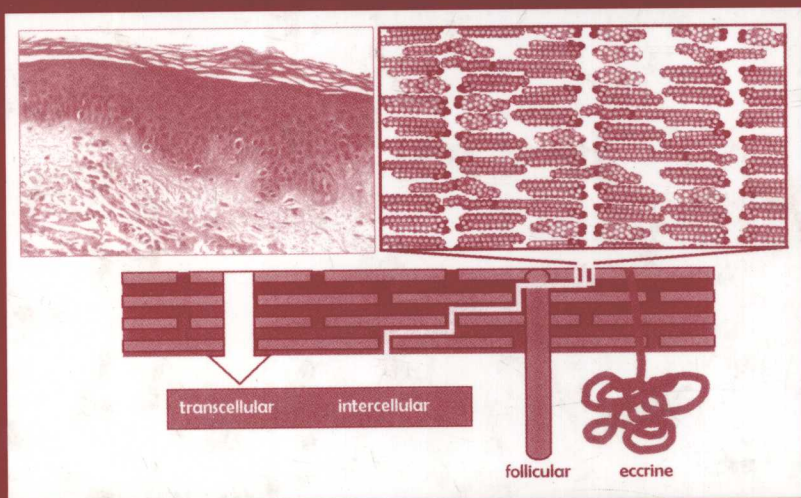


Transdermal Drug Delivery

Second Edition, Revised and Expanded



edited by
Richard H. Guy
Jonathan Hadgraft

Transdermal Drug Delivery

Second Edition, Revised and Expanded

edited by

Richard H. Guy

*Universities of Geneva and Lyon, Archamps, France
and University of Geneva, Geneva, Switzerland*

Jonathan Hadgraft

NRI, University of Greenwich, Chatham, England



Y2000264



MARCEL DEKKER, INC.

NEW YORK • BASEL

Library of Congress Cataloging-in-Publication Data

A catalog record for this book is available from the Library of Congress.

ISBN: 0-8247-0861-X

The first edition was published as *Transdermal Drug Delivery: Developmental Issues and Research Initiatives*, edited by Jonathan Hadgraft and Richard H. Guy.

This book is printed on acid-free paper.

Headquarters

Marcel Dekker, Inc.
270 Madison Avenue, New York, NY 10016
tel: 212-696-9000; fax: 212-685-4540

Eastern Hemisphere Distribution

Marcel Dekker AG
Hutgasse 4, Postfach 812, CH-4001 Basel, Switzerland
tel: 41-61-260-6300; fax: 41-61-260-6333

World Wide Web

<http://www.dekker.com>

The publisher offers discounts on this book when ordered in bulk quantities. For more information, write to Special Sales/Professional Marketing at the headquarters address above.

Copyright © 2003 by Marcel Dekker, Inc. All Rights Reserved.

Neither this book nor any part may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, microfilming, and recording, or by any information storage and retrieval system, without permission in writing from the publisher.

Current printing (last digit):

10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

Transdermal Drug Delivery

DRUGS AND THE PHARMACEUTICAL SCIENCES

Executive Editor

James Swarbrick

*PharmaceuTech, Inc.
Pinehurst, North Carolina*

Advisory Board

Larry L. Augsburger University of Maryland Baltimore, Maryland	David E. Nichols Purdue University West Lafayette, Indiana
--	--

Douwe D. Breimer Gorlaeus Laboratories Leiden, The Netherlands	Stephen G. Schulman University of Florida Gainesville, Florida
--	--

Trevor M. Jones The Association of the British Pharmaceutical Industry London, United Kingdom	Jerome P. Skelly Alexandria, Virginia
--	--

Hans E. Junginger Leiden/Amsterdam Center for Drug Research Leiden, The Netherlands	Felix Theeuwes Alza Corporation Palo Alto, California
--	---

Vincent H. L. Lee University of Southern California Los Angeles, California	Geoffrey T. Tucker University of Sheffield Royal Hallamshire Hospital Sheffield, United Kingdom
---	--

Peter G. Welling
Institut de Recherche Jouveinal
Fresnes, France

DRUGS AND THE PHARMACEUTICAL SCIENCES

A Series of Textbooks and Monographs

1. Pharmacokinetics, *Milo Gibaldi and Donald Perrier*
2. Good Manufacturing Practices for Pharmaceuticals: A Plan for Total Quality Control, *Sidney H. Willig, Murray M. Tuckerman, and William S. Hitchings IV*
3. Microencapsulation, *edited by J. R. Nixon*
4. Drug Metabolism: Chemical and Biochemical Aspects, *Bernard Testa and Peter Jenner*
5. New Drugs: Discovery and Development, *edited by Alan A. Rubin*
6. Sustained and Controlled Release Drug Delivery Systems, *edited by Joseph R. Robinson*
7. Modern Pharmaceutics, *edited by Gilbert S. Banker and Christopher T. Rhodes*
8. Prescription Drugs in Short Supply: Case Histories, *Michael A. Schwartz*
9. Activated Charcoal: Antidotal and Other Medical Uses, *David O. Cooney*
10. Concepts in Drug Metabolism (in two parts), *edited by Peter Jenner and Bernard Testa*
11. Pharmaceutical Analysis: Modern Methods (in two parts), *edited by James W. Munson*
12. Techniques of Solubilization of Drugs, *edited by Samuel H. Yalkowsky*
13. Orphan Drugs, *edited by Fred E. Karch*
14. Novel Drug Delivery Systems: Fundamentals, Developmental Concepts, Biomedical Assessments, *Yie W. Chien*
15. Pharmacokinetics: Second Edition, Revised and Expanded, *Milo Gibaldi and Donald Perrier*
16. Good Manufacturing Practices for Pharmaceuticals: A Plan for Total Quality Control, Second Edition, Revised and Expanded, *Sidney H. Willig, Murray M. Tuckerman, and William S. Hitchings IV*
17. Formulation of Veterinary Dosage Forms, *edited by Jack Blodinger*
18. Dermatological Formulations: Percutaneous Absorption, *Brian W. Barry*
19. The Clinical Research Process in the Pharmaceutical Industry, *edited by Gary M. Matoren*
20. Microencapsulation and Related Drug Processes, *Patrick B. Deasy*
21. Drugs and Nutrients: The Interactive Effects, *edited by Daphne A. Roe and T. Colin Campbell*
22. Biotechnology of Industrial Antibiotics, *Erick J. Vandamme*

23. *Pharmaceutical Process Validation*, edited by Bernard T. Loftus and Robert A. Nash
24. *Anticancer and Interferon Agents: Synthesis and Properties*, edited by Raphael M. Ottenbrite and George B. Butler
25. *Pharmaceutical Statistics: Practical and Clinical Applications*, Sanford Bolton
26. *Drug Dynamics for Analytical, Clinical, and Biological Chemists*, Benjamin J. Gudzinowicz, Burrows T. Younkin, Jr., and Michael J. Gudzinowicz
27. *Modern Analysis of Antibiotics*, edited by Adjoran Aszalos
28. *Solubility and Related Properties*, Kenneth C. James
29. *Controlled Drug Delivery: Fundamentals and Applications*, Second Edition, Revised and Expanded, edited by Joseph R. Robinson and Vincent H. Lee
30. *New Drug Approval Process: Clinical and Regulatory Management*, edited by Richard A. Guarino
31. *Transdermal Controlled Systemic Medications*, edited by Yie W. Chien
32. *Drug Delivery Devices: Fundamentals and Applications*, edited by Praveen Tyle
33. *Pharmacokinetics: Regulatory • Industrial • Academic Perspectives*, edited by Peter G. Welling and Francis L. S. Tse
34. *Clinical Drug Trials and Tribulations*, edited by Allen E. Cato
35. *Transdermal Drug Delivery: Developmental Issues and Research Initiatives*, edited by Jonathan Hadgraft and Richard H. Guy
36. *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*, edited by James W. McGinity
37. *Pharmaceutical Pelletization Technology*, edited by Isaac Ghebre-Sellassie
38. *Good Laboratory Practice Regulations*, edited by Allen F. Hirsch
39. *Nasal Systemic Drug Delivery*, Yie W. Chien, Kenneth S. E. Su, and Shyi-Feu Chang
40. *Modern Pharmaceutics: Second Edition, Revised and Expanded*, edited by Gilbert S. Banker and Christopher T. Rhodes
41. *Specialized Drug Delivery Systems: Manufacturing and Production Technology*, edited by Praveen Tyle
42. *Topical Drug Delivery Formulations*, edited by David W. Osborne and Anton H. Amann
43. *Drug Stability: Principles and Practices*, Jens T. Carstensen
44. *Pharmaceutical Statistics: Practical and Clinical Applications*, Second Edition, Revised and Expanded, Sanford Bolton
45. *Biodegradable Polymers as Drug Delivery Systems*, edited by Mark Chasin and Robert Langer
46. *Preclinical Drug Disposition: A Laboratory Handbook*, Francis L. S. Tse and James J. Jaffe
47. *HPLC in the Pharmaceutical Industry*, edited by Godwin W. Fong and Stanley K. Lam
48. *Pharmaceutical Bioequivalence*, edited by Peter G. Welling, Francis L. S. Tse, and Shrikant V. Dinghe

49. Pharmaceutical Dissolution Testing, *Umesh V. Banakar*
50. Novel Drug Delivery Systems: Second Edition, Revised and Expanded, *Yie W. Chien*
51. Managing the Clinical Drug Development Process, *David M. Cocchetto and Ronald V. Nardi*
52. Good Manufacturing Practices for Pharmaceuticals: A Plan for Total Quality Control, Third Edition, *edited by Sidney H. Willig and James R. Stoker*
53. Prodrugs: Topical and Ocular Drug Delivery, *edited by Kenneth B. Sloan*
54. Pharmaceutical Inhalation Aerosol Technology, *edited by Anthony J. Hickey*
55. Radiopharmaceuticals: Chemistry and Pharmacology, *edited by Adrian D. Nunn*
56. New Drug Approval Process: Second Edition, Revised and Expanded, *edited by Richard A. Guarino*
57. Pharmaceutical Process Validation: Second Edition, Revised and Expanded, *edited by Ira R. Berry and Robert A. Nash*
58. Ophthalmic Drug Delivery Systems, *edited by Ashim K. Mitra*
59. Pharmaceutical Skin Penetration Enhancement, *edited by Kenneth A. Walters and Jonathan Hadgraft*
60. Colonic Drug Absorption and Metabolism, *edited by Peter R. Bieck*
61. Pharmaceutical Particulate Carriers: Therapeutic Applications, *edited by Alain Rolland*
62. Drug Permeation Enhancement: Theory and Applications, *edited by Dean S. Hsieh*
63. Glycopeptide Antibiotics, *edited by Ramakrishnan Nagarajan*
64. Achieving Sterility in Medical and Pharmaceutical Products, *Nigel A. Halls*
65. Multiparticulate Oral Drug Delivery, *edited by Isaac Ghebre-Sellassie*
66. Colloidal Drug Delivery Systems, *edited by Jörg Kreuter*
67. Pharmacokinetics: Regulatory • Industrial • Academic Perspectives, Second Edition, *edited by Peter G. Welling and Francis L. S. Tse*
68. Drug Stability: Principles and Practices, Second Edition, Revised and Expanded, *Jens T. Carstensen*
69. Good Laboratory Practice Regulations: Second Edition, Revised and Expanded, *edited by Sandy Weinberg*
70. Physical Characterization of Pharmaceutical Solids, *edited by Harry G. Brittain*
71. Pharmaceutical Powder Compaction Technology, *edited by Göran Alderborn and Christer Nyström*
72. Modern Pharmaceutics: Third Edition, Revised and Expanded, *edited by Gilbert S. Banker and Christopher T. Rhodes*
73. Microencapsulation: Methods and Industrial Applications, *edited by Simon Benita*
74. Oral Mucosal Drug Delivery, *edited by Michael J. Rathbone*
75. Clinical Research in Pharmaceutical Development, *edited by Barry Bleidt and Michael Montagne*

76. The Drug Development Process: Increasing Efficiency and Cost Effectiveness, *edited by Peter G. Welling, Louis Lasagna, and Umesh V. Banakar*
77. Microparticulate Systems for the Delivery of Proteins and Vaccines, *edited by Smadar Cohen and Howard Bernstein*
78. Good Manufacturing Practices for Pharmaceuticals: A Plan for Total Quality Control, Fourth Edition, Revised and Expanded, *Sidney H. Willig and James R. Stoker*
79. Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms: Second Edition, Revised and Expanded, *edited by James W. McGinity*
80. Pharmaceutical Statistics: Practical and Clinical Applications, Third Edition, *Sanford Bolton*
81. Handbook of Pharmaceutical Granulation Technology, *edited by Dilip M. Parikh*
82. Biotechnology of Antibiotics: Second Edition, Revised and Expanded, *edited by William R. Strohl*
83. Mechanisms of Transdermal Drug Delivery, *edited by Russell O. Potts and Richard H. Guy*
84. Pharmaceutical Enzymes, *edited by Albert Lauwers and Simon Scharpé*
85. Development of Biopharmaceutical Parenteral Dosage Forms, *edited by John A. Bontempo*
86. Pharmaceutical Project Management, *edited by Tony Kennedy*
87. Drug Products for Clinical Trials: An International Guide to Formulation • Production • Quality Control, *edited by Donald C. Monkhouse and Christopher T. Rhodes*
88. Development and Formulation of Veterinary Dosage Forms: Second Edition, Revised and Expanded, *edited by Gregory E. Hardee and J. Desmond Baggot*
89. Receptor-Based Drug Design, *edited by Paul Leff*
90. Automation and Validation of Information in Pharmaceutical Processing, *edited by Joseph F. deSpautz*
91. Dermal Absorption and Toxicity Assessment, *edited by Michael S. Roberts and Kenneth A. Walters*
92. Pharmaceutical Experimental Design, *Gareth A. Lewis, Didier Mathieu, and Roger Phan-Tan-Luu*
93. Preparing for FDA Pre-Approval Inspections, *edited by Martin D. Hynes III*
94. Pharmaceutical Excipients: Characterization by IR, Raman, and NMR Spectroscopy, *David E. Bugay and W. Paul Findlay*
95. Polymorphism in Pharmaceutical Solids, *edited by Harry G. Brittain*
96. Freeze-Drying/Lyophilization of Pharmaceutical and Biological Products, *edited by Louis Rey and Joan C. May*
97. Percutaneous Absorption: Drugs–Cosmetics–Mechanisms–Methodology, Third Edition, Revised and Expanded, *edited by Robert L. Bronaugh and Howard I. Maibach*

98. Bioadhesive Drug Delivery Systems: Fundamentals, Novel Approaches, and Development, *edited by Edith Mathiowitz, Donald E. Chickering III, and Claus-Michael Lehr*
99. Protein Formulation and Delivery, *edited by Eugene J. McNally*
100. New Drug Approval Process: Third Edition, The Global Challenge, *edited by Richard A. Guarino*
101. Peptide and Protein Drug Analysis, *edited by Ronald E. Reid*
102. Transport Processes in Pharmaceutical Systems, *edited by Gordon L. Amidon, Ping I. Lee, and Elizabeth M. Topp*
103. Excipient Toxicity and Safety, *edited by Myra L. Weiner and Lois A. Kotkoskie*
104. The Clinical Audit in Pharmaceutical Development, *edited by Michael R. Hamrell*
105. Pharmaceutical Emulsions and Suspensions, *edited by Francoise Nielloud and Gilberte Marti-Mestres*
106. Oral Drug Absorption: Prediction and Assessment, *edited by Jennifer B. Dressman and Hans Lennernäs*
107. Drug Stability: Principles and Practices, Third Edition, Revised and Expanded, *edited by Jens T. Carstensen and C. T. Rhodes*
108. Containment in the Pharmaceutical Industry, *edited by James P. Wood*
109. Good Manufacturing Practices for Pharmaceuticals: A Plan for Total Quality Control from Manufacturer to Consumer, Fifth Edition, Revised and Expanded, *Sidney H. Willig*
110. Advanced Pharmaceutical Solids, *Jens T. Carstensen*
111. Endotoxins: Pyrogens, LAL Testing, and Depyrogenation, Second Edition, Revised and Expanded, *Kevin L. Williams*
112. Pharmaceutical Process Engineering, *Anthony J. Hickey and David Ganderton*
113. Pharmacogenomics, *edited by Werner Kalow, Urs A. Meyer, and Rachel F. Tyndale*
114. Handbook of Drug Screening, *edited by Ramakrishna Seethala and Prabhavathi B. Fernandes*
115. Drug Targeting Technology: Physical • Chemical • Biological Methods, *edited by Hans Schreier*
116. Drug–Drug Interactions, *edited by A. David Rodrigues*
117. Handbook of Pharmaceutical Analysis, *edited by Lena Ohannesian and Anthony J. Streeter*
118. Pharmaceutical Process Scale-Up, *edited by Michael Levin*
119. Dermatological and Transdermal Formulations, *edited by Kenneth A. Walters*
120. Clinical Drug Trials and Tribulations: Second Edition, Revised and Expanded, *edited by Allen Cato, Lynda Sutton, and Allen Cato III*
121. Modern Pharmaceuticals: Fourth Edition, Revised and Expanded, *edited by Gilbert S. Banker and Christopher T. Rhodes*
122. Surfactants and Polymers in Drug Delivery, *Martin Malmsten*
123. Transdermal Drug Delivery: Second Edition, Revised and Expanded, *edited by Richard H. Guy and Jonathan Hadgraft*

124. Good Laboratory Practice Regulations: Second Edition, Revised and Expanded, *edited by Sandy Weinberg*
125. Parenteral Quality Control: Sterility, Pyrogen, Particulate, and Package Integrity Testing: Third Edition, Revised and Expanded, *Michael J. Akers, Dan Larrimore, and Dana Morton Guazzo*
126. Modified-Release Drug Delivery Technology, *edited by Michael J. Rathbone, Jonathan Hadgraft, and Michael S. Roberts*
127. Simulation for Designing Clinical Trials, *edited by Hui C. Kimko and Stephen Duffull*

ADDITIONAL VOLUMES IN PREPARATION

Pharmaceutical Process Validation: An International Third Edition, Revised and Expanded, *edited by Robert A. Nash and Alfred H. Wachter*

Affinity Capillary Electrophoresis in Pharmaceuticals and Biopharmaceuticals, *edited by Reinhard H. H. Neubert and Hans-Hermann Rüttinger*

Ophthalmic Drug Delivery Systems: Second Edition, Revised and Expanded, *edited by Ashim K. Mitra*

Pharmaceutical Gene Delivery Systems, *edited by Alain Rolland and Sean M. Sullivan*

Biomarkers in Clinical Drug Development, *edited by John Bloom*

Preface

The previous edition of our book was compiled in the late '80s at the height of academic and industrial activity in transdermal research. While this route of administration continues to be limited by the number of suitable drug candidates available, it still attracts considerable worldwide interest, and, importantly, the pharmaceutical industry is now prepared to consider new chemical entities for transdermal delivery. This will reinvigorate the field, which, until now, has depended on the development of existing compounds that typically do not possess optimal physicochemical properties for dermal delivery.

The second edition reflects our increased knowledge of the mechanisms of absorption and how these can be used to advantage in the development of medicinal agents and formulations for both dermal and transdermal delivery. The barrier properties of the skin, thanks to the use of sophisticated biophysical techniques, are much better understood and their modulation by both chemical and physical techniques has achieved impressive results. Consequently, the manner in which the basic physicochemical properties of a drug determine the amount that can be transported across the stratum corneum can now be explained in detail. The revised text shows the importance of these properties and how predictive models can be established to examine the feasibility of delivering molecules into and through the skin. Over the last 15 years, considerable advances have been made in the use of physical approaches to promote absorption. These techniques, which include electrical, ultrasound, and other minimally invasive strategies, are reviewed here in some detail. Chemical enhancers, on the other hand, have been fully examined in multiple other texts and are therefore not covered in this edition.

The fact that the skin is a metabolically active organ means that its barrier properties can be modulated by interference with lipid synthesis. This novel approach is reviewed in this book, as is the application of supersaturation as a mechanism for enhanced delivery. Finally, as no transdermal system can be successful until it has passed through stringent regulatory control, the final chapter considers the steps required for the registration of dermal delivery systems.

In summary, this text attempts to achieve two broad objectives. The first is to provide a "snapshot" of the field and an evaluation of some creative ideas under examination. The second objective is to serve as a reference work that summarizes the state of the art and can be used to guide the interested reader into the fascinating world (and associated challenges) of transdermal drug delivery.

Richard H. Guy
Jonathan Hadgraft

Contributors

Annette L. Bunge Chemical Engineering Department, Colorado School of Mines, Golden, Colorado, U.S.A.

Adrian Davis GlaxoSmithKline Consumer Healthcare, Weybridge, England

M. Begoña Delgado-Charro Centre Interuniversitaire de Recherche et d'Enseignement, Universities of Geneva and Lyon, Archamps, France, and School of Pharmacy, University of Geneva, Geneva, Switzerland

James A. Down BD Technologies, Research Triangle Park, North Carolina, U.S.A.

Peter M. Elias Departments of Dermatology and Medicine, University of California, San Francisco, San Francisco, California, U.S.A.

Kenneth R. Feingold Departments of Dermatology and Medicine, University of California, San Francisco, San Francisco, California, U.S.A.

Richard H. Guy Centre Interuniversitaire de Recherche et d'Enseignement, Universities of Geneva and Lyon, Archamps, France, and School of Pharmacy, University of Geneva, Geneva, Switzerland

Jonathan Hadgraft Skin and Membrane Transfer Research Center, NRI, University of Greenwich, Chatham, England

Noel G. Harvey BD Technologies, Research Triangle Park, North Carolina, U.S.A.

Victor Meidan New Jersey Center for Biomaterials, Newark, New Jersey, U.S.A.

Gopinathan Menon Avon Products, Inc., Suffern, New York, U.S.A.

Mark Pellett Wyeth Consumer Healthcare, Havant, England

Véronique Préat Unité de Pharmacie Galénique, Université Catholique de Louvain, Brussels, Belgium

S. Lakshmi Raghavan Skin and Membrane Transfer Research Center, NRI, University of Greenwich, Chatham, England

Vinod P. Shah Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, Maryland, U.S.A.

Carl Thornfeldt Cellegy Pharmaceuticals, Inc., Foster City, California, U.S.A.

Janice Tsai Department of Dermatology, University of California, San Francisco, San Francisco, California, U.S.A.; Department of Clinical Pharmacy, National Cheng Kung University, Taiwan; and Cellegy Pharmaceuticals, Inc., Foster City, California, U.S.A.

Rita Vanbever Unité de Pharmacie Galénique, Université Catholique de Louvain, Brussels, Belgium

Brent E. Vecchia* Chemical Engineering Department, Colorado School of Mines, Golden, Colorado, U.S.A.

* *Current affiliation:* Blakely Sokoloff Taylor & Zafman LLP, Denver, Colorado, U.S.A.

Contents

<i>Preface</i>	<i>iii</i>
<i>Contributors</i>	<i>vii</i>
1. Feasibility Assessment in Topical and Transdermal Delivery: Mathematical Models and In Vitro Studies <i>Jonathan Hadgraft and Richard H. Guy</i>	1
2. Evaluating the Transdermal Permeability of Chemicals <i>Brent E. Vecchia and Annette L. Bunge</i>	25
3. Skin Absorption Databases and Predictive Equations <i>Brent E. Vecchia and Annette L. Bunge</i>	57
4. Partitioning of Chemicals into Skin: Results and Predictions <i>Brent E. Vecchia and Annette L. Bunge</i>	143
5. Iontophoresis: Applications in Drug Delivery and Noninvasive Monitoring <i>M. Begoña Delgado-Charro and Richard H. Guy</i>	199
6. Skin Electroporation for Transdermal and Topical Drug Delivery <i>Véronique Préat and Rita Vanbever</i>	227

7.	Sonophoresis: Ultrasound-Enhanced Transdermal Drug Delivery <i>Victor Meidan</i>	255
8.	Metabolic Approach to Transdermal Drug Delivery <i>Peter M. Elias, Kenneth R. Feingold, Janice Tsai, Carl Thornfeldt, and Gopinathan Menon</i>	285
9.	The Application of Supersaturated Systems to Percutaneous Drug Delivery <i>Mark Pellett, S. Lakshmi Raghavan, Jonathan Hadgraft, and Adrian Davis</i>	305
10.	Minimally Invasive Systems for Transdermal Drug Delivery <i>James A. Down and Noel G. Harvey</i>	327
11.	Transdermal Drug Delivery System Regulatory Issues <i>Vinod P. Shah</i>	361
	<i>Index</i>	369