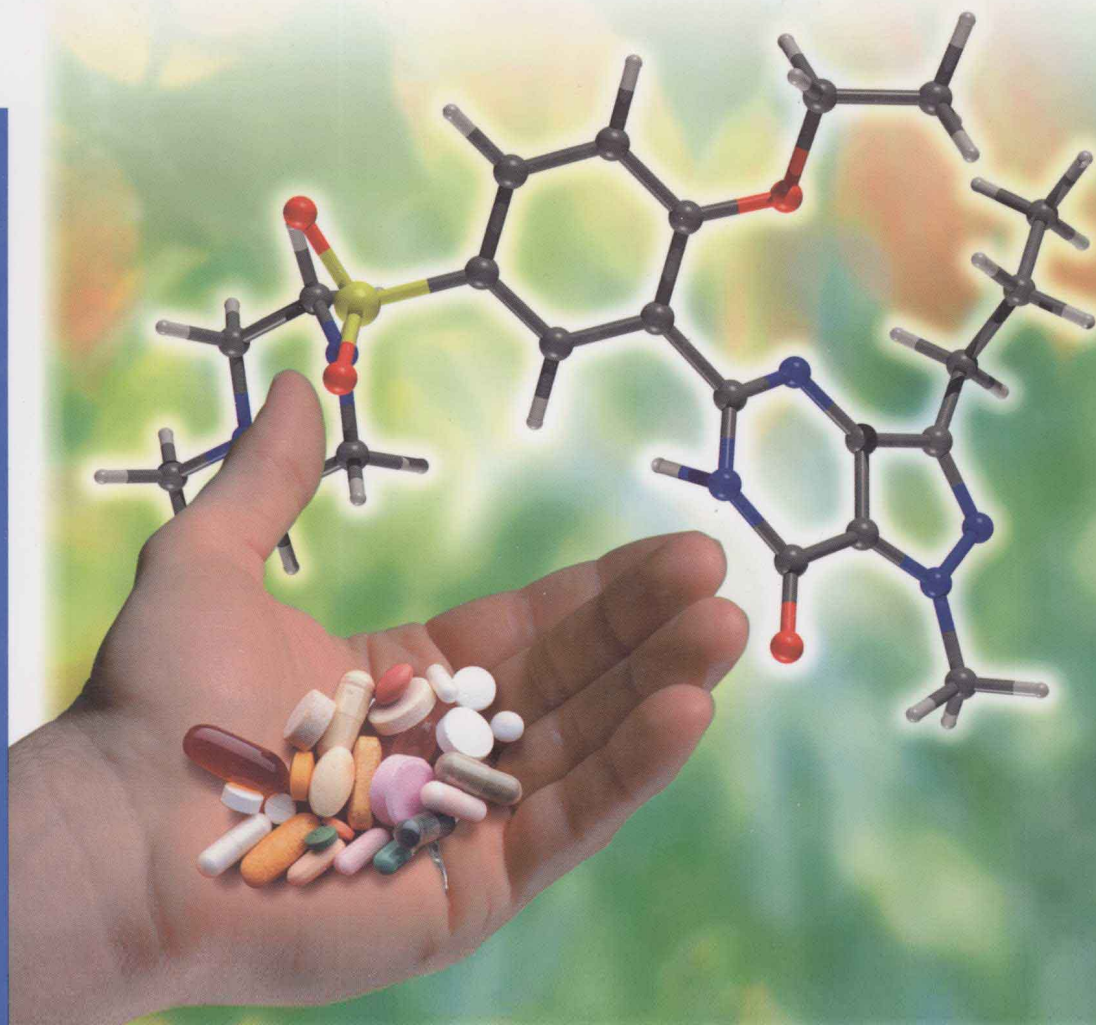


Edited by Peter J. Dunn, Andrew S. Wells,
and Michael T. Williams

 WILEY-VCH

Green Chemistry in the Pharmaceutical Industry



Green Chemistry in the Pharmaceutical Industry

*Edited by Peter J. Dunn, Andrew S. Wells, and
Michael T. Williams*



WILEY-
VCH

WILEY-VCH Verlag GmbH & Co. KGaA

Foreword

While we all recognize the value and benefits to mankind of the healing drugs that are used worldwide, we often take for granted how these precious materials are discovered and made. The expectations of modern society for improved safety, lower environmental impact, more sustainable practices, and lower energy use at a fair cost place tremendous demands and responsibility on us all, and the complex task of manufacturing pharmaceuticals has to balance current knowledge and the robustness and durability of the chemical and biological processes used with these regulatory pressures and escalating costs. Nevertheless, chemists and production engineers owe it to their profession and to future generations to adopt a charter which promotes the 'Green' agenda.

I therefore welcome this new text, which promotes improved and sustainable practices. It demonstrates clearly how through innovation, understanding, and commitment one can effect change and drive standards even higher. The chapters discuss all the relevant issues of the day as they relate to solvents, energy, new technologies, metrics, and lifecycle appreciation. The articles describing illustrative processes used by the major practitioners for producing worked-up pharmaceutical products amply demonstrate the attitude and advantages that can accrue by a more reflective and committed approach. Clean chemo-enzymatic processes alone, with continuous flow methods and improved optimization protocols, are beginning to make an impact and are certainly trends for the future. Our ability to better and more rapidly profile for impurities and evaluate alternative routes is leading to new opportunities and creating better understanding.

The future image of the industry and society's respect for it will hinge upon a clear demonstration of its belief in and stewardship of the principles of Green Chemistry. Indeed, there is nothing more worthy than our desire to improve our ability to meet healthcare needs for the betterment of everyone through sustainable practices.

Steven V. Ley
Cambridge, UK

List of Contributors

Joseph D. Armstrong III

Merck Research Laboratories
Department of Process Research
PO Box 2000
Rahway, NJ 07065
USA

Jaume Balsells

Merck Research Laboratories
Department of Process Research
PO Box 2000
Rahway, NJ 07065
USA

Rakeshwar Bandichhor

Center of Excellence, Research &
Development Integrated Product
Development
Dr. Reddy's Laboratories Ltd.
Survey Nos. 42, 45, 46 & 54
Bachupally
Qutubullapur
Ranga Reddy Dist 500072
Andhra Pradesh
India

Apurba Bhattacharya

Texas A&M University
Department of Chemistry
920 W. Santa Gertrudes
Kingsville, TX 78363
USA

John Blacker

University of Leeds
Institute of Process R + D
School of Chemistry
Woodhouse Lane
Leeds, LS2 9JT
UK

Jean Bléhaut

Groupe Novasep SAS
82, Boulevard de la Moselle-BP50
Pompey-54340
France

William A. Carole

Rowan University
Department of Chemical Engineering
Glassboro, NJ 08028
USA

Andrew Clausen

Amgen Inc.
Chemical Process R&D
One Kendall Square
Bldg 1000
Cambridge, MA02139
USA

David J.C. Constable

V.P. Energy, Environment, Safety and
Health Lockheed Martin
6801 Rockledge Drive
MP: CCT-246
Bethesda, MD 20817
USA

Vyvyann T. Coombe

AstraZeneca Gloal SHE
Brixham Environmental Laboratory
Freshwater Quarry
Brixham, Devon
TQ5 8BA
UK

Peter J. Dunn

Pfizer Global Research and
Development
Ramsgate Road
Sandwich
Kent
CT13 9NJ
UK

Trevor Grinter

Roystons
New Road
Rotherfield
East Sussex
TN6 3JS
UK

Karl B. Hansen

Amgen Inc.
Chemical Process R&D
One Kendall Square
Bldg 1000
Cambridge, MA02139
USA

Joel M. Hawkins

Pfizer Global R&D
Chemical R&D Department
MS 4073, Eastern Point Road
Groton, CT 06340
USA

Catherine E. Headley

University of Manchester
Business Relations Team
Oxford Road
Manchester, M13 9PL
UK

Richard K. Henderson

GlaxoSmithKline Plc
Park Road
Ware, Herts. SG12 0DP
UK

Kevin Hettenbach

Pfizer Global R&D
Chemical R&D Department
MS 4073, Eastern Point Road
Groton, CT 06340
USA

Sa V. Ho

Pfizer Global Biologics
700 Chesterfield Parkway BB3D
Chesterfield, MO 63017
USA

Yi Hsiao

Bristol Myers Squibb
NB50-358
One Squibb Drive
New Brunswick, NJ 08903
USA

Norihiro Ikemoto

Merck Research Laboratories
Department of Process Research
PO Box 2000
Rahway, NJ 07065
USA

Concepción Jiménez-González

GlaxoSmithKline Pharmaceuticals
Five Moore Drive
Research Triangle Park, NC 27709
USA

Patrick Kelleher

Pfizer Global Manufacturing
Process Development Centre
Loughbeg
Ireland

Hans Kierkels

DSM Pharma Chemicals
Department: DSM Innovative
Synthesis BV
P.O. Box 18
6160 MD Geleen
The Netherlands

Eric Lang

Groupe Novasep SAS
82, Boulevard de la Moselle-BP50
Pompey-54340
France

Olivier Ludemann-Hombourger

Lonza Braine SA
Chausée de Tubize 297
Braine-l'Alleud-1420
Belgium

Wiesław Majewski

Novasep Process SAS
81, Boulevard de la Moselle-BP50
Pompey-54340
France

Carlos Martinez

Pfizer Global R&D
Chemical R&D Department
MS 4073, Eastern Point Road
Groton, CT 06340
USA

Pia G. Mountford

Bristol Myers Squibb
777 Scudders Mill Road
Plainsboro, NJ 08536
USA

Sven Panke

ETH Zürich
Department of Biosystems Science
and Engineering
Mattenstrasse 26
4058 Basel
Switzerland

Lee Proctor

Phoenix Chemicals Ltd.
Croft Business Park
34 Thursby Road
Bromborough
Wirral CH62 3PW
UK

Mariano J. Savelski

Rowan University
Department of Chemical Engineering
Glassboro, NJ 08028
USA

Yasuhiro Sawai

Takeda Pharmaceutical Company Ltd.
Chemical Development Laboratories
17-85 Jusohonmachi 2-Chome
Yodogawa-ku
Osaka 532-8686
Japan

Martin Schürmann

DSM Pharma Chemicals
Department: DSM Innovative
Synthesis BV
P.O. Box 18
6160 MD Geleen
The Netherlands

Roger Sheldon

Delft University of Technology
Julianalaan 136
2628 BL Delft
The Netherlands

C. Stewart Slater

Rowan University
Department of Chemical Engineering
Glassboro, NJ 08028
USA

David Taylor

WCA Environment Ltd
Brunel House
Volunteer Way
Farington
Oxfordshire SN7 7YR
UK

Eric Valéry

Novasep Process SAS
81, Boulevard de la Moselle
54340 Pompey
France

Andrew S. Wells

Astra Zeneca
Process Research & Development
Bakewell Road
Loughborough
LE11 5RH
United Kingdom

Michael T. Williams

CMC Consultant
133, London Road
Deal
Kent CT14 9TY
UK

Michael Wolberg

DSM Pharma Chemicals-ResCom
DPC Regensburg GmbH
Donaustauer Str. 378
93055 Regensburg
Germany

Feng Xu

Merck Research Laboratories
Department of Process Research
PO Box 2000
Rahway, NJ 07065
USA

Mitsuhisa Yamano

Takeda Pharmaceutical Company Ltd.
Chemical Development Laboratories
17-85 Jusohonmachi 2-Chome
Yodogawa-ku
Osaka 532-8686
Japan

Related Titles

Blaser, H.-U., Federsel, H.-J. (eds.)

**Asymmetric Catalysis on
Industrial Scale**
Challenges, Approaches and Solutions

Second Edition

2010

ISBN: 978-3-527-32489-7

Series Editor: Anastas, P.
Volume Editor: Crabtree, R. H.

**Handbook of Green
Chemistry – Green Catalysis**

3-Volume Set

2009

ISBN: 978-3-527-31577-2

Series Editor: Anastas, P.
Volume Editors: Leitner, W., Jessop, P. G.,
Li, C.-J., Wasserscheid, P., Stark, A.

**Handbook of Green
Chemistry – Green Solvents**

3-Volume Set

2010

ISBN: 978-3-527-31574-1

Tanaka, K.

**Solvent-free Organic
Synthesis**

2009

ISBN: 978-3-527-32264-0

Wasserscheid, P., Welton, T. (eds.)

Ionic Liquids in Synthesis

2008

ISBN: 978-3-527-31239-9

Sheldon, R. A., Arends, I., Hanefeld, U.

**Green Chemistry and
Catalysis**

2007

ISBN: 978-3-527-30715-9

Loupy, A. (ed.)

**Microwaves in Organic
Synthesis**

2006

ISBN: 978-3-527-31452-2

Kemmere, M. F., Meyer, T. (eds.)

**Supercritical Carbon Dioxide
in Polymer Reaction Engineering**

2005

ISBN: 978-3-527-31092-0

Contents

Foreword	V
List of Contributors	XV

1	Introduction to Green Chemistry, Organic Synthesis and Pharmaceuticals	1
	<i>Roger Sheldon</i>	
1.1	The Development of Organic Synthesis	1
1.2	The Environmental Factor	4
1.3	The Role of Catalysis	7
1.4	Green Chemistry: Benign by Design	10
1.5	Ibuprofen Manufacture	11
1.6	The Question of Solvents: Alternative Reaction Media	11
1.7	Biocatalysis: Green Chemistry Meets White Biotechnology	15
1.8	Conclusions and Prospects	18
	References	18
2	Green Chemistry Metrics	21
	<i>Richard K. Henderson, David J.C. Constable, and Concepción Jiménez-González</i>	
2.1	Introduction	21
2.2	Measuring Resource Usage	24
2.2.1	Focus on Solvents	26
2.2.2	Focus on Renewables	28
2.2.3	Cleaning and Maintenance	30
2.3	Life Cycle Assessment (LCA)	30
2.4	Measuring Chemistry and Process Efficiency	34
2.5	Measuring Process Parameters and Emissions	35
2.6	Real Time Analysis	36
2.6.1	Scalability	36
2.6.2	Controllability	37
2.6.3	Robustness	38

2.7	Operational Efficiency	38
2.8	Measuring Energy	39
2.9	Measuring the Toxicity of All the Substrates	40
2.9.1	Occupational Exposure Hazard and Risk	40
2.10	Measuring Degradation Potential	43
2.11	Measuring the Inherent Safety or Lack of Inherent Safety	45
2.12	Conclusions	45
	References	46

3 Solvent Use and Waste Issues 49

C. Stewart Slater, Mariano J. Savelski, William A. Carole, and David J.C. Constable

3.1	Introduction to Solvent Use and Waste Issues	49
3.1.1	Introduction	49
3.1.2	Process Efficiency Metrics	50
3.1.3	Impact Beyond the Plant – Solvent Life Cycle	51
3.1.4	Solvent Utilization	52
3.1.5	Solvents Used in the Pharmaceutical Industry	54
3.1.6	Solvent Use in Process Development	57
3.1.7	Consequences of Excessive Solvent Use	59
3.1.8	Waste Management Practices in the United States	61
3.2	Solvent and Process Greenness Scoring and Selection Tools	64
3.2.1	Review of Solvent and Process Scoring Methods	64
3.2.1.1	Greenness Assessment of Pharmaceutical Processes and Technology	64
3.2.1.2	Greenness Scoring Methods for Solvents	66
3.2.1.3	The GSK Solvent Selection Guide	68
3.2.1.4	The Rowan Solvent Greenness Index Method	70
3.3	Waste Minimization and Solvent Recovery	73
3.3.1	Minimizing Solvent Use	73
3.3.1.1	Batch versus Continuous Reactors	74
3.3.1.2	Biosynthetic Processes	74
3.3.1.3	Solid-State Chemistry	75
3.3.1.4	Telescoping	75
3.3.2	Recycling Solvents	76
3.3.2.1	Methods to Recover and Reuse Solvents	76
3.3.2.2	Issues with Solvent Recovery and Reuse	79
	Acknowledgments	80
	References	81

4 Environmental and Regulatory Aspects 83

David Taylor and Vyvyan T. Coombe

4.1	Historical Perspective	83
4.2	Pharmaceuticals in the Environment	84
4.2.1	Presence	84
4.2.2	Persistence	86
4.2.3	Bioaccumulation	86

4.2.4	Ecotoxicology	87
4.2.5	The Current State of the Science	90
4.3	Environmental Regulations	90
4.3.1	Product Regulations	91
4.3.2	Process Regulations	93
4.3.2.1	Chemicals Control	93
4.3.2.2	Integrated Pollution Control	95
4.3.3	Environmental Quality Regulations	97
4.4	A Look to the Future	98
	References	99
5	Synthesis of Sitagliptin, the Active Ingredient in Januvia® and Janumet®	101
	<i>Jaume Balsells, Yi Hsiao, Karl B. Hansen, Feng Xu, Norihiro Ikemoto, Andrew Clausen, and Joseph D. Armstrong III</i>	
5.1	Introduction	101
5.2	First-Generation Route	102
5.3	Sitagliptin through Diastereoselective Hydrogenation of an Enamine. The PGA Enamine-Ester Route	105
5.4	The Triazole Fragment	109
5.5	Direct Preparation of β -Keto Amides	112
5.6	Second-Generation Chiral Auxiliary Route. The PGA Enamine-amide Route	115
5.7	The Asymmetric Hydrogenation Route	116
5.8	Purification and Isolation of Sitagliptin (Pharmaceutical Form)	122
5.9	The Final Manufacturing Route	123
	Acknowledgments	125
	References	125
6	The Development of Short, Efficient, Economic, and Sustainable Chemoenzymatic Processes for Statin Side Chains	127
	<i>Martin Schürmann, Michael Wolberg, Sven Panke, and Hans Kierkels</i>	
6.1	Introduction: Biocatalysis	127
6.2	The Relevance of Statins	128
6.3	Biocatalytic Routes to Statin Side Chains	129
6.4	2-Deoxy-D-Ribose 5-Phosphate Aldolase (DERA)-Based Routes to Statin Intermediates	131
6.4.1	Chemical Transformations of the DERA Product Toward Statins	131
6.4.2	Optimization and Scale-Up of the DERA Reaction	133
6.4.2.1	Deactivation of DERA	136
6.4.2.2	Enzyme Kinetics	136
6.4.2.3	Conclusions and Outlook	138
6.4.3	Improvement of DERA by Directed Evolution	139
6.5	Conclusions	142
	Acknowledgments	143
	References	143

7	The Taxol® Story—Development of a Green Synthesis via Plant Cell Fermentation	145
	<i>Pia G. Mountford</i>	
7.1	Introduction	145
7.2	Discovery and Early Development	146
7.3	From Extraction of Taxol® from Pacific Yew Tree Bark to Semi-Synthetic Taxol®	147
7.4	Taxol® from Plant Cell Fermentation	150
7.5	Comparison of Semi-Synthetic versus PCF Taxol® Processes: The Environmental Impact	154
7.5.1	Semi-Synthetic Process	154
7.5.1.1	<i>Taxus Baccata</i> Plantations	154
7.5.1.2	Biomass Waste from Isolating 10-DAB	154
7.5.1.3	Chemical Synthesis	154
7.5.2	Plant Cell Fermentation Process	155
7.5.2.1	Plant Cell Fermentation	155
7.5.2.2	Crude Paclitaxel Isolation	155
7.5.2.3	Chromatographic Purification of Crude Paclitaxel	155
7.6	Comparison of Semi-Synthetic versus PCF Taxol®: Green Chemistry Principles	156
7.6.1	Reagent Use	156
7.6.2	Solvent Use	156
7.6.3	Energy and Handling Implications	157
7.7	Final Words	158
	Acknowledgments	158
	References	159
8	The Development of a Green, Energy Efficient, Chemoenzymatic Manufacturing Process for Pregabalin	161
	<i>Peter J. Dunn, Kevin Hettenbach, Patrick Kelleher, and Carlos A. Martinez</i>	
8.1	Introduction	161
8.2	Process Routes to Pregabalin	161
8.2.1	Classical Resolution Route	162
8.2.2	Asymmetric Hydrogenation Route to Pregabalin	163
8.2.3	Non-Pfizer/Parke-Davis Routes to Pregabalin	165
8.3	Biocatalytic Route to Pregabalin	165
8.3.1	Enzyme Screening, Optimization, and Recycling of Undesired Enantiomer	166
8.3.2	Subsequent Chemical Steps to Pregabalin	170
8.4	Green Chemistry Considerations	171
8.4.1	Material Usage	172
8.4.2	Energy Usage	173
8.5	Conclusions	176
	Acknowledgments	176
	References	176

9	Green Processes for Peptide Mimetic Diabetic Drugs	179
	<i>Yasuhiro Sawai and Mitsuhiro Yamano</i>	
9.1	Introduction	179
9.2	Green Chemistry Considerations in Peptide-like API Manufacture	179
9.3	Purification Process to Manufacture Amorphous API	182
9.3.1	Cation Exchange Chromatography	184
9.3.2	Extraction	186
9.4	Preparation of Unnatural Amino Acids	187
9.4.1	Crystallization-Induced Diastereomer Transformation	188
9.4.2	Optical Resolution via Diastereomeric Salt Formation	191
9.5	Summary	193
	Acknowledgments	193
	References	193
10	The Development of an Environmentally Sustainable Process for Radafaxine	197
	<i>Trevor Grinter</i>	
10.1	Introduction	197
10.1.1	Background	198
10.2	Chemistry Process and the Dynamic Kinetic Resolution (DKR)	199
10.2.1	General Description of the Chemistry	201
10.2.2	Route 2	202
10.2.3	Route 3	202
10.3	Multicolumn Chromatography—Development of Route 4	206
10.4	Environmental Assessment	212
10.4.1	Life Cycle Metrics	214
10.4.2	Eco-Efficiency Benefits	216
10.5	Summary	217
	Acknowledgments	218
	References	218
11	Continuous Processing in the Pharmaceutical Industry	221
	<i>Lee Proctor, Peter J. Dunn, Joel M. Hawkins, Andrew S. Wells, and Michael T. Williams</i>	
11.1	Introduction	221
11.2	Continuous Production of a Key Intermediate for Atorvastatin	223
11.2.1	Laboratory Screening	223
11.2.2	Reaction Scale-up	225
11.2.3	Product Isolation and Waste Treatment	226
11.3	Continuous Process to Prepare Celecoxib	228
11.4	Continuous Oxidation of Alcohols to Aldehydes	232
11.5	Continuous Production of Bromonitromethane	234
11.6	Continuous Production and Use of Diazomethane	235
11.7	A Snapshot of Some Further Continuous Processes Used in the Preparation of Pharmaceutical Agents	238

11.8	Conclusions	241
	Acknowledgments	241
	References	241
12	Preparative and Industrial Scale Chromatography: Green and Integrated Processes	243
	<i>Eric Lang, Eric Valéry, Olivier Ludemann-Hombourger, Wieslaw Majewski, and Jean Bléhaut</i>	
12.1	Introduction	243
12.2	Basic Principles of Chromatography	244
12.3	Process Optimization to Reduce Eluent Consumption	246
12.3.1	Batch Processes	247
12.3.1.1	Increasing Injected Amount	247
12.3.1.2	Reducing Cycle Time with Stacked Injections (Case of Isocratic Eluents)	247
12.3.1.3	Reducing Cycle Time Using Gradients	248
12.3.2	Continuous Processes	249
12.4	Use of a Green Solvent: Supercritical Carbon Dioxide	252
12.5	Solvent Recycling Technologies	255
12.5.1	Recycling Devices for Isocratic Chromatography	256
12.5.2	Recycling Devices for Gradient Chromatography	257
12.5.3	Recycling Devices for Supercritical Carbon Dioxide	258
12.6	Application Examples	259
12.6.1	Optimization of a Batch Process	259
12.6.2	Selection of the Chromatographic Conditions	259
12.6.3	Scale-up on a Pilot SFC Unit	261
12.6.4	Optimization of an MCC Process	264
12.7	Conclusion: An Environmentally Friendly Solution for Each Separation	264
	Acknowledgment	266
	References	266
13	Dynamic Resolution of Chiral Amine Pharmaceuticals: Turning Waste Isomers into Useful Product	269
	<i>John Blacker and Catherine E. Headley</i>	
13.1	Background	269
13.1.1	Chiral Amine Resolution Processes	269
13.1.2	Homochiral Amine Racemization Processes	272
13.2	Integration of Chiral Amine Resolution and Racemization	276
13.2.1	Dynamic Resolution Processes	276
13.3	Case Studies	279
13.3.1	Asymmetric Transformation of (S)-7-Methoxy-1,2,3,4-tetrahydronaphthalen-2-amine	279
13.3.2	Asymmetric Transformation of (R)-1-tert-butyloxycarbonyl-3-aminopyrrolidine	281

13.3.3	Sertraline	282
13.4	Conclusions	286
	Acknowledgments	287
	References	287
14	Green Technologies in the Generic Pharmaceutical Industry	289
	<i>Apurba Bhattacharya and Rakeshwar Bandichhor</i>	
14.1	Introduction	289
14.2	'Waste': Definition and Remedy	292
14.3	Amidation	293
14.3.1	Carbodiimide and Acid Chloride Mediated Transformation	293
14.3.2	Metal-Catalyzed Oxidative Amide Synthesis	294
14.3.2.1	Copper-Catalyzed Amide Synthesis	294
14.3.2.2	Palladium-Catalyzed Amide Synthesis	294
14.3.2.3	Ruthenium-Catalyzed Amide Synthesis	295
14.3.3	N-Heterocyclic Carbene (NHC-Catalyzed Amidation)	296
14.3.4	Amidation Catalyzed by Boric Acid Derivatives	297
14.4	Synthesis of Galanthamine	298
14.5	Synthesis of Solefinacin	298
14.5.1	Precedented Approach	298
14.5.2	A Greener Approach	299
14.6	Synthesis of Levetiracetam	300
14.6.1	Established Approach	300
14.6.2	A More Eco-Friendly Synthesis	301
14.7	Synthesis of a Finasteride Intermediate	301
14.7.1	The Classical Approach	301
14.7.2	Problems with the Existing Synthesis	302
14.7.3	A Catalytic Approach	302
14.8	Bromination	304
14.8.1	Current Zafirlukast Bromination Method	304
14.8.2	Environmental Burden	305
14.8.3	Waste-Minimized Bromination	305
14.9	Sulfoxidation in the Synthesis of Rabeprazole	306
14.9.1	The Traditional Approach	306
14.9.2	A Greener Approach	307
14.10	Conclusions	307
	Acknowledgments	308
	References	308
15	Environmental Considerations in Biologics Manufacture	311
	<i>Sa V. Ho</i>	
15.1	Introduction	311
15.2	Therapeutic Biologics	312
15.2.1	Types of Therapeutic Biologics	312
15.2.2	General Features of Therapeutic Protein Manufacture	314

15.3	Environmental Impact Considerations	317
15.3.1	Microbially Produced Proteins	317
15.3.1.1	Insulin Production Process	317
15.3.1.2	Production of a Typical Medium-Sized Protein	318
15.3.1.3	Highly Efficient Protein Manufacturing Process	319
15.3.2	Monoclonal Antibodies and Mammalian Cell Culture Processes	321
15.3.2.1	Typical-to-Optimized Manufacturing Process for mAbs	322
15.3.2.2	Projected 'Intensified' Large-Scale Monoclonal Antibody Manufacturing Process	322
15.4	Overall Comparison	324
15.5	Environmental Indices for Therapeutic Protein Manufacture	325
15.6	Technologies with Potential Environmental Impact	327
15.7	Single-Use Biologics Manufacture	328
15.8	Summary	329
	Acknowledgments	330
	References	330
16	Future Trends for Green Chemistry in the Pharmaceutical Industry	333
	<i>Peter J. Dunn, Andrew S. Wells, and Michael T. Williams</i>	
16.1	Introduction	333
16.2	Waste Minimization in Drug Discovery	334
16.3	Greener Synthetic Methods in Primary Manufacturing	338
16.3.1	Synthesis Design and Execution	338
16.3.2	Reduction and Oxidation	339
16.3.3	C–C Bond Formation	340
16.3.4	Heteroatom Alkylation and Acylation	341
16.3.5	Biocatalysis Now and Into the Future	341
16.3.6	Application of Technology	343
16.4	Alternative Solvents in the Pharmaceutical Industry	344
16.4.1	Water	345
16.4.2	Ionic Liquids (ILs)	345
16.4.3	Fluorous Solvents	346
16.4.4	Supercritical CO ₂ (SC-CO ₂) and Gas-Expanded Liquids (GXL)	346
16.4.5	Molecular Solvents from Renewable Sources	347
16.4.6	Solid-Phase Reactions	348
16.4.7	The Work-Up	348
16.4.8	Obstacles to Change	349
16.5	Green Chemistry in Secondary Pharmaceutical Operations	349
16.6	Global Cooperation in Green Chemistry	351
16.6.1	The Pharmaceutical Roundtable	351
16.6.2	Recognition	352
16.6.3	The Global Impact	352
16.7	Conclusions	353
	References	353
	Index	357

1

Introduction to Green Chemistry, Organic Synthesis and Pharmaceuticals

Roger Sheldon

1.1

The Development of Organic Synthesis

The well-being of modern society is unimaginable without the myriad products of industrial organic synthesis. Our quality of life is strongly dependent on, *inter alia*, the products of the pharmaceutical industry, such as antibiotics for combating disease and analgesics or anti-inflammatory drugs for relieving pain. The origins of this industry date back to 1935, when Domagk discovered the antibacterial properties of the red dye, prontosil, the prototype of a range of sulfa drugs that quickly found their way into medical practice.

The history of organic synthesis is generally traced back to Wöhler's synthesis of the natural product urea from ammonium isocyanate in 1828. This laid to rest the *vis vitalis* (vital force) theory, which maintained that a substance produced by a living organism could not be produced synthetically. The discovery had monumental significance, because it showed that, in principle, all organic compounds are amenable to synthesis in the laboratory.

The next landmark in the development of organic synthesis was the preparation of the first synthetic dye, mauveine (aniline purple) by Perkin in 1856, generally regarded as the first industrial organic synthesis. It is also a remarkable example of serendipity. Perkin was trying to synthesize the anti-malarial drug quinine by oxidation of *N*-allyl toluidine with potassium dichromate. This noble but naïve attempt, bearing in mind that only the molecular formula of quinine ($C_{20}H_{24}N_2O_2$) was known at the time, was doomed to fail. In subsequent experiments with aniline, fortuitously contaminated with toluidines, Perkin obtained a low yield of a purple-colored product. Apparently, the young Perkin was not only a good chemist but also a good businessman, and he quickly recognized the commercial potential of his finding. The rapid development of the product, and the process to make it, culminated in the commercialization of mauveine, which replaced the natural dye, Tyrian purple. At the time of Perkin's discovery Tyrian purple, which was extracted from a species of Mediterranean snail, cost more per kg than gold.