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Biopharmaceutical Innovation at a Glance

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Summary

Biopharmaceutical Research & Development (R&D) aims at finding new modalities to diagnose, prevent, and treat human diseases. Prototypes of innovative approaches are tested in biological systems of increasing size, complexity, and relevance. The early phase spans from individual receptors over cell, organ systems to first therapeutic exploration in small and well-defined patient populations. This exploratory phase ends once clinical proof of concept (PoC) is established. Subsequently, large clinical programs are undertaken to confirm the efficacy and (if applicable) superiority of the new approach by means of long clinical programs. Health authorities around the world play a key role in this process. During the clinical test phase, together with the biopharmaceutical companies, they surveil and ensure the scientifically sound and safe conduct of clinical trials. In a second step, health authorities review the entire data set that has been generated during both the exploratory and the confirmatory phases. If, based on these data, they come to conclude that the benefits conferred to the patients outweigh the risks, authorization to market the drug in the respective country is conferred. In order to get reimbursed, approved new drugs need to undergo an economic review process. There the decision is made if the new drug confers enough clinical benefits to justify its price. The drug approval process and the economic evaluation/reimbursement process are two distinct processes carried out by different institutions.

Although R&D leverages a number of academic disciplines like epidemiology, genetics, biology, chemistry, bioinformatics, pharmacology, toxicology, pharmacy, and medicine, it is not primarily an academic discipline and cannot be studied in one program at a university. It is difficult to find coherent overarching information on

Principles of Biomedical Sciences and Industry: Translating Ideas into Treatments, First Edition. Edited by Markus Hinder, Alexander Schuhmacher, Jörg Goldhahn, and Dominik Hartl.

concepts generally applicable to the industry beyond individual company processes. Thus, this book attempts to bridge this gap and provide an overview and concepts and reliable details which apply across the industry and are valuable for everyone working in or with the biopharmaceutical industry.

Tools

- Pharmacology
- Pharmacokinetics
- Toxicology
- Clinical studies
- Project and portfolio management
- IP management

Regulatory framework

- National and regional drug approval regulations
- International Conference on Harmonization (ICH)
- Declaration of Helsinki (DoH)

Risks

- Strategic risks, such as enormous R&D investments
- External risks, such as drug approval regulations
- Internal risks, such as degree of predictivity of early trials for late-stage development

Success factors

- Understanding molecular mechanisms
- Disease understanding
- Biomarkers

1.1 Biopharmaceutical Innovation and Drug Development, the Past and Present

'Définissez les termes, vous dis-je, ou jamais nous ne nous entendrons'.
Voltaire (François-Marie Arouet 1694–1778)
If you wish to converse with me, define your terms.

To alleviate or even cure human disease has always been an area of paramount interest and activity of mankind. Documentation from around the globe (e.g. Middle East, India, China, America) indicates that since ancient times people observed and collected information about techniques to treat human disease. The oldest available documents are approximately 4000 years old and date from approximately 2000

B.C. (papyrus Ebers (1500 BC) and papyrus Kahun (1800 BC)). From ancient times up to the Middle Ages, the key source to finding ways to treat human disease were trial and observation and in many cases folk memory to preserve useful knowledge. Thus, the first treatments were rather found by chance than actively discovered.

Pharmacology as a scientific discipline, which deals with the discovery and characterization of xenobiotics to treat diseases, is a relatively young discipline and had to wait until physics, chemistry, and biology had established themselves as sciences and laid the foundations for a scientific understanding of human health and disease.

Until the 1950s, classical (forward) pharmacology dominated the scientific approach to find new medicines. During this time, most of the discoveries focused mainly on medications providing symptomatic amelioration or relief as opposed to changing long-term prognosis of patients suffering from a disease or treatment of risk factors (Drews 2000).

Drug approval in the early days was often restricted to small series of clinical tests demonstrating that the desired effects were detectable. Systematic testing in broad populations of interest and a systematic approach to investigating a drug's preclinical and clinical safety only became a prerequisite on both sides of the Atlantic after two drug disasters became public (1930 Sulfanilamide and 1960 Thalidomide) (Paine 2017; Silverman 2002). Subsequently, more and more processes and standards which were related to drug discovery and more importantly drug approval became standardized and regulated – thus today's notion of a highly regulated industry.

In 1990, the Japanese Ministry of Health, Labour and Welfare (MHLW), the American Food and Drug Administration (FDA), and the European Medicines Evaluation Agency (EMEA, today EMA) agreed on common procedures and standards that apply to the investigation approval of new drugs in all three countries and regions. These standards are laid down in the documents of the 'International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use', often just called ICH (ICH, n.d.). From the 1990s on, some researchers started to discuss a 'productivity crisis' in the biopharmaceutical industry. Since these times, productivity, determined as the number of new drugs approved, and efficiency, determined as the ratio of investments needed by the number of new drugs approved, are figures that are constantly watched by decision makers inside and outside of the biopharmaceutical industry. Recent analyses indicate that discovering and bringing a new drug to the market need investments in the range of US$ 5–10 billion (Schuhmacher et al. 2016).

The more drugs became available to treat a specific condition and the more drugs were used as chronic or preventive treatments, the more long-term clinical safety became a focus area. Altered benefit/risk assessments in this context led to marketing withdrawals for numerous approved drugs from nearly all therapeutic areas. Prominent examples include some fluoroquinolone antibiotics, some peroxisome proliferator-activated receptor agonists, cyclooxygenase 2 inhibitors and anti-histaminics and ant-psychotics, just to name a few. Based on these experiences, health authorities started to require prior to approval of a new medicine an active risk exclusion approach. In other words, the long accepted 'no difference approach'

to demonstrate clinical safety was abandoned by an active process able to rule out a certain degree of hazard (Brass et al. 2006).

The core responsibility of a pharmaceutical company towards society is to discover and develop solutions which help patients to lead a better and longer life. In order to generate the necessary cash flow which can be invested in R&D, many companies have focused in the past on the so-called blockbuster model, i.e. on products with worldwide sales in excess of US$ 1 billion/year. Traditionally, these were products at relatively low daily dosage cost in highly prevalent diseases and thus large worldwide populations. Triggered by an improved mechanistic understanding of diseases and genetics enhancing the identification of new drug targets, the biopharmaceutical sector has developed in recent years more and more medicines to treat so-called orphan diseases which by definition affect less than 1 in 2000 people (Trusheim et al. 2007). By today, orphan drugs represent around one-eighth of worldwide prescription drug sales indicating the importance of this new market segment (Waters and Urquhart 2019).

With more and more competitive drugs entering the market and the availability of a plethora of therapeutic options in the highly prevalent diseases, the question arises, how to best invest scarce healthcare resources. As a reaction, payors around the globe have at different pace and to different extent started to ask the 'value for money' question. This has led to a situation, where a new drug today needs to conform or exceed the quality, safety efficacy (QSE) requirements set forth by health authorities to gain marketing authorization on the one hand. On the other hand, these new medicinal products need to demonstrate their cost-effectiveness before they can be reimbursed by national health insurers and other payors.

1.2 Why We Wrote This Book and What Readers Can Expect to Gain from Reading It

Biopharmaceutical sciences and pharmaceutical innovation belong to the highly innovative, cost-intense, high tech endeavours which can provide important progress to both the individual and the society.

Finding and developing a new medicine is a complex undertaking which requires many diverse scientific disciplines with different scientific languages and ways of thinking to collaborate effectively and efficiently towards a common goal over many years.

The editors of this book realized through own experience as academicians and as associates in the biopharmaceutical industry, as well as university lecturers that becoming a drug hunter or developer is a year-long, often unstructured process and that biopharmaceutical innovation and the art and science of drug development are not yet established as an academic university discipline. Universities are home to excellent disciplines wh are an essential part of the pharmaceutical value chain. As academic institutions, their scope is broader and contributions to pharmaceutical innovation often are a more peripheral aspect of their overall work. Equally important, the integrating, connective band between the multiple critical academic

disciplines is frequently not established. Accordingly, it is challenging to gather coherent overarching information on concepts generally applicable to the industry beyond individual company processes.

This book aims to provide a comprehensive and coherent insight into pharmaceutical R&D and related functions, such as business development and market entry. In general, biopharmaceutical R&D relies on external innovation and on qualified academics transitioning from basic and clinical research into pharmaceutical industry. Drug discovery and development in biopharmaceutical companies, however, usually is an internally focused process and easily perceived by industry outsiders as a 'black-box' without insights into strategies and operations, making it difficult for academics to consider and prepare for a career in R&D in pharmaceutical industry. Based on feedback from industry-internal and academic-external colleagues and stakeholders, we identified the clear unmet need to map out the different phases and frameworks of drug discovery, drug development, business development, and market access within the pharmaceutical industry. Pharmaceutical R&D makes intensive use of a broad number of academic disciplines, including epidemiology, genetics, biology, chemistry, biochemistry, bioinformatics, pharmacology, toxicology, pharmacy, veterinary medicine, and medicine.

This book covers all relevant disciplines along the pharmaceutical value chain, introduces key success-critical concepts to find, select, and develop new drugs, as well as introduces the reader into basic concepts and the technical jargon of integrated drug developers. All book authors are recognized experts in their respective areas. They know the ins and outs of their disciplines from a theoretical perspective, they all know from own practical work which parts of the theory are critically important and wrote their respective chapters with the reader and future application of knowledge in mind. The chapters include comprehensive referencing for readers who want to get down to the primary sources and in many cases contain practical examples and illustrations.

The editors believe that this book can bridge and close the existing knowledge gap and therefore provides a comprehensive overview on different components, phases, and frameworks of biopharmaceutical R&D, with broad relevance across pharmaceutical industries and valuable for a broad readership working either in, together with or interested in joining the biopharmaceutical industry.

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