, or during IND/CTA review of the data, is enormous. Having input from regulators at this early stage ensures that you have this information before the extremely expensive later stage clinical trials are undertaken.

The IND (and the CTA) will include a Clinical Investigator's Brochure (CIB), which is a detailed summary of all of the background information on the compound and all details of both previous trials and the planned trial to allow clinical investigators to conduct the trial safely in the correct population or patient group. This section also ensures that the clinical investigators have the relevant knowledge and experience to undertake the trials. The Clinical section will also contain information as to the ethical review of the studies and how the investigators will obtain consent from patients and how they will be treated once the study ends, although this is explained in more detail in the trial protocol and patient information.

10.3.2 New Drug Application (NDA)

An NDA is a formal application for a licence to market and sell a compound in the USA, equivalent to the EU Marketing Authorisation Application (MAA) (Fig 10.1). It is the culmination of the process of developing a product and the key step required before commercialising it. It comprises three main sections: CMC, Non-clinical and Clinical Proof that the compound is safe and effective in the target patient population must be shown. In addition to the CMC and preclinical material such as that contained in the IND, the NDA contains a full description of the clinical trials, a thorough description of their conduct and analysis, and explanations of any anomalies in the data

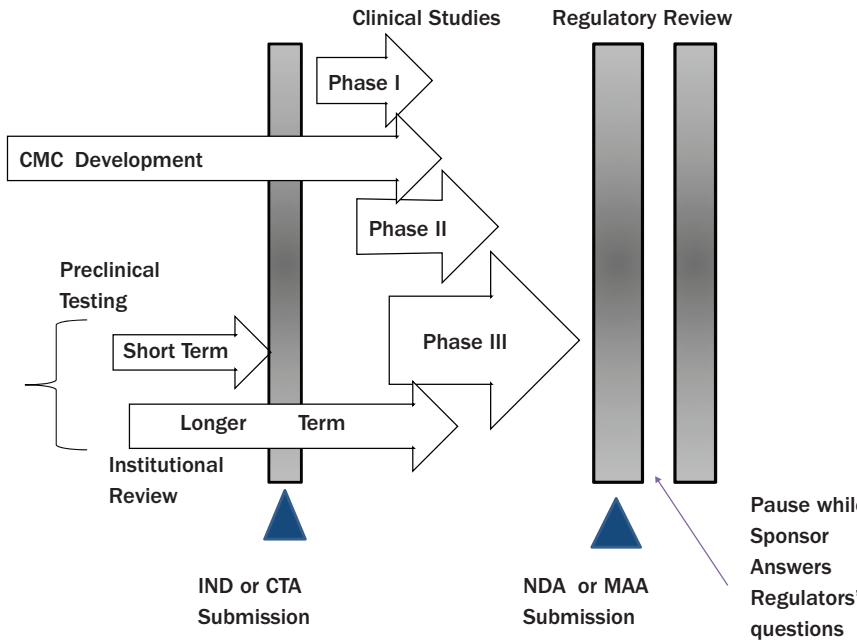


Figure 10.1 Diagrammatic representation of the ICH Common Technical Document.

Source: http://www.fda.gov/RegulatoryInformation/Guidances/ucm129901.htm

or deviations from the agreed protocols (see Table 10.1 for checklist). As you will read in Chapter 11 on clinical trials, double-blind, randomized, placebo-controlled trials are the gold standard by which compounds are judged. It is also often expected that a positive control is included as a comparator in the programme of trials, i.e. a new compound will usually be expected to have at least equal efficacy to an established marketed product in the relevant indication.

One requirement is a draft of the packet insert that will be given to the patient with a full description of permitted use. Details of dosing and likely side effects are also included. This last item might sound like a relatively minor matter but in fact it is absolutely key to the success of a compound. Some companies will actually use the projected or draft label insert as their guide for the entire drug development process (see Chapter 9). The label is the patient information included in the medicine pack when it is finally

Table 10.1 Marketing Authorisation Application (MAA – EU) and New Drug Application (NDA – USA): contents checklist

1. Draft Package Insert (Label)
2. Overall summary
3. Integrated summary of safety – FDA only
4. Integrated summary of efficacy – FDA only
5. Chemistry, manufacturing and control (CMC)
6. Non-clinical pharmacology and toxicology
7. Microbiology (if applicable)
8. Human pharmacokinetics and bioavailability
9. Clinical Data Summary/statistical methods used
10. Risk Management Plan
11. Raw data – FDA only
12. Case report forms – FDA only
13. Case report form tabulations – FDA only

launched. The label outlines, for example, the conditions for which the treatment can be used. If, for example, your company is developing a novel anti-inflammatory agent this label will state which conditions it can be used for. If your product is used to treat, for instance, rheumatoid arthritis (RA) you will have to have this on your label and it will probably specify what type of RA patients, e.g. those who have already tried non-steroidal anti-inflammatory (NSAID) or other drugs, it is appropriate for. To get this label agreed you will have to show efficacy in this group specifically and present the data within the NDA. The label will also list all of the safety issues for the treatment that you might have found during development, for example that the treatment is not tolerated well in elderly patients. This will be included on the label by the regulatory agency during review. Regulatory authority insistence on detailing adverse effects that you may not agree with can represent a severe blow to the product's acceptance in the market and lead to ultimate commercial failure. Specifically, any major safety concerns can lead to a Black Box Warning (BBW) in the USA, a specific warning against using the medication in certain circumstances or in certain patient groups. Antipsychotic treatments had been used for many

years in very disturbed elderly patients with dementia. Pharmacovigilance studies showed that these drugs as a class were associated with elevated risk of sudden death in these patients, from a variety of causes. This led to a BBW on the label of most antipsychotics strictly restricting their use in this patient group. Likewise, fears of increased suicidal tendencies in younger people with some antidepressants have led to a BBW being placed on most SSRI (selective serotonin reuptake inhibitor) antidepressants, except Prozac (fluoxetine). A BBW can have a severe impact on the willingness of physicians to prescribe a drug, especially if a safer, even if less efficacious, alternative is available.

The label will also contain all of the relevant information on the production, packing, storage and even transportation if these conditions are relevant to the safety or efficacy of the drug.

There is a large amount of information available on the FDA website where forms and guidance for specific indications can be downloaded. It is a good idea, however, to get advice first from someone who has been through the system rather than trying to do everything yourself.

10.4 The three pillars of drug development and registration

No matter which regulatory system your treatment goes through to obtain marketing approval, quality, safety and efficacy are the three pillars of drug legislation. The overall regulatory challenge for sponsors is to show that their products meet tight quality standards and are sufficiently safe and efficacious to provide evidence of a positive benefit–risk evaluation based on all studies conducted during development.

10.4.1 Quality

Only a brief summary of the large and highly specialised area of Quality and CMS is possible in this chapter. Adequate quality and quality

control must be demonstrated for the product and the production process. The manufacturing process must ensure that it can consistently reproduce batches of a medicine to the same quality standards, e.g. a 10-mg tablet must contain the precise amount of drug stated in the specification as well as adhering to all of the other components of the specification – impurities, polymorphism characteristics, residual solvents, endotoxins, shelf-life, etc. The manufacturing process must comply with good manufacturing practice regulations both during the clinical development programme and once the product is marketed (cf. 2003/94/EC). The process must be validated according to good manufacturing practice principles and regulations.

10.4.2 Safety

Early indicators of drug safety can be obtained for molecules that emerge from the early stages of structure–activity relationship development. It is possible to determine if certain structural moieties are associated with undesirable characteristics such as hERG activity which would indicate a liability towards cardiovascular problems for the drug in the clinic. Other potential indicators could be mutagenesis, indicating genotoxicity or liability to interact with major metabolising enzymes. As these are a source of major inter-individual variation in response to drugs it is important that compounds with these liabilities are identified early and removed from the drug development process. This is dealt with in more detail in Chapter 9.

The product's safety profile in non-human species must be demonstrated with safety pharmacology, pharmacokinetics and toxicology data reflecting its anticipated usage in humans. The active, clinical dose should be at least 5–10 times less than the non-toxic dose in the most relevant species in your longest toxicology study (the actual margin depends on the indication). The product must also not be genotoxic, carcinogenic, toxic to reproduction, immunogenic or irritant. You must show that the product produces sufficient exposure to relevant receptors over an appropriate time (not too long or short) at the clinically active, non-toxic dose. New approaches to substituting traditional safety analyses are being developed, such as

cellular toxicity testing and human tissue testing, but it will be some time before these become standard practice. The drug must be demonstrated to be as safe as possible for use in the target patient population. This is an increasing challenge to companies as it is accepted that it is impossible to *prove* safety during the clinical trial programme. One can only show that the treatment has not caused any major problems so far in the studies undertaken. For this reason regulatory agencies often require a post-marketing risk management programme (see Chapter 11). Safety data must be collected over a treatment period that reflects the actual use of the drug. This may be a matter of some weeks with antibiotics, but in the case of chronic treatment such as with most psychotropic drugs which patients may take for several years, data must be collected over at least 12 months. All manner of safety analyses must be done on the database: serious adverse events, treatment of emergent adverse events, deaths, withdrawals (from treatment), events by organ, etc.

10.4.3 Efficacy

Drug discovery depends on knowledge of the disease being targeted so that a specific molecular target can be identified as the basis of a drug testing programme. This is now generally conducted on a very large scale with the use of high-throughput screening technologies and modern techniques in chemistry which allow for the testing of a large number of molecules against those molecular targets.

Although serendipity or chance findings have guided drug discovery in the past, the process now is more often driven by rational drug design. In almost every area from the central nervous system to oncology, a molecular target such as an enzyme or receptor is chosen and an extensive structure–activity analysis is performed to find the molecule with the best fit to that target. So successful is this marriage of molecular biology and medicinal chemistry, aided by advanced computational techniques that can help chemists to decide which molecules to make based on knowledge of the structure of the target protein (molecular modelling or computer-aided drug design), that there is time to think about what other features can be identified and built in to the molecule at this early stage.

The aim of all of this activity is to show that the mechanism by which the test compound is acting alters the disease state in patients. The novel treatment must show a measurable improvement in the condition of patients. You must show that the minimum effective dose is non-toxic and is suitable for administration by an acceptable route (oral, intravenous, etc) in phase I and II studies. You then demonstrate, usually in at least two phase III studies, that the product is sufficiently safe and efficacious, the latter in terms of statistical significance against selected primary endpoints in the pivotal studies, and in terms of a clinically meaningful result. The precise endpoint will depend on the condition under investigation. For oncology treatments, for example, it may be necessary to show an improved survival time for patients suffering from the particular cancer. In non-fatal conditions efficacy will be a statistically and clinically meaningful reduction in the disease burden in patients. It is important to note the phrase 'clinically meaningful' as it does not mean merely statistical significance. A small but statistically significant effect alone might not be sufficient to convince regulators that the proposed treatment merits authorisation. The panel of clinical experts who review the data package on behalf of the regulatory authorities will assess the evidence on the basis of potential benefit to patients.

10.5 How regulatory requirements guide drug discovery and development

If it is not already evident, we would like to stress at this point that keeping regulatory requirements in mind and if necessary referring to them often during development is essential to successful development of a new product. Failing to plan for an essential study demanded by regulatory requirements can spell disaster for a drug development programme.

If there is one common failing of 'biotech' drug development programmes it is that there is too much emphasis on demonstrating efficacy at the preclinical stage to the detriment of other factors such as bioavailability, formulation, key ADME factors and adequate dose finding, which can be major determinants of the clinical utility of a new treatment. This may be understandable from the perspective

of those whose aim is to help the company reach 'value inflexion points', which is (often mistakenly) driven solely by the goal of 'getting the drug into the clinic' to demonstrate clinical efficacy. The determination to prove efficacy over all else is interesting: there is little additional marginal value in data from a fourth or fifth *in vivo* efficacy model whereas showing that the drug does reach its target in therapeutic quantities and is eliminated quickly and safely can be vital in determining if the compound has real clinical potential as a treatment for the target disease. It is dangerous to try to infer ADME characteristics from efficacy models, i.e. 'it worked in model X so therefore it must be getting to the target'. This ignores the importance of linking dose administered to efficacious concentration at the target. If 100 mg/kg of a compound is required to produce an effect even though it has 1 nM affinity for its target, there could be something very wrong with the pharmacokinetics of the compound, and this will sound alarm bells with regulators. They will be very concerned, for example, about the fate of the 'left over' compound and its liability to cause deleterious effects elsewhere in the body. Many biotech companies also leave crucial safety studies until too late in development. Put bluntly, in trying to balance what can be done with available funds and what might be required by regulators it is essential to focus on the latter. There are no prizes for 'effort' in drug development. Achieving regulatory approval is the goal and if a company does not have the resources to do this, it might need to think very seriously about how it intends to proceed.

10.5.1 Regulatory affairs and non-clinical development, including key CMC matters

Only a tiny percentage of molecules ever make it through development due mainly to the difficulty of meeting criteria for efficacy (does it work at the desired target?) and safety (it should not adversely affect other vital systems). Of those that reach phase I clinical trials, still only about 10% will make it to market. Once a molecule has displayed appropriate activity and a favourable profile in its biodistribution in preclinical studies, it goes for evaluation as a

development candidate (see Table 10.2). The primary purpose of this stage is to determine the safety profile of a drug before it is administered to humans. Preclinical development therefore requires the sponsor to:

- establish pharmacokinetics and pharmacodynamics (ADME) in non-human species
- assess safety in a range of *in vitro* and *in vivo* models
- assess efficacy in appropriate models where possible.

In addition to, and often simultaneously with, non-clinical safety studies, a range of CMC work is conducted, including studies to:

- develop formulations for clinical trials
- develop analytical methods for drug substance and drug product
- evaluate product stability under various conditions
- develop and refine a scalable manufacturing process for drug substance and drug product.

Assessment of quality and safety is the key regulatory concern at this point. As noted above, assessment of applications by regulatory authorities for approval to run early clinical trials is almost totally focused on CMC, toxicology and exposure. In addition to the

Table 10.2 Regulatory and clinical objectives of phase I studies

1. Effect of treatment in healthy subjects (except in exemptions such as compassionate use)
2. Single- and multiple-dose studies
3. Pharmacokinetic data
4. Pharmacodynamic data
5. Maximum tolerated dose (MTD)
6. Adverse events profile
7. Initial elucidation of dose range and route of administration
8. Other parameters as necessary, especially safety in special groups

assessment of quality, the safety assessment will include a whole range of designated tests for special populations (e.g. elderly, paediatric) or situations. The key preclinical requirements are summarised in text Box 10.1.

10.5.2 Regulatory affairs and clinical development

The process of clinical trials is outlined in detail in Chapter 11 but some mention of what is involved is necessary here. The FDA, EMA and other regulatory bodies publish very clear testing requirements

Box 10.1 Non-clinical development and CMC basic requirements: summary 1

Pharmacokinetics and efficacy

1. Establish pharmacokinetics and pharmacodynamics (ADME)
2. Assess safety *in vitro*
3. Assess efficacy in animal models

Chemistry, manufacturing controls (CMC)

1. Develop formulations for clinical trials
2. Develop analytical and chemical methods
3. Evaluate product stability
4. Develop manufacturing process

Assess toxicity

1. Acute intoxication [max. tolerated dose, median lethal dose (LD50)]
2. Effect of repeated administration
3. Effects on reproductivity/fertility in males/females
4. Embryotoxicity
5. Genotoxicity
6. Tumorigenicity
7. Sensitisation
8. Immunogenicity
9. Local or other special adverse effects

for compounds (see Table 10.2). In very general terms, a treatment must first be shown to be well tolerated in healthy volunteers (phase I) and have kinetics appropriate to its dosing regime in patients. The compound should be available in therapeutic concentrations relevant to its intended labelling, e.g. once a day or once a week dosing. The precise patient population must be defined and this frequently changes from phase II to phase III programme. Due to its overarching importance to development and commercialization, the product label approved by regulators will only allow use of the product in precisely the population studied in phase III, except in special circumstances. Phase II studies will give preliminary evidence that the treatment is effective and well tolerated in patients with the target condition but it is well known that phase II results from highly controlled studies in a few specialist centres are often not easily replicated in large, multicentre phase III studies. What many companies overlook is that regulators, at least in the EU, usually only advise but do not insist on specific phase II studies or patient numbers, whereas they are much more prescriptive on phase III requirements. Phase III studies will examine efficacy and safety in larger samples of patients and necessarily constitute the pivotal evidence that MAA approval or rejection is based on. So there is some sense from the regulator's perspective in not stipulating what phase II studies are required. In fact, it would be very difficult for regulators to advise simultaneously on phase II and phase III as the latter is driven by the former. Many biotech companies see this approach as providing an opportunity to skip much of the phase II work and go precipitously into phase III, thinking that a successful phase III programme will probably lead to approval but ignoring the evidence and inherent risks in a truncated phase II. This together with the desperate attempts to establish 'efficacy' of any type (noted above) are typical and important errors committed by many biotech companies. It is perhaps not surprising, therefore, that many seasoned professionals suspect that regulatory authorities are sceptical about the ability of small companies to develop new medicines, especially for larger indications such as cardiovascular disease, diabetes and depression. The EMA has, in fact, published data showing that larger companies certainly fare better in terms of gaining approvals than small ones in the

centralised procedure. The other side of this coin is seen in the biotech company developing a product for a condition with few or no current treatments. In this case, the company tries to generate sufficient clinical data in phase II to obtain approval, thus skipping phase III. This may be an even less successful approach and one that requires intense discussion with the regulators before starting the clinical trials. There are many examples of failures here, although most of them are not published. One example in the public domain was the initial failure of the soft tissue sarcoma drug Yondelis to gain approval in EU with phase II data. This was developed by a small EU biotech company. On the other hand, Gleevec from Novartis was approved with phase II data, but a review of approvals shows that approval with phase II data alone is rare, even for orphan drugs (see below).

10.5.3 Benefit versus risk – the final regulatory decision?

Most drugs have some side effects which limit their use, particularly at higher doses or on prolonged administration. This is normally dealt with by limiting treatment either by reducing the maximum dose given or by restricting the period of time for which the drug is administered. The risk to the sponsor rests on producing sufficient evidence of product efficacy within the dose and exposure range that does not cause serious or severe adverse effects. The benefits of each drug must be measured against the risk of administration, particularly prolonged dosing and exposure, and the seriousness of the condition for which it is indicated. Thus, the benefit–risk calculation will depend on the nature of the disease being treated, the level of activity of the treatment, and the nature and extent of the risks of treatment to the patient. A life-threatening side effect such as prolongation QTc interval (an alteration of cardiac function with potentially lethal consequences) would mean that it would be unlikely that a drug with this property would ever receive approval for general use, particularly where other safer alternatives are available. However, the benefit–risk assessment is not usually as clear cut as this and requires more subtle consideration of the efficacy benefits versus the safety risks as evidenced by both non-clinical and clinical data. A

product that causes undesirable effects but provides either significant symptom alleviation, or especially a cure, for a serious or life-threatening condition may well have a positive benefit–risk profile. This is very often the case for oncology products which are intended to be toxic to the targeted cancer cells but may also cause toxicity to normal cells or some other systemic effect. The benefit–risk assessment is the final technical assessment in the regulatory review that leads to either a positive or a negative opinion on approval.

The review process is a complex one that can take a long time. Increasing regulatory requirements and review times are among the causes frequently cited for reductions in productivity of the biopharmaceutical industry (Munos, 2010). Exactly how long a review of an MAA takes is difficult to say as it depends on a number of factors, particularly the time that the sponsor takes to respond to Agency questions on the file. The EMA has a median review time in the region of 420 days, consistent across therapeutic area and over time, since 2003 (CMR, 2010). The FDA has a shorter median review time, closer to 300 days, but a much larger variation depending on the therapeutic area. Both the FDA and EMA operate fast-track review procedures although it is more commonly used in the USA. This only applies to products used to treat conditions of a very high medical need, such as certain tumours and orphan diseases.

10.6 Post-marketing requirements and activities

It is increasingly common for products to be subject to risk management programmes prior to approval being granted. It is also common for companies to have to conduct paediatric studies as part of a commitment to the EMA paediatric committee (PDCO) following a deferral for these studies during development. The FDA can also require such studies. It should also be noted that in Europe drugs have traditionally been subject to renewal of their licences every five years, although the legislation is currently being changed in this respect. Any significant changes to the terms or content of a marketing authorisation, including new evidence of safety issues requiring changes to the product label (Summary of Product

Characteristics, or SPC in the EU) or patient information, will need to be the subject of a variation to the Marketing Authorisation Application (MAA) in the EU. Pharmacovigilance is, of course, a key pillar to the continued approval and marketing of medicinal products. The legislation on pharmacovigilance is currently under review in the EU, as explained at the start of this chapter, and the likely outcome is enhanced and more onerous pharmacovigilance affecting companies. It is a good idea therefore to regularly consult the relevant sections of the FDA and EMA websites for updates on these topics.

10.6.1 Pharmacovigilance

The constant monitoring of the safety of medicines after authorisation ('pharmacovigilance') is an important part of the work of the EU national competent authorities and EMA, and the FDA in the USA. The EMA receives safety reports from within and outside the EU concerning centrally authorised medicinal products and co-ordinates action relating to the safety and quality of medicinal products. Approval of a drug for marketing is therefore not the end of a company's regulatory obligations.

Given the relatively prolonged time periods required to produce comprehensive safety data, regulatory authorities accept that this can only be done once the drug has been licensed for use in the general population. At this point companies may also seek to alter the formulation (injectable, transdermal, nanoparticles, etc.) or extend its use in additional indications and/or sub-populations. This is often referred to as 'phase IV' clinical work (Table 10.3).

Table 10.3 Types of phase IV studies

• Comparisons with competitor treatments
• Health economic studies (cost–benefit analyses)
• Labelling changes (e.g. new formulations, different patient population, new dosing regimen)
• Conditional approval studies
• Post-marketing surveillance studies (pharmacovigilance)
• Information/utilisation studies

10.7 Your drug is on the market, what can possibly go wrong?

It is hard to imagine after all of this scrutiny that anything can go wrong with a drug but the sad fact is that a significant number of drugs that get to the market never make any money. Even worse, some drugs that get to the market are commercial successes but are suddenly faced with a major problem which can either limit their use or, in the worst case scenario, lead to their withdrawal from the market.

It is worth taking a look at these problems and seeing what can be learned from them.

10.7.1 Safety issues

It can emerge on prolonged treatment that a drug produces an undesirable or even lethal effect in some patients. In recent years this has been seen with products used for a range of conditions from anti-inflammatory pain killers (Cox-II agents), to some anti-diabetic drugs (referred to as a group as glitazones), to a number of central nervous system products. Antipsychotic drugs help to control the symptoms of schizophrenia in most patients. As such they have been an enormous clinical success, allowing severely mentally ill patients to have better and happier lives. However, it has also become apparent that many of the most effective and successful drugs also have significant drawbacks, one of which is the propensity to induce weight gain. This problem seems to have been largely missed in the pre-registration trials where patients were confined in hospitals and their food intake was restricted. Once the drugs were made available to the general patient population whose condition was managed in the community, where their food intake was not controlled, patients began to register with significant weight gain. This might have been seen merely as an inconvenience and perhaps regarded as a small price to pay for greater mental health. However, a significant subgroup of patients recorded weight gain in excess of 10–20 kg and began to show other health effects of obesity, including raised blood pressure and diabetes. The

sponsoring companies have been involved in protracted and complex legal issues surrounding these issues ever since.

An even more stark example of a major blockbuster hitting problems was a successful inflammatory treatment for rheumatoid arthritis, Vioxx, that was found to be associated with significantly enhanced risk of cardiovascular side effects up to and including increased mortality from cardiac arrest. This led not only to the company withdrawing that particular drug but also to the abandonment of the entire class of drugs. The legal and financial impact of this on the industry was enormous. Many companies also had similar compounds in various stages of development from early drug discovery to late-stage clinical trials and these had to be dropped.

10.7.2 Dependence/withdrawal

Any treatment should allow for a restoration of function once the period of treatment has ceased. If normal function is not possible without the treatment, even though the disease condition has been resolved, this means that the drug has produced physical or psychological dependence in the patient. Prolonged exposure has also been associated with 'withdrawal syndrome', where some patients experience unpleasant effects when drug administration is discontinued. Benzodiazepine drugs are effective in reducing anxiety and inducing sleep. The drugs also have a tendency to induce dependence, with the patient being unable to sleep normally without the drug. Concerns about these effects have severely limited the use of benzodiazepine drugs for these conditions. Studies are required to show that drugs do not create dependence or induce withdrawal syndromes on discontinuation of treatment.

10.7.3 Inadequate health economic benefit

Healthcare providers and insurers are becoming ever more conscious of the cost of treatment and drug budgets have been under particular scrutiny in recent years. As a consequence merely showing safety and

efficacy in patients is not enough; the benefit must be shown to be worth the cost to the health system. A minor improvement in quality of life might not be regarded as sufficient. Drugs used in the treatment of Alzheimer's disease (AD) offer a significant benefit to some patients for up to a year of treatment. The UK's government advisory body, the National Institute for Clinical Excellence, initially decided that the overall benefit as measured across all patients for the 10 years that patients survive on average with AD was insufficient to justify giving the drug to all patients. Complex legal, political and social issues were involved and the debate is still ongoing in the UK but the issue will become more important as paying for health care becomes critical for both private and state providers.

10.8 Specific strategies and targets for biotech companies: orphan drugs and rare diseases

The last decade has seen the decline of the blockbuster and the arrival of niche, specialised and personalised medicines. The latter usually serve small but often highly lucrative markets. They are exemplified by a number of types of products that are subject to recent regulation, including cell therapies, gene therapies, drug device combinations, certain branded generics and re-positioned products, tissue engineered products, and sophisticated biotechnology-derived products. A detailed analysis of the regulatory environment for all of these types of products, many of which are covered by the Advanced Therapy Medicinal Product (ATMP) legislation (Regulation 1394/2007), is outside the scope of this chapter, although one area that has seen a great impact deserves special mention, namely orphan medicinal products (Table 10.4). The reason for this is that not only are orphan drugs very often a target for biotechnology companies, but they now account for a significant amount of the EMA and FDA workload and are increasingly a focus of attention for larger pharma companies. The latter therefore represents an opportunity for smart biotechs to foster collaborations with pharma companies. See text Box 10.2 for a summary.

Table 10.4 Orphan treatments approved in the EU in 2009–2010

Treatment	Indicated use
Afinitor	Renal cell carcinoma
Arcalyst	Cryopyrin-associated periodic syndromes (rare autoinflammatory diseases)
Cayston	Gram-negative bacterial lung infection in cystic fibrosis
Firdapse	Lambert–Eaton myasthenic syndrome (LEMS)
Ilaris	Cryopyrin-associated periodic syndromes (rare autoinflammatory diseases)
Mozobil	Mobilisation of progenitor cells prior to stem cell transplantation
Nplate	Idiopathic thrombocytopenic purpura
Nymusa	Primary apnoea in premature newborns
Revolade	Chronic immune (idiopathic) thrombocytopenic purpura (ITP)
Tepadina	Autologous or allogeneic haematopoietic progenitor cell transplantation
Arzerra	Chronic lymphocytic leukaemia (CLL)

10.8.1 Why orphan drug designation and development?

There are streamlined regulatory procedures outlined by the FDA and the EMA to encourage the registration of medicines for rare diseases although there are minor differences between the requirements and benefits in the different jurisdictions. Small companies unable to undertake the clinical development of a treatment for major illnesses have benefited from being able to direct their efforts towards obtaining licences for treatments in rare diseases.

Contrary to what many people, including experienced industry professionals, often believe or imagine, the regulatory requirements for orphan drugs are very similar to those for other drugs. The requirement to demonstrate adequate quality is the same as for a non-orphan product. Non-clinical requirements are very similar. The overall requirement for numbers of patients in the database for registration is usually less than for a drug to treat a widespread condition. The lower prevalence of the more rare orphan diseases means that requirements with regard to numbers of patients *may* be relaxed in some trials, although the sponsor must demonstrate the

Box 10.2 Equivalent regulatory requirements in the EU and USA: orphan drugs

Orphan Drug Status: EU

Aim: Encourage the registration of medicines for rare diseases

Requires:

Prevalence < 5 in 10,000 of population EU for debilitating or life-threatening condition
Some non-clinical activity and safety data at least for designation
Full development programme for registration but reductions in amount of data/studies can sometimes be negotiated, especially for super-orphans.

Benefits

Assistance with development programme
10-year market exclusivity
Tax exemptions
Reduced regulatory fees

Orphan Drug Status: USA

Aim: Encourage the registration of medicines for rare diseases

Requires:

Prevalence <200,000 people in the US for debilitating or life-threatening condition
Some non-clinical activity and safety data at least for designation
Full development programme for registration but reductions in amount of data/studies can sometimes be negotiated, especially for super-orphans.

Benefits

Assistance with development programme
7-year marketing exclusivity in the US
Tax exemptions
Reduced regulatory fees

impossibility of recruiting sufficient patients in a reasonable time frame. This is agreed very much on a product by product basis with the Agency (see comments below). In addition to the possibility of having smaller clinical development programmes, orphan designation in the EU currently allows applicants to benefit from free scientific advice during the development process and exemptions for certain regulatory fees. Tax incentives are also available to encourage companies to develop treatments for these rare diseases which might otherwise be regarded as 'uneconomic'. Most importantly, however, a successful orphan marketing authorisation gives the product a 10-year marketing exclusivity in the EU or 7 years in the US. In the 10 years from 2000 to 2010, of 1114 applications for orphan drug status, 760 positive opinions have been granted on orphan designations and 724 medicines have been granted orphan status in the EU (EMA, 2010). In the US the programme has been in place since 1983 and over 350 drugs have been approved for marketing with orphan designations. There is now a common application format that will allow sponsoring companies to make the same submission to the FDA and the EMA for designation. The on-line form has a format that allows input of information that is required by both agencies and also sections for the additional specific requirements for either the EMA or FDA.[3]

According to EU legislation a medicinal product is designated as an orphan medicinal product if:

> "It is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting no more than five in 10,000 persons in the European Union at the time of submission of the designation application (prevalence criterion), or;
>
> It is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and without incentives it is unlikely that expected sales of the medicinal product would cover the investment in its development, and;

> No satisfactory method of diagnosis, prevention or treatment of the condition concerned is authorised, or, if such method exists, the medicinal product will be of significant benefit to those affected by the condition."

The FDA set the prevalence criterion at fewer than 200,000 people in the US affected by the relevant condition.

The strategy of seeking orphan drug status for a new medication is attractive to many small drug and biotech companies primarily because it often allows them to get a treatment into clinical development more quickly, with the resulting positive effect on perceived value inflexion and on public relations. In certain circumstances, most notably re-positioned drugs for orphan diseases, it is possible to get the product on the market more quickly as the product may already have a reasonable data package, especially safety data. The aim is often to follow this application up with additional data to extend the use of the drug to other (sometimes non-orphan) indications.

10.8.2 Potential difficulties with orphan drug strategies

There are issues to bear in mind when considering an orphan indication. First, it will, by definition, be a small market and it is essential to ensure that the economic case that providing for that small market is strong. The prices of some orphan treatments are sometimes set very high to recover the costs of development for very small patient populations. Alglucerase, a treatment for Gaucher's disease, can cost up to $300,000 per year. The oncology drug Gleevec (Imantinib) for the treatment of rare cancers, including chronic myeloid leukaemia, can seem relatively modest in comparison but still requires an annual budget in excess of $40,000 per patient. These are relatively novel treatments for patients with a life-threatening condition who had no other option at the time of approval. A large number of such products would certainly impact negatively on reimbursement or procurement policies, and governments are aware of this. The market exclusivity incentive only applies to *similar* products and therefore companies should be aware that there

can be different orphan drugs on the market for the same condition. As not all orphan diseases are life-threatening, the premium price scenario is not always replicated for all orphan products. Similarly, not all orphan drugs are equally novel. Some biotech companies have made the mistake of assuming that health authorities will pay a premium price for a product simply because it meets the prevalence criteria, whereas the reality is that authorities will also consider the real medical need and, albeit informally, often the innovative value of the product too. In many countries such costly treatments will simply be beyond the reach of individuals or even healthcare systems.

Secondly, as the disease is, by definition, rare, the clinical development can be slow and unexpectedly expensive. The trials may need to recruit patients from specialist centres in many countries, including countries or regions not experienced in clinical development of drugs, and far less in development of novel drugs for difficult-to-treat patients. Even though the regulatory clinical requirements may in some cases be slightly relaxed (e.g. a surrogate may be accepted as a trial endpoint rather than a clinical endpoint such as survival), this can lead to greater scrutiny of pharmacokinetics, dosing or the non-clinical safety package.

Finally, as noted above, quality requirements are usually non-negotiable. It can be as difficult to make a drug for a small market as for a large one. It is not uncommon for companies to be faced with the need to manufacture large batches of drug substance or drug product to meet validation or other requirements even though the cost of manufacturing is prohibitive (e.g. certain recombinant or advanced therapy products) and the drug batch will ultimately be destroyed. The science around rare diseases can be just as intractable as it is around major therapeutic areas, and in many cases more so.

10.8.3 Advantages of orphan designation

Many of these difficulties can all be managed with careful planning and they have not deterred companies from pursuing orphan indications. Often companies seek orphan authorisations for additional indications for drugs that have already been approved for

other conditions where the cost of early development is already mitigated or has been recouped.

In addition to the streamlined regulatory procedures and undoubted help that the EMA and FDA provide to orphan disease companies, the other major advantage of the orphan area, as discussed above, is that *in certain cases* much higher prices can be charged compared with the high-volume, low-margin, mass-market drugs. It is probably true that most orphan drugs are more expensive than more frequently used products and therefore for companies operating on a lower fixed-cost basis, they may contribute significantly to company profits. Even larger companies have noted that the 6000 orphan diseases represent an untapped market and some are heavily involved in developing new orphan medicines, usually of the more novel type. As such, orphan drugs have been a major growth area. The total worldwide market for orphan drugs, including sales of such drugs in non-orphan applications, exceeded $28 billion in 2003. This market has risen at an average annual growth rate of 9.1%, to reach $43.6 billion in 2008, with increasingly exponential growth as the global orphan drugs market is expected to reach $81.8 billion by 2011. A few orphan products, such as Aglucarse, have sales in excess of $1 billion annually. The global orphan disease therapeutics market is forecast to show increased growth due to increased approval of orphan drugs. Analysis of the market shows that the potential annual turnover for one indication varies between $100 million and $1.5 billion. As mentioned above, once approved orphan drugs can later be developed for other non-orphan indications. Thus an orphan drug approval can sometimes be a relatively rapid route to the market, and can later be leveraged for other uses, but a detailed analysis of the specific product scenario should be conducted to ascertain this in each case due to the technical difficulties in orphan drug development.

10.9 And finally … the regulatory affairs expert

Many people used to find their way into regulatory affairs from a laboratory job, typically someone who was tired of lab work and wanted a desk job. Often these people were pharmacists or chemists,

and since CMC forms a large and highly regulated section of most regulatory applications, there was some sense in this type of person being in regulatory affairs. Moreover, the non-clinical and especially the clinical data tended (and to some extent still tends) to be handled more within the various non-clinical and clinical departments with the regulatory professional having more of a reviewing role. In the last 25 years, however, companies have woken up to the fact that as all of the data from all departments eventually have to be handled by the regulatory department for a number of purposes (CTA, scientific advice, MAA, etc), and as drug development is a highly regulated activity, it makes sense to involve the regulatory professional in a strategic, technical and regulatory advisory role from early development. This not only helps the company to follow a development pathway acceptable to the regulatory authorities but helps prepare the regulatory professional for future negotiations with the regulatory authorities in order to gain approval of the company's various applications. There is now a greater range of experiences within regulatory affairs in general and the role is a much more active one than it was in the 1980s. Typically, the regulatory affairs role in a small company requires interaction with many disciplines and is very 'hands-on', whereas in multinationals the regulatory roles are split up into, for example, development product and marketed product roles, or roles by geographical region, or by focus on particular disciplines (CMC, non-clinical, clinical, labelling). Sometimes, companies will hire someone with a specific therapeutic experience. It is an area with its own career path and a number of professional bodies exist and prosper such as The Organisation for Professionals in Regulatory Affairs, the Regulatory Affairs Professionals Society and the Drug Information Association. So, all in all, for a person with an enquiring mind there is lots to do in a regulatory affairs role. The danger, however, is becoming bogged down in the purely administrative activities that are necessarily associated with a function that routinely deals with public sector authorities. It is certainly a role that will continue to take on greater importance in companies as regulation in the EU, USA and Japan evolves in the many ways discussed in this chapter, and as drug development becomes more complicated with our burgeoning scientific knowledge and the implementation of an increasing amount of regulation.

Seven key points to remember about the regulatory process

- Use the Regulatory Process to guide your product development. Don't ignore it or put it off – it won't go away.
- Don't think that regulatory affairs only matter at registration. Your pharma partners will also judge your product by regulatory standards, e.g. during deal negotiations.
- Remember that regulatory standards are minimum requirements that are likely to get tougher throughout the time of your product development. You have to aim high.
- The regulatory process is a dialogue. Constructive engagement with regulators is a very good policy. Ignore their advice at your peril.
- Keep a keen eye on commercial imperatives versus regulatory standards, and especially keep control of external pressures to generate efficacy data and 'get into the clinic' too early.
- Use experienced professionals to help guide you, particularly in your interactions with the regulatory authorities. This is a complex, evolving, difficult to interpret and often ignored area of drug development.
- Orphan designation and approval is a potential fast track to the market and is often a viable model for small companies.

Notes

1. See http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000187.jsp&murl=menus/special_topics/special_topics.jsp&mid=
2. http://www.fda.gov/
3. http://www.fda.gov/downloads/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/UCM135127.pdf [last accessed 7 February 2011].

References and recommended reading

CMR International Factbook 2010 Pharmaceutical R&D (2010) Thomson Reuters.

Committee on Safety of Medicines. (2010). http://medicines.mhra.gov.uk/aboutagency/regframework/csm/csmhome.htm [accessed March 2010]

European Medicines Evaluation Agency. (2010). http://www.emea.eu.int/ [accessed March 2010]

Food and Drug Administration. (2010). http://www.fda.gov/default.htm [accessed March 2010]

International Convention on Harmonisation (ICH). (2010). www.ICH.org [accessed March 2010]

Licensing of medicines: European licensing. http://medicines.mhra.gov.uk/ourwork/licensingmeds/european/europelic.htm [accessed March 2010]

Medicines and Healthcare products Regulatory Agency. (2010). http://www.mhra.gov.uk/ [accessed March 2010]

Munos B. (2009). Lessons from 60 years of pharmaceutical innovation. *Nature Reviews: Drug Discovery* 6: 959–68.

Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment and Prevention of Bipolar Disorder. (2001). http://www.emea.eu.int/pdfs/human/ewp/056798en.pdf [accessed March 2010]

Orphan Designation EMA. (2010). http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/05/WC500090812.pdf

Simmons J, Bernstein D. (2006). Navigating differences between FDA and EMEA for regulatory compliance during drug development. http://biopharminternational.findpharma.com/biopharm/Article/Navigating-Differences-Between-FDA-and-EMEA-for-Re/ArticleStandard/Article/detail/371018