Process Chemistry in the Pharmaceutical Industry

Volume 2

Challenges in an Ever Changing Climate

Edited by
Kumar Gadamassetti
Tamim Braish

CRC Press
Taylor & Francis Group
Process Chemistry in the Pharmaceutical Industry

Volume 2

Challenges in an Ever Changing Climate
Process Chemistry in the Pharmaceutical Industry

Volume 2
Challenges in an Ever Changing Climate

Edited by
Kumar Gadamsasetti
Tamim Braish
Dedication

KG would like to dedicate this book to his wife Vidya, daughter Stuthi, and son Pratik.

TFB would like to dedicate this book to his wife Teresa and son Fehme.
# Table of Contents

**Chapter 1**  
Process Chemistry in the Pharmaceutical Industry: Challenges in an Ever Changing Climate—An Overview.................................................................1  
*Kumar Gadamasetti*

**Chapter 2**  
Emerging Trends in Process Chemistry .................................................................13  
*Tamim F. Braish, Fons De Knaep, and Kumar Gadamasetti*

**Chapter 3**  
Varenicline: Discovery Synthesis and Process Chemistry Developments...................23  
*Jotham W. Coe, Harry A. Watson Jr., and Robert A. Singer*

**Chapter 4**  
The SUTENT® Story .......................................................................................................49  
*Rajappa Vaidyanathan*

**Chapter 5**  
An Efficient and Scalable Process for the Preparation of a Potent MC4 Receptor Agonist .................................................................................................................65  
*Cécile Savarin, John Chung, Jerry A. Murry, Raymond J. Cvetovich, Chris McWilliams, Dave Hughes, Joseph Amato, Geneviève Boice, Karen Conrad, Edward Corley, Robert Reamer, and Lisa DiMichele*

**Chapter 6**  
Process Research and Development of LY414197, a 5HT_{3B} Antagonist ................89  
*Alfio Borghese and Alain Merschaert*

**Chapter 7**  
To Overcome the Hurdles: Coping with the Synthesis of Robalzotan, a Complex Chroman Antidepressant.............................................................111  
*Hans-Jürgen Federsel and Anders Sveno*

**Chapter 8**  
Chiral Amine Synthesis—Strategies, Examples, and Limitations.................................137  
*Thomas C. Nugent*
Chapter 9
Unnatural Amino Acids
David J. Ager

Chapter 10
The Chemical Development of a Potential Manufacturing Route to the Endothelin Antagonists UK-350,926 and UK-349,862
Christopher P. Ashcroft, Stephen Challenger, Andrew M. Derrick, Yousef Hajikarimian, and Nicholas M. Thomson

Chapter 11
Cefovecin Sodium: A Single-Dose Long-Acting Antibiotic for Use in Companion Animals
Timothy Norris

Chapter 12
The Lithium–Halogen Exchange Reaction in Process Chemistry
William F. Bailey and Terry L. Rathman

Chapter 13
Oxetan-3-one: Chemistry and Synthesis
Georg Wuitschik, Erick M. Carreira, Mark Rogers-Evans, and Klaus Müller

Chapter 14
Well-Defined (NHC)Pd (II) Complexes and Their Use in C–C and C–N Bond-Forming Reactions
Oscar Navarro and Steven P. Nolan

Chapter 15
Toward Truly Efficient Organic Reactions in Water
Chikako Ogawa and Shu Kobayashi

Chapter 16
The Chemical Development of the Commercial Route to Sildenafil Citrate
Peter J. Dunn

Chapter 17
Stereoselective Enzymatic Synthesis of Intermediates Used for Antihypertensive, Antiinfective, and Anticancer Compounds
Ronald L. Hanson

Chapter 18
Designing Robust Crystallization Processes for Active Pharmaceutical Ingredients—From Art to Science
Dierk Wieckhusen
## Table of Contents

**Chapter 19**  
*In Situ Mid-Infrared Spectroscopy for Process Development* ......................................................313  
*David A. Conlon, Bill Izzo, J. Christopher McWilliams, Robert A. Reamer, Feng Xu, and Paul Collins*

**Chapter 20**  
Optimizing an Asymmetric Homologation in a Tandem Asymmetric Homologation–Homoaldol Process ...............................................................................................317  
*J. Christopher McWilliams and Robert A. Reamer*

**Chapter 21**  
Development of Efficient One-Pot Process in the Synthesis of Sitagliptin: Application of Online-Infrared for Kinetic Studies to Probe the Reaction Mechanism..............333  
*Feng Xu*

**Chapter 22**  
Mid-Infrared Monitoring Applications during Development of the Vinyl Ether Formation Step in the Preparation of Aprepitant (Emend™) ...............................................349  
*David A. Conlon, Bill Izzo, and Paul Collins*

**Chapter 23**  
Process Analytical Technology in the Manufacture of Bulk Active Pharmaceuticals—Promise, Practice, and Challenges ..........................................................361  
*C.A. Mojica, L. St. Pierre-Berry, and F. Sistare*

**Chapter 24**  
PEGylation of Biological Macromolecules...................................................................................383  
*John J. Buckley, Rory F. Finn, Jianming Mo, Laura A. Bass, and Sa V. Ho*

**Chapter 25**  
Microwave Technology in Process Optimization..........................................................................403  
*Farah Mavandadi*

**Chapter 26**  
Process Development Considerations for Therapeutic Monoclonal Antibodies in Mammalian Cell Culture ..........................................................427  
*Susan Casnocha, Ronald Fedechko, Paul Mensah, John Mott, and Sandeep Nema*

**Chapter 27**  
Reaction Progress Kinetic Analysis: A Powerful Methodology for Streamlining Pharmaceutical Reaction Steps ..................................................................................455  
*Natalia Zotova, Suju P. Mathew, Hiroshi Iwamura, and Donna G. Blackmond*

**Chapter 28**  
Trends in Outsourcing....................................................................................................................465  
*John Lu and Ichiro Shinkai*
Chapter 29
Sourcing Pharmaceutical Products in China and India.................................................................471
David Robins and Steve Hannon

Index...............................................................................................................................................481
Preface

The pharmaceutical industry is committed to finding new ways and new medicines to alleviate the burden of disease and come up with cures to improve human life. Advancements in science and growth in technology are leading to personalized medicine that may someday be the norm rather than the exception. Symptoms may be forecasted immediately and treatment may be instantaneous to ultimately stop the progression of disease and lead to better life. For now, a paradigm shift in therapeutics from small molecules to biologics and macromolecules has become prominent toward the end of the last millennium, and this change is poised to remain and grow.

The first volume of this series has gained enormous respect and popularity in both the pharmaceutical and academic arenas. The theme, Process Chemistry in the Pharmaceutical Industry, led one of us (Gadamasetti) to work on a global forum to set the stage for key personnel from the pharmaceutical industry, academia, and regulatory agencies to gather to discuss the topics related to active pharmaceutical ingredients (APIs) and find solutions in chemistry, morphology, engineering, and regulatory compliance. With the help of the American Chemical Society (ACS), one of us (Gadamasetti) led the ACS ProSpectives, “Process Chemistry in the Pharmaceutical Industry,” as the chairman (2002–2004). During the meetings and on several occasions over the years, we have had numerous opportunities to discuss the burning issues and the need for a second volume. Even though the first volume addressed many of these issues with real-life examples, the second volume became absolutely necessary, as the pharmaceutical industry has been faced with a magnitude of change never seen before. It is an evolution in an industry known for its stability. Small molecule therapeutics are no longer the only drugs that companies can develop, and in many cases, existing therapies are not adequate. New medicines are needed, and quickly. How can we develop medicines faster and cheaper without jeopardizing patient safety?

The purpose of this book is to highlight the importance of an area of research in the pharmaceutical industry known as process research and development and the challenges ahead. In the pharmaceutical industry, the medicinal chemist is faced with the daunting task of finding the next drug buster. This is by far the toughest job, because many medicinal chemists could work all their lives synthesizing molecules that may never make it to the market.

Drug candidates progress through development slowly, requiring 9 to 12 years before reaching the patient. What stems as an idea in the lab could become a reality, after agonizing preclinical and clinical investments, benefiting patients worldwide, which makes the journey extremely rewarding but also enormously expensive.

The process chemist must develop a commercial route for a drug candidate that addresses cost issues, environmental concerns, atom economy, and ease of synthesis, and with the specified quality attributes that will ensure patient safety during development and post-launch, underscoring the importance of process research and development disciplines in the industry.

We sincerely believe and hope that the subject material of this current volume will reach a wider array of readers and will help them understand and apply the knowledge in teaching and in solving problems at work.

Kumar Gadamasetti
Tamim Braish
Acknowledgments

We would like to thank all of the contributors to this volume for their hard work, contributions, and most importantly their patience. We want to thank the reviewers as guardians of the science for their critical feedback, their constructive criticism, and their invaluable effort that helped shape the book.

We also want to thank colleagues within the pharmaceutical industry for their encouragement and ideas on what they thought would be a good contribution to the book that made the volume an enjoyable project and a great addition to the literature.

Additionally, we are indebted to many people who provided support and mentorship: Steve Ley (Cambridge University), Mauaricio Futran (Bristol-Myers Squibb), and Trevor Laird (Scientific Update) for their suggestions and foreword; Philip Fuchs (Purdue University) and Victor Snieckus (Queens University) for their support and guidance; Nancy Jacoby for her assistance in reviewing several manuscripts. Colleagues from Pfizer: Frank Urban, Tom Crawford, Sarah Kelly, Ed Kobeliski, Roger Nosal, Jodi Gaynor, Stephane Caron, Lynne Handanyan, Jeff Blumenstein, and former colleagues (of KG) from Bristol-Myers Squibb for their critical feedback and support.

We thank the staff at Taylor and Francis for their outstanding efforts and support especially for last minute changes and additions.

Kumar & Tamim
The Editors

**Kumar Gadamasetti** is the founder and president of Delphian Pharmaceuticals, a cancer therapy start-up [2003] company, located in the San Francisco Bay area. Previously he held positions at Bristol Myers-Squibb Company, New Brunswick, New Jersey, as a senior research investigator in the Process Research Group and at Amgen, Thousand Oaks, California, as the head of the Process Research and Development Department. At Bristol Myers-Squibb, he worked on syntheses of anticancer drug taxol (Paclitaxel™) and monoclonal antibody drug conjugates, and at Amgen, he directed the Process Research and Development Group to advance small molecules in the areas of calcimimetics and the cardiovascular and central nervous systems, and supported other drug discovery programs. Prior to starting Delphian Pharmaceuticals, he was the chief operating officer of X-Mine, a bioinformatics company (South San Francisco, California), and senior director of chemistry research and development at Discovery Partners International Inc., located in South San Francisco. A winner of a Presidential Award at Bristol Myers-Squibb, Gadamasetti edited the first volume, entitled *Process Chemistry in the Pharmaceutical Industry* (1999). He has authored several papers and U.S. patents. He was the founder and chairman of the American Chemical Society’s ProSpectives, “Process Chemistry in the Pharmaceutical Industry” (2002–2004). Currently he serves as an editorial board member of the American Chemical Society journal, *Organic Process Research and Development*.

Gadamasetti has been a visiting professor at Catholic University of Louvain, Louvain-la-Neuve, Belgium (2000), and a visiting scholar at Humboldt University, Berlin, Germany (2005). He obtained his Ph.D. degree in 1987 from the University of Vermont, Burlington (Research Advisor: Martin Kuehne). He conducted his postdoctoral studies at University of Virginia, and Virginia Polytechnic Institute and State University, Blacksburg, before joining Bristol Myers-Squibb in 1991. He obtained his B.S. and M.S. from Osmania University, Hyderabad, India.

**Tamim Braish** started his career as a bench chemist in the process group at Pfizer in Groton, Connecticut, working in the area of quinolone antibacterials where he developed several commercial routes to drug candidates currently in production. He became a manager in 1997 in charge of the preparations laboratory, and was involved with governance at the project and the portfolio levels, and in 2003 he became a senior director responsible for the Full Development Group within the Chemical Research and Development Group at Pfizer. He serves on the editorial board of the *Organic Process Research and Development* journal and is the author of many publications and patents. His interests span both the synthetic chemistry arena as well as the regulatory arena. Braish was born in Lebanon and grew up in Indiana. He earned a B.S. degree in chemistry from Indiana University–Purdue University, Fort Wayne, and a Ph.D. from Purdue University in 1986 with Professor Philip Fuchs on the synthesis of natural products.
Contributors

David J. Ager  
DSM, PMB 150  
9650 Strickland Road Suite 103  
Raleigh, North Carolina 27615, USA  
e-mail: david.ager@dsm.com

Joseph Amato  
Department of Process Research  
Merck Research Laboratories  
P.O. Box 2000  
Rahway, NJ 07065 USA

Christopher P. Ashcroft  
Chemical Research and Development  
Pfizer Global Research and Development  
Sandwich, CT13 9NJ, Kent, UK  
e-mail: christopher.ashcroft@pfizer.com

William F. Bailey  
University of Connecticut  
Department of Chemistry  
Storrs, CT 06269-3060 USA  
e-mail: bailey@uconnvm.uconn.edu

Laura A. Bass  
Pfizer Global Biologics  
Pharmaceutical Sciences  
700 Chesterfield Village Parkway  
Chesterfield, MO 63017 USA  
e-mail: laura.a.bass@pfizer.com

Donna G. Blackmond  
Department of Chemistry  
Department of Chemical Engineering and Chemical Technology  
Imperial College, London SW7 2AZ UK  
e-mail: d.blackmond@imperial.ac.uk

Geneviève Boice  
Department of Process Research  
Merck Research Laboratories  
P.O. Box 2000  
Rahway, NJ 07065 USA

Alfio Borghese  
Solvay Pharmaceuticals  
P.O. Box 9001380  
DA Weesp  
The Netherlands  
e-mail: a.borghese@hotmail.com

Tamim F. Braish  
Pfizer Global R&D  
Groton, CT 06340 USA  
e-mail: tamim.f.braish@pfizer.com

John J. Buckley  
Pfizer Global Biologics  
Pharmaceutical Sciences  
700 Chesterfield Village Parkway  
Chesterfield, MO 63017 USA  
e-mail: john.joseph.buckley@pfizer.com

Erick M. Carreira  
Laboratorium für Organische Chemie HCI  
H335  
ETH Zürich  
8093 Zürich, Switzerland  
e-mail: carreira@org.chem.ethz.ch

Susan Casnocha  
Pfizer Global Biologics  
Pharmaceutical Sciences  
700 Chesterfield Village Parkway  
Chesterfield, MO 63017 USA  
e-mail: susan.a.casnocha@pfizer.com
Stephen Challenger  
Chemical Research and Development  
Pfizer Global Research and Development  
Sandwich, CT13 9NJ, Kent, UK  
e-mail: stephen.challenger@pfizer.com

John Chung  
Department of Process Research  
Merck Research Laboratories  
P.O. Box 2000  
Rahway, NJ 07065 USA

David A. Conlon  
Process Research & Development  
Bristol-Myers Squibb Company  
One Squibb Drive  
48-1-1031  
New Brunswick, NJ 08903-0191 USA  
e-mail: david.conlon@bms.com

Karen Conrad  
Department of Process Research  
Merck Research Laboratories  
P.O. Box 2000  
Rahway, NJ 07065 USA

Edward Corley  
Department of Process Research, Merck  
Research Laboratories  
P.O. Box 2000  
Rahway, NJ 07065 USA

Jotham W. Coe  
Neuroscience Medicinal Chemistry  
Pfizer Global Development and Research  
Eastern Point Road  
Groton, CT 06340 USA  
e-mail: jotham.w.coe@pfizer.com

Paul Collins  
Department of Process Research  
Merck Research Laboratories  
P.O. Box 2000  
Rahway, NJ 07065 USA

Raymond J. Cvetovich  
Department of Process Research  
Merck Research Laboratories  
P.O. Box 2000  
Rahway, NJ 07065 USA

Fons De Knaep  
Johnson & Johnson, Beerse B-2340  
Belgium  
e-mail: fdnkaep@prdbe.jnj.com

Andrew M. Derrick  
Chemical Research and Development  
Pfizer Global Research and Development  
Sandwich, CT13 9NJ, Kent, UK  
e-mail: andrew.derrick@pfizer.com

Lisa DiMichele  
Department of Process Research  
Merck Research Laboratories  
P.O. Box 2000  
Rahway, NJ 07065 USA

Peter J. Dunn  
Chemical Research and Development  
Pfizer Global Research and Development  
Sandwich, CT13 9NJ, Kent, UK  
e-mail: peter.dunn@pfizer.com

Ronald Fedechko  
Pfizer Global Biologics  
700 Chesterfield Village Parkway  
Chesterfield, MO 63017 USA  
e-mail: ronald.w.fedechko@pfizer.com

Hans-Jürgen Federsel  
AstraZeneca, Process R&D  
151 85 Södertälje, Sweden  
e-mail: hans-jurgen.federsel@astrazeneca.com

Rory F. Finn  
Pfizer Global Biologics  
Pharmaceutical Sciences  
700 Chesterfield Village Parkway  
Chesterfield, MO 63017 USA  
e-mail: rory.f.finn@pfizer.com

Mauricio Futran  
Process R&D  
Bristol-Myers Squibb  
New Brunswick, NJ 08903 USA  
Mauricio.futran@bms.com
Contributors

Kumar Gadamasetti  
Delphian Pharmaceuticals  
Pharmaceutical R&D  
Belmont, CA 94002 USA  
e-mail: delphianpharma@aol.com

Yousef Hajikarimian  
Chemical Research and Development  
Pfizer Global Research and Development  
Sandwich, CT13 9NJ, Kent, UK  
e-mail: yousef.hajikarimian@pfizer.com

Steve Hannon  
Davos  
600 East Crescent Avenue  
Upper Saddle River, NJ 07458 USA  
e-mail: hannons@DAVOS.com

Ronald L. Hanson  
Bristol-Myers Squibb  
New Brunswick, NJ 08903-0191 USA  
e-mail: ronald.hanson@bms.com

Sa V. Ho  
Pfizer Global Biologics  
Pharmaceutical Sciences  
700 Chesterfield Village Parkway  
Chesterfield, MO 63017 USA  
e-mail: sa.v.ho@pfizer.com

Dave Hughes  
Department of Process Research  
Merck Research Laboratories  
P.O. Box 2000  
Rahway, NJ 07065 USA

Hiroshi Iwamura  
Department of Chemistry  
Imperial College  
London SW7 2AZ UK

Bill Izzo  
Chemical Engineering Research and  
Department of Process Research  
Merck Research Laboratories  
P.O. Box 2000  
Rahway, NJ 07065 USA  
e-mail: bill_izzo@merck.com

Shu Kobayashi  
Graduate School of Pharmaceutical Sciences  
The University of Tokyo,  
The HFRE Division  
ERATO  
Japan Science and Technology Agency (JST)  
Hongo, Bunkyo-ku, Tokyo 113-0033, Japan  
e-mail: skobayas@mol.f.u-tokyo.ac.jp

Steven V. Ley  
The University of Cambridge  
Trinity College, Cambridge, UK  
e-mail: Svl1000@cam.ac.uk

John Lu  
Mitsui & Co., (U.S.A.)  
New York, USA

Suju P. Mathew  
Department of Chemistry  
Imperial College  
London SW7 2AZ UK

Farah Mavandadi  
Discovery Drive  
Charlottesville, VA 22911 USA  
e-mail: farah.mavandadi@biotage.com

J. Chris McWilliams  
Department of Process Research  
Merck Research Laboratories  
P.O. Box 2000, Rahway, NJ 07065 USA  
e-mail: jmcmath@boehringer-ingelheim.com

Paul Mensah  
Pfizer Global Biologics  
Pharmaceutical Sciences  
700 Chesterfield Village Parkway  
Chesterfield, MO 63017 USA  
e-mail: paul.mensah@pfizer.com

Alain Merschaert  
Eli Lilly & Company  
Chemical Product R & D  
Lilly Development Centre S.A.  
Parc Scientifique de Louvain-la-Neuve  
Rue Granbonpré 11  
B-1348 Mont-Saint-Guibert, Belgium
Jianming Mo  
Pfizer Global Biologics  
Pharmaceutical Sciences  
700 Chesterfield Village Parkway  
Chesterfield, MO 63017 USA  
e-mail: jianming.mo@pfizer.com

Carlos. A. Mojica  
Pfizer Global R&D  
Groton, CT 06340 USA  
e-mail: carlos.mojica@pfizer.com

John Mott  
Pfizer Global Biologics  
Pharmaceutical Sciences  
700 Chesterfield Village Parkway  
Chesterfield, MO 63017 USA  
e-mail: john.e.mott@pfizer.com

Klaus Müller  
F. Hoffmann-La Roche AG  
Pharmaceuticals Division  
4070 Basel, Switzerland  
e-mail: klaus.mueller@roche.com

Jerry A. Murry  
Department of Process Research  
1 Amgen Center Dr.  
Newbury Park, CA 91320 USA  
e-mail: jmurray@amgen.com

Oscar Navarro  
ICIQ  
Av Paisos Catalans 16  
43007 Tarragona  
Spain  
e-mail: onavarro@uci.edu

Sandeep Nema  
Pfizer Global R&D  
Groton, CT 06340 USA

Steven P. Nolan  
ICIQ  
Av Paisos Catalans 16  
43007 Tarragona  
Spain  
e-mail: snolan@iciq.es

Timothy Norris  
Pfizer Global R&D  
Groton, CT 06340 USA  
e-mail: timothy.norris@pfizer.com

Thomas C. Nugent  
Department of Chemistry  
School of Engineering and Science  
International University Bremen  
Campus Ring 1  
28759 Bremen, Germany  
e-mail: t.nugent@iu-bremen.de

Chikako Ogawa  
Eisai Research Institute  
Lead Identification  
4 Corporate Drive  
Andover, MA 01810 USA  
e-mail: chikako_ogawa@eri.eisai.com

Terry L. Rathman  
t-Links Consulting  
100-29 Willow Run, Suite Li, Gastonia, NC 28056  
e-mail: trathman@carolina.rr.com

Robert A. Reamer  
Department of Process Research  
Merck Research Laboratories  
P.O. Box 2000  
Rahway, NJ 07065 USA

David Robins  
Davos  
600 East Crescent Avenue  
Upper Saddle River, NJ 07458 USA  
e-mail: darobins@DAVOS.com

Mark Rogers-Evans  
F. Hoffmann-La Roche AG  
Pharmaceuticals Division  
4070 Basel, Switzerland

Cécile Savarin  
Department of Process Research  
1 Amgen Center Dr.  
Newbury Park, CA 91320 USA  
e-mail: csavarin@amgen.com
Contributors

Ichiro Shinkai  
Beta Chem Inc.  
1-2-1 Ohtemachi  
Chiyoda-Ku  
Tokyo 100-0004, Japan  
e-mail: shinkai.ichiro@beta-chem.com

Robert A. Singer  
Chemical R&D  
Pfizer Global Development and Research  
Eastern Point Road  
Groton, CT 06340 USA  
e-mail: robert.a.singer@pfizer.com

L. St. Pierre-Berry  
Pfizer Global R&D  
Groton, CT 06340 USA  
e-mail: laurie.a.st.pierre@pfizer.com

Anders Sveno  
AstraZeneca  
Process R&D  
151 85 Södertälje, Sweden  
e-mail: andres.sveno@astrazeneca.com

Nicholas M. Thomson  
Chemical Research and Development  
Pfizer Global Research and Development  
Sandwich, CT13 9NJ, Kent, UK  
e-mail: nick.thomson@pfizer.com

Rajappa Vaidyanathan  
Chemical R & D  
Pfizer Global Research and Development  
Groton, CT 06340 USA  
e-mail: Rajappa.vaidyanathan@pfizer.com

Harry A. Watson Jr.  
Chemical R&D  
Pfizer Global Development and Research  
Eastern Point Road  
Groton, CT 06340 USA

Dierk Wieckhusen  
Novartis Pharma AG  
Process Technology  
WSJ145.10.01A, Lichtstr. 35  
CH-4002 Basel, Switzerland  
e-mail: dierk.wieckhusen@novartis.com

Georg Wuitschik  
Laboratorium für Organische Chemie HCI  
H335  
ETH Zürich  
8093 Zürich, Switzerland  
e-mail: wuitschik@org.chm.ethz.ch

Xu Feng  
Process Research Department  
Merck Research Laboratories  
P.O. Box 2000  
Rahway, NJ 07065 USA  
e-mail: feng_xu@merck.com

Natalia Zotova  
Department of Chemical Engineering and  
Chemical Technology  
Imperial College  
London SW7 2AZ UK
Affiliations

AstraZeneca, Process R&D, 151 85 Södertälje, Sweden
Beta-Chem, Inc. 1-2-1 Ohtemachi, Chiyoda-Ku, Tokyo 100-0004, Japan
Biotage, Discovery Drive, Charlottesville, VA 22911 USA
Bristol-Myers Squibb, New Brunswick, NJ 08903-0191 USA
Davos, 600 East Crescent Avenue, Upper Saddle River, NJ 07458 USA
Delphian Pharmaceuticals, Pharmaceutical R&D, Belmont, CA 94002 USA
DSM, PMB 150, 9650 Strickland Road Suite 103, Raleigh, North Carolina 27615, USA
Eli Lilly & Company, Chemical Product R&D, Lilly Development Centre S.A., Parc Scientifique de Louvain-la-neuve, Rue Granbonpré, 11, B-1348 Mont-Saint-Guibert, Belgium
Eisai Research Institute, Lead Identification, 4 Corporate Drive Andover, MA 01810 USA
ETH Zürich, Laboratorium für Organische Chemie HCI H335, 8093 Zürich, Switzerland
F. Hoffmann-La Roche AG, Pharmaceuticals Division, 4070 Basel, Switzerland
Imperial College, Department of Chemistry, Department of Chemical Engineering and Chemical Technology, London SW7 2AZ UK
International University Bremen, Department of Chemistry, School of Engineering and Science, Campus Ring 1, 28759 Bremen, Germany
Johnson & Johnson, Beerse B-2340, Belgium
Merck Research Laboratories, Rahway, NJ 07065 USA
Mitsui & Co., New York, USA.
Novartis Pharma AG, Process Technology, WSJ145.10.01A, Lichtstr. 35, CH-4002 Basel, Switzerland
Pfizer Global Research and Development, Sandwich, CT13 9NJ, Kent, UK
Pfizer Global Biologics, Pharmaceutical Sciences, Chesterfield, MO 63017 USA
Pfizer Global R&D, Groton, CT 06340 USA

t-Links Consulting, 100-29 Willow Run, Suite Li, Gastonia, NC 28056 USA

The University of Cambridge, Trinity College, Cambridge, UK

University of Connecticut, Department of Chemistry, Storrs, CT 06269-3060 USA

University of New Orleans, Department of Chemistry, 2000 Lakeshore Dr., New Orleans, LA 70148 USA

The University of Tokyo, Graduate School of Pharmaceutical Sciences, The HFRE Division, ERATO, Japan Science and Technology Agency (JST), Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
1 Process Chemistry in the Pharmaceutical Industry: Challenges in an Ever Changing Climate—An Overview

Kumar Gadamasetti

CONTENTS

1.1 Introduction...........................................................................................................................1
1.2 Change and Challenges........................................................................................................2
  1.2.1 Technology: APIs in the 21st Century.................................................................2
    1.2.1.1 Small and Large Molecules .................................................................2
    1.2.1.2 Growth Forecast for Small and Large Molecules and Generics............3
  1.2.2 Globalization.............................................................................................................3
  1.2.3 Regulatory Compliance............................................................................................3
1.3 Green Chemistry.............................................................................................................4
1.4 Prescription Pharmaceutical Drugs...................................................................................4
1.5 Outline of Contents.........................................................................................................5
  1.5.1 Case Studies ..............................................................................................................5
  1.5.2 Asymmetric Synthesis, Macromolecules, and Special Topics .........................9
  1.5.3 Enzymatic Intervention, Crystallization, and Morphology and Chemical Engineering .................................................................9
  1.5.4 Regulatory Compliance, Process Patents, and Instrumentation .......................10
  1.5.5 Outsourcing.............................................................................................................10
1.6 Future Trends...............................................................................................................10

References and Notes...........................................................................................................10

1.1 INTRODUCTION

The pharmaceutical industry strives to produce medical breakthroughs to improve the quality of human life. The average cost to develop and advance a new chemical entity (NCE) from inception to market, as a successful drug, is about $1 billion.¹ There are no guarantees of sustained success or longevity for any given drug in the market as evidenced by the recent withdrawal from market of Vioxx.² In spite of a higher degree of attrition at various stages of development and the statistics indicating a downward trend in the number of NCEs in the past 3 to 4 years, the worldwide pharmaceutical market growth was positive to the tune of 6 to 7% in 2006, and it is projected that
global sales will reach $665 billion to $685 billion in 2007. The pharmaceutical industry is going through a continuous ferment of change and reinvention to cope with attrition, high development cost, and the potential lack of substrate. Adaptation to growing change has become a norm in an industry that was known for its stability over the last several decades of the 20th century. The mission of process chemistry in the pharmaceutical industry is to provide documented, controlled, economic, green, and safer synthetic processes for development and large-scale manufacturing under regulatory guidance to support clinical trials and future commercial requirements of an active pharmaceutical ingredient (API). The main focus of this volume is twofold:

1. Outline approaches to synthetic processes and realistic solutions to some problems associated with process development and manufacturing in industry
2. Discuss changes that the pharmaceutical industry has been going through and how these changes have affected the process scientist, engineer, or technologist in tackling the challenges in this constantly evolving environment

The subject matter and the authors from academia and industry were carefully selected to make an attempt to lay out the mosaic of comprehensive information with real case studies to present to the process personnel and the individuals interested in such sciences and technology. It is hoped that the subject matter in this volume will help you to learn, develop, and eventually contribute positively by tackling challenges toward improving the quality of human life.

1.2 CHANGE AND CHALLENGES

The pharmaceutical industry has experienced an enormous array of change in terms of management, accountability, and ultimately productivity, toward the end of the 20th century. Process chemists constitute a small fraction of the whole development discipline, yet they are known to play a vital role in making significant contributions in the industry. Although changes focused toward process optimization, controls, and equipment were categorized as “anticipated change,” the changes due to advances in technology and the new forms of APIs (active pharmaceutical ingredients: small molecules and biologics) led to new paradigms in the process technology disciplines. Outlined below are a few selected elements in terms of technology (small versus large molecules), global regulatory compliance, and globalization, relevant to process chemists, technologists, and engineers.

1.2.1 TECHNOLOGY: APIs IN THE 21ST CENTURY

Advances in the human genome project and the identification of genes and proteins that underlie diseases led to a plethora of targets in biologics as APIs for the treatment of human diseases. The amalgamation of fermentation experts, cell biologists, enzymologists, and process engineers/scientists has helped accelerate the recent biologic drugs to market. Process personnel have taken the task to learn, cross-train, and bridge the gap to address the needs to meet the development timelines. A paradigm shift in therapeutics from small molecules to biologics and macromolecules became prominent toward the end of the last millennium, and this change is poised to remain and grow. Roughly 60% of the revenue growth for “Big Pharma” is projected to come from biologic products through 2010.

1.2.1.1 Small and Large Molecules

Small molecule drugs, defined as drugs with typical molecular weights <500 daltons, have been the main drivers of sales growth for Big Pharma. The projections lean toward a change in this trend by the turn of this decade. The pharmaceutical industry is expected to move rapidly toward biologic products, defined usually, but not exclusively, as protein-based therapeutic agents. Therapeutic
proteins, monoclonal antibodies, and vaccines, are expected to complement or replace many small molecules over the next decade or two. Herceptin®, Lucentis® from Genentech, Epogen® and Aranesp® from Amgen, Procrit® from Johnson & Johnson, Humulin® from Eli Lilly, and Novo- lin® from Novo Nordisk, are a few selected examples of large molecule therapeutics.

1.2.1.2 Growth Forecast for Small and Large Molecules and Generics

Datamonitor, which forecasts revenue growth, predicts the compound annual growth rate (CAGR) of 13% for Big Pharma during 2004–2010. In contrast, the CAGR for small molecule products is expected to be about 1% over the same period. On the flip side, the generics companies see small molecules as blockbuster drugs that continue to drive their market in the future with the belief that “the end of blockbusters is not upon us, despite what some analysts are saying.”

The global market for generic drugs is poised for strong (11 to 13%) growth by 2007. According to Datamonitor (London, UK), generic drugs are expected to reach sales of $160 billion by 2015 as drug patents continue to expire.

1.2.2 Globalization

Contract manufacturing organizations (CMOs) in Italy, Spain, Eastern bloc countries, China, and India have become major partners for the pharmaceutical and biotech companies. Cost reductions and competition to manufacture API formulations and the manufacturing of generic drugs have created this market and have led to the growth in globalization. The industry has benefited from enormous improvements in the quality of work and the timely delivery of the APIs that are well within the set parameters (cost, timeline, and quality). Outsourcing has become a part of the development strategy for most fully integrated pharmaceutical companies (FIPCOs) as well as mid-to small-size pharmaceutical and biotech companies. Most Big Pharma companies develop the processes in-house and transfer the robust processes to CMOs overseas. Globalization has necessitated that process personnel develop practical technical transfer methods, tight controls on releasing specifications, and thorough knowledge of regulatory compliance. In essence, globalization created a healthy worldwide competition in the process community. Although initially the benefits were enjoyed mutually between pharmaceutical/biotech industry and the contract research organizations (CROs)/CMOs, lately the industry seems to be facing tough competition due to the growth of generic drugs overseas.

1.2.3 Regulatory Compliance

Pharmaceutical industrial globalization brought a general awareness that it was essential to make pharmaceutical manufacturing more efficient and less wasteful. The pressure is enormous on regulators globally to focus on the most critical issues affecting product quality and assuring patient safety. The International Conference on Harmonization (ICH) issued a series of quality standards (Q series: Q8, Q9, Q10, etc.) to ensure efficiency and quality assurance in drug substance (API) and drug product manufacturing. A continuous exchange of dialogue between U.S. as well as worldwide regulatory agencies with the pharmaceutical counterparts on global regulatory awareness and advancements is the mantra for today’s industrial survival and longevity. The need for process development to encompass regulatory compliance, current good manufacturing practice (cGMP) guidelines, 21 CFR Part 11, utilizing process analytical technology (PAT) tools in advancing the APIs through various phases of drug development, is an added responsibility for the process scientist in the modern era of pharmaceutical industry. As the regulatory environment changes, it is likely that many small biotech companies may not have sufficient in-house expertise in good manufacturing practice (GMP) compliance and will as a result underestimate what it takes to manufacture drugs safely. However, these small biotech companies will now benefit greatly from
the already established market of CROs/CMOs that have honed their process development and regulatory skills with Big Pharma over the years.

An in-depth discussion of PAT and its applications in industrial processes is presented by Merck and Pfizer process scientists in Chapters 19, 20, 21, 22, and 23. Readers are encouraged to read the plethora of information, guidance and updates provided by the U.S. Food and Drug Administration (FDA) and international agencies.

1.3 GREEN CHEMISTRY

The focus for pharmaceutical industries is to find ways to develop chemical products and environmentally friendly, efficient processes that require fewer reagents and minimize the production of toxic gases and toxic waste, while being operationally safe and economical. Chapters 15 and 16 in this volume, one from academia (Ogawa and Kobayashi) and the other from industry (Dunn), are dedicated to green chemistry.

The accomplishments by Codexis and Merck, recipients of the Presidential Green Chemistry Challenge Award in 2006, are noteworthy, and they highlight a future trend in the industry (Scheme 1.1 and Scheme 1.2). Some companies have created organized plans for developing environmentally friendly processes.

1.4 PRESCRIPTION PHARMACEUTICAL DRUGS

“Growth in the global pharmaceutical market is expected to moderate in 2007 although opportunities for biologics and generics loom large and Asia shifts the balance of API power.” Global pharmaceutical sales are expected to increase 5 to 6% by 2007 to reach $665 billion to $685 billion down from a growth of 6 to 7% in 2006, according to recent analysis by IMS Health (Fairfield, Connecticut). Growth of biologics, like Epogen® and Neupogen® (Amgen), Herceptin® and Lucentis® (Genentech), Gardasil (Merck), Humulin® (Eli Lilly), and Novolin (Novo Nordisk), is projected

[Diagram of green chemistry process]

SCHEME 1.1 Green chemistry efficiency in the synthesis of atorvastatin (Lipitor®) by Codexis scientists. Codexis researchers engineered three enzymes to create a more efficient biocatalytic process to make hydroxynitrile, the intermediate that forms the chiral dihydroxy acid side chain essential to atorvastatin’s synthesis. (From Angewandte Chemie International Edition, 44, 362, 2005. With permission.)
Biologics are often very expensive, injectable medicines used for hard-to-treat diseases like cancer, severe anemia, and rheumatoid arthritis. Table 1.1 lists the 20 top-selling prescription drugs currently on the market. Macromolecules are prominent on this list (30%) and will likely continue to grow.

### 1.5 OUTLINE OF CONTENTS

In classifying the division of chapters and in selecting the specific contents of individual chapters, the editors made a conscientious effort to identify the changes the pharmaceutical industry has been going through during the past decade, while preserving the basic mosaic of elements (methodology, optimization, controls, scale-up, and engineering and commercial processes) on which process chemistry is built. The topics in a given chapter may cover classical case studies of process development, the manufacturing processes of current specific drugs in advanced stages of development, the drugs in market, and specific classes of compounds of significant value for the industry. With the intent of addressing the changes the industry has been going through, the chapters focus on globalization, outsourcing, regulatory compliance, and biologics.

### 1.5.1 CASE STUDIES

Case studies include taking the drug discovery processes to commercial processes via process research and development. An in-depth discussion on varenicline (Chapter 3) and sunitinib (Chapter 4), both recently approved drugs, originated from Pfizer’s discovery and process development group by Coe and Vaidyanathan and coworkers, respectively. Savarin and coworkers from Merck, in Chapter 5, outline a detailed work on efficiency and scalable process of a potent MC4 receptor antagonist followed by the work on LY414038, a 5HT2 antagonist from Eli Lilly process scientists, in Chapter 6. A contribution from AstraZeneca in Chapter 7 on the synthesis of robalzotan originated from Federsel’s group. The subsequent two specific drug development projects were submitted by Pfizer—one from Challenger and colleagues from United Kingdom, on the endothelin antagonists, UK-350926 and UK-349,862. Norris outlined the details of the development and scale-up of

---

**SCHEME 1.2** Green chemistry in the synthesis of sitagliptin (Januvia™) by Merck process scientists. Merck process chemists redesigned and significantly shortened the original synthesis of type 2 diabetes drug candidate sitagliptin (Januvia) to include an unprecedented efficient hydrogenation of an unprotected enamine. (From C&EN, July, 24–27, 2006. With permission.)
TABLE 1.1
Top 20 Prescription Drugs

<table>
<thead>
<tr>
<th>Rank</th>
<th>Drug</th>
<th>Manufacturer</th>
<th>Condition</th>
<th>Revenue 1</th>
<th>Revenue 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lipitor</td>
<td>Pfizer</td>
<td>High cholesterol</td>
<td>$8.4B</td>
<td>$13.3B</td>
</tr>
<tr>
<td>2</td>
<td>Zocor</td>
<td>Merck &amp; Co.</td>
<td>High cholesterol</td>
<td>$4.4B</td>
<td>$5.5B</td>
</tr>
<tr>
<td>3</td>
<td>Nexium</td>
<td>AstraZeneca</td>
<td>Heartburn</td>
<td>$4.4B</td>
<td>$6.2B</td>
</tr>
<tr>
<td>4</td>
<td>Prevacid</td>
<td>Abbott &amp; Takeda</td>
<td>Heartburn</td>
<td>$3.8B</td>
<td>$4.0B</td>
</tr>
<tr>
<td>5</td>
<td>Advair (Seretide)</td>
<td>GlaxoSmithKline</td>
<td>Asthma</td>
<td>$3.6B</td>
<td>$5.9B</td>
</tr>
</tbody>
</table>
### TABLE 1.1 (CONTINUED)
Top 20 Prescription Drugs

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Cl COOCH₃</td>
<td>A. Plavix</td>
<td>B. Clopidogrel</td>
<td>C. Bristol-Myers Squibb &amp; Sanofi-Aventis</td>
</tr>
<tr>
<td></td>
<td>(optically active)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>H₂ NHCH₃</td>
<td>A. Zoloft</td>
<td>B. Sertraline</td>
<td>C. Pfizer</td>
</tr>
<tr>
<td></td>
<td>(optically active)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Hormone</td>
<td>A. Epogen</td>
<td>B. Erythropoietin</td>
<td>C. Amgen</td>
</tr>
<tr>
<td>9</td>
<td>Hormone</td>
<td>A. Procrit</td>
<td>B. Erythropoietin</td>
<td>C. Johnson &amp; Johnson</td>
</tr>
<tr>
<td>11</td>
<td>Protein (recombinant tumor necrosis factor alfa receptor)</td>
<td>A. Enbrel</td>
<td>B. Etanercept</td>
<td>C. Amgen and Wyeth</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>A. Norvasc</td>
<td>B. Amlodipine</td>
<td>C. Pfizer</td>
</tr>
</tbody>
</table>
### TABLE 1.1 (CONTINUED)
**Top 20 Prescription Drugs**

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A. Seroquel
B. Quetiapine
C. AstraZeneca
d. Schizophrenia
E. $2.6B

A. Effexor XR
B. Venlafaxine
C. Wyeth
d. Depression
E. $2.6B
F. $3.8B

A. Zyprexa
B. Olanzapine
C. Eli Lilly
d. Schizophrenia
E. $2.5B
F. $4.7B [7]

A. Singulair
B. Montelukast
C. Merck & Co.
d. Asthma and allergies
E. $2.5B

A. Protonix
B. Pentoprazole
C. Wyeth
d. Heartburn
E. $2.4B

A. Risperdal
B. Risperidone
C. Johnson & Johnson
d. Schizophrenia
E. $2.3B
F. $4.3B [8]

Glycoprotein (growth factor or cytokine)
A. Neulasta
B. Granulocyte colony-simulating factor
C. Amgen
d. Chemotherapy side effects
E. $2.2B
tesocefovecin sodium. Three specific case studies entail chiral amines (Nugent, University of Bremen, Germany), unnatural amino acids (Ager, DSM), and lithium–halogen exchange reactions (Bailey and Rathman, University of Connecticut). These constitute important building blocks and useful methodologies for the process chemist.

1.5.2 ASYMMETRIC SYNTHESIS, MACROMOLECULES, AND SPECIAL TOPICS

Single isomers have gained enormous popularity in the pharmaceutical world. Potential generic competition of select single enantiomer drugs interested the chemists as well as the legal firms. Plavix, Nexium, Zocor, Pravacol (or Mevalotin), Zoloft, Ciralex (or Lexapro), and Zithromax are among the selection of drugs that gained popularity. Structures and sales are represented in Table 1.1.

A large number of drugs marketed today are chiral in nature. In 2005, single-enantiomer therapies had sales of $225 billion, representing 37% of the total final formulation pharmaceutical sales of $602 billion. Among the small molecules, single-enantiomer drugs are not only critical in new drug development, but they also can be used as a defense strategy by innovator drug companies against generic competition. The success of optically active Nexium by AstraZeneca and on the downside the litigations surrounding clopidogrel by Sanofi-Aventis and Bristol-Myers Squibb are noteworthy. Oxetan-3-one chemistry and synthesis by Carreira and colleagues in Chapter 13 and a discussion of C–C and C–N bond-forming reactions (Chapter 14) by Navarro and Nolan provide outstanding material.

Among the special topics, two chapters from the Pfizer process development group have focused on therapeutic monoclonal antibodies (Chapter 26) and pegylation of biological molecules (Chapter 24). Hopefully, the readers will appreciate the first-hand knowledge of the science and technology of the challenges of handling, modifying, and purifying large molecules. Microwave-mediated organic synthesis in the laboratories gained popularity in recent years. Chapter 25 enlists the merits and applications of such reactions.

1.5.3 ENZYMATIC INTERVENTION, CRYSTALLIZATION, AND MORPHOLOGY AND CHEMICAL ENGINEERING

Microbial technology enables enzymatic interventions for a given building block (e.g., β-keto esters to β-(S)-hydroxy esters) or generates the whole drug (e.g., pravachol from Bristol-Myers Squibb). Both approaches are very valuable in the pharmaceutical industry. Hanson from Bristol-Myers Squibb provided an outstanding discussion with schematics of building blocks and drugs in Chapter 17. Crystallization, in the early years, was considered more an art than a science. Chapter 18 by Wieckhusen from Novartis outlines an excellent step-by-step tutorial to achieve control in large-scale industrial crystallizations. Blackmond and colleagues from Imperial College, London, UK,
portray the “reaction progress kinetic analysis” and the applications to the pharmaceutical world in Chapter 27.

### 1.5.4 Regulatory Compliance, Process Patents, and Instrumentation

Contributions in Chapters 19, 20, 21, and 22 are focused on in situ reaction monitoring using mid-infrared (IR) spectroscopy, stemming from McWilliams and coworkers of the Merck process group. Detailed discussion on process analytical technology (PAT) and associated tools is outlined by Mojeca and the Pfizer group, and an outline of regulatory compliance and the effect on process scientists’ outlook is summarized in Chapter 1 and in Chapter 2.

### 1.5.5 Outsourcing

Globalization in the modern era has led to worldwide outsourcing. Two chapters were dedicated to the changes in the pharmaceutical industry in terms of outsourcing. In Chapter 28, Lu and Shinkai (Beta Chem, Japan), formerly from Merck, discuss the trends. Robins and Hannon (Davos), in Chapter 29, outline the importance of sourcing pharmaceutical products to China and India.

### 1.6 Future Trends

The title of this book is centered on the challenges in an ever-changing climate in the pharmaceutical industry’s process development and manufacturing disciplines. Highlighted in this chapter are key factors influencing such challenges, addressing the need for change. The second chapter in this volume entitled “Emerging Trends in Process Chemistry,” by Braish, De Knaep, and Gadamasetti delineates the essence of the function of the process development chemist in the pharmaceutical industry subject to a continuous state of change.

### REFERENCES AND NOTES

2. Vioxx, the Merck blockbuster drug, was withdrawn from the market for the risk of serious cardiovascular side effects.

References

2 Chapter 2. Emerging Trends in Process Chemistry


7. For a 60 mg daily dose, \( 1.5 \times 10^{-6} \) g of impurity/day/\( 60 \times 10^{-3} \) g of drug/day \( \times 1000 = 25 \) ppm. Hence, for a drug with a 60 mg daily dose, the guidance allows 25 ppm of one genotoxic impurity.


9. This is not a guidance, but an approach that later appeared as a guidance in ICH Q8, Q9, and Q10.


13.


16. Personal communication with Chris Watts of the FDA PAT policy team, Center for Drug Evaluation and Research (CDER), office of Pharmaceutical Science. From a talk by Chris Watts presented at Pittcon Conference, March 2, 2005, Orlando, FL.


3 Chapter 3. Varenicline: Discovery
Synthesis and Process Chemistry
Developments

1. “Counterblaste to Tobacco,” King James, 1604.


8. Mansbach, R.S.; Chambers, L.K.; Rovetti, C.C. Effects of


34. Ratio determined using HPLC and GC-MS. The major component was determined to be the cis-isomer, as it is rapidly consumed in the subsequent cyclization, whereas the minor isomer is consumed more slowly.

35. The diastereoselectivity approaches 1:1 upon increased reaction time, indicative of acid-catalyzed isomerization of the ester.


37. (a) Brown, H.C.; Heim, P.; Yoon, N.M. Selective reductions. XV. Reaction of diborane in tetrahydrofuran


43. It has been shown that hydroxide bridged dimeric palladium complexes can form and impede catalysis, see Hartwig, J.F. Palladium-catalyzed amination of aryl halides: mechanism and rational catalyst design. Synlett 1997, 4, 329-340.

44. We observed less-efficient reactions with tricyclohexylphosphine that had been exposed to the air, presumably due to oxidation of the phosphine. For best results on scale, we used new containers of the phosphine to minimize opportunity for air oxidation before use. For improved reliability, we found that dicyclohexylphenylphosphine was less susceptible to air oxidation and provided a more stable catalyst (as did dialkylbiarylphosphine ligands; see Reference 42).

45. The sodium salt of 50 was crystallized from acetonitrile and toluene and isolated as a single olefin isomer. The structure was elucidated by single-crystal X-ray diffraction.
4 Chapter 4. The SUTENT® Story


Chapter 5. An Efficient and Scalable Process for the Preparation of a Potent MC4 Receptor Agonist


7. (a) Savarin, C.G.; Boice, G.N.; Murry, J.A.; Corely, E.; DiMichele, L.; Hughes, D. Org. Lett. 2006, 8, 3903–3906. (b) Boice, G.; McWilliams, C.; Murry, J.; Savarin, C.; Stereoselective Preparation of 4-Arylpiperidine Amides by Asymmetric Hydrogenation of a Prochiral Enamide and


13. This intermediate is common to other pharmaceuticals (e.g., fluconazole and voriconazole).

6 Chapter 6. Process Research and Development of LY414197, a 5HT 2B Antagonist


22. Even though we have shown that recovery of the CBZ-(S)-proline is feasible.


24. The experiment was conducted with the (S,S) chiral catalyst that afforded the unwanted (R)-4.

Coping with the Synthesis of Robalzotan, a Complex Chroman Antidepressant*


23. Paiocchi, M. et al. PCT WO 02-00575, 2002; [to Zambon group, Italy].

24. Lane, C.F., Sodium cyanoborohydride: a highly selective reducing agent for organic functional groups, Synthesis,
25. Johansen, C. and Fiksdahl, A., Inversion of chiral 
α-methylbenzylamine, Chirality, 6, 161, 1994.


descriptions of three different approaches.
Chapter 8. Chiral Amine Synthesis—Strategies, Examples, and Limitations

1. The author worked as a process research chemist for three years with Catalytica/DSM (Mountain View, CA) and then 2 years with Pharmacia/Pfizer (South San Francisco, CA) before joining Jacobs University (Bremen, Germany) as an assistant professor of organic chemistry in October 2003. Email address: t.nugent@jacobs-university.de.


3. Unfunctionalized amines here implies the exclusion of substrates requiring functional groups that are intimately involved in the transition state for production formation, e.g., ester chelation to a metal center.

4. The term ‘chiral amine’ is used in the title, but refers to an α-chiral amine, i.e., an α-carbon stereocenter adjacent to a nitrogen atom.

5. The time honored adage, especially in sophomore organic chemistry courses, of teaching students that over alkylation of amines makes their substitution chemistry unfit for consideration is outdated; though limited the strategy should not be ignored for the mono-alkylation of amines, see, for example, Hayler, J. D.; Howie, S. L. B.; Giles, R. G.; Negus, A.; Oxley, P. W.; Walsgrove, T. C.; Whiter, M. Org. Process. Res. Dev. 1998, 2, 3-9.


8. Similar examples of ketone reduction, followed by alcohol activation, and nucleophilic displacement thereof by an amine, have been demonstrated for other drug classes, see Reference 5 and Noyori, R.; Ohkuma, T. Angew. Chem. 2001, 113, 40-75; Angew. Chem., Int. Ed. 2001, 40, 40-73.


10. Note that very specialized syntheses, i.e., specialized for one substrate in particular, are not considered here.


23. No experimental description could be found.

24. See the Supporting Information section of Ref. 15b.


48. The Ellman method for sulfinyl ketimine synthesis would similarly suffer, but perhaps can be alleviated by using the Lewis acids B(OiPr)3 or Al(OiPr)3.


50. For a brief overview regarding imine formation, see page 1291 of Ref. 46.


Chapter 9. Unnatural Amino Acids

Scheme 9.39: $H_2N\text{CO}_2H\ R\ 36,\ R = \text{SPh}\ 37,\ R = \text{S(CH}_2\text{)}_2\text{OH}\ 38,\ R = \text{SePh}\ \text{PHN}\ \text{CO}_2H\ R\ \text{NaBH}_4\ \text{PHN}\ \text{R\ OH}\ \text{PDPI, I 2 imidazole, CH}_2\text{Cl}_2\ \text{PHN}\ \text{R\ I\ Et}_4\text{N\ +\ CN\\SH}_2\text{Cl}_2\ \text{PHN}\ \text{R\ I\ MeOH}\ \text{PHN}\ \text{R\ CO}_2\text{Me}\ where\ P = \text{Boc\ or\ Cbz}\ \text{B. Liu, H.}}$


10. Ware, E. Chem. Rev. 1950, 46, 403.


80. Taylor, P.P.; Pantaleone, D.P.; Senkpeil, R.F.;


Chapter 10. The Chemical Development of a Potential Manufacturing Route to the Endothelin Antagonists UK-350,926 and UK-349,862


7. For the three-step preparation of sulfonyl chloride 14 from 4-bromo-3-methylanisole see Reference 3.


9. Peakdale Molecular and EMS-Dottikon AG supplied N-methylindole-6-carboxylic acid methyl ester.


**Scheme 11.12**

\[ \text{acetone}/\text{H}_2\text{O} \text{ NaOH pH 6.8–8.2 } + (\text{ii}) \text{ C treatment (iii)} \]


12. This is true for both cyclization options; however, in the Horner-Wadsworth-Emmons chemistry, the cephem 29 is isolated before conversion into 30.

13. Sodium dithionite.


Chapter 12. The Lithium-Halogen Exchange Reaction in Process Chemistry


25. Ende, D.J. and Braish, T., The heat generated during the in situ formation of LiBr in a THF-hydrocarbon solvent mixture typically used for the exchange reaction is
approximately twice as large as the heat measured during
the lithium-bromine exchange, personal communication, 2006.


62, 8237 1997. (b) The selective monolithiation of
2,5-dibromopyridine has also been reported, see Wang, X.,
Rabbat, P., O’Shea, P., Tillyer, R., Grabowski, E.J.J., and

28. Scott, R.W., Fox, D.E., Wong, J.W., and Burns, M.P.,

29. Atkins, R.J., Breen, G.F., Crawford, L.P., Grinter,
T.J., Harris, M.A., Hayes, J.F., Moores, C.J., Saunders,
R.N., Share, A.C., Walsgrove, T.C., and Wicks, C., Org.

30. Denni-Dischert, D., Marterer, W., Banziger, M., Yusuff,
N., Batt, D., Ramsey, T., Geng, P., Michael, W., Wang,
R.-M.B., Taplin Jr., F., Versace, R., Cesarz, D., and

31. (a) Hutton, J., Jones, A.D., Lee, S.A., Martin, D.M.G.,
Meyrick, B.R., Patel, I., Peardon, R.F., and Powell, L.,
Atkinson, S., Cornwall, P., Foster, A.C., Gill, D.M.,
Humphries, L.A., Keegan, P.S., Kemp, R., Merifield, E.,
Perkins, J., Rowan, P., Sadler, P., Singleton, J.T.,

5404, 1990.


34. (a) Köbrich, G. and Trapp, H., Chem. Ber., 99, 600,
1966. (b) Köbrich, G., Angew. Chem., Int. Ed. Engl., 6, 41,
1967.

35. (a) Seebach, D. and Neumann, H., Chem. Ber., 107, 847,
1974. (b) Neumann, H. and Seebach, D., Chem. Ber., 111,


Chapter 13. Oxetan-3-one: Chemistry and Synthesis


21. Fernandez, J., Myers, R.J., and Gwinn, W.D., Microwave
spectrum and planarity of the ring of trimethylene oxide,

22. Gwinn, W.D., Information pertaining to molecular structure, as obtained from the microwave spectra of molecules of the asymmetric rotor type, Discuss. Faraday. Soc. (19), 43, 1955.


29. Nair, J.K., Reddy, T.S., Satpute, R.S., Mukundan, T., and Asthana, S.N., Synthesis and characterization of energetic thermoplastic elastomers (ETPEs) based on


derivs., methods for their preparation and their use as
herbicides. 19920116.

44. Koeppe, M.K. and Brown, H.M., Sulfonylurea herbicide
plant-metabolism and crop selectivity, Agro Food Ind.
Hi-Tech 6 (6), 9, 1995.

45. Forsberg, G., Rate constants and reaction products of
the alkaline hydrolysis of ethylene and trimethylene
chlorohydrins with alkyl substituents, Acta Chem. Scand. 8
(1), 135, 1954.

46. Ruzicka, L., On the understanding of carbon rings I. On
the constitution of zibetone, Helv. Chim. Acta 9, 230,
1926.

47. Welch, S.C. and Rao, A.S.C.P., Convenient one-step
synthesis of 2,2-disubstituted oxetanes from ketones, J.

48. Fitton, A.O., Hill, J., Jane, D.E., and Millar, R.,
Synthesis of simple oxetanes carrying reactive

49. Büchli, G., Inman, C.G., and Lipinsky, E.S.,
Light-catalyzed organic reactions. 1. The reaction of
carbonyl compounds with 2-methyl-2-butene in the presence
of ultraviolet light, J. Am. Chem. Soc. 76 (17), 4327,
1954.

50. Paterno, E. and Chieffi, G., Synthesis in organic
chemistry using light. Note II. Compounds of unsaturated
39, 341, 1909.

51. Bach, T., Stereoselective intermolecular
[2+2]-photocycloaddition reactions and their application in

molar volumes of organic compounds in water. Part 1.

53. Moore, J.C., Battino, R., Rettich, T.R., Handa, Y.P.,
and Wilhelm, E., Partial molar volumes of gases at infinite
22, 1982.


65. Coppola, G.M., Amberlyst-15, a superior acid catalyst

14 Chapter 14. Well-Defined (NHC)Pd (II) Complexes and Their Use in C-C and C-N Bond-Forming Reactions


13. (IPr)Pd(allyl)Cl and (SIPr)Pd(allyl)Cl are commercially available from Strem Chemicals (Newburyport, MA) for small quantities (hundreds of mg) and from Umicore AG (Brussels, Belgium) for larger quantities.


17. From 10 mmol (3.66 g), 15 mmol (5.49 g), and 10 mmol (3.66 g) of [Pd(allyl)Cl] 2, respectively.


34. For a review, see Alonso, F.; Beletskaya, I.P.; Yus, M. Chem. Rev. 2002, 102, 4009-4092.


38. To highlight the stability of these complexes, subjecting them to 90°F and nearly 100% humidity for 2 months resulted in no decomposition of these precatalysts. Furthermore, their activity was unaffected after this treatment. We can thank Hurricane Katrina for this ultimate stability test.
Chapter 15. Toward Truly Efficient Organic Reactions in Water


7. Fringuelli and coworkers reported use of Al(III), Ti(IV), and Sn(IV) as Lewis acids for epoxide opening reactions in acidic water. The pH was adjusted by adding H 2 SO 4 . Fringuelli, F., Pizzo, F., and Vaccaro, L. J. Org. Chem., 2001, 66, 3554.


27. (a) Ishikawa, S.T., Hamada, T., Manabe, K., Kobayahi, S. J. Am. Chem. Soc., 2004, 126, 12236. We performed the hydroxymethylation of 2 using 20 mol% of an Sc 3+ source and 24 mol% of 3 in H 2 O/1,4dioxane at 0ºC. As a result, Sc(OTf) 3 and ScBr 3 afforded almost the same results (Sc(OTf) 3 : (b) 15 h, 86% yield, 84% enantiomeric excess; ScBr 3 : 22 h, 75% yield, 83% enantiomeric excess).


32. Sc(OTf) 3 is a water-compatible Lewis acid, and it works well for hydroxymethylation even in the absence of a basic ligand. Kobayashi, S., et al. Synlett, 1993, 472.


34. The angle of O–Bi–O is 165º, whereas that of O–Sc–O is 151º. The torsional angle of two pyridines in the Bi complex is 27.0º, and that in the Sc complex is 19.4º. For the Sc complex, see Reference 27(a).

35. For reviews on the asymmetric synthesis and use of


41. Schneider et al. reported the same reactions in an organic solvent. See Reference 36(d).


45. After our first report (Reference 46), other reports on


16 Chapter 16. The Chemical Development of the Commercial Route to Sildenafil Citrate


14. Muller, N. and Matzke, M., U.S. Patent 6 444 828. (Note that under certain conditions the regiochemistry for the methylhydrazine reaction can be 13:1.)


17 Chapter 17. Stereoselective Enzymatic Synthesis of Intermediates Used for Antihypertensive, Antiinfective, and Anticancer Compounds


Chapter 19. Mid-Infrared Spectroscopy for Process Development


17. Reference 3.

20 Chapter 20. Optimizing an Asymmetric Homologation in a Tandem Asymmetric Homologation-Homoaldol Process

SCHEME 20.12


7. The mechanism involving acyl Meldrum’s acids in solution was never clarified. Several proposed reaction pathways are often found in the same publication.


14. Although 3 can be obtained in high yield by acylating Meldrum’s acid with 2,4,5-trifluorophenylacetyl chloride in the presence of various amine bases, without aqueous workup, the next through process step to the ketoamide 5 does not perform well in terms of impurity profile and conversion.

15. 1 H NMR studies showed that the background reaction between pivaloyl chloride and Meldrum’s acid in CD3CN in the presence of i-Pr2NEt and 10 mol% DMAP at 0°C to ambient temperature is slow. Under these reaction conditions, formation of 14 is negligible in comparison to the reaction rate for formation of 3.

16. It is known that acyl Meldrum’s acids are not always stable. For example, see Reference 8b.


19. This process has been successfully and reproducibly carried out in 300-kg scales.
20. For a less-complicated consideration, all the tautomers, rotamers, as well as resonance structures are not specifically considered here. For example, although these equilibriums can be included in the kinetic analyses, the outcome reaction rate results in the same kinetic effects on $[HA]$ or $[A]$ as described in the text. In order to have more focused discussion in the text, detailed kinetic analyses of all other possible mechanisms, which can be done as described in the text, are not listed here.


27. Previously known as ASI Applied Systems, Millersville, Maryland.

28. The obtained online IR kinetic profiles of the combination of anion and free acid form of 3 as well as the formation of the product matched very well with the HPLC kinetic profile as shown later in Figure 21.6.

29. A stepwise formation of the oxoketene by loss of acetone to form intermediates such as 10, followed by decarboxylation, cannot be ruled out. The fact that the reaction rate is unaffected by the increasing concentration of acetone formed during the reaction provides some evidence against the pathway via intermediates such as 10, if reversible formation of these intermediates is the
rate-determining step.


22 Chapter 22. Mid-Infrared Monitoring Applications during Development of the Vinyl Ether Formation Step in the Preparation of Aprepitant (Emend)

1. Formerly ASI.


8. Additional service requirements for the MP unit included high-pressure instrument air (>80 psig) for purging the explosion-proof enclosure, low-pressure nitrogen (5 psig) for purging the optical conduit, and 20 to 25 °C deionized water for internal temperature control of the explosion-proof enclosure. An attempt to use nitrogen to purge the MP was made; however, supply pressure deviations were experienced, resulting in discontinuous purging of the unit and loss of power. This necessitated the use of
high-pressure instrument air for instrument purging. The main concern with using air versus nitrogen was the presence of pump oil which could potentially damage the instrument optics. To avoid such contamination, an oil trap was placed between the instrument air header and the MP unit.


14. A reliable NIR method was developed and implemented in the pilot plant. Y. Chen, unpublished results. NO Bz O F HC CF 3 CF 3 ethyl impurity CH 3
23 Chapter 23. Process Analytical Technology in the Manufacture of Bulk Active Pharmaceuticals—Promise, Practice, and Challenges


24 Chapter 24. PEGylation of Biological Macromolecules


11. Molineux G., Kinstler O., Briddell, B., Hartley, C.,


29. Francis G E; Fisher D; Delgado C; Malik F; Gardiner A; Neale D. PEGylation of cytokines and other therapeutic proteins and peptides: the importance of biological optimization of coupling techniques. International journal of hematology (1998), 60(1), 1-10.


34. Dolence, Eric K.; Hu, Chen-Ze; Tsang, Ray; Sanders, Clifton G.; Osaki, Shigemasa. Electrophilic polyethylene oxides for the modification of polysaccharides, polypeptides (proteins) and polymer surfaces. (Surface Engineering Technologies, Division of Innerdyne, Inc., USA). US patent 55650234 1997.


38. Beauchamp, C.O.; Gonias, S.L.; Menapace, D.P.; Pizzo, S.V., A new procedure for the synthesis of polyethylene glycol-protein adducts; effects on function, receptor


41. Dhalluin, Christophe; Ross, Alfred; Leuthold, Luc-Alexis; Foser, Stefan; Gsell, Bernard; Mueller, Francis; Senn, Hans. Structural and Biophysical Characterization of the 40 kDa PEG-Interferon-α2a and Its Individual Positional Isomers, Bioconjugate Chemistry (2005), 16(3), 504-517.


44. Arutselvan, N.; Xiong Cheng-Yi; Albrecht Huguette; DeNardo Gerald L; DeNardo Sally J Characterization of site-specific ScFv PEGylation for tumor-targeting pharmaceuticals, Bioconjugate Chemistry (2005), 16(1), 113-21.


47. Rosendahl, Mary S.; Doherty, Daniel H.; Smith, Darin J.; Bendele, Alison M.; Cox, George N. Sitespecific protein PEGylation: Application to cysteine analogs of recombinant human granulocyte colony-stimulating factor,

49. Zalipsky, S. and Barany, G., Preparation of polyethylene glycol derivatives with two different functional groups at the termini, Polymer Preprints (American Chemical Society, Division of Polymer Chemistry), 1986, 27(1), 1-2.


66. Goodson, R.J. and Katre, N.V., Site directed PEGylation
of recombinant interleukin-2 at its glycosylation site, Biotechnology, 8(4), 343, 1990.


76. Felix, A.M., Site-specific poly(ethylene glycol)ylation


Chapter 25. Microwave Technology in Process Optimization


60. The three case studies described herein consist of unpublished data from Personal Chemistry, Inc. (Biotage). The reaction conditions for individual steps are available from www.biotagepathfinder.com


70. Cymerman-Craig, J.; Moyle, M. Organic Synthesis, 1963,
All attempts to purify compound 47 by crystallization or chromatography failed, probably because of the instability of 47. Additionally, the product can exist both in "acrylonitrile" form 47 or "cinnamyl nitrile" form 47a. Moreover, Z and E isomers are possible. These substances have not been fully characterized in the literature.

HPLC analysis of intermediate 47 was not possible because of the instability and high molecular weight of this product.

Variations in other reaction parameters did not further improve the yield. The excess of solvents guanine and ethanol and the use of the highest possible temperature are essential. Other solvents, additional bases, and lower temperatures diminish yields of trimethoprim.

Because compound 55 is unstable, it was not isolated, and the reaction was controlled by HPLC using weakly acidic buffer (pH 5.5).

Measured by the disappearance of the imine derivative 54.
Chapter 26. Process Development
Considerations for Therapeutic Monoclonal Antibodies in Mammalian Cell Culture


25. Feldhaus, M.J. and Siegel, R.W., Yeast display of


34. Keen, M.J. and Hale, C., The use of serum-free medium for the production of functionally active humanized monoclonal antibody from NS0 mouse myeloma cells engineered using glutamine synthetase as a selectable marker, Cytotechnology, 18, 287, 1995.


Chapter 27. Reaction Progress Kinetic Analysis: A Powerful Methodology for Streamlining Pharmaceutical Reaction Steps


5. An analogous equation may be written to normalize the rate by [2]: it is most practical to carry out the normalization using the limiting substrate.


9. A full kinetic study of the proline-mediated aldol reaction based on a detailed catalytic reaction mechanism will be published separately.