Part I
Introduction

Pharmacokinetics and Pharmacodynamics of Biotech Drugs: Principles and Case Studies in Drug Development. Edited by Bernd Meibohm

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The Role of Pharmacokinetics and Pharmacodynamics in the Development of Biotech Drugs

Bernd Meibohm

1.1
Introduction

During the past two decades, advances in biotechnology have triggered the development of numerous new drug products. This group of so-called biotech drugs is a subset of the therapeutic group of biologics. Therapeutic biologic products, or biologics, are defined by the U.S. Food and Drug Administration (FDA) as any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man. Biologics are a subset of drug products distinguished by their manufacturing process. While classical drugs are synthesized via a chemical process, biologics are manufactured utilizing biological processes and are typically derived from living material – human, plant, animal, or microorganism. Biotech drugs can be considered as those biologics that are manufactured using biotechnology-based production processes.

The similarity in the drug development and evaluation process for biotech drugs and conventional, chemically synthesized drugs has recently been acknowledged in the FDA's 2003 decision to transfer certain product oversight responsibilities from the Center for Biologics Evaluation and Research (CBER) to the Center for Drug Evaluation and Research (CDER). The biologics for which oversight was transferred include monoclonal antibodies for *in vivo* use, proteins intended for therapeutic use, including cytokines (e.g., interferons), enzymes (e.g., thrombolytics), growth factors, and other novel proteins that are derived from plants, animals, or microorganisms, including recombinant versions of these products, and other non-vaccine and non-allergenic therapeutic immunotherapies. Classical biologics such as blood, blood components and vaccines remain under the regulatory authority of the CBER. Even under this new structure, however, the biologic products transferred to the CDER will continue to be regulated as licensed biologics – that is, a Biologic License Application (BLA) must be submitted to obtain marketing authorization as compared to a New Drug Application (NDA) which is used for traditional, chemically manufactured drug products.

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For the purpose of this book, biotech drugs include not only therapeutically used peptides and proteins, including monoclonal antibodies, but also oligonucleotides and DNA preparations for gene therapy. Although oligonucleotides are, due to their chemically defined production process, classified by the FDA as classical drugs requiring an NDA prior to marketing authorization, and DNA preparations for gene therapy are regulated by the CBER, they are both included in the class of biotech drugs as their therapeutic application relies heavily on the principles of molecular biology and they are considered by analysts as biotech compounds.

1.2 Biotech Drugs and the Pharmaceutical Industry

In parallel with the development of the discipline of biotechnology during the past two decades, an increasing fraction of pharmaceutical R&D has been devoted to biotechnology-derived drug products. It has been estimated that more than 250 million patients have benefited from already approved biotechnology medicines to treat or prevent heart attacks, stroke, multiple sclerosis, leukemia, hepatitis, rheumatoid arthritis, breast cancer, diabetes, congestive heart failure, kidney cancer, cystic fibrosis and other diseases [1]. This number is expected to increase significantly with the introduction of new biotech drugs into the marketplace. According to a survey by the Pharmaceutical Research and Manufacturers of America (PhRMA) in 2004, 324 biotechnology medicines were in development for almost 150 diseases. These include 154 medicines for cancer, 43 for infectious diseases, 26 for autoimmune diseases, and 17 for AIDS/HIV and related conditions. These potential medicines – all of which were at the time of the survey either in human clinical trials or under review by the FDA – will enlarge the list of 108 biotechnology medicines already approved and available to patients (Fig. 1.1) [1].

Biotech and genomic companies currently perform almost one-fifth of all pharmaceutical R&D, and this figure is set to double during the next 10 years [2]. It has been suggested that over half of all the New Active Substances developed during the next 10–15 years will result from research into antibodies alone. Biotechnology products accounted for more than 35% of the 37 New Active Substances that were launched in 2001 [2]. This success in drug development is underlined by the fact that several biotech drugs have achieved blockbuster status, earning more than US$ 1 billion in annual sales, including Epoetin-α (Epogen/Procrit/Eprex), interferon-α2b (IntronA, PEG-Intron/Rebetron combination therapy), and filgrastim (Neupogen) [3].

Since the development of biotech drugs generally rests on a fundamental understanding of the related disease, their clinical development has also proven to be more successful than for conventional, chemically derived small-molecule drugs. Only 8% of the new chemical entities that entered the clinical phases of drug development between 1996 and 1998 reached the market, compared to 34% of biotech drugs (Fig. 1.2). This means that biologics have, at the time of their first-in-

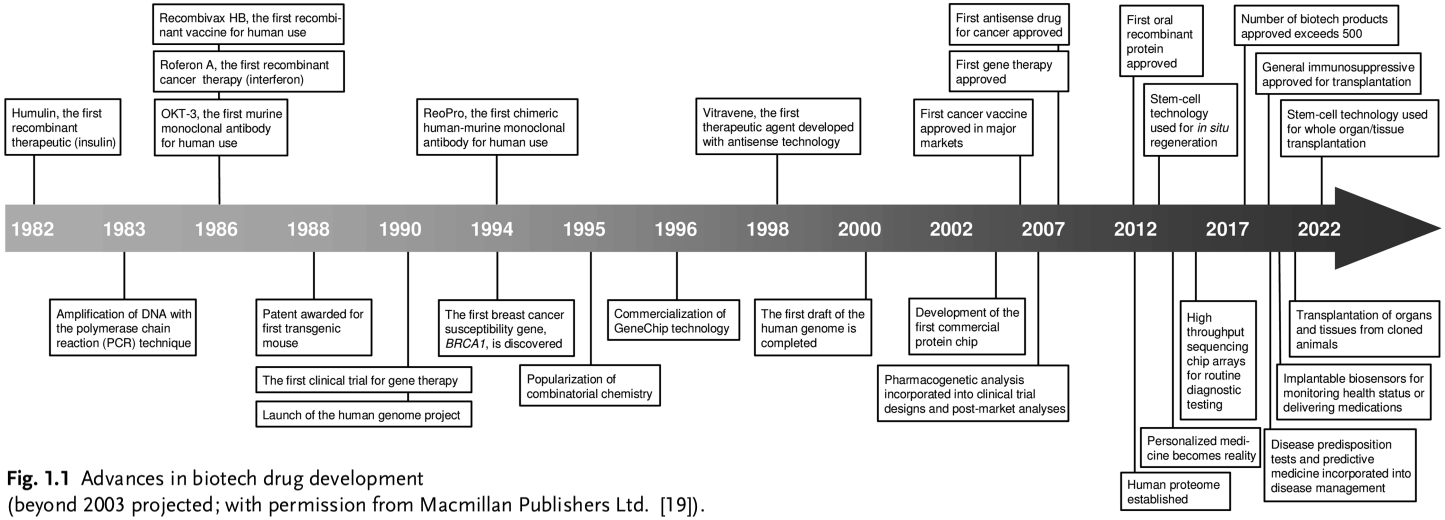

Fig. 1.1 Advances in biotech drug development
(beyond 2003 projected; with permission from Macmillan Publishers Ltd. [19]).

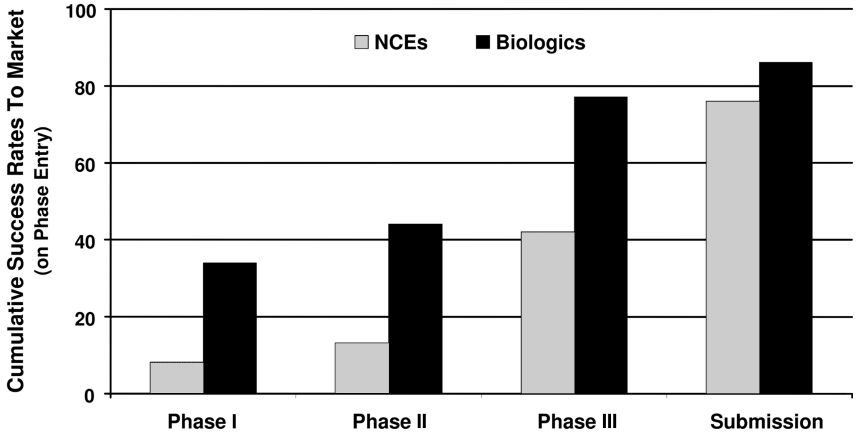

Fig. 1.2 Success rates for clinical drug development are much higher for biologics than for traditional, chemically defined drug compounds. NCE: New chemical entity (modified from [2]).

man studies, a fourfold greater chance than traditional, chemically defined drugs of making it into the marketplace. Thus, greater use of biologics will likely reduce the attrition rate at every stage of the clinical drug development process [2]. Based on these facts, it can be predicted that biotech drugs will play a major – if not dominant – role in the drug development arena of the next decades.

1.3 Pharmacokinetics and Pharmacodynamics in Drug Development

The general paradigm of clinical pharmacology is that administration of a dose or the dosing regimen of a drug results in defined drug concentrations in various body compartments and fluids. These are, in turn, the driving force for the drug's desired and undesired effects on the human body that collectively constitute the drug's efficacy and safety profile. Based on this paradigm, the basis for the pharmacotherapeutic use of biotech drugs is similar to that of small molecules – a defined relationship between the intensity of the therapeutic effect and the amount of drug in the body or, more specifically, the drug concentration at its site of action (i. e., an exposure–response relationship). The relationship between the administered dose of a drug, the resulting concentrations in body fluids and the intensity of produced outcome may be either simple or complex, and thus obvious or hidden. However, if no simple relationship is obvious, it would be misleading to conclude *a priori* that no relationship exists at all rather than that it is not readily apparent [4, 5].

The dose–concentration–effect relationship is defined by the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of a drug. Pharmacokinetics comprises all processes that contribute to the time course of drug concentrations

in various body fluids, generally blood or plasma – that is, all processes affecting drug absorption, distribution, metabolism, and excretion. In contrast, pharmacodynamics characterizes the effect intensity and/or toxicity resulting from certain drug concentrations at the assumed effect site. When simplified, pharmacokinetics characterizes "what the body does to the drug", whereas pharmacodynamics assesses "what the drug does to the body" [6]. Combination of both pharmacological disciplines by integrated PK/PD modeling allows a continuous description of the effect–time course resulting directly from the administration of a certain dose (Fig. 1.3) [4, 5].

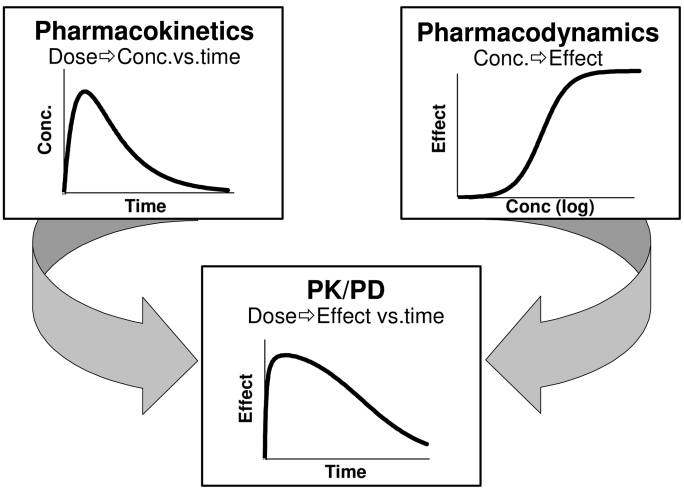

Fig. 1.3 Pharmacokinetic/pharmacodynamic (PK/PD) modeling as combination of the classic pharmacological disciplines pharmacokinetics and pharmacodynamics (from [5]).

The increased application and integration of PK/PD concepts in all stages of preclinical and clinical drug development is one potential tool to enhance the information gain and the efficiency of the decision-making process during drug development [7]. PK/PD analysis supports the identification and evaluation of drug response determinants, especially if mechanism-based modeling is applied [8]. PK/PD analysis also facilitates the application of modeling and simulation (M&S) techniques in drug development, and allows predictive simulations of effect intensity-time courses for optimizing future development steps.

Pharmaceutical drug development has traditionally been performed in sequential phases, preclinical as well as clinical Phases I to III, in order to answer the two basic questions – which compound should be selected for development, and how it should be dosed. This information-gathering process has recently been characterized as two successive learning-confirming cycles (Fig. 1.4) [8, 9]. The first cycle (traditional Phases I and IIa) comprises learning – in healthy subjects – what dose is tolerated and confirming that this dose has some measurable bene-

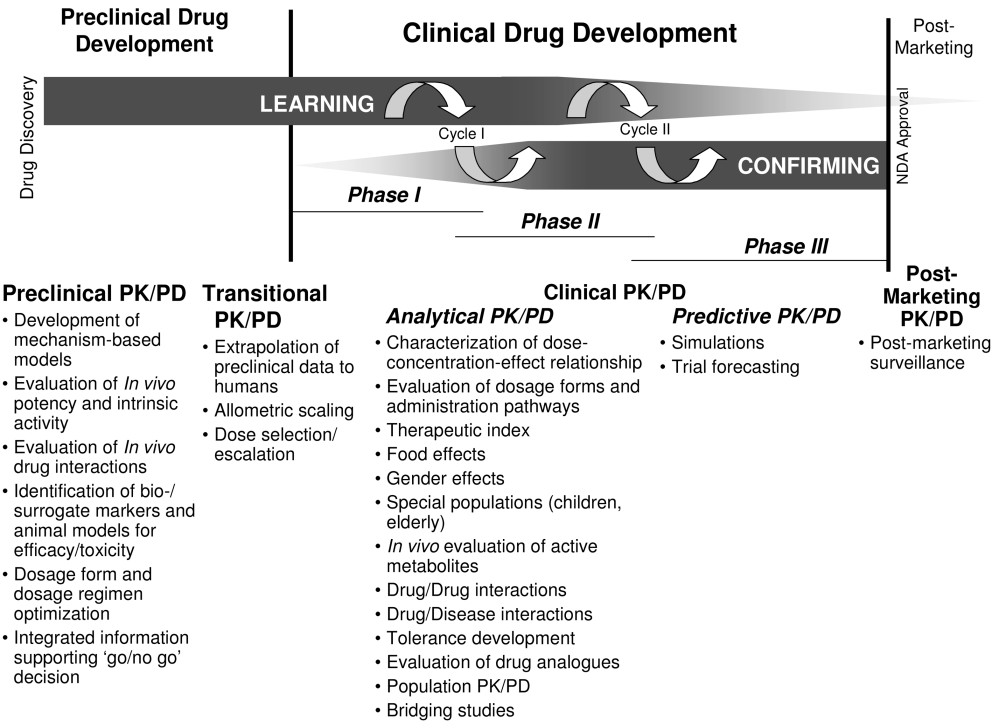

Fig. 1.4 Examples of the application of pharmacokinetic/pharmacodynamic (PK/PD) concepts in preclinical and clinical drug development (from [10]).

fits in the targeted patients. An affirmative answer at this first cycle provides the justification for a larger and more costly second learn–confirm cycle (Phases IIb and III), where the learning step is focused on how to use the drug in representative patients for maximizing its benefit/risk ratio, while the confirming step is aimed at demonstrating an acceptable benefit/risk ratio in a large patient population. It has repeatedly been suggested to leave the sequential approach of preclinical/clinical phases and to streamline drug development by combining preclinical and early clinical development as parallel, exploratory endeavors and to expand the learning process to all phases of drug development. Such a strategy might provide a deeper understanding of the drug's action prior to taking it further in development. This will ensure that the limited resources available in drug development are allocated to the most promising drug candidates [10].

For several years, the widespread application of PK/PD concepts in all phases of drug development has repeatedly been promoted by industry, academia, and regulatory authorities [11–16]. Rigorous implementation of PK/PD concepts in drug product development provides a rationale, scientifically based framework for efficient decision-making regarding the selection of potential drug candidates, for

maximum information gain from the performed experiments and studies, and for conducting fewer, more focused clinical trials with improved efficiency and cost-effectiveness [2, 10]. Examples of applications of PK/PD in drug development are provided in Figure 1.4.

1.4 PK and PK/PD Pitfalls for Biotech Drugs

Pharmacokinetic and pharmacodynamic principles are equally applicable to conventional small-molecule drugs and biotech drugs such as peptides, proteins, and oligonucleotides. Since biotech drugs are frequently identical or similar to endogenous substances, however, they often exhibit unique pharmacokinetic and pharmacodynamic properties that are different from traditional small-molecule drugs and resemble more those of endogenous macromolecules.

The distribution and metabolism of protein-based biotech drugs, for example, generally follows the mechanisms of endogenous and nutritional proteins. This includes, for example, unspecific proteolysis as a major elimination pathway for proteins rather than oxidative hepatic metabolism typical for the majority of small-molecule drugs. As a consequence, drug interactions studies focused on cytochrome P-450 enzymes do not usually need to be performed for protein-based biotech drugs [17].

Due to their structural similarity as polypeptides, it is generally much easier for peptide-based biotech drugs to predict how they will be distributed, metabolized and eliminated, and they typically have much faster development cycles. As the handling of peptides is relatively well preserved between different mammalian species, this also implies that knowledge generated in pharmacokinetic studies in animals can be extrapolated to predict the situation in humans with a relatively high reliability. Thus, allometric scaling is usually much more successful for biotech drugs than for traditional small-molecule compounds [17].

Another pharmacokinetic feature frequently observed for biotech drugs, but only rarely seen for traditional small-molecule drugs, is target-mediated drug disposition [18]. In this case, interaction of the drug with its pharmacological target is not reversible, but initiates the elimination of the drug, for example through intracellular metabolism after internalization of a drug–receptor complex. If the number of pharmacological target molecules is in the same magnitude or larger than the number of drug molecules, drug elimination via interaction with the pharmacological target may constitute a substantial fraction of the overall elimination clearance of the drug. In this case, pharmacokinetics and pharmacodynamics are no longer independent processes, but become inseparable and bidirectionally interdependent, in contrast to being unidirectionally interdependent as is the case if drug concentrations determined by pharmacokinetics are the driving force of drug effect via the concentration–effect relationship described by pharmacodynamics.

Target-mediated drug disposition is often associated with nonlinearity in the pharmacokinetics of the affected drug, as the elimination pathway mediated via

interaction with the pharmacological target is frequently saturated at therapeutic concentrations. The consequence is an over-proportional increase in systemic exposure with increasing dose once this elimination pathway becomes saturated.

As mentioned earlier, one of the reasons for the success of biotech compounds in drug development is the fact that the biological approach rests on a fundamental understanding of the disease at the molecular level [2, 19]. Nevertheless, nonlinear pharmacokinetics, target-mediated disposition, as well as their metabolic handling may not only pose extra challenges, but also provide opportunities during the preclinical and clinical development of biotech drugs that are different from small-molecule drug candidates and may require additional resources and unique expertise. Some of the associated challenges, pitfalls and opportunities will be addressed in the subsequent chapters of this textbook.

1.5 Regulatory Guidance

Regulatory guidance documents supporting the drug development process with regard to pharmacokinetics and PK/PD evaluations have, in general, a similar relevance for biotech drugs as they have for traditional, chemically defined small-molecule compounds. These include for example the exposure–response guidance document from 2003 [20] and the population pharmacokinetics guidance document from 1999 [20] as issued by the FDA, and the ICH E4 guideline on "Dose Response Information To Support Drug Registration" [21] of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

Additional guidance documents, however, have been issued that address the specific needs of and requirements for biotech drugs. Besides specific guidance documents for biologics with regard to chemical characterization, stability and manufacturing, there are also documents affecting clinical pharmacology evaluations. The ICH S6 guideline on "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals", for example, addresses among other topics preclinical pharmacokinetics and pharmacodynamics as well as exposure–response and drug metabolism studies [22].

1.6 Future

Biotech drug development is frequently described as occurring in waves. The initial wave occurred following the introduction of recombinant human insulin in 1982, and comprised recombinant endogenous proteins. The introduction of multiple monoclonal antibodies into pharmacotherapy constitutes the second wave of

innovation. Further waves are expected to occur during the second part of this decade, with the widespread introduction of humanized or fully human monoclonal antibodies and the marketing approval of antibody-derived products such as antibody fragments and fusion proteins [23].

The further development and promotion of model-based drug development through the FDA's critical path initiative is likely to further foster the application of PK/PD concepts and M&S in the development of biotech drug compounds. This move is further bolstered by initiatives of the pharmaceutical industry as well as professional organizations in pharmaceutical sciences and clinical pharmacology to embrace a more holistic and integrated approach to quantitative methods in drug development stretching from drug discovery to post-marketing surveillance, with PK/PD-based M&S at its core.

In the near future, one of the major challenges for the biotech industry, as well as for the regulatory authorities, will be the introduction of biogeneric drugs, also termed biosimilar drugs or "follow-on" biologics. This group of drugs is the biotech analogue of generic drug products for traditional small-molecule compounds. Biogenerics have been defined as new protein drug products that are pharmaceutically and therapeutically equivalent to a reference product, for example an innovator product after expiration of its patent protection.

The activity of those biotech drugs that are macromolecules is often dependent upon their conformation, which is based on the secondary, tertiary and sometimes quaternary structure. As conformational changes can result in changes of the drug's activity profile, it is crucial to ensure that the essential conformational features are maintained in biogeneric compared to innovator products. This situation is further complicated by the fact that the manufacturing conditions are largely determining the final product, and that changes in this process may already result in activity changes, for example conformational changes or changes in the glycosylation pattern. In addition, there is often only limited knowledge available as to which features are essential for the biotech drug's *in-vivo* effectiveness [24]. Although the extensive discussions on biogeneric products are still ongoing, the European Medicines Agency (EMEA) has recently issued a "Guideline on Similar Biological Medicinal Products" [25]. In this document, the EMEA argues that the standard generic approach for the establishment of bioequivalence applied to chemically derived small-molecule drugs is not appropriate for biologics or biotechnology-derived drug products due to their complexity. Instead, a "similar biological medicinal products" approach, based on a comparability exercise, must be applied. The issue of biogenerics is discussed in detail in Chapter 8.

Biotech drugs, including peptides, proteins and antibodies, oligonucleotides and DNA, are projected to cover a substantial market share in the healthcare systems of the future. It will be crucial for their widespread application in pharmacotherapy, however, that their respective drug development programs are successfully completed in a rapid, cost-efficient and goal-oriented manner. Model-based drug development utilizing pharmacokinetic and pharmacodynamic concepts including exposure–response correlations has repeatedly been promoted by industry, academia, and regulatory authorities for all preclinical and clinical phases of

drug development, and is believed to result in a scientifically driven, evidence-based, more focused and accelerated drug product development process [10]. Thus, PK/PD concepts are likely to continue expanding their role as a cornerstone in the successful development of biotech drug products in the future.

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