

DRUGS AND THE PHARMACEUTICAL SCIENCES

VOLUME 203

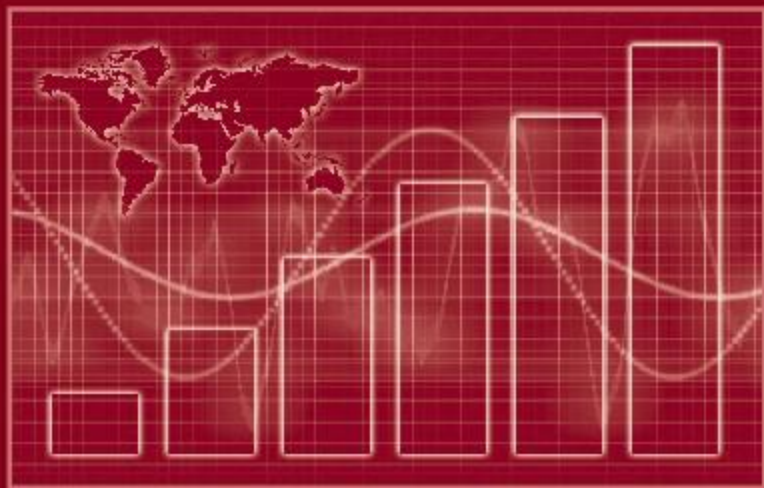
CD Included

FIFTH EDITION



Pharmaceutical Statistics

Practical and Clinical Applications



Sanford Bolton
Charles Bon

informa
healthcare

Pharmaceutical Statistics

DRUGS AND THE PHARMACEUTICAL SCIENCES

A Series of Textbooks and Monographs

Executive Editor

James Swarbrick

*PharmaceuTech, Inc.
Pinehurst, North Carolina*

Advisory Board

Larry L. Augsburger

*University of Maryland
Baltimore, Maryland*

Jennifer B. Dressman

*University of Frankfurt Institute of
Pharmaceutical Technology
Frankfurt, Germany*

Anthony J. Hickey

*University of North Carolina
School of Pharmacy
Chapel Hill, North Carolina*

Ajaz Hussain

*Sandoz
Princeton, New Jersey*

Joseph W. Polli

*GlaxoSmithKline
Research Triangle Park
North Carolina*

Stephen G. Schulman

*University of Florida
Gainesville, Florida*

Yuichi Sugiyama

University of Tokyo, Tokyo, Japan

Geoffrey T. Tucker

*University of Sheffield
Royal Hallamshire Hospital
Sheffield, United Kingdom*

Harry G. Brittain

*Center for Pharmaceutical Physics
Milford, New Jersey*

Robert Gurny

*Universite de Geneve
Geneve, Switzerland*

Jeffrey A. Hughes

*University of Florida College
of Pharmacy
Gainesville, Florida*

Vincent H. L. Lee

*US FDA Center for Drug
Evaluation and Research
Los Angeles, California*

Kinam Park

*Purdue University
West Lafayette, Indiana*

Jerome P. Skelly

Alexandria, Virginia

Elizabeth M. Topp

*University of Kansas
Lawrence, Kansas*

Peter York

*University of Bradford
School of Pharmacy
Bradford, United Kingdom*

**For information on volumes 1–151 in the *Drugs and Pharmaceutical Science Series*,
Please visit www.informahealthcare.com**

152. *Preclinical Drug Development*, edited by Mark C. Rogge and David R. Taft
153. *Pharmaceutical Stress Testing: Predicting Drug Degradation*, edited by Steven W. Baertschi
154. *Handbook of Pharmaceutical Granulation Technology: Second Edition*, edited by Dilip M. Parikh
155. *Percutaneous Absorption: Drugs–Cosmetics–Mechanisms–Methodology*, Fourth Edition, edited by Robert L. Bronaugh and Howard I. Maibach
156. *Pharmacogenomics: Second Edition*, edited by Werner Kalow, Urs A. Meyer and Rachel F. Tyndale
157. *Pharmaceutical Process Scale-Up*, Second Edition, edited by Michael Levin
158. *Microencapsulation: Methods and Industrial Applications*, Second Edition, edited by Simon Benita
159. *Nanoparticle Technology for Drug Delivery*, edited by Ram B. Gupta and Uday B. Kompella
160. *Spectroscopy of Pharmaceutical Solids*, edited by Harry G. Brittain
161. *Dose Optimization in Drug Development*, edited by Rajesh Krishna
162. *Herbal Supplements-Drug Interactions: Scientific and Regulatory Perspectives*, edited by Y. W. Francis Lam, Shiew-Mei Huang, and Stephen D. Hall
163. *Pharmaceutical Photostability and Stabilization Technology*, edited by Joseph T. Piechocki and Karl Thoma
164. *Environmental Monitoring for Cleanrooms and Controlled Environments*, edited by Anne Marie Dixon
165. *Pharmaceutical Product Development: In Vitro-In Vivo Correlation*, edited by Dakshina Murthy Chilukuri, Gangadhar Sunkara, and David Young
166. *Nanoparticulate Drug Delivery Systems*, edited by Deepak Thassu, Michel Deleers, and Yashwant Pathak
167. *Endotoxins: Pyrogens, LAL Testing and Depyrogenation*, Third Edition, edited by Kevin L. Williams
168. *Good Laboratory Practice Regulations*, Fourth Edition, edited by Anne Sandy Weinberg
169. *Good Manufacturing Practices for Pharmaceuticals*, Sixth Edition, edited by Joseph D. Nally
170. *Oral-Lipid Based Formulations: Enhancing the Bioavailability of Poorly Water-soluble Drugs*, edited by David J. Hauss
171. *Handbook of Bioequivalence Testing*, edited by Sarfaraz K. Niazi
172. *Advanced Drug Formulation Design to Optimize Therapeutic Outcomes*, edited by Robert O. Williams III, David R. Taft, and Jason T. McConville
173. *Clean-in-Place for Biopharmaceutical Processes*, edited by Dale A. Seiberling
174. *Filtration and Purification in the Biopharmaceutical Industry*, Second Edition, edited by Maik W. Jornitz and Theodore H. Meltzer
175. *Protein Formulation and Delivery*, Second Edition, edited by Eugene J. McNally and Jayne E. Hastedt
176. *176 Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*, Third Edition, edited by James McGinity and Linda A. Felton
177. *Dermal Absorption and Toxicity Assessment*, Second Edition, edited by Michael S. Roberts and Kenneth A. Walters
178. *Preformulation Solid Dosage Form Development*, edited by Moji C. Adeyeye and Harry G. Brittain
179. *Drug-Drug Interactions*, Second Edition, edited by A. David Rodrigues
180. *Generic Drug Product Development: Bioequivalence Issues*, edited by Isadore Kanfer and Leon Shargel
181. *Pharmaceutical Pre-Approval Inspections: A Guide to Regulatory Success*, Second Edition, edited by Martin D. Hynes III
182. *Pharmaceutical Project Management*, Second Edition, edited by Anthony Kennedy
183. *Modified Release Drug Delivery Technology*, Second Edition, Volume 1, edited by Michael J. Rathbone, Jonathan Hadgraft, Michael S. Roberts, and Majella E. Lane

184. Modified-Release Drug Delivery Technology, Second Edition, Volume 2, *edited by Michael J. Rathbone, Jonathan Hadgraft, Michael S. Roberts, and Majella E. Lane*
185. The Pharmaceutical Regulatory Process, Second Edition, *edited by Ira R. Berry and Robert P. Martin*
186. Handbook of Drug Metabolism, Second Edition, *edited by Paul G. Pearson and Larry C. Wienkers*
187. Preclinical Drug Development, Second Edition, *edited by Mark Rogge and David R. Taft*
188. Modern Pharmaceutics, Fifth Edition, Volume 1: Basic Principles and Systems, *edited by Alexander T. Florence and Jürgen Siepmann*
189. Modern Pharmaceutics, Fifth Edition, Volume 2: Applications and Advances, *edited by Alexander T. Florence and Jürgen Siepmann*
190. New Drug Approval Process, Fifth Edition, *edited by Richard A. Guarino*
191. Drug Delivery Nanoparticulate Formulation and Characterization, *edited by Yashwant Pathak and Deepak Thassu*
192. Polymorphism of Pharmaceutical Solids, Second Edition, *edited by Harry G. Brittain*
193. Oral Drug Absorption: Prediction and Assessment, Second Edition, *edited by Jennifer J. Dressman, Hans Lennernas, and Christos Reppas*
194. Biodrug Delivery Systems: Fundamentals, Applications, and Clinical Development, *edited by Mariko Morishita and Kinam Park*
195. Pharmaceutical Process Engineering, Second Edition, *Anthony J. Hickey and David Ganderton*
196. Handbook of Drug Screening, Second Edition, *edited by Ramakrishna Seethala and Litao Zhang*
197. Pharmaceutical Powder Compaction Technology, Second Edition, *edited by Metin Celik*
198. Handbook of Pharmaceutical Granulation Technology, *Dilip M. Parikh*
199. Pharmaceutical Preformulation and Formulation, Second Edition: A Practical Guide from Candidate Drug Selection to Commercial Dosage Form, *edited by Mark Gibson*
200. International Pharmaceutical Product Registration, Second Edition, *edited by Anthony C. Cartwright and Brian R. Matthews*
201. Generic Drug Product Development: International Regulatory Requirements for Bioequivalence, *edited by Isadore Kanfer and Leon Shargel*
202. Proteins and Peptides: Pharmacokinetic, Pharmacodynamic, and Metabolic Outcomes, *edited by Randall J. Mersny and Ann Daugherty*
203. Pharmaceutical Statistics: Practical and Clinical Applications, Fifth Edition, *Sanford Bolton and Charles Bon*

FIFTH EDITION

Pharmaceutical Statistics

Practical and Clinical Applications

Sanford Bolton

Consultant

Tucson, Arizona, USA

Charles Bon

Biostudy Solutions, LLC

Wilmington, North Carolina, USA

informa

healthcare

New York London

Informa Healthcare USA, Inc.
52 Vanderbilt Avenue
New York, NY 10017

© 2010 by Informa Healthcare USA, Inc.
Informa Healthcare is an Informa business

No claim to original U.S. Government works
Printed in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

International Standard Book Number-10: 1-4200-7422-9
International Standard Book Number-13: 978-1-4200-7422-2 (Hardcover)

This book contains information obtained from authentic and highly regarded sources. Reprinted material is quoted with permission, and sources are indicated. A wide variety of references are listed. Reasonable efforts have been made to publish reliable data and information, but the author and the publisher cannot assume responsibility for the validity of all materials or for the consequence of their use.

No part of this book may be reprinted, reproduced, transmitted, or utilized in any form by any electronic, mechanical, or other means, now known or hereafter invented, including photocopying, microfilming, and recording, or in any information storage or retrieval system, without written permission from the publishers.

For permission to photocopy or use material electronically from this work, please access www.copyright.com (<http://www.copyright.com/>) or contact the Copyright Clearance Center, Inc. (CCC) 222 Rosewood Drive, Danvers, MA 01923, 978-750-8400. CCC is a not-for-profit organization that provides licenses and registration for a variety of users. For organizations that have been granted a photocopy license by the CCC, a separate system of payment has been arranged.

Trademark Notice: Product or corporate names may be trademarks or registered trademarks, and are used only for identification and explanation without intent to infringe.

Library of Congress Cataloging-in-Publication Data

Bolton, Sanford, 1929–
Pharmaceutical statistics : practical and clinical applications / Sanford Bolton,
Charles Bon. – 5th ed.
p. ; cm. – (Drugs and the pharmaceutical sciences ; 203)
Includes bibliographical references and index.
ISBN-13: 978-1-4200-7422-2 (hardcover : alk. paper)
ISBN-10: 1-4200-7422-9 (hardcover : alk. paper) 1. Pharmacy–Statistical methods.
I. Bon, Charles, 1949– II. Title. III. Series: Drugs and the pharmaceutical sciences ; 203.
[DNLM: 1. Pharmacy–methods–Laboratory Manuals. 2. Statistics as Topic–Laboratory
Manuals. W1 DR893B v.203 2009 / QV 25 B694p 2009]
RS57.B65 2009
615'.1072–dc22

2009039659

For Corporate Sales and Reprint Permission call 212-520-2700 or write to: Sales Department, 52 Vanderbilt Avenue, 7th floor, New York, NY 10017.

Visit the Informa Web site at
www.informa.com

and the Informa Healthcare Web site at
www.informahealthcare.com

To my wife, Phyllis
always present,
always sensitive,
always inspirational
—S. B.

To Sanford Bolton
my mentor who kindled my love of statistics,
and to my wife, Marty,
who did the same for the other areas of my life
—C. B.

Preface

This is the fifth edition of *Pharmaceutical Statistics*. The first edition was published 25 years ago when there were no statistical texts, as far as I know, which were directed toward nonstatistician researchers in academia or the pharmaceutical industry. Although, such a book was not immediately recognized as being an important adjunct to pharmaceutical research, soon after its publication, the passage of time has clearly confirmed the need for a statistics book that is useful for the pharmaceutical scientist. The practical examples with a discussion of the pharmaceutical and clinical consequences have helped to give the pharmaceutical researcher another dimension.

When I first wrote this book in the early 1980s, using a typewriter and two fingers, one of my aims was to document my experience and have a book that could be my personal reference. In each new edition, I have added new material based on new experiences that I think will be useful to the pharmaceutical community as well as to enhance the book as my own reference.

This new edition has some new features. We have expanded some of the tables in the appendix to make them more complete. A more detailed explanation of one- and two-sided statistical tests and when they are applicable has been included. We have updated some of the material related to clinical trials. We have updated statistical applications to bioequivalence, as well as various designs used in bioequivalence studies. A program to calculate the number of subjects in bioequivalence trials under a number of assumptions has been added to the disk accompanying the book. We have also added some new material explaining in more detail the assumptions and applications of nonparametric methods, including application of the binomial distribution to put upper confidence limits on the proportion of successes and failures in a sample. We have included the application of confidence intervals for a ratio, using a method based on Fieller's Theorem. An interesting relationship between the mean and median of a sample is included, with a derivation.

Finally, we have done our best to remove typos and any errors that we have discovered from the fourth edition. Unfortunately, with so much material, it seems impossible to be perfect. However, we strive for perfection, to do our best, and we look forward to comments, criticisms, and ideas from our readers to improve the book, or include new material for the sixth edition.

Before leaving this introduction, again I give thanks to my teachers, my students, my colleagues, my readers, and my work with pharmaceutical problems from pharmaceutical firms of all sizes and shapes that continue to challenge and teach me.

I want to acknowledge those who have helped me both as a person and scientist, and helped me grow. In particular, I owe debts of gratitude to two mentors, now deceased, Dr. Takeru Higuchi and Dr. John Fertig. I acknowledge the institutions that encouraged me to write this book, and allowed me to apply the knowledge to apply statistical applications to pharmaceutical problems, that is, University of Wisconsin, Columbia University and St. John's University in Queens, NY. Finally, thanks to my family, friends, and students, all of whom have made my life more full and have been my family. Special thanks to my wife, Phyllis Bolton, Mohan Sondhi, Salah Ahmed, Spiro Spireas, Charles DiLiberti, Chuck Bon Jerry Reinstein, Robert and Maria Bell, Lama Pema, Mrs. Popoff, and The University of Arizona Guitar Department, to mention only a few.

Sanford Bolton

Contents

Preface ix

- 1. Basic Definitions and Concepts 1**
 - 1.1 Variables and Variation 1
 - 1.2 Frequency Distributions and Cumulative Frequency Distributions 3
 - 1.3 Sample and Population 8
 - 1.4 Measures Describing the Center of Data Distributions 9
 - 1.5 Measurement of the Spread of Data 13
 - 1.6 Coding 18
 - 1.7 Precision, Accuracy, and Bias 20
 - 1.8 The Question of Significant Figures 22
 - Key Terms 23
 - Exercises 24
 - References 25

- 2. Data Graphics 26**
 - 2.1 Introduction 26
 - 2.2 The Histogram 26
 - 2.3 Construction and Labeling of Graphs 28
 - 2.4 Scatter Plots (Correlation Diagrams) 33
 - 2.5 Semilogarithmic Plots 34
 - 2.6 Other Descriptive Figures 35
 - Key Terms 38
 - Exercises 38
 - References 39

- 3. Introduction to Probability: The Binomial and Normal Probability Distributions 40**
 - 3.1 Introduction 40
 - 3.2 Some Basic Probability 40
 - 3.3 Probability Distributions—The Binomial Distribution 44
 - 3.4 Continuous Data Distributions 52
 - 3.5 Other Common Probability Distributions 63
 - 3.6 The Log-Normal Distribution 66
 - Key Terms 68
 - Exercises 69
 - References 70

- 4. Choosing Samples 71**
 - 4.1 Introduction 71
 - 4.2 Random Sampling 72
 - 4.3 Other Sampling Procedures: Stratified, Systematic, And Cluster Sampling 75
 - 4.4 Sampling in Quality Control 78
 - Key Terms 79
 - Exercises 79
 - References 81

- 5. Statistical Inference: Estimation and Hypothesis Testing 82**
 - 5.1 Statistical Estimation (Confidence Intervals) 82
 - 5.2 Statistical Hypothesis Testing 89
 - 5.3 Comparison Of Variances In Independent Samples 118
 - 5.4 Test Of Equality Of More Than Two Variances 121
 - 5.5 Confidence Limits For A Variance 122
 - 5.6 Tolerance Intervals 123
 - Key Terms 124
 - Exercises 124
 - References 127

- 6. Sample Size and Power 128**
 - 6.1 Introduction 128
 - 6.2 Determination Of Sample Size For Simple Comparative Experiments For Normally Distributed Variables 129
 - 6.3 Determination Of Sample Size For Binomial Tests 133
 - 6.4 Determination Of Sample Size To Obtain A Confidence Interval Of Specified Width 136
 - 6.5 Power 138
 - 6.6 Sample Size And Power For More Than Two Treatments (Also See Chap. 8) 141
 - 6.7 Sample Size For Bioequivalence Studies (Also See Chap. 11) 143
 - Key Terms 145
 - Exercises 145
 - References 146

- 7. Linear Regression and Correlation 147**
 - 7.1 Introduction 147
 - 7.2 Analysis Of Standard Curves In Drug Analysis: Application Of Linear Regression 151
 - 7.3 Assumptions In Tests Of Hypotheses In Linear Regression 152
 - 7.4 Estimate Of The Variance: Variance Of Sample Estimates Of The Parameters 153
 - 7.5 A Drug Stability Study: A Second Example Of The Application Of Linear Regression 155
 - 7.6 Confidence Intervals In Regression Analysis 159
 - 7.7 Weighted Regression 163
 - 7.8 Analysis Of Residuals 164
 - 7.9 Nonlinear Regression 166
 - 7.10 Correlation 170
 - 7.11 Comparison Of Variances In Related Samples 175
 - Key Terms 177
 - Exercises 178
 - References 180

- 8. Analysis of Variance 182**
 - 8.1 One-Way Anova 182
 - 8.2 Planned Versus A Posteriori (Unplanned) Comparisons In Anova 187
 - 8.3 Another Example Of One-Way Anova: Unequal Sample Sizes And The Fixed And Random Models 196
 - 8.4 Two-Way Anova (Randomized Blocks) 198
 - 8.5 Statistical Models** 209
 - 8.6 Analysis Of Covariance** 210
 - 8.7 Anova For Pooling Regression Lines As Related To Stability Data** 215

** A more advanced topic.

Key Terms 218
Exercises 218
References 221

9. Factorial Designs 222**

- 9.1 Definitions (Vocabulary) 222
- 9.2 Two Simple Hypothetical Experiments To Illustrate The Advantages Of Factorial Designs 225
- 9.3 Performing Factorial Experiments: Recommendations And Notation 228
- 9.4 A Worked Example Of A Factorial Experiment 229
- 9.5 Fractional Factorial Designs 234
- 9.6 Some General Comments 237
 - Key Terms 237
 - Exercises 238
 - References 239

10. Transformations and Outliers 240

- 10.1 Transformations 240
- 10.2 Outliers 249
 - Key Terms 256
 - Exercises 256
 - References 257

11. Experimental Design in Clinical Trials 258

- 11.1 Introduction 258
- 11.2 Some Principles Of Experimental Design And Analysis 259
- 11.3 Parallel Design 262
- 11.4 Crossover Designs And Bioavailability/Bioequivalence Studies 266
- 11.5 Repeated Measures (Split-Plot) Designs 301
- 11.6 Multiclinic Studies 306
- 11.7 Interim Analyses 307
 - Key Terms 309
 - Exercises 309
 - References 310

12. Quality Control 312

- 12.1 Introduction 312
- 12.2 Control Charts 312
- 12.3 Acceptance Sampling And Operating Characteristic Curves 324
- 12.4 Statistical Procedures In Assay Development 327
- 12.5 Establishing In-House Limits 336
- 12.6 Some Statistical Aspects Of Quality And The "Barr Decision" 339
- 12.7 Important QC Tests For Finished Solid Dosage Forms (Tablets And Capsules) 342
- 12.8 Out Of Specification (OOS) Results 345
 - Key Terms 346
 - Exercises 346
 - References 347

13. Validation 349

- 13.1 Process Validation 349
- 13.2 Assay Validation 358
- 13.3 Concluding Remarks 364

** A more advanced topic.

	Key Terms	364
	Exercises	364
	References	365
14.	Computer-Intensive Methods	366
14.1	Monte Carlo Simulation	366
14.2	Bootstrapping	384
	References	389
15.	Nonparametric Methods	390
15.1	Data Characteristics And An Introduction To Nonparametric Procedures	390
15.2	Sign Test	393
15.3	Wilcoxon Signed Rank Test	394
15.4	Wilcoxon Rank Sum Test (Test For Differences Between Two Independent Groups)	398
15.5	Kruskal–Wallis Test (One-Way Anova)	402
15.6	Friedman Test (Two-Way Analysis Of Variance)	404
15.7	Nonparametric Analysis Of Covariance	408
15.8	Runs Test For Randomness	409
15.9	Contingency Tables	411
15.10	Nonparametric Tolerance Interval	420
	Key Terms	421
	Exercises	421
	References	424
16.	Optimization Techniques and Screening Designs**	425
16.1	Introduction	425
16.2	Optimization Using Factorial Designs	427
16.3	Composite Designs To Estimate Curvature	435
16.4	The Simplex Lattice	439
16.5	Sequential Optimization**	446
16.6	Screening Designs	449
	Key Terms	451
	Exercises	451
	References	452
	Glossary	453
	Appendix I: Some Properties of the Variance	455
	I.1 Pooling Variances	455
	I.2 Components Of Variance	455
	I.3 Variance Of Linear Combinations Of Independent Variables	456
	Reference	456
	Appendix II: Comparison of Slopes and Testing of Linearity: Determination of Relative Potency	457
	Reference	461
	Appendix III: Multiple Regression	462
	References	466
	Appendix IV: Tables	467

** A more advanced topic.

Appendix V: Outlier Tests and Chemical Assays 487

- V.1 Introduction 487
- V.2 Can Outlier Tests Be Justified? 487
- V.3 Why Is There Not A USP Test For Outliers For Chemical Assays? 488
- V.4 Some Comments On The Nature Of Outliers And Outlier Tests, And Other Inconsistencies In The Decision That Outlier Tests Be Used For Biological Assays But Not For Chemical Assays 489
- V.5 What Is The Purpose Of Performing Replicate Assays And When Is Averaging Appropriate 490
- V.6 In What Situations Might Outlier Tests Be Applicable? 490
- References 491

Appendix VI: Should a Single Unexplained Failing Assay be Reason to Reject a Batch? 493

- VI.1 Case 1 494
- VI.2 Case 1A 494
- VI.3 Case 1B 495
- VI.4 Case 2 496
- VI.5 Case 2A 496
- VI.6 Case 2B 498
- VI.7 Conclusion 499
- References 499

Appendix VII: When is it Appropriate to Average and its Relationship to the Barr Decision 500

- VII.1 Background: Assay And Content Uniformity Tests 500
- VII.2 Averaging Replicates From A Homogeneous Sample 500
- VII.3 How Do We Deal With Single OOS Results When The Average Conforms? 501
- VII.4 Discussion 503
- Reference 503

Appendix VIII: Excel Workbooks and SAS Programs 504

- Excel Workbooks 504
- SAS Programs 555

Appendix IX: An Alternative Solution to the Distribution of the Individual Bioequivalence Metric 613

- IX.1 Derivation And Results 614
- References 615

Appendix X: Some Statistical Considerations and Alternate Designs and Considerations for Bioequivalence 623

- X.1 Parallel Design In Bioequivalence 623
- X.2 Outliers 626
- X.3 Dichotomous Outcome 627
- X.4 Steady State Studies 628
- X.5 Bioequivalence Studies Performed In Groups 629
- X.6 Replicate Study Designs 630

Answer to Exercises 633

Index 649

