

# **Recalls of Pharmaceutical Products**

**Eliminating Contamination and  
Adulteration Causes**

**Tim Sandle**

**PDA**

**Bethesda, MD, USA**

**DHI Publishing, LLC**

**River Grove, IL, USA**

10 9 8 7 6 5 4 3 2 1

**ISBN: 978-1-942911-42-5**  
**Copyright © 2020 Tim Sandle**  
**All rights reserved.**

All rights reserved. This book is protected by copyright. No part of it may be reproduced, stored in a retrieval system or transmitted in any means, electronic, mechanical, photocopying, recording, or otherwise, without written permission from the publisher. Printed in the United States of America.

Where a product trademark, registration mark, or other protected mark is made in the text, ownership of the mark remains with the lawful owner of the mark. No claim, intentional or otherwise, is made by reference to any such marks in the book. Websites cited are current at the time of publication. The author has made every effort to provide accurate citations. If there are any omissions, please contact the publisher.

While every effort has been made by the publisher and the author to ensure the accuracy of the information expressed in this book, the organization accepts no responsibility for errors or omissions. The views expressed in this book are those of the author and may not represent those of either Davis Healthcare International or the PDA, its officers, or directors.



*Connecting People, Science and Regulation®*



This book is printed on sustainable resource paper approved by the Forest Stewardship Council. The printer, Gasch Printing, is a member of the Green Press Initiative and all paper used is from SFI (Sustainable Forest Initiative) certified mills.

**PDA Global Headquarters**  
Bethesda Towers, Suite 150  
4350 East-West Highway  
Bethesda, MD 20814  
United States  
[www.pda.org/bookstore](http://www.pda.org/bookstore)  
001-301-986-0293

**Davis Healthcare International Publishing, LLC**  
2636 West Street  
River Grove  
IL 60171  
United States  
[www.DHIBooks.com](http://www.DHIBooks.com)

# About the Author

Tim Sandle, PhD, CBiol, RSB, FIScT

Dr. Sandle is an experienced pharmaceutical microbiologist and quality assurance professional with over 25 years' experience in the life sciences sector. He is currently the Head of Microbiology and Sterility Assurance at a UK sterile products manufacturer. His previous experience includes working for the NHS Blood Service and in medical research.

A visiting lecturer at the University of Manchester (where he teaches pharmaceutical microbiology), he is also affiliated with University College London (where he teaches aspirant Qualified Persons in sterilization technology). Dr. Sandle has served on various committees, including contributing to the development of the ISO 14644 cleanroom standards and in relation to disinfection controls for the Blood Transfusion Services for England and Wales. Dr. Sandle is also the editor of the publication *GMP Review*.

He has written or edited 27 books, contributed 100 chapters to books edited by others, contributed 160 peer-reviewed papers, and authored around 400 technical articles for a range of publications. His subjects include pharmaceutical microbiology, clinical microbiology, quality assurance, quality control, sterility assurance, general biology, and the history of science. Dr. Sandle also serves on the editorial boards of several science journals, and he has delivered over 160 conference presentations and webinars.

His voluntary work includes serving as a member of the Pharmaceutical Microbiology Interest Group (Pharmig) committee since 2002. He has been a governor for two schools (one position for 16 years), and he was a Labour and Co-operative Party councillor, serving on Hertsmere Borough Council, where he was chairman of leisure services and parks. Dr. Sandle was also a non-executive

director of the Hertsmere Homelessness charity and a non-executive director of Elstree Film Studios.

Among Dr. Sandle's qualifications are a PhD from Keele University, UK, and Chartered Status from the Royal Society of Biology. In addition, he is a Fellow of the Institute of Science and Technology. Dr. Sandle has received several awards, including PDA Author of the Year, the Pharmig Excellence in Pharmaceutical Microbiology Award, the George Sykes Award from the Pharmaceutical and Healthcare Sciences Society, and the Kenneth G. Chapman Award for contributions to validation excellence from the Institute of Validation Technology.

The professional bodies which Dr. Sandle is a member of include the Parenteral Drug Association (PDA), Pharmaceutical and Healthcare Science Society (PHSS), Royal Society of Biology, Pharmig, Microbiology Society, and the Institute of Science and Technology (IST).

In his spare time, Dr. Sandle runs a website called Pharmaceutical Microbiology Resources, which provides topical news interspersed with new standards and regulations. He is also a science and technology journalist and is a science editor-at-large for the Canadian-based global news site Digital Journal.

Dr. Sandle's interests include walking, politics, film, jazz and folk music, history, and a splattering of science fiction. He lives just outside the city of St. Albans, which is in the county of Hertfordshire in England.

---

---

# CONTENTS

<b>I</b>	<b>SETTING THE RECALL CONTEXT</b>	<b>I</b>
	Reasons for Recalls	4
	Review of the Chapters	27
	Summary	32
	References	33
<b>2</b>	<b>RECALLS AND GMP: WHAT ARE THE REGULATORS SAYING?</b>	<b>35</b>
	Introduction	35
	US FDA	37
	Canada	38
	European Union	41
	World Health Organization (WHO)	45
	ICH	48
	Coordination Between Regulators	49
	Summary	50
	References	50
	Appendix I: Model GMP checklist	53
<b>3</b>	<b>RECALL TRENDS AND THE PRIMARY CAUSES FOR PRODUCT RECALLS</b>	<b>67</b>
	Introduction	67
	US Recalls	68

European Recalls	75
Reasons for Recalls	77
International Recalls	81
Why Do Recalls Occur?	83
Summary	89
References	90
<b>4 ECONOMIC CONSEQUENCES OF PHARMACEUTICAL RECALLS</b>	<b>95</b>
Introduction	95
Economic Costs of Recalls	96
Loss of Sales	99
Internal Costs	100
Negative Publicity	101
Recall Strategy	104
Impact on Competitor Firms	105
Insurance Costs	107
Corporate Social Responsibility and the Supply Chain	108
Summary	108
References	109
<b>5 A HISTORY OF ERRORS: THE MOST SERIOUS GLOBAL DRUG INCIDENTS AND RECALLS</b>	<b>113</b>
Introduction	113
Early Years	114
Thalidomide (1960s)	116
Diethylstilbestrol (1971)	118
Tylenol (1982)	119
Omniflox (Temafloracin) (1992)	120
Fenfluramine and Dexfenfluramine (1997)	121
Seldane (Terfenadine) (1998)	121
Posicor (Mibefradil) (1998)	122
Duract (Bromfenac) (1999)	123
Rezulin (Troglitazone) (2000)	123
PPA Drugs (2000)	124
Baycol (Cerivastatin) (2001)	124
Vioxx (Rofecoxib) (2004)	125
Bextra (Valdecoxib) (2005)	126

Palladone (Hydromorphone) (2005)	127
Able Labs Drugs (2005)	127
My Pikin (2008)	129
Accutane (Isotretinoin) (2009)	130
Darvon and Darvocet (Propoxyphene) (2010)	131
Meridia (Sibutramine) (2010)	131
Specialty Pharmacies/NECC (2012–2015)	132
Cook Medical (2016)	133
Bella Pharmaceuticals (2017)	134
Blood Pressure Medications (2018–2019)	135
Ranitidine-Containing Medicinal Products (2019)	137
Nitrosamines	138
Summary	138
References	139
<b>6 PREDICTIVE MODELS TO ASSESS PHARMACEUTICAL RECALLS</b>	<b>147</b>
Introduction	147
Regulatory Inspections as Predictors for Recall	149
Predictive Analytics Models	150
Pharma 4.0	153
Implementation	154
Application	155
Errors with Predictive Models	163
Summary	164
References	164
<b>7 STERILE PHARMACEUTICAL PRODUCTS: NOTABLE RECALLS AND PERTINENT LESSONS</b>	<b>169</b>
Introduction	169
What are Sterile Products?	172
Major Recalls in Relation to Sterile Pharmaceuticals	174
Sterile Products Recalls with Compounding	180
Reasons for Sterile Products Recalls	191
Summary and Further Thoughts	195
References	197

<b>8</b>	<b>PHARMACEUTICAL PRODUCT RECALLS ASSOCIATED WITH FUNGAL CONTAMINATION</b>	<b>205</b>
	Introduction	205
	Fungal Infections	207
	Pharmaceutical Recalls with Fungal Contamination	208
	Fungal Contamination Cases	212
	Hazards to Patients from Fungal Contamination	218
	Types of Fungi Associated with Cleanrooms	220
	Fungal Risks in Pharmaceutical Environments	229
	Where Fungi Are Found and Why Fungi Survive	229
	Summary	233
	References	233
<b>9</b>	<b>BURKHOLDERIA CEPACIA COMPLEX: EXAMPLE OF NON-STERILE PRODUCT RECALL DUE TO MICROBIOLOGICAL CONTAMINATION</b>	<b>241</b>
	Introduction	241
	Organism Characteristics	243
	Association with Recalls	244
	Ubiquity of <i>B. Cepacia</i> Organisms	249
	Potential Risk to Patients	250
	FDA Alert and the Testing Debate	251
	Testing Scope	259
	Tests For BCC	260
	Assessment of Test Data	264
	Summary	266
	References	268
<b>10</b>	<b>CHEMICAL ADULTERATION OF PHARMACEUTICAL PRODUCTS AND ANALYTICAL METHODS FOR THE ASSESSMENT OF ADULTERANTS</b>	<b>277</b>
	Introduction	277
	Adulteration	279
	Chemical Adulteration	281
	Historical Cases	282
	Risks in Relation to Undeclared Materials	284



Importance of Data	284
Case Study: Herbal Supplements	285
Case Study: Chinese Medicine	288
Case Study: Dietary Supplements	289
Analytical Testing of Pharmaceuticals	290
Physical Tests	290
Chemical Tests	294
Analytical Assessments for Adulteration	295
Summary	305
References	306

<b>11 BATCH PROCESSING RECORDS: GOOD DESIGN AND THE MISSTEPS WITH HUMAN ERROR</b>	<b>313</b>
Introduction	313
Batches and Batch Records	314
Good Documentation Design for Batch Records	316
Potential Problems with Batch Records	317
Improving and Tracking the Batch Record Process	323
Designing Batch Record Processes	327
Electronic Batch Records	330
Reviewing Batch Records	336
There Is More to Quality than Batch Records	339
Distribution Records	340
Conclusion	340
References	341

<b>12 LABELS AND PACKAGING: ERRORS AND MISAPPLICATION</b>	<b>345</b>
Introduction	345
Good Manufacturing Practice and Labels	348
Good Manufacturing Practice and Packaging	352
Types of Errors with Labeling and Packaging	353
Risk to Patients from Label Errors	356
Recalls	357
Reasons for Errors	359
Detecting Errors	361
Addressing Errors and Best Practices	361
Auditing	375

Counterfeit Products	376
Summary	378
References	379

### **13 AVOIDING ERRORS WITH THE BATCH RELEASE PROCESS 385**

Introduction	385
Batch Release	386
Recalls and the Batch Release Process	387
Global Differences for Batch Release	392
Batch Documentation	395
Batch Release Processes	397
Parametric Release	400
Electronic Records	401
Process Analytical Technology	402
Distribution	403
Customer Complaints	405
Outsourcing and Batch Release	405
Summary	406
References	407

### **14 DATA INTEGRITY FAILURES AND THE RECALL OF MEDICINES 411**

Introduction	411
Data Integrity	412
Challenges in Meeting Data Integrity Requirements	416
Auditing Organizations for Data Integrity	419
Data and Data Governance	420
Regulatory Perspectives	422
Risks	426
Risk Assessment	428
Data Integrity and Recalls	430
Data and Computerized Systems	436
Cybersecurity	438
Summary	439
References	439

<b>15 EFFECTIVE GOOD DISTRIBUTION PRACTICE TO AVOID RECALLS</b>	<b>443</b>
Introduction	443
Quality Management Systems and GDP	445
Falsified Medicines	448
QMS Elements for Effective GDP	452
Constituent Parts of the GDP Process	459
Examples of GDP Regulatory Issues	472
Quality Assessments of GDP	477
Summary	480
References	481
<b>16 ESSENTIAL REQUIREMENTS FOR A GLOBAL RECALL STRATEGY</b>	<b>487</b>
Introduction	487
Stages of Recall	489
Notification of a Recall	491
Actions in Response to a Complaint	491
Classifying Recalls	496
Recall Strategy	498
Reconciliation	503
Reviewing Manufacturing Data in Response	503
Interim and Post-Recall Responsibilities	504
Evaluation of the Recall	505
Summary of the Recall Process	505
Recommencing Supply of a Recalled Product	506
Role of Healthcare Professionals	507
Summary	508
References	512
<b>17 ANATOMY OF A RECALL STANDARD OPERATING PROCEDURE</b>	<b>515</b>
Introduction	515
Recall Procedure	516
Reviewing the Recall Procedure	525
Simulated Recall	528
Vendor-Initiated Recall	529
Wholesalers	531
Summary	534
References	535

<b>18 PUTTING THE REPORT TOGETHER: HOW TO RESPOND EFFECTIVELY TO REGULATORS AND CUSTOMERS</b>	<b>537</b>
Introduction	537
Responding to Regulators: Dealing with Recalls	538
Responding to Customers	552
Internal Training	555
Summary	556
References	557
<b>19 PHARMACEUTICAL ADVERTISING AND MARKETING IN THE DIGITAL AGE</b>	<b>559</b>
Introduction	559
Pharmaceuticals in the Digital Age	560
Digital Marketing and Advertising	561
Regulation	571
Conclusion and Toward a Future Framework	572
References	574
<b>20 CONNECTING RECALLS AND THE GMP INSPECTION PROCESS</b>	<b>579</b>
Introduction	579
GMP Inspections	579
FDA and EU Inspections	581
Recall-Related Inspections	584
Inspection Preparation	586
Managing the Inspection	588
Inspection Format	592
Inspection Outcomes	592
Post-Inspection Activities	597
Conclusion	597
References	598
<b>21 SAFE DISPOSAL OF RECALLED AND UNWANTED MEDICINES</b>	<b>601</b>
Introduction	601
Impact on Antimicrobial Resistance	602

Environmental Concerns	605
Government Responsibilities	607
Pharmaceutical Organizations	608
Consumers	618
Pharmacies	619
Summary	622
References	623
<b>22 QUALITY METRICS—IMPROVING PERFORMANCE TO REDUCE RECALLS</b>	<b>627</b>
Introduction	627
What are Metrics?	628
Using Metrics	631
Reviewing Metrics	632
Weakness with Metrics	632
Setting Metrics	633
Evolution of Measures	634
Changing Metrics	635
Reviewing and Setting Quality Metrics	635
Examples of Metrics	640
Risk Management	642
Management and Culture	643
Summary	645
References	646
<b>23 AVOIDING RECALLS BY APPLYING RISK MANAGEMENT TO THE SUPPLY CHAIN</b>	<b>649</b>
Introduction	649
Supply Chain Risks	653
Summary	671
References	671
<b>24 SUPPLY CHAIN: AVOIDING RECALLS AND APPLYING TECHNOLOGIES TO SAFEGUARD THE MEDICINAL FLOW</b>	<b>675</b>
Introduction	675

Supply Chain	677
Global Concerns with Falsified Medicines	680
Regulatory Responses	681
Using New Technologies	691
Summary	701
References	702