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MANAGING THE DRUG DISCOVERY PROCESS

HOW TO MAKE IT MORE EFFICIENT AND COST-EFFECTIVE

SUSAN M. MILLER, WALTER H. MOOS,
BARBARA H. MUNK AND STEPHEN A. MUNK

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Managing the Drug Discovery Process

Foreword

It is indeed simultaneously the best of times and worst of times in biotech and pharma research and development (R&D).

We are pleased to write this Foreword for *Managing the Drug Discovery Process: How to Make It More Efficient and Cost-Effective*, by Susan Miller, Walter Moos, Barbara Munk, and Stephen Munk. The authors are leaders in their fields, but more importantly they are critical thinkers and innovators. A frequently quoted book (Foster & Kaplan, 2001) highlighted the need for continuous innovation as the only way to survive "creative destruction" in industries, pharmaceutical, and biotechnology being no exception. It is important for readers to know that Drs. Miller, Moos, Munk, and Munk wholly understand this need.

In recent years, a number of reviews and books have appeared on the topic of drug discovery. Many of them cataloged different technologies used; others described various stages of pharmaceutical development, and some delved into the nitty-gritty of molecules and structures. The present volume is, perhaps most importantly, the first to address the role and need of focused education and higher learning as part of the drug discovery "process." Traditionally, scientists trained in one or more key disciplines of biochemistry, chemistry, and pharmacology or physiology, and acquired the skills to conduct experiments in an academic setting. Clinicians with an understanding of disease processes often joined to help advance the project(s). Thus, when combined with an applied cause in an industrial setting that could bring together expert teams from multiple disciplines to focus on a given problem, basic research emerging from academic centers could often be translated into a marketable product. One major drawback of this scenario was that, more often than not, junior scientists would acquire their "drug discovery" skills through on-the-job training. That started to change with the emergence of molecular biology as a discipline, and biotechnology as an industry. Increased needs in patenting regimes and regulatory oversight required additional trained staff. Time being of the essence, the industry looked for talent with specific and exact skillsets who could immediately jump into the project flow rather than after a training hiatus. Consequently, the traditional training grounds in colleges and universities had to evolve their curricula to prepare the next generations of the workforce. The authors have wisely devoted two sections of the book to the preprofessional and professional aspects of learning, which are undeniably critical for development of a skilled workforce of the future.

As the authors propose, the present book shows the ongoing revolution in biomedical R&D from a chemist's perspective. Chemistry and its practitioners have contributed immensely to the quest for better life, be it through herbal remedies from time

immemorial or with safe and effective medicines in the last 100 years (Sneader, 2005). However, the trial and error approach to finding a cure has given way to designed therapies. Yesterday's chemistry and pharmacology of drug discovery has morphed into today's "biomedical research." The single most important driver for that transition is probably total sequencing of the human genome (and at times the misplaced optimism it generated) at the end of the last century, which was made possible when basic research was combined with high technology. So, transitioning from yesterday's disease- and target-centric mindsets to the more person- and phenotype-centric therapeutic solutions of tomorrow brings us back, once again, to chemistry and chemists! However, the introduction of far more complex treatments and lifesaving remedies (discovered through advanced science and technology) leads to significantly increased costs to develop and provide access to them. Adding to the mix, cutting edge technologies, higher regulatory and compliance burden, and diverse global patent regimes all contribute to the cost. Therefore, any process improvement(s) aimed at reducing the time, cost, and improved effectiveness of the treatment will reduce the overall economic burden on the individual consumer and society in general.

In recent years, perhaps chemistry (more so in its pharmaceutical applications) is the only scientific discipline to be impacted by globalization. Worldwide access to talent, infrastructure, favorable tax and treaty regimes, and the onset of generic drugs (with resultant regulatory changes) led to intense shareholder pressure on companies to reduce time and cost in bringing new medicines to market. As in other areas of high technology, the pharmaceutical industry in the United States and Europe started to reap the benefit of lower costs of sourcing products and services from overseas. An unfortunate "side effect" of this attempt to manage a worldwide resource supply chain is the mistaken belief that process enhancement(s) catalyzed by technology will magically accelerate development of new lifesaving therapies.

Another important factor is probably the ebb and flow of cultures in learning and practicing chemistry and biology, and then tying them together in an applied context (Kornberg, 1987). Padmanabhan Balaram, a mentor to one of us (KK), using examples taken from the period literature, outlined numerous misconceptions that were being propagated in the name of drug discovery (Balaram, 2004). Unfortunately, many of today's practices are unchanged from the time of those writings.

As long-time students and practitioners of biotechnology and pharmaceutical R&D, we know that it is essential to have an in-depth understanding of the pharmacological and chemical underpinnings of the drug discovery process, and that some aspects of it are not suited for the production line. At least for the foreseeable future, drug discovery will remain largely an intellectually driven process requiring its practitioners to have a deep understanding of chemistry principles, particularly concepts in organic and medicinal chemistry, as applied to human biology. This perception is critical for knowledge transfer in process optimization. Generational loss of institutional memory, both in academia and in industry, has exacerbated the problem.

Drug discovery practitioners often embrace new technologies to find innovative solutions for advancing projects. Automated combinatorial chemistry, the polymerase chain reaction, high-throughput screening, bioinformatics, computer-aided drug design, molecular and cellular imaging, and many other techniques had their origins

in academic laboratories, but rapidly progressed to drug discovery applications in industry. Hopefully, the advent of epigenetic-targeted drugs and breakthrough technologies like "CRISPR-Cas9," and engineered microbes as endogenous diagnostic and or drug releasing synthetic units (living pills), elegantly discussed and presented in this book, will offer new insights and help overcome many of the shortcomings (Moos, Faller, et al., 2016; Moos, Maneta, et al., 2016; Irwin, Moos, Faller, Steliou, & Pinkert, 2016).

It is indeed the best of times for nurturing creativity and innovation in an era of abundance. The good aspects of global access to talent, resources, and new technologies are highly relevant to the pharmaceutical and biotechnology industries. It is also the worst of times, with the ever increasing cost of higher education, reduced funding support for research in the universities (particularly in the United States), more competition, regulatory burden across continents, and many old scourges still needing new remedies, all adding to the misery. But there is hope. A recent report describes significant increases in new drug candidates obtaining approval (Smietana, Siatkowski, & Moller, 2016). It was observed that 11.9% of drug candidates were approved during 2012–2015—a substantial increase from only a 7.5% success rate during 2008–2011. The higher success rates are attributed to better pipeline quality, and the pharma industry getting better at "fail early, fail cheap," a process improvement!

As we look ahead, the next phase of the biomedical revolution will be measured by the significant improvement in the quality of life of those burdened with disease and their caregivers, and counted in the number of lives saved. The authors of this book have effectively painted a broad-brush picture of the many touch points in the drug discovery process, be it in educating a future workforce, discovery *itself*, or of products entering the market. The overview is refreshing, thorough and timely. Hopefully you, the reader, will share the same sense of our excitement.

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Preface

Dear Readers,

With apologies to the famous English novelist (Dickens, 1859), it is simultaneously the best of times and the worst of times in biotechnology and pharmaceutical research and development (biotech/pharma R&D), as usual…

Key point

It is simultaneously the best of times and the worst of times in biotech and pharma R&D, as usual.

As usual? Indeed, biotech/pharma R&D is seemingly balanced at a tipping point (Gladwell, 2000) on a perpetual basis, sometimes sliding back, and at other times catapulting forward. The challenges abound, daily—even for cures that provide both a significant improvement in a patient's quality of life and a reduction in the pharmacoeconomic toll of healthcare—thereby garnering unwanted drug pricing attention all the way to the US Senate (Wyden & Grassley, 2016). Predictably, on almost any day, another R&D issue will be in the news, such as an unexpected death in an early-stage clinical trial (Butler & Callaway, 2016), the need to improve the reproducibility of biomedical research (Anonymous, 2016), or cybersecurity risks in healthcare (Perakslis & Stanley, 2016).

But wait! On a more positive note, major advances are evident in many fields of medicine (Turkoski, 2016), including new therapies for congestive heart failure (Sible, Nawarskas, Alajajian, & Anderson, 2016), novel diabetes drugs and diagnostics (Curtis, Holt, Richardson, Knott, & Partridge, 2016; Grönholm & Lenardo, 2015; Nauck, 2016), injectable proteins acting on new molecular targets for patients whose lipids are not controlled well by existing drugs or who cannot tolerate the side effects of statins (Sible, Nawarskas, & Anderson, 2016), and the possibility that the overall incidence in dementia is now in decline (Satizabal et al., 2016). And we could go on and on! You *can* chart a course to success, contributing to enabling discoveries that ultimately lead to products that save and improve countless lives, as we have. And it is our goal that this book will help current and future generations do so on a grander scale than ever before.

As an aside, note that throughout this book we resort to shortening some long words and phrases like "biotechnology and pharmaceutical research and development" to a more digestible "biotech/pharma R&D." And we try to avoid the so-called three-letter acronym or "TLA" disease, but a list of abbreviations is readily at hand regardless. Further, we have tried not to digress too much. But we digress…

Returning to our sober yet hopeful message, we understand fully that the journey through drug discovery and development can be a difficult one. Put simply, it is a highly technical and heavily regulated process that takes a long time and costs a lot of money. However, if you attack the issues with the right mindset, as we describe in this book, you will save lives, reduce healthcare costs, gain respect, and feel good about yourself, and everyone involved can make money. This is truly a story about "doing well and doing good" (a saying credited to Benjamin Franklin, among others). It is exactly that superlative outcome that underpins our core mission in writing this book.

As chemists, to be true to our heritage, we must focus on the *chemistry* of biomedical R&D. (By the way, how did "chemistry" get lost in "biomedical"?) Our focus is not biology, but we often talk about biological sciences in this book. Our focus is not medical, but we mention medicine, clinical trials, and patients on a number of occasions. We cover both undergraduate and graduate prerequisites and then carry this all the way through employment and a lifetime career. Thus, herein we provide a chemistry perspective on biomedical research for students, practitioners, reporters, and anyone else willing to listen.

Key point

Herein we provide a chemistry perspective on biomedical research for students, practitioners, reporters, and anyone else willing to listen.

At the risk of repeating ourselves, we underscore the realities of the biotech/pharma R&D arena throughout the book, for example, by presenting the ever increasing challenges when costs continue to skyrocket and failure by attrition reigns. However, at every step of the way, the healthcare enterprise writ large learns and uncovers new opportunities to improve health and well-being. That is the opportunity that makes the challenges fade into the background and the reason to pen this book now. Few writers can provide such a window on the hidden and unexpected insights from the trenches, which serves as a guide to current and next-generation healthcare innovators across the full range of research, development, business, and the innumerable related considerations necessary for success. Other books of this type provide valuable perspectives from a different cross-section of biotech/pharma R&D adventures. We have jumped into the fray anticipating that our deep, personal, real-life familiarities with multiple R&D venues, including big pharma, large biotech, start-up ventures, academia, and nonprofit research institutes, will be of unique value to a diverse cadre of readers. Students at any age, both early career and seasoned professionals, and anyone who finds himself or herself at the interface of science and business in healthcare, as well as others on the following partial list of potential interested parties, will hopefully benefit from this book:

- Biotechnology and pharmaceutical industry employees
- Industry writers, editors, analysts, and economists
- Venture capitalists (VCs) and their investors and recipients

- Investment bankers, major consulting firms, and professional meeting organizations
- Government researchers, funding agencies, budget offices, and politicians and staff
- Academic faculty, students, administrators, and technology transfer professionals in health and related sciences, broadly inclusive, for example, also touching on bioengineering
- Medical practitioners with an interest in R&D, such as physician scientists and pharmacists

Surprise! Education and training are important, as is experience and life-long learning, if efficiency and cost-effectiveness are your targets.

Key point

Education and training are important, as is experience and life-long learning, if efficiency and cost-effectiveness are your targets.

In the chapters on undergraduate and graduate education, we discuss degree programs that are often stepping stones to the biotech/pharma team. Not only does this book describe educational opportunities and pathways to a degree in the sciences, but also we describe the diverse range of career opportunities and challenges that a degree in the sciences can provide. We talk about research and discovery (discovery being the essential "little d" in terms of cost and commercialization) leading to development (development being the ultimate payoff "BIG D") of product candidates, both new chemical entities and protein biologics. In the process we provide roadmaps of both small molecule drug development and large-molecule biologic development, finally reaching the pinnacle of proof-of-concept in patients. Throughout, we provide objective insights that are valuable regardless of your perspective or stage of development.

Importantly, the present book builds on prior works of the authors, including Moos (2007) and Munk (2007), for example. Thus we ask you to consider at least part of this book to be similar to the next edition of a textbook, updated and broadened, "new and improved!" While the primary literature is essential for those who want to become experts, we have purposely decided to cite a varied collection of books, review articles, basic research articles, websites, and blogs, in order to provide easy entry points for those who are new to the scene and want to learn more on their own. Original literature and other citations herein include "the usual suspects" plus diverse "off-the-beaten-track" references and venues to reduce the sameness of so much scientific writing and to provide more colorful and memorable insights than might be found in other books and reviews.

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Watch for the different "voices" that you "hear" as you read the various sections and chapters, reflecting the very nature of the topics and fields of interest therein.

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That is, there are some areas and discussions that are open to informal, even conversational, playful, and almost interactive, prose. Other passages are historical, philosophical, poetic, or once in a while a soap box where we drive home a point. Yet other topics are more "cut and dried"—not boring, but serious—medical facts or regulatory realities, for example, where "the facts, just the facts" reign. Here and there we provide sage advice, offering alternatives to current thinking, especially of value for students. Of course you are the one to decide and judge which path to take, but possibly we will make your guess more educated as to which course will be best for you, your skills, your interests, and your organization.

As you page through this scientific, business, and literary offering, reading or scanning or just looking at the pictures, please keep several wise sayings in mind. They should serve you well.

- Do well by doing good (see note about Franklin, above).
- The difficult we do immediately—the impossible takes only a little longer (unknown author, but similar phrases were used by the US military in the 1940s).
- I have to live with myself, and so, I have to be fit for myself to know (Guest, 1977).
- It is hard to have too many friends (unknown origin, possibly derived from writings of the ancient Greek historian, Plutarch).
- Keep your eye on the donut, not on the hole (Anonymous, 1904), for the best is yet to come (Sinatra, 1964).

We anticipate the question, *Why a book in 2016?* Our purpose is simple. Books create an enduring foundation, allowing readers to develop their own nuanced understanding of a topic in order to be able to apply that understanding confidently. In today's over-connected 24/7 online lifestyle, a book provides a personal refuge from a planet of noise and chaos. Moreover, worries of "Idiocracy" (Judge, 2006) and "Is Google Making Us Stoopid?" (Carr, 2008) are not unfounded, and we believe that the right books guard against such an erosion of personal knowledge and raw intelligence. Importantly, books retain value regardless of one's viewpoint. Our plan has thus been to write an enduring set of messages and guideposts addressed to those who wish to make a real difference in the world of healthcare. Some of what we describe is "old" wisdom, reapplied, but wisdom of the ages never goes out of date, even if forgotten, ignored, or lost at times. So, just as fine wines get better with age, we hope this book proves to outlive the latest fads, becoming a treasured companion in our readers' journeys through life.

Key point

Why a book in 2016? Books create an enduring foundation, allowing readers to develop their own nuanced understanding of a topic in order to be able to apply that understanding confidently.

In closing, we thank our current and past collaborators, colleagues, mentors, postdocs, and students for many contributions to the current state-of-the-art, and to our understanding of the field of biomedical R&D, drug discovery, and chemical development, altogether from the following outstanding organizations: Allergan, Ash Stevens, Chiron/Novartis, MitoKor/Mimotopes/Migenix, ShangPharma/ChemPartner, SRI, the University of California San Francisco, the University of Michigan, Warner-Lambert/Parke-Davis/Pfizer, and Wayne State University.

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Read on!

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Conflict of Interest/Disclosure Statement

WHM and SMM are married, BHM and SAM are married, and they each own stock or stock options individually and/or as married couples in selected biotechnology and pharmaceutical companies. WHM holds stock options in selected biotechnology and pharmaceutical companies. WHM consults and serves as an advisor and board member for certain biotechnology, pharmaceutical, and related life science organizations, including contract research and related organizations. SAM is an employee of and holds stock and stock options in a contract manufacturing organization. WHM, SMM, and BHM hold faculty positions at major universities. WHM serves on the editorial boards of journals at major publishing houses, including Elsevier. All four authors will share any royalties accruing from publication of this book.

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List of abbreviations

3D	3-dimensional
5HT or 5-HT	5-hydroxytryptamine or serotonin
5HTTLPR or 5-HTTLPR	long promoter region of SERT
7TM	7 transmembrane(s) (as in GPCRs)
μM	micromolar (10^{-6} molar)
AA	amino acid
AACC	American Association of Community Colleges
AACP	American Association of Colleges of Pharmacy
AACSB	Association to Advance Collegiate Schools of Business
AALAS	American Association for Laboratory Animal Science
AAMI	age-associated memory impairment
AAUP	American Association of University Professors
Ab	antibody
ABC	ATP-binding cassette (transporter)
ABET	Accreditation Board for Engineering and Technology
ACE	angiotensin converting enzyme
ACICS	Accrediting Council for Independent Colleges and Schools
ACS	American Chemical Society
AD	Alzheimer or Alzheimer's disease
ADA	adenosine deaminase or anti-drug antibody
ADC	antibody drug conjugate
ADHD	attention deficit hyperactivity disorder
ADME	absorption, distribution, metabolism, elimination (or excretion)
ADMET or ADME/T	absorption, distribution, metabolism, elimination (or excretion), toxicology
ado	adenosine
AI	artificial intelligence
AIDS	acquired immune deficiency syndrome
ALAT	Assistant Laboratory Animal Technician
ALL	acute lymphoblastic leukemia
ALS	amyotrophic lateral sclerosis
AMS	accelerator mass spectrometry
ANDA	abbreviated NDA
ANT	adenine nucleotide transporter
AP	Advanced Placement
API	active pharmaceutical ingredient
APR	annual product review
AR	adenosine receptor
ARB	angiotensin receptor blocker
ARRA	American Recovery and Reinvestment Act (of 2009)
ASCP	American Society for Clinical Pathology
ASHP	American Society of Health-System Pharmacists

ASMS	affinity selection mass spectrometry or spectroscopy
ATP	adenosine triphosphate
ATPase	a class of enzymes and transporters
AVMA	American Veterinary Medical Association
B	billion or byte
BA	Bachelor of Arts degree (also AB)
BARDA	US Biomedical Advanced Research and Development Authority
BB	building block
BBB	blood brain barrier
BBA	Bachelor of Business Administration degree
BCE	before current era
Bcl-2	B-cell lymphoma 2 protein
BCP	biochemical pharmacology
BD	business development
BDDCS	biopharmaceutics drug disposition classification system
BDZ	benzodiazepine
BGT	a GABA transporter
BIO	Biotechnology Industry Organization
biotech	biotechnology (industry)
BLA	biologics license application
BLS	US Bureau of Labor Statistics
BS	Bachelor of Science degree (also SB)
C&E	Chemical and Engineering (C&E News)
CADD	computer-assisted or -aided drug design
CAMD	computer-assisted or -aided molecular design
cAMP	cyclic adenosine monophosphate
CAS	Chemical Abstracts Service or CRISPR-associated protein (Cas)
CBER	US FDA Center for Biologics Evaluation and Research
CCK	cholecystokinin
CDER	US FDA Center for Drug Evaluation and Research
CDMRP	US Congressionally Directed Medical Research Programs
CDN	cyclic-dinucleotide
cDx	companion diagnostic
CEDD	Center of Excellence for Drug Discovery
CEO	Chief Executive Officer
CFA	Chartered Financial Analyst
CFDA	China FDA
CFP	Certified Financial Planner
CFR	US Code of Federal Regulations
CFTR	cystic fibrosis transmembrane conductance regulator
cGMP	current good manufacturing practice or cyclic guanosine monophosphate
CHEA	Council for Higher Education Accreditation
ClogP	calculated (rather than measured) log P
CMC	chemistry, manufacturing, and controls
CMC-II	Comprehensive Medicinal Chemistry II
CML	chronic myeloid (or myelogenous) leukemia
CMO	Chief Medical Officer or contract manufacturing organization
CMV	cytomegalovirus

CN	cyano group
CNS	central nervous system
COO	Chief Operating Officer or Chief of Operations
COOH or CO_2H	carboxy or carboxyl group (–COOH or $-CO_2H$)
COOP	cooperative
COTS	commercial off-the-shelf
COX	cyclooxygenase (as in COX-1 or COX-I and COX-2 or COX-II)
CPA	Certified Public Accountant
CPI	consumer price index
CPPs	critical process parameters
CQAs	critical quality attributes
CRISPR	clustered regularly-interspaced short palindromic repeats
CRO	contract or clinical research organization
crRNA	CRISPR RNA
CSO	Chief Scientific Officer
CTC	circulating tumor cell
CTD	common technical document
CTS	C-terminal segment
CV	curriculum vitae
CXO	combined CMO/CRO
CYP or CYP450	cytochrome P-450
Da	Dalton
DA	dopamine
DARPA	US Defense Advanced Research Projects Agency
DAT	dopamine transporter
DDI	drug–drug interaction
DDR	Drug Development Research (a scientific journal)
DEC	Digital Equipment Corporation
DEL	DNA-encoded library
DIY	do it yourself
DM	drug metabolism
DMF	Drug Master File or dimethyl formamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DoE or DOE or DoEs	design of experiments or US Department of Energy
DOEd	US Department of Education
DOI	discipline(s) of innovation
DOS	diversity-oriented synthesis
DSC	differential scanning calorimetry
EAA	excitatory amino acid
EAAC1	EAAT3
EAAT	an EAA transporter
EB	exabyte (10^{18} bytes)
EC_{50}	half-maximal effective concentration (e.g., of a drug)
ED_{50}	half-maximal effective dose (e.g., of a drug)
EDB	Singapore Economic Development Board
EFMD	European Foundation for Management Development (see also EQUIS)
eIND	exploratory IND application