Practical Process Research and Development

A guide for organic chemists

Second Edition

Neal G. Anderson
Anderson's Process Solutions
Jacksonville, Oregon

ELSEVIER

AMSTERDAM • BOSTON • HEIDELBERG • LONDON
NEW YORK • OXFORD • PARIS • SAN DIEGO
SAN FRANCISCO • SYDNEY • TOKYO

Academic Press is an imprint of Elsevier

Academic Press is an imprint of Elsevier
The Boulevard, Langford Lane, Kidlington, Oxford, OX5 1GB, UK
225 Wyman Street, Waltham, MA 02451, USA
Radarweg 29, PO Box 211, 1000 AE Amsterdam, The Netherlands

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
Anderson, Neal G.
Practical process research and development : a guide for organic chemists / Neal G. Anderson. – 2nd ed.
p. cm.
Rev. ed. of: Practical process research & development. c2000.
ISBN 978-0-12-386537-3 (hardback)
1. Chemical processes. I. Anderson, Neal G. Practical process research & development. II. Title. III. Title: Practical process research and development.
TP155.7.A55 2000
541'.39–dc23
2011051049

ISBN: 978-0-12-386537-3

Chapter 1

Introduction

Chapter Outline

I. Introduction 1
II. Equipment Considerations on Scale 7
III. Operations Preferred on Scale 12
IV. Patent Considerations 15
V. Summary and Perspective 16
References 19

"The world doesn't move because of idealism…. [i]t moves because of economic incentives."

– Fernando Canales Clariond, formerly Mexico's secretary of the economy [1]

"It is well-known that there are no technical optima in industry, only economic optima…."

– G. Guichon et al. [2]

"Today, green chemistry is simply a good business choice."

– Paul Anastas [3]

I. INTRODUCTION

The driving forces of the pharmaceutical industry are to develop medicines that maintain or improve health and the quality of life for people, and to provide a reasonable return for investors. The many unknowns of the business, especially our imperfect understanding of biology, make for a high-risk environment. Yet the rewards are high as well. In Table 1.1 are presented some statistics associated with developing drugs, and these statistics explain some of the pressures of the business.

Significant financial gains are possible by developing drugs, as indicated by the penalties and fines levied against firms and people recently. For instance, in 2010 AstraZeneca was fined $520,000,000 for promoting Seroquel for off-label uses [4] and GlaxoSmithKline was fined $150,000,000 for violations of current Good Manufacturing Practices (cGMPs) [5]. In 2009, Pfizer was fined $2,300,000,000 for illegally promoting

Practical Process Research and Development. DOI: 10.1016/B978-0-12-386537-3.00001-0

TABLE 1.1 Some Statistics Relevant to the Pharmaceutical Industry

Value	Factor
$1,300,000,000	Cost to bring a drug to market (1)
5–20% of drug product price	CoG of API
30% of the CoG for drug product	Cost of QC (2)
Millions of dollars	Cost of failed drug formulation (3)
As high as market will bear	Price of drug product to consumer (higher for US than for most countries) (4)
$75,000	The value of one additional year of life, set in 2005 by health economists (5)
$200,000–$300,000	Annual cost of US chemist or engineer for an employer
About 95%	Portion of drug candidates that fail in pre-clinical or clinical studies
About 30%	Portion of approved drugs that recoup development costs (6)
8 years	Average time of development (goal is 5 years)
20 years	Period for exclusive sales of a patented drug (US)
20 − Development time	Years to recoup investment costs
$1,000,000	Sales lost for every day that a filing is delayed, if drug sales are $400 MM/year

(1) Undoubtedly includes the cost of advancing drug candidates that failed. Jarvis, L. M. Chem. Eng. News ***2010,*** *88(23), 13. May be higher: Vertex developed Incivek (telaprevir) over 20 years at the cost of around $4,000,000,000: Jarvis, L. Chem. Eng. News* ***2011,*** *89(22), 8.*

(2) Mullin, R. Chem. Eng. News ***2009,*** *87(39), 38.*

(3) May be higher for formulations involving spray drying. A huge cost may be incurred if the physical form of an API is not controlled and a dosage form fails specifications, thus interrupting clinical trials or discontinuing sales of a drug (Chapter 13). Thayer, A. M. Chem. Eng. News ***2010,*** *88(22), 13.*

(4) http://www.economist.com/node/4054095 (June 16, 2005).

(5) The Washington Post, July 17, 2005: http://www.washingtonpost.com/wp-dyn/content/article/2005/07/16/AR2005071600941_pf.html.

(6) Mod. Drug Discov. ***2001,*** *4(10), 47.*

Bextra and three other medications [6], and Bristol–Myers Squibb (BMS) was fined $2,100,000 for making agreements with Apotex to delay the launch of generic Plavix [7]. In 2009, the FDA stopped reviewing applications from Ranbaxy and prohibited Ranbaxy from importing 30 generic drugs, due to falsified QC data [8]. In 2007, a former top official of China's state organization approving drugs was executed for taking bribes [9]. In 2004, BMS was fined $150,000,000 for "channel stuffing," an accounting practice that artificially boosted the sale of drugs [10]. The reputation of the pharmaceutical industry has been sullied over the past few decades, but many people, including this author, enter this industry because they want to be able to help others.

The development and sales of drugs are influenced by an interplay of financial, political, governmental and personal considerations. For example, Bayer reduced the cost of a pill of ciprofloxacin from $1.77 to $0.75 after the horrific crashes of September 11, 2001 [11]. As of August 2009 the pharmaceutical lobby had 1544 lobbyists, or almost three lobbyists per congressman in Washington DC [12]; this is a sizeable increase from the 625 registered lobbyists in 2001 [11]. No major US pharmaceutical company would develop RU-486, an abortifacient, due to backlash anticipated from conservative groups. The sale of anti-AIDS drugs at reduced prices to the third world is a nice example of philanthropy; probably some income tax write-offs are also involved. Philanthropic efforts exist, such as Merck's gifts of ivermectin to prevent river blindness and the development of tenofovir by the Clinton Health Access Initiative to treat AIDS in the developing world [13]. Pharmaceutical industries may need support from government to continue developing drugs for the third world, such as compounds to treat malaria [14]. Efforts to minimize wastes and decrease impacts on the environment have increased, due to sensible and altruistic reasons, and due to penalties imposed. Although bacteria resistant to powerful antibiotics are continually emerging, the development of antibiotics has slowed due to the anticipated longer times to recoup development costs from drugs that are not taken on a chronic basis. The development of new chemical entities (NCEs) is becoming more difficult with increased scrutiny by regulatory authorities; for instance, the third or fourth entry into a therapeutic category may have to demonstrate superior benefits to win FDA approval [15], and control of potentially genotoxic impurities at the ppm level demands additional efforts. And everything is influenced by people striving for personal advancement.

As a result of increasing pressure to bring compounds to market, business trends within the pharma sector have been changing. Working smarter and faster is stressed, for instance, using high-throughput screening and statistically designed experiments. Pharmaceutical industries are being pressured to develop more efficient processes [16]. The FDA has advanced process analytical technology (PAT), and this may decrease manufacturing costs [17]. The importance of solid process development efforts has been recognized [18].

The complexity of compounds that has emerged as active pharmaceutical ingredients (APIs) may be increasing, as shown in Figure 1.1, and structural complexity increases the cost of development. Drug development is expensive: Vertex's first approved drug was developed in-house over 20 years at the cost of around $4,000,000,000. Incivek (telaprevir) will treat hepatitis C, at a projected price of $49,200, competing with Merck's Victrelis (boceprevir) at a projected price of $31,000–$44,000. Each company has set up assistance programs to help with the co-payments of insured patients [19].

The foundation of thorough processes is the work carried out by academicians. Some brilliant total syntheses have been described by academic chemists, such as the syntheses of codeine by the groups of Stork [20] and Magnus [21]. Total synthesis in an academic sense [22,23] is often not suitable for scale-up on an industrial scale; scaling up in an academic setting to millimoles or grams may not be enough to uncover and address processing difficulties. Prof. Hudlicky has described many practical considerations for syntheses [24] that are applicable to process R&D efforts in the pharmaceutical industry.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.