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Introduction to the Book

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"Value Creation in the Pharmaceutical Industry: The Critical Path to Innovation" is intended to review the current state of the art and to provide cutting-edge knowledge in the pharmaceutical research and development (R&D) process. All authors are well-known experts in their field of activity and provide first-hand scientific, regulatory, management, or business information. They share their personal vision on how their field of expertise will or need to develop to finally keep pace with the changes that will happen in the pharmaceutical industry.

With this book, we examine the situation of pharmaceutical innovation from three different perspectives:

- Technically from the sequence of R&D
- Operationally when we answer the question of what can be done to increase R&D efficiency
- Strategically by examining environmental factors and trends that may influence pharmaceutical R&D in the future

Due to its unique structure and content, we expect that this book will be a way to update knowledge and spark new ideas for R&D managers, industry specialists, academics, and other stakeholders interested in pharmaceutical R&D.

As depicted in Figure 1.1, this book addresses the critical path of value creation in the pharmaceutical industry from the view points of research, development, and business. The articles on epidemiology, antibodies, and drug discovery may be assigned best to the section on "research." At the interface of "research" to the part of "development," we provide the articles on preclinical safety, translational medicine (TM), and drug costs. The section on "development" is represented by the articles on pharmaceutical, clinical, and translational development. A more holistic view on pharmaceutical R&D with an interface to the topic "business" is provided by the texts on portfolio management, financing of R&D, open innovation, licensing, outsourcing, innovation models, leadership in R&D, and management of intellectual assets. The business part is represented by the articles on marketing, vaccines, and pharmacoeconomics.

We will start this introduction by describing in general how does the highly regulated and standardized R&D process in the pharmaceutical industry look like.

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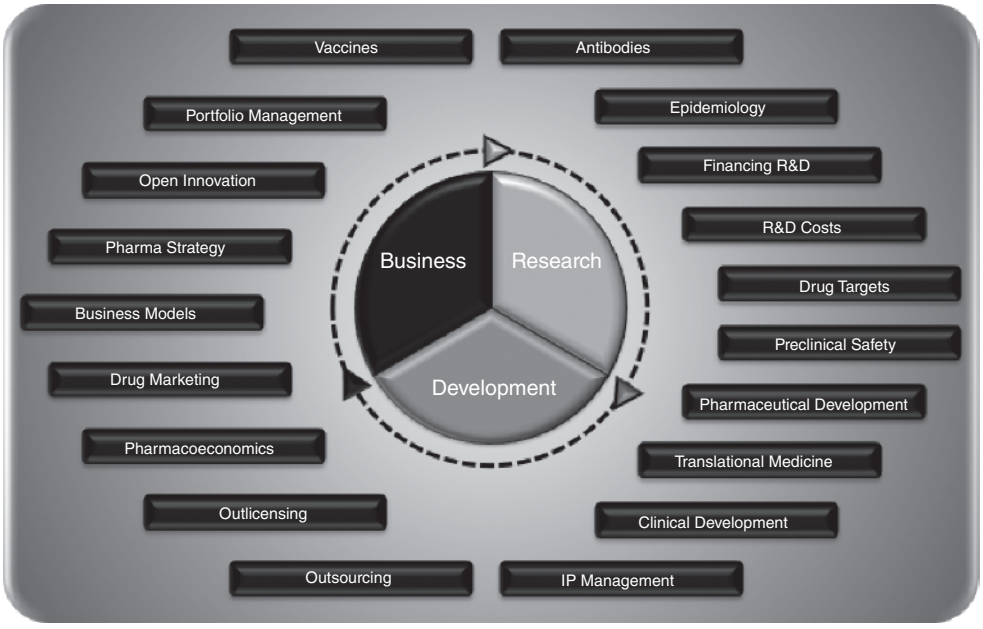

Figure 1.1 The pharmaceutical innovation hemisphere.

The first step of pharmaceutical R&D is the identification and validation of a suitable drug target that, if up- or downregulated, activated, or inhibited, may play a role in a disease. Thus, an in-depth understanding of the disease and its molecular mechanism is key to search for new drug targets. In a next step, researchers search for lead compounds that potentially influence the drug target in the aforementioned way. If a lead compound is discovered, researchers optimize the potential of the compound to become a drug candidate. In preclinical development, it is analyzed as to whether this candidate can be used in the human situation, and it undergoes a series of preclinical testing primarily intended to understand how the compound works and as to whether it is safe in animal models. Next, safe drug candidate can be used for test series in the human situation. First and in view of the US market, an Investigational New Drug Application (IND) needs to be filed at the Food and Drug Administration (FDA). In the following years, several clinical trials are conducted to analyze the efficacy and safety profile of the drug candidate. Principally, the clinical trial process is conducted in three phases. In phase I, the drug candidate is tested in a small group of healthy volunteers to analyze its pharmacokinetic. Phase II trials are conducted to analyze the safety and the efficacy of the drug candidate in a selected group of patients that have the disease under investigation. In the phase III trials, the drug candidate is tested in large groups of patients to provide statically well-founded data on the efficacy and safety of the drug and the overall risk–benefit ratio. Finally, a new drug application (NDA) is filed to get market approval for the new drug. The FDA reviews all

data and assesses the benefit versus the risk of the drug candidate and decides as to whether an approval can be granted.

Today, this R&D process lasts on average for about one to two decades and is related with a very low probability of success (PoS) from discovering a new drug candidate to its launch to the first market. The complexity of drug R&D combined with the increasing permeation by technology, the costs related with failed drugs, and the capitalization of costs over the long timelines are the main drivers of the enormous high costs that need to be invested per new molecular entity (NME). Today, the average costs per NME are probably above USD 2 billion (Figure 1.2).

With a total of 22 chapters, this book reviews the whole value chain of pharmaceutical R&D from drug discovery to marketing of a new drug. In detail, this book starts with three chapters that set the stage for the pharmaceutical industry, namely, epidemiology, healthcare needs, and a definition of value in the pharmaceutical business and the shrinking R&D efficiency.

First, **Stephan Luther** provides an overview and introduction on "*Global Epidemiological Developments.*" He reviews the basic models which describe the burden of disease in different geographical areas and under different socioeconomic and climate conditions. Based on these factors, he reviews the healthcare needs

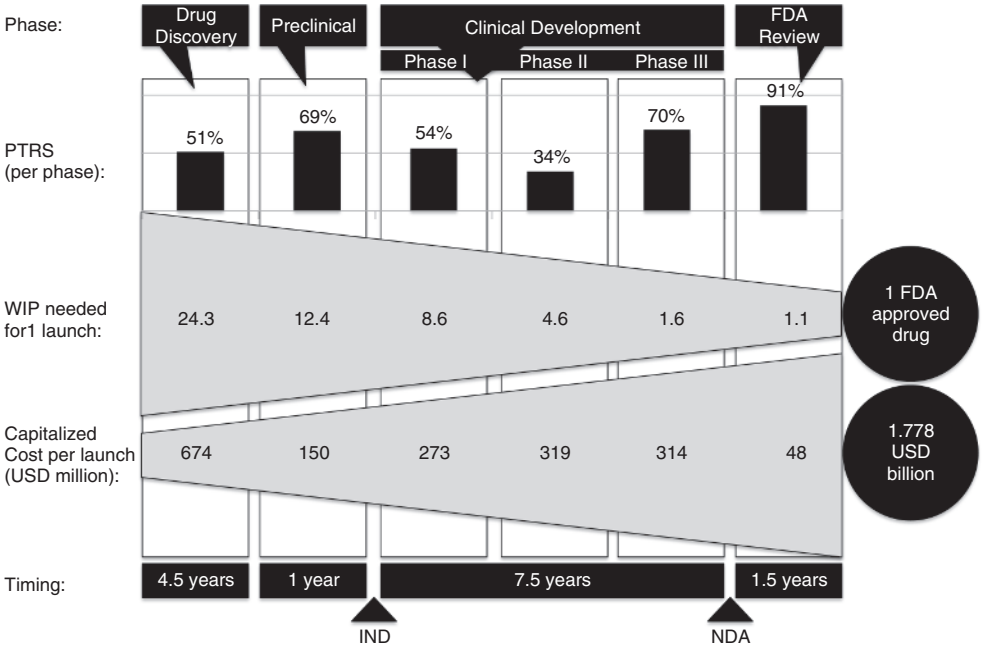

Figure 1.2 The traditional R&D phase model; IND (Investigational New Drug), NDA (New Drug Application), FDA (Food and Drug Administration), PTRS (probability of technical and regulatory success), WIP (work in progress), USD (U.S. Dollar), data derived from Paul S. et al. (2010)

for specific areas and provides an outlook on likely future developments worldwide. The chapter explains why on a global scale, there is a shift from communicable disease to noncommunicable disease and why in addition to mortality the disability-adjusted life years (DALYs) will become a prominent estimate for the overall global burden of disease.

The chapter by **Sam Salek and Paul Kamudoni** on "*The Value of Pharmaceutical Innovation: Concepts and Assessment*" introduces the reader to the different concepts of value and its assessment. Importantly the authors describe value from different perspectives of the multiple stakeholders in the healthcare sector and how the concept of value has evolved over time. They review on how value is assessed today and describe the consequences for pharmaceutical R&D. Based on recent developments, they provide an outlook how the pharmaceutical industry and regulatory agencies decision makers in the healthcare sector can work together in a more unified and transparent way to improve outcomes for the patients and the healthcare systems.

In the following chapter ("*A Review of the Pharmaceutical R&D Efficiency: Costs, Timelines, and Probabilities*"), we review the efficiency of the current R&D, namely, the R&D costs, the cycle times, the PoS of pharmaceutical R&D, and the number of NMEs that have been launched in past years. **Alexander Schuhmacher, Oliver Gassmann, and Markus Hinder** describe the traditional R&D phase model, highlight the reasons of the low success rates, and answer the question of why pharmaceutical R&D takes so long. We also detail the drivers of the enormous R&D costs and summarize our research on the question of how much does an NME cost today. Finally, further impact factors on R&D efficiency are discussed.

It is realistic to say that today more than USD 2 billion is required to bring one NME to the market, in a process that takes one to two decades. Accordingly, and as provided by the chapter of **Sviataslau Sivagrakau** ("*Financing Pharmaceutical Innovation*"), drug development is concentrated almost exclusively in advanced economies. The United States is the global leader with market share of 60% in scientifically novel new drugs. Globally, two-thirds of the investments in biomedical R&D come from the industry, whereas one-third are publicly funded. Since the 1980s, multinational pharmaceutical companies lost their dominance in providing NME. Whereas in the 1980s the big players originated three quarters of all NMEs, they have lost today's majority market share to smaller companies. In light of this, the financing landscape has become more fragmented and includes venture capital, university funds, public and charity grants, alliances, private–public partnerships, corporate and state venture capital, acquisitions by larger firms, and initial public offerings for companies with late-stage compounds. The last 5 years exhibited very favorable market conditions for exchange-listed drug developers: high valuations and strong industry-level performance. On the other hand, funding at early stages, particularly translational phase, remains scarce.

The next seven book chapters focus more specifically on the R&D process and the related potential of value creation in the phases of drug discovery and preclinical and clinical development.

In "*Challenges and Options for Drug Discovery*," **Werner Kramer** analyzes the different approaches taken in research–discovery and compares historical promises and delivery in these disciplines. He identifies the key obstacles, which need to be overcome to provide sustained success in the discovery space. He proposes and describes a new model, which unites scientific scrutiny, decisions based on understanding of human and molecular physiology. This includes the weighing of target-related safety and efficacy and the stringent application of decision trees in the assessment of projects. The chapter is especially valuable because the author does not forget to build the bridge to neighboring discipline TM.

The transition of a new molecule from animals to humans is a key event in the development of a new medicine. On the one hand, this is important to ensure adequate clinical safety for study participants. On the other hand, TM up to clinical proof of concept can offer precious information on a molecule's mode of action, pharmacokinetics (PKs), and pharmacodynamics (PDs) and its therapeutic potential. **Gezim Lahu and John Darbyshire** review in "*Translational Medicine: Enabling the Proof of Concepts*" the overall process and show the benefit of established and emerging tools and skills to enable informed and better decision making. By embedding TM into the bigger context between drug discovery and development, they provide a perspective of how TM can become a value driver in both directions.

In their chapter "*Preclinical Safety and Risk Assessment*," **Paul Germann and Rob Caldwell** review the state of the art in preclinical safety assessment. The authors give an overview of today's preclinical test strategies to support drug candidate testing in the early phases of drug development. They also provide an overview on the general components that are required for regulatory acceptable preclinical data package. Furthermore, the authors give information on the interaction of therapeutic use, route of application, treatment duration, and therapeutic indication and its influence on the safety assessment and the determination of the therapeutic window.

In the next book chapter on pharmaceutical development, it is described that more and more biological molecules (peptides, proteins, monoclonal antibodies (mAbs)) in not only oncological indications but also general medicine indications (e.g., diabetes, rheumatoid arthritis, or psoriasis) are reaching the market today and more will follow in the future. Thus, **Galina Hesse**'s chapter ("*Developing Commercial Solutions for Therapeutic Proteins*") describes the challenges associated with this switch from low-molecular-weight orally available molecules to parenterals. The chapter describes all key steps of pharmaceutical development from formulation over devices and quality design to ensure a successful and target product profile-driven formulation development.

Clinical development's remit is under full transformation, from a discipline whose primary deliverable was drug approval to an area of expertise where new and neglected aspects of the right use of medications come together. **Markus Hinder and Alexander Schuhmacher** review in "*The Evolution of Clinical Development: From Technical Success to Clinical Value Creation*" how the road to technical success has continued and will continue to evolve and which new

aspects need to be integrated during the process of clinical development to finally provide a drug which benefits the individual and society. The chapter highlights and provides concrete examples how this process will become more patient-centric, successful, and efficient by integrating knowledge early on the different customer's needs in the field.

Finally and in a more holistic way, **Nigel McCracken** describes the role of "*Translational Development*" within today's pharmaceutical business to help translate basic research into clinical utility. He also outlines the multidisciplinary tools and the highly collaborative approaches that are used to deliver a specific development solution designed to maximize the risk–benefit ratio of a new drug. Therefore, he answers the following questions: what is translational development, and where does it fit into the drug development process? What are the main types of activities where translational development provides a value for the development of a new drug?

In a next step to examine the critical path of value creation in the pharmaceutical industry, the book focuses more on business-related aspects of pharmaceutical R&D.

In a book chapter with the title "*40 Years of Innovation in Biopharmaceuticals: Will the Next 40 Years Be as Revolutionary?*," **Mathias Schmidt** and colleagues present that the invention of recombinant DNA technology and the ability to generate mAbs have revolutionized the pharmaceutical industry and the way serious diseases are treated. The chapter will review milestones and innovations along the success path of mAbs and other biologics and will critically challenge successes and setbacks. They also introduce the next wave of innovation for mAbs that is focusing on miniaturized antibodies, novel binding scaffolds, bispecific antibodies, oral availability, antibody–drug conjugates, permeation of the blood–brain barrier, and targeting of biologics to the cytoplasm.

Pierre Morgon's first chapter in this book ("Vaccines: *Where Inertia, Innovation, and Revolution Create Value, Simultaneously and Quietly*") provides an overview on the space and role of vaccines within the healthcare sector, the emergence of novel immunization approaches, the drivers of immunization, and its fast growth as a product segment. In addition, we will analyze why innovation is needed along the whole value chain of the vaccine business and who will be a player that might drive this business in the future.

In his second book chapter ("*The Patient-Centric Pharma Company: Evolution, Reboot, or Revolution?*"), **Pierre Morgon** provides new trends that are affecting the players in the healthcare sector and that are driving the increasing focus on real-life patient data in the course of the process of clinical development. And we will illustrate why patient satisfaction should be the ultimate performance indicator of healthcare procurement.

Subsequently, the authors of the Chapters 15–21 address the more management-related topics that impact the value-creation potential of pharmaceutical R&D. Chapters 15–19 review the impact of open innovation, outsourcing, out-licensing, new business models, and leadership styles on the efficiency and productivity of pharmaceutical R&D and illustrate the newest

trends in these fields. Chapters 20 and 21 describe portfolio management and the management of intellectual property (IP) rights as key success factors.

With the book chapter on open innovation ("*The Pharmaceutical Industry Is Opening Its R&D Boundaries*"), we provide a sound basis to understand the complex of open innovation. It begins with a comparison of closed versus open innovation and an insight into the open innovation process. **Alexander Schuhmacher and Ulrich Betz** offer an overview of the more traditional elements of open innovation in the pharmaceutical industry, such as target scouting, research collaborations, drug licensing, outsourcing, and joint ventures. In addition, they provide examples of new open innovation initiatives in the pharmaceutical business, for example, new frontier sciences, drug discovery alliances, private–public partnerships, innovation incubators, virtual R&D, crowdsourcing, open-source innovation, innovation camps, and fluctuating open teams. Finally, the role of open innovation in new R&D business models is examined, and the open and virtual innovation model "knowledge leverager" is explained in detail.

While in-licensing is a key source of new drug development, out-licensing does not play a central role in pharmaceutical companies' R&D strategies yet. **Oliver Gassmann** and colleagues describe in their book chapter "*Out-Licensing in Pharmaceutical Research and Development*" how out-licensing can contribute to an increase in R&D efficiency. Therefore, the authors address the following questions: What is the relevance of R&D collaborations in the pharmaceutical industry? What are the drivers of out-licensing? And how is out-licensing managed in R&D organizations?

Outsourcing has originally been established as an off-the-shelf service in the pharmaceutical industry decades ago to reduce R&D costs and to increase R&D flexibility. **Antal K. Hajos** ("*Trends and Innovations in Pharmaceutical R&D Outsourcing*") describes the fundamental changes in the clinical research organization (CRO) industry that have happened in the past years and the development of outsourcing as a strategic partnership option. In addition, he illustrates how the CRO industry has started to become more differentiated into global players, specialist, and niche providers.

Next, the book chapter on "*New Innovation Models in Pharmaceutical R&D*" illustrates the consequences and measures that have been taken in the past years as a result of the historically low success rates in R&D. We outline the development in pipeline sizes of multinational pharmaceutical companies as we illustrate the R&D investments and the measures that have been taken in the past years to reduce the R&D costs. Finally, **Alexander Schuhmacher, Markus Hinder, and Oliver Gassmann** discuss and review some R&D models that were developed to increase R&D efficiency.

In his book chapter on "*The Influence of Leadership Paradigm and Styles on Pharmaceutical Innovation*," **Aubyn Howard** sets the topic of innovation within the context of leadership. He shows how both collective leadership paradigms and individual leadership styles influence the process of innovation in the pharmaceutical industry. Furthermore, he shows how the challenges that the industry is facing are contextualized within a wider process of transformation and evolution

within organizations and society today. Finally, we are providing information of how leadership paradigms and styles can impact the capacity of pharmaceutical companies to enable innovation.

With Chapters 20 and 21, the authors complete our view on pharmaceutical R&D by providing their insights on both portfolio and IP management in today's pharmaceutical world.

As it is becoming more and more expensive and risky to develop an NCE (New Chemical Entity), pharmaceutical companies need to make sure that their portfolio of drug candidates is well balanced financially and risk-wise. According to the authors **Joachim Greuel and Axel Wiest**, a primary goal of portfolio management is to ensure that an entire R&D portfolio is successful while allowing individual projects to fail. With their book chapter "*The Role of Modern Portfolio Management in the Pharmaceutical Industry*," they describe that since H. M. Markowitz was awarded the Nobel Memorial Prize in Economic Sciences in 1990 for his pioneering work in modern portfolio theory, portfolio management has been a main pillar in asset allocation and financial investment. However, the benefit of portfolio management for the pharmaceutical industry is still controversial. Although most larger pharmaceutical companies report to have implemented portfolio management processes, some question whether a portfolio management system leads to a higher R&D productivity. The authors put a hypothesis forward suggesting that pharmaceutical portfolio management is not only important to allocate resources and optimize project management from a strategic perspective. It may be seen as a crucial enabling element in the entire pharmaceutical innovation process.

Finally, the purpose of the book chapter "*Patent Management Through the innovation Lifecycle*" is to provide an overview of the role of patents in today's pharmaceutical business. The authors **Martin Bader and Oliver Gassmann** provide best practice examples of the pharmaceutical industry and outline how patent management is done in the environment of low R&D efficiency. Therefore, the authors answer the questions of what are the challenges that companies face when managing patents and how can patents be managed throughout the product life cycle.

Reference

Paul, S.M. *et al.* (2010) *Nat. Rev. Drug Discovery*, **9**, 203–214.