

# HANDBOOK OF PHARMACEUTICAL GENERIC DEVELOPMENT



VOLUME **XI** Part **ONE**  
Drug Development - Solid Oral Dosage Forms

Handbook of Pharmaceutical  
Generic Development *Series*

## HPGD 24 Vol. SERIES - ORAL ER CAPSULES - Part I

First & Second Int. Edition - 01 & 02 (First & second print run) Published 1995/6/7/8.

Third International Edition - 03 (1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> printing) - Published 1999/2000/2001.

Fourth International Edition - 04 (First & second print) - Jan / July 2002 & 2003.

Fifth International Edition - 05 (1<sup>st</sup> Print) - Publishing November Effective January 2004

Published and distributed in UK, US, EU, Israel, Asia, and Japan in by Locum International Publishing House (Houston, Israel, South Africa) in Hard Cover; Soft and Spiral Cover; Electronic CD ROM; and Online Editions. All print and electronic editions are identical in content and format.

Sixth International Edition - 06 (1<sup>st</sup> Print) - Publishing November Effective January 2005

Seventh International Edition - 07 (1<sup>st</sup> Print) - Publishing November Effective January 2006

Eight International Edition - 08 (1<sup>st</sup> Print) - Publishing November Effective January 2007

Copyright © 1995 Handbook of Pharmaceutical Generic Development.

Text Copyright © 1995 Handbook of Pharmaceutical Generic Development.

Illustration copyright © 1995 Handbook of Pharmaceutical Generic Development.

Locum International Group Publishing House 562 Monaco L Monaco Blvd. Delray Beach Florida 33446-1938 USA. - All right reserved

ISBN 0793 8691

ISBN 0793 8705 - Electronic Version (CD ROM and On-line editions)

Handbook Development 24 volume series

General Generic Development ISSN Series number 0793 7407

General Generic Development ISSN Series number 0793 7792 - Electronic Issue (CD ROM and On-line are identical in size and content to the printed hard or soft cover version.)

**Duplication:** No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, microfilming, recording or otherwise, without the prior written permission of the copyright owner or subject to the following conditions:

Authorization to photocopy items for internal or personal use or internal or personal use of specific company personnel is granted by Locum International Publishing House, provided that the base fee of \$1 per page is paid directly to the Copyright Clearance Center (CCC) 222 Rosewood Drive, Danvers, MA 01923 USA.

For organizations that have been granted a photocopy license by CCC, a separate system of payment has been arranged.

US printing Locum USA Publishers 562 Monaco L Delray Beach 33446 Florida USA

For additional information, contact the Group Publications Department Locum International Publishing House; PO Box 874, 50 Gilad Street, Kochav Yair, 44864 Israel.



US Fax: +(1) 561-431 2620

Global Fax: +972-97-494-532

E-mail: [info@iagim.org](mailto:info@iagim.org)

<http://www.locum.co.il>

<http://www.locumeuro.com>

<http://www.locumusa.com>

[info@locumgroup.org](mailto:info@locumgroup.org)

Current Printing (last digit): 10 9 8 7 6 5 4 3.

SERIAL NUMBER - DO NO REMOVE! - REGISTERED WITH

LOCUM INTERNATIONAL PUBLISHERS REGISTRATION SERVICES  
WARNING: THIS ISSUE A IS MULTIPLE PAGE UV ENCODED EDITION.

☒ PRINTED IN USA

PRINTED IN ISRAEL

PRINTED IN IRELAND

PRINTED IN REPUBLIC OF SOUTH AFRICA

# HANDBOOK OF PHARMACEUTICAL GENERIC DEVELOPMENT



**B L O C K   J   D   &   B E L L E   D**

# Electronic Handbook Series of Pharmaceutical Generic Development

ISSN 0793 8667 - Electronic Version Handbook Development 24 Volume Series  
ISSN Series Number 0793 761X - Electronic Version

## Handbook of Pharmaceutical Generic Development

Part I (Development) & Part II (Formulation ; Development & ANDA)

Vol. 1 **Tablets IR Oral**

## Handbook of Pharmaceutical Generic Development

Part I (Development) & Part II (Formulation ; Development & ANDA)

Vol.2 **Capsules IR Oral**

## Handbook of Pharmaceutical Generic Development

Part I (Development) & Part II (Formulation ; Development & ANDA)

Vol.3 **Semisolids Topical**

## Handbook of Pharmaceutical Generic Development

Part I (Development) & Part II (Formulation ; Development & ANDA)

Vol.4 **Liquids Oral**

## Handbook of Pharmaceutical Generic Development

Part I (Development) & Part II (Formulation ; Development & ANDA)

Vol.5 **Soft Gelatin Capsules**

## Handbook of Pharmaceutical Generic Development

Part I (Development) & Part II (Formulation ; Processes & ANDA)

Vol.6 **e-SOPs / SOPs**

## Handbook of Pharmaceutical Generic Development

Part I (Development) & Part II (Formulation ; Processes & ANDA)

Vol.7 **Suspensions IR Oral  
Standard & Reconstituted**

## Handbook of Pharmaceutical Generic Development

Part I (Development) & Part II (Formulation ; Processes & ANDA)

Vol.8 **Sterile Eye Preparations**

## Handbook of Pharmaceutical Generic Development

Part I (Development) & Part II (Formulation ; Processes & ANDA)

Vol.9 **Nasal Preparations**

## Handbook of Pharmaceutical Generic Development

Part I (Development) & Part II (Formulation ; Processes & ANDA)

Vol.10 **Oral Tablets CR / MR**

## Handbook of Pharmaceutical Generic Development

Part I (Development) & Part II (Formulation ; Processes & ANDA)

Vol.11 **Oral Capsules ER**

## Handbook of Pharmaceutical Generic Development

Part I (Development) & Part II (Formulation ; Processes & ANDA)

Vol.12 **Oral EC Tablets DR**

## Handbook of Pharmaceutical Generic Development

Part I (Development) & Part II (Formulation ; Processes & ANDA)

Vol.13 **Chewable IR Tablets**

## Handbook of Pharmaceutical INNOVATIVE Development

Handbook of Pharmaceutical INNOVATIVE Development

Vol.14 **Tablets IR Oral**

Handbook of Pharmaceutical INNOVATIVE Development

Vol.15 **Capsules IR Oral**

Handbook of Pharmaceutical DRUG Development  
(TITLE 17 SERIES Master Formula & Process Instructions)

Vol.16 **Suspensions IR Oral**

Handbook of Pharmaceutical DRUG Development  
(TITLE 17 SERIES Master Formula & Process Instructions)

Vol.17 **MF & MMI Parts 1 - 5**

## Handbook of Pharmaceutical DRUG Development

Part I, II & III (Development, Manufacturing & Engineering

Vol.18 **MF & MMI Parts 6 - 10**

## Handbook of Pharmaceutical DRUG Development

Part I (Development) & Part II (Formulation ; Development & ANDA)

Vol.19 **SOPs / PAI-Checklist**

## Handbook of Pharmaceutical Generic Development

Part I (Method Validation) & Part II (Analytical Methods 1994-2008)

Vol.20 **STERILE INJECTIONS**

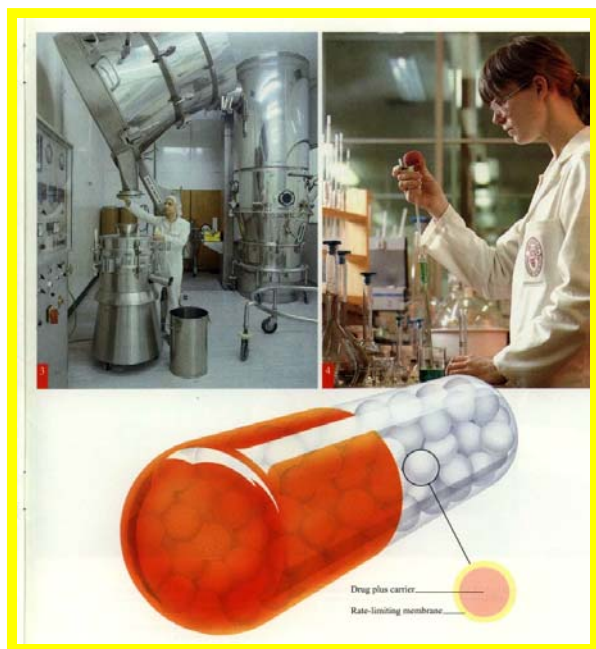
Vol.21 **S I Assays HPLC**  
50 Stability Indicating Assays

Available either as Hard Bound, Soft Bound or Soft Spiral Cover (for Updating) or CD ROM.  
Additional Drug Specific Volumes in Preparation. An on-going electronic and print series



# Handbook of Pharmaceutical Generic Development

## Oral Extended Release CAPSULES



Part ONE  
DRUG Development



# Acknowledgments

I.A.G.I.M. (R&D) Foundation.  
 I.A.G.I.M. Research Council.  
 Contributions - Generic & Research Firms.  
 Associate Universities, Technicons and Consultants.  
 Handbook Series Coordinating Committee.  
 International Journal of Drug Development.  
 International Journal of Drug Formulation.  
 Journal of Pharmaceutical Development.  
 International Journal of Generic Drugs.  
 International Journal of Drug R&D  
 I.A.G.I.M. Drug Development Archives  
 Locum International Archives.  
 FDA/OGD/CDER Maryland  
 Guides and Guidelines  
 Library of Congress.  
 AIC Conferences.  
 Editorial Board.  
 Pharm. Eur.  
 USP/NF.  
 USPC.  
 BP  
 ☼

To Doribelle  
 for her years of support and help  
 to Sean for his expert knowledge on computerization  
 to David and Ari for running the project's computers  
 and lastly to Pat for his inestimable  
 contribution.

**24 Volume Series**  
 Handbook of Pharmaceutical Generic Development  
**International Edition**

LOCUM PUBLISHING HOUSE

ཨ ཨ ཨ  
 ཨ Locum Press ཨ  
 ཨ ཨ ཨ

# INTRODUCTION

## Handbook of Generic Development - Oral Capsule Dosage Form

This Handbook is the **current** edition of the ongoing 24 volume *series* on the Handbook of Generic Drug Development. It is a hands-on technical presentation that portrays the current drug development requirements at the time of going to print necessary for an Abbreviated New Drug Application for an oral capsule dosage form.

The Handbook is available in PDF electronic format and the **e-format** CD ROM is updated annually to association members of IAGIM as required.

The pellet manufacturing method in this application highlights the similarity between the various sphere coating manufacturing processes for pellet encapsulation. Two basic types of dissolution-controlled pulse delivery systems for capsules spheres are common (a) beads/spheres containing the drug with different thickness of dissolving barrier coats (as in this handbook) or (b) pellets of beads/spheres with *alternate* drug and rate controlling barrier layers (i.e. drug / coat / drug / coat / layering etc.). Very soluble active drug materials such as Slow Release Potassium Chloride may be sized and then spray coated with multiple layers of a modern rate controlling barrier coat. The data that changes, for manufacturing procedure is simply the processing, in-process and finished product specifications provided for in Sections 11 and 12 of the **Part Two** of the model Abbreviated New Drug Application.

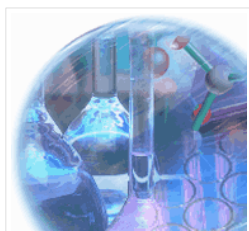
This international edition of the Handbook has been redesigned and updated to meet the **current** Guidance for Industry - Organization of an Abbreviated New Drug Application and an Abbreviated Antibiotic Application as well as all current approved and *draft* FDA guideline requirements of the Center of Drug Evaluation and Research (CDER) up to current edition date.

Editor-in-Chief.



*Additional Volumes in Preparation*

General Drug Development Series ISSN 0973 7601  
Electronic Drug Development Series ISSN 0973 761X



# Contents

## PHARMACEUTICAL DEVELOPMENT

|                                 |             |
|---------------------------------|-------------|
| <b>Table of Contents</b>        | <b>VII</b>  |
| <b>Acronyms - Abbreviations</b> | <b>XIII</b> |
| <b>Introduction</b>             | <b>XIV</b>  |
| <b>Preface</b>                  | <b>XV</b>   |
| <b>Forward</b>                  | <b>XVI</b>  |

### Chapter 1

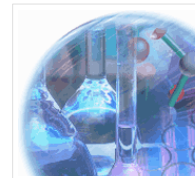
|  |            |
|--|------------|
| <b>Regulatory</b>                            | <b>1.1</b> |
| - Pre-formulation checklist                  | 1.3        |
| <b>Documentation</b>                         |            |
| - getting the right Documentation            | 1.5        |
| - SOP control and checklist                  | 1.7        |
| <b>Development Notebooks</b>                 | <b>1.8</b> |
| - Development Notebooks checklist            | 1.10       |
| - SOP Control and Development Notebooks SOPs | 1.11       |

### Chapter 2

|  |             |
|--|-------------|
| <b>Developing the Formula -an Overview</b>                             | <b>2.1</b>  |
| - Formulation checklist  | 2.2         |
| - Formula Development  | 2.3         |
| <b>Drug Development Checklist</b>                                      | <b>2.4</b>  |
| <b>Development Formula SOPs</b>  | <b>2.5</b>  |
| <b>Biopharmaceutical guidance</b>                                      | <b>2.6</b>  |
| <b>Developing the Formula</b>  | <b>2.7</b>  |
| <b>Product Development Flow Chart</b>                                  | <b>2.13</b> |
| <b>Product Development Guide</b>                                       | <b>2.15</b> |
| <b>Purified water - An ingredient in solid dosage form development</b> | <b>2.23</b> |
| <b>Do and Don'ts in Development</b>                                    | <b>2.26</b> |
| <b>Purified water check list</b>                                       | <b>2.27</b> |



# Contents



## Chapter 3

|   |     |
|---|-----|
| <b>Active Ingredients</b>                             | 3.1 |
| - Do's and Don'ts                                     | 3.2 |
| - Active checklist                                    | 3.3 |
| - Approved Suppliers Checklist                        | 3.5 |
| - Standard Operating Procedures, Actives              | 3.6 |
| - Alternative Active Ingredients -Regulatory Guidance | 3.7 |

## Chapter 4

|  |     |
|--|-----|
| <b>Release Controlling Excipients</b>              | 4.1 |
| <b>Release Coat Material</b>                       | 4.2 |
| <b>Developing ER Formula</b>                       | 4.3 |
| <b>Semi active ingredients</b>                     | 4.4 |
| -Validating the Semi-active ingredients, Checklist | 4.6 |
| <b>Antioxidant Tabulations</b>                     | 4.7 |

## Chapter 5

|   |     |
|---|-----|
| <b>Non active materials (excipients)</b>    | 5.1 |
| -Checklist non active ingredient            | 5.3 |
| -Standard Operating Procedures, Non actives | 5.4 |

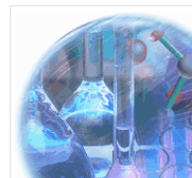
## Chapter 6

|   |      |
|---|------|
| <b>Container closure systems</b>                      | 6.1  |
| - Container-liner-closure systems, checklist          | 6.2  |
| - Container-liner-closure systems, SOPs               | 6.4  |
| - Packaging Components                                | 6.5  |
| - Packaging Components Documentation Requirements SOP | 6.6  |
| - Packaging Characteristics                           | 6.11 |
| - Packaging Component Descriptions                    | 6.12 |
| - Packaging Component                                 | 6.16 |

## Chapter 7

|  |      |
|--|------|
| <b>Developing Extended Release Capsules</b>        | 7.1  |
| - Manufacturing Instructions                       | 7.5  |
| - The manufacturing Instructions and Controls      | 7.7  |
| - Diltiazem ER Capsules - Manufacturing & Controls | 7.11 |
| - Large scale manufacturing Instructions           | 7.14 |
| - Large scale Master Formula                       | 7.18 |
| - Large scale Manufacturing Flow Charts            | 7.26 |

# Contents



## Chapter 8

|   |     |
|---|-----|
| <b>In-process Quality Controls</b>                    | 8.1 |
| - Manufacturing in-process controls; checklist        | 8.2 |
| - In-process Specifications - overview                | 8.5 |
| - In-process Specifications - production              | 8.6 |
| - In-process Control Specifications - quality control | 8.7 |
| - In-process SOPs - Quality Control                   | 8.9 |

## Chapter 9

|  |     |
|--|-----|
| <b>Finished Product Specifications</b>                       | 9.1 |
| - Finished Product Specifications - Release                  | 9.2 |
| - Finished Product Specifications; - Stability               | 9.3 |
| - Finished Product Specifications; Required Checklist & SOPs | 9.5 |

## Chapter 10

|  |      |
|--|------|
| <b>Process Optimization and Procedures Flowchart</b> | 10.1 |
|--|------|

## Chapter 11

|   |       |
|---|-------|
| <b>Bioavailability &amp; Bioequivalence</b> | 11.1  |
| <b>Formula Composition</b>                  | 11.3  |
| <b>Qualitative Comparison</b>               | 11.7  |
| - Dissolution                               | 11.9  |
| - Comparative Dissolution Tabulations       | 11.11 |
| - Comparative Dissolution Graphs            | 11.13 |
| - Certificate of Analysis Chromatograms     | 11.15 |
| - Biostudy Packaging Disbursements          | 11.19 |

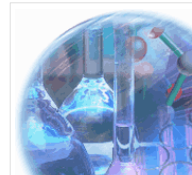
## Chapter 12

|   |       |
|---|-------|
| <b>Cleaning Procedures and Guidelines</b> | 12.1  |
| <b>Cleaning Limits</b>                    | 12.9  |
| <b>Cleaning Limits Checklists</b>         | 12.14 |
| <b>Cleaning Validation Requirements</b>   | 12.6  |
| <b>Cleaning Procedures Do's and Don's</b> | 12.19 |

## Chapter 13

|   |       |
|---|-------|
| <b>Analytical Validation guidelines</b>           | 13.1  |
| - Analytical Testing Out of Specification         | 13.21 |
| - Potassium Chloride Pellets - Monograph          | 13.33 |
| - Out-of-Specifications Checklists                | 13.34 |
| - Ruggedness and Robustness                       | 13.52 |
| - Impurities in Drug Substances                   | 13.56 |
| - Impurities Rules to Remember & Do's and Don'ts  | 13.66 |
| - Bioanalytical Methods                           | 13.70 |
| - Impurities Decision Trees                       | 13.53 |
| <b>Analytical Post approval Changes -PAC-ALTS</b> | 13.82 |
| <b>PAC-ALTS Checklist</b>                         | 13.85 |

# Contents



## Chapter 14

|  |       |
|--|-------|
| <b>Process Qualification Batch</b>                       | 14.1  |
| - Process Qualification Batch; Checklist                 | 14.2  |
| - Process Qualification Batch; SOPs                      | 14.3  |
| - Process Qualification Blend Analysis                   | 14.5  |
| - Process Qualification Blend Analysis - Do's and Don'ts | 14.8  |
| - Process Qualification - Encapsulation process          | 14.9  |
| <b>Process Qualification Chart</b>                       | 14.10 |

## Chapter 15

|  |       |
|--|-------|
| <b>Pivotal batch</b>                     |       |
| - The Pivotal Batch                      | 15.1  |
| - Pivotal batch Checklist                | 15.2  |
| - Pivotal batch SOPs                     | 15.3  |
| - Sampling and Testing the Pivotal Batch | 15.5  |
| - Auditing the Pivotal batch             | 15.11 |
| - Auditing the Pivotal batch Checklist   | 15.13 |

## Chapter 16

|   |        |
|---|--------|
| <b>Bioequivalence vs. RLD</b>                                     | 16.1   |
| <b>Test Designs - Overview</b>                                    | 16.2   |
| <b>Statistical Bioequivalence</b>                                 | 16.13  |
| <b>IBE Equation explained</b>                                     | 16.14  |
| <b>IBE - Big Picture (Pros and Cons)</b>                          | 16.15  |
| <b>Comparing IBE and ABE</b>                                      | 16.16  |
| <b>Generic Drug Dissolution Testing</b>                           | 16.19  |
| <b>Typical IVIVC Models</b>                                       | 16.21  |
| <b>Choosing IVIVC levels</b>                                      | 16.22  |
| <b>Dissolution Testing in MR Solid Dosage Forms</b>               | 16.27  |
| <b>Biowaivers</b>   | 16.39  |
| <b>Overall Dissolution Picture</b>                                | 16.42  |
| <b>Biopharmaceutics Classification System</b>                     | 16.43  |
| <b>Performance Verification in Dissolution testing</b>            | 16.45  |
| <b>BA and BE Overview</b>   | 16.58  |
| <b>Food-Effects in BA-BE Studies</b>                              | 16.84  |
| <b>Similarity Testing - Chow, Pitt and Others</b>                 | 16.92  |
| <b>Installation and Operational requirements of Lab Equipment</b> | 16.100 |



# Contents

## Chapter 17

|   |       |
|---|-------|
| <b>Technical Transfer Documentation</b>                 | 17.1  |
| - Technical Transfer Documentation; Checklist           | 17.6  |
| - Technical Transfer Documentation; Pharmaceutical Part | 17.9  |
| - Technical Transfer Documentation; Analytical Part     | 17.13 |

## Chapter 18

|   |       |
|---|-------|
| <b>Process Validation Batches</b>           | 18.1  |
| - The Process Validation Batches; Checklist | 18.2  |
| - Process Validation Requirements; SOPs     | 18.4  |
| - Process Validation Master Plans           | 18.5  |
| - Process Optimization Protocol Design      | 18.16 |
| - Process Optimization Master Charts        | 18.18 |
| - Process Optimization Master Charts        | 18.19 |
| - Process Optimization Master Charts        | 18.20 |

## Chapter 19

|   |       |
|---|-------|
| <b>Pre--Approval Inspections</b>                        | 19.1  |
| <b>PAI Summary</b>                                      | 19.9  |
| <b>Pre--Approval Inspection Audit - Team Set Up</b>     | 19.10 |
| <b>Pre--Approval Inspection Audit - Team Activities</b> | 19.11 |

## Chapter 20

|  |       |
|--|-------|
| <b>Stability Testing of Drug Substance and Drug Product - overview</b> | 20.1  |
| <b>Stability Testing of Drug Substance and Drug Product - ANDAs</b>    | 20.15 |
| <b>Stability Testing Significant Change</b>                            | 20.21 |
| <b>Significant Change SOP</b>  | 20.25 |
| <b>Stability Storage Conditions</b>                                    | 20.29 |
| <b>Photostability in Drug Substances</b>                               | 20.31 |
| <b>Setting up a Functional Stability Unit</b>                          | 20.40 |
| <b>Stability SOPs Development</b>                                      | 20.48 |

## Chapter 21

### Standard Operational Procedures

|   |       |
|---|-------|
| <b>Development SOPs</b>                                       | 21.1  |
| <b>Index of Pharmaceutical Standard Operating Procedures</b>  | 21.3  |
| <b>Index of Analytical Standard Operating Procedures</b>      | 21.10 |
| <b>Index of Microbiological Standard Operating Procedures</b> | 21.16 |
| <b>Index of Stability Standard Operating Procedures</b>       | 21.20 |

ISSN 0793 8756

ISBN 0793 8640 - Electronic Version

Handbook Development 24 Volume Series

ISSN Series Number 0793 7792 - Electronic Version

## EDITORIAL PREFACE

## Handbook of Generic Development - Oral Capsule Dosage Form

This handbook represents the **new** International Edition of the ongoing **24** volume series of Generic Drug Development and appears under the cumulative title of the Handbook series of Generic Drug Development. The ongoing 24 volume series are updated reviewed and expanded annually.

This is an ongoing process as new data, specifications and process techniques are added on a continual and expanding basis. This handbook is fact, never fully complete, as each new annual edition brings an enlarged and extended profile in the drug development process, as well as new agency rules, guidelines and guidance to industry which continue to be added year by year as the global product data base expands.

Currently over 150 scientific publications and drug development conferences are annually referenced in the **24** volume Handbook series of Generic Drug Development.

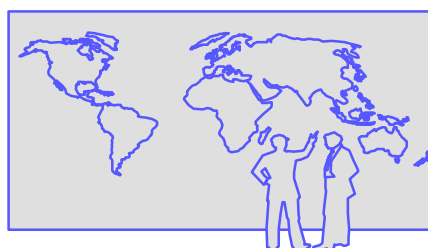
This mammoth task presents a continual ongoing commitment by the scientific review committee to the improvement of the technical databases and the product specific drug development requirements and know-how technology accessed through the world wide IAGIM joint ventures and know-how projects currently active in over 15 countries.

The Handbook is available in electronic format (Online and CD ROM) and the e-format is up-dated annually to association members of IAGIM.

This **updated** international edition of the Handbook has been redesigned and updated to meet the latest Guidance for Industry - Organization of an Abbreviated New Drug Application as well as all current approved and key *draft* and final FDA guideline requirements of the Center of Drug Evaluation and Research (CDER).

Editorial      Advisory

Board.



ISSN 0793 8632

*An on-going series*

*Additional Volumes in Preparation*

General Drug Development Series ISSN 0973 7601

Electronic Drug Development Series ISSN 0973 761X

ÓŠÎ

International Edition

p 2005 p

© COPYRIGHT Locum Int.

İ > Đ