PRECLINICAL SAFETY EVALUATION OF BIOPHARMACEUTICALS

A SCIENCE-BASED APPROACH TO FACILITATING CLINICAL TRIALS

Edited by

Joy A. Cavagnaro
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FOREWORD

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Biopharmaceutical research represents the use of various biotechnology techniques to discover and manufacture potential new medicines, to test their safety, and to prove their value in treating or preventing disease in humans and animals. It employs the skills and hard work of discovery and development scientists, pharmacologists, immunologists, toxicologists, pharmacokineticists, pharmacists and manufacturers, clinical scientists, and clinical research organizations representing the public interest, healthy and patient volunteers, ethics committees, and regulatory agencies.

The public, venture capitalists, media, and even novelists have looked to biotechnology for health care solutions with high expectations. Bringing the safest possible new medicines into public use is critical for society as a whole, from human and veterinary medical and economic perspectives, and also to maintain public trust in the industry. However, no drug can ever be "100% safe." Drugs are developed and approved because they show benefits that outweigh foreseeable risks for specific indications in specific populations. Once marketed, a drug can be less safe if it is used in a way that decreases foreseeable benefits, or that increases risks if the actual risks are greater than or differ from the predicted risks. What then are the most appropriate and reasonable ways to answer the essential questions about possible risks versus benefits during the lengthy process of developing a new drug? What can be predicted from preclinical studies and of what value are the predictions?

Before testing new medicines in humans, various in vitro and in vivo preclinical studies are performed in selecting the lead candidate for clinical development. In particular, studies are designed to support a first in human (FIH) dose for phase 1 clinical trials. Phase 1 trials are principally designed to examine safety of single and sometimes several doses in about 20 to 80 study subjects, usually healthy volunteers. Phase 2 trials are designed to confirm safety, determine clinical activity, and help define an optimal dose, usually following one- to three-month dosing, for the subsequent phase 3 trials. Phase 2 are controlled studies of approximately 100 to 300 volunteer subjects with disease. Phase 3 trials are designed to prove efficacy and safety of the drug. These trials are double-blinded and placebo-controlled involving hundreds to

thousands of research subjects with the intended disease in clinics and hospitals. The duration of dosing for drugs administered chronically can last six months or longer. Each phase is supported by in vivo animal studies based on consideration of the population being tested and the duration of the clinical trial. Following the completion of all three phases of clinical trials, the sponsor of the trial analyzes all the data and files a marketing application with one or more regulatory authorities. Once approved, the new medicines become available for physicians to prescribe. For some drugs the process from discovery to approval can take as long as 10 years or more. Sponsors are also required to submit periodic reports, including any cases of adverse reactions and appropriate quality control records even after a product is approved. The phase 4 or postmarketing study commitments, which may involve additional preclinical as well as clinical studies, are for evaluation of long-term effects as well as detection and definition of previously unknown or inadequately quantified adverse reactions and related risk factors.

A pre-approved capitalized cost estimate for development of a new biopharmaceutical has recently been estimated at over $1 billion (US dollars) with $615 million estimated for all R&D costs, including basic research and preclinical development prior to initiation of clinical testing and $626 million for clinical testing [1]. These estimates take into account the significant attrition rates over the course of clinical development.

In order to facilitate clinical development, it is important to define risk and benefit in the most reasonable and appropriate way. Preclinical studies are the foundation for the initial and ongoing assessment of potential risks and as such should be designed in order to realize their maximum value. The primary objective of preclinical safety evaluation studies is to provide data that clinical investigators can use to better predict adverse effects in study subjects and to help researchers design clinical studies that will minimize their occurrence. The same information will also help to guide research toward new, less toxic drugs and, if harmful effects cannot be entirely avoided, to suggest means to lessen or alleviate the adverse actions.

In this context the term "nonclinical" is often used interchangeably with "preclinical," particularly to define the preclinical studies performed after a product has advanced into the clinic (and thus is no longer in the preclinical development phase). Diverse studies are performed at different times to answer specific questions that only become relevant during particular phases of clinical development; for example, carcinogenicity studies are done to answer questions that ultimately arise at the end of lifetime administration to patients. Based on the explicit objective of safety studies to reveal or exclude potential adverse effects *before* they occur in healthy subjects or patients, the term "preclinical" will be used throughout this book to highlight the importance of the data to be derived *prior* to the specific clinical phase they are designed to support.

The expanding role of preclinical safety evaluation has changed the discovery/development interface for conventional small-molecule pharmaceuticals

as well as large-molecule biopharmaceuticals. A larger proportion of scientific staff and resources are required to support research and screening efforts. There has been an increasing emphasis on mechanistic studies, exploratory research, and a systems biology approach to detect and investigate an expanding range of predictable and unexpected harmful effects, always with the intention of improving the predictive value of the positive and negative information obtained.

Major technological advances in platform technologies have had a major impact on the pathways and timelines of pharmaceutical development. These include high-throughput assays for profiling and probing new molecules: "omics" technologies, exposure technologies, delivery technologies, and "informatics" technologies. A number of strategies have evolved to improve the predictive value and increase the safety knowledge based including the validation and acceptance of alternative methods, in vitro cellular models, in silico techniques and animal-based simulation models, use of nontraditional animal models and animal models of disease including humanized transgenic mice, development of noninvasive and minimally invasive technologies, and increased efforts in computational toxicology and data mining have also evolved to improve predictive value and increase the safety knowledge base and provide feedback from failed and successful development programs. A practical challenge has been the prioritization and validation of these innovative technologies.

Integration and optimization of results from early evaluation models have been essential components in improving the predictive value of preclinical studies. Programs have been accelerated through innovative study designs that can incorporate efficacy, pharmacokinetics, and safety/toxicity endpoints in the same model, thus speeding the delivery of safer therapeutic and prophylactic medicines. Lead candidate selection has been advanced by the clinical exploration and acceptance of microdosing and exploratory investigational new drug application (IND) regulatory mechanisms that support early investigation of new drugs in humans based on the results of focused preclinical information sufficient to exclude unacceptable risks and obtained with limited but proportionate expenditure of time and resources. Such strategies meet the goal of hastening development without increasing risks to the subjects involved.

Conventional FIH studies designed to determine the maximum safe dosage while ensuring the greatest possible safety in healthy volunteers may not always suffice to meet clinical needs and development and financial timelines. For accelerated development plans, FIH studies should be designed not only to identify development-limiting adverse effects but to establish proof of concept or initial effectiveness, ideally this may mean studying in an index population (i.e., a disease population). Accordingly preclinical development strategies need to be designed to support early treatment of patients and seamless progress into full clinical development.

Sometimes a product will be shown not to be ready for the widespread use and must go back for refinement. It is, however, very difficult from preclinical

studies or during the early stages of clinical trials to make the decision to stop or delay development because of findings that point to potentially unacceptable risks. When a product is delayed in meeting certain milestones or if it never reaches registration and marketing at all, the consequences can be devastating for the developer, particularly for small, one-product companies. The challenge of preclinical work is to be efficient and effective in order to be able to make the "no go" decision as early as possible in the process to conserve resources and gain insight for future products. This opportunity to discontinue a product's development early and to redirect research and development effort should ultimately lead to better products.

The history of drug development, especially its preclinical aspects, has been one of irregular advances, often based on ad hoc means intended to detect recent clinical problems and adverse effects and commonly based on national expertise and practices. The result was a patchwork of overlapping and even conflicting but commonly mutually exclusive data requirements in different countries. Additional barriers to facilitating clinical development have been the various multiple national and local standards and guidance that often resulted in duplication, inefficiency, and delays. By common consent this "internationally disharmonized state of drug development" slowed and inhibited the development of new treatments for rare and common diseases and led to much waste of scarce and precious resources.

It took many years but eventually careful discussions between regulatory agencies representing the public interest, drug industry, and academic experts led to a continuing international process to agree on guidelines for the different aspects of drug development. In the early 1990s the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) representing industry and regulators in the United States, Europe, and Japan was established to work on international guidelines in the areas of manufacturing (quality), preclinical evaluations (safety), and clinical evaluations (efficacy).

For small molecules, experience with conventional pharmaceuticals (new chemical entities, NCEs) has shown that relatively standardized approaches have generally been appropriate to support clinical development, but for biopharmaceuticals (novel biological entities, NBEs), scientific and clinical appreciation of their special properties has shown that it is unwise to provide detailed general guidelines applicable to every NBE because their nature, actions, and the reactions of the treated recipient differ so greatly between products and biological and clinical circumstances. Thus the broad nature of the information required to assess probable safety prior to obtaining clinical experience can be and has been defined but not the detailed procedures and investigative strategies required in providing it.

In 1997 the ICHS6 guidance on preclinical safety evaluation of biotechnology-derived products [2] introduced the concept of the "case-by-case" approach. This means that each new test article (product) or product class must have a science-based testing program custom prepared for that product

based on its chemistry, pharmacology, kinetics and biological properties and effects, and its clinical indication. This strategic approach replaced naive reliance on what had been done for the last product tested. The testing program is expected to be iterative, as we should learn from and adapt testing to what has been discovered from all previous testing with the product and from advances in biological, physiological, immunological, and pathological understanding. "Science-based" means that the testing program is defendable in terms of the scientific understanding of the biological effects of the product and the testing is performed with an appropriate scientific rationale.

Preclinical safety evaluation of biopharmaceuticals has evolved through the application of scientific insight, historical and anecdotal experiences, and common sense. The scientific community has relied on the exchange of ideas among academia, industry, and regulatory scientists. However, despite the implementation of up-to-date, optimal preclinical testing strategies to assess safety and rigorous product surveillance programs in the clinic, novel biopharmaceuticals sometimes still cause unanticipated adverse clinical effects, contributing to skepticism by some as to the purpose and/or relevance of preclinical studies. It should be realized that unexpected effects may occur because of unknown changes in the product, because of unanticipated actions of the substance and individual or idiosyncratic responses by treated subjects. Tighter pharmaceutical control and better-focused preclinical studies, both guided by past experience of adverse actions, will minimize the first two risks, and cautious investigation of carefully increased doses will limit the potential harm of unusual individual responses. There can be no direct defense against idiosyncratic responses. Fortunately, they are rare, and cautious investigation of each novel substance in humans has protected us against this form of harm, as every clinical study has to balance risk to every subject against the possible benefit to the participant and to humankind in general. The value of prudently designed and conducted clinical studies is so great that they are justifiable provided that precautions are taken that reflect the nature and activities of the biopharmaceutical product and any special features of the subjects to be given it, all interpreted in the light of the basic and preclinical knowledge of the product's actions.

In a world of more fully informed patients, increased public scrutiny, and greater debate about ethics, manufacturers, developers, and regulators are demonstrating increased interest in patient welfare. Many small start-up biotech companies still enter the business to take on the challenges of producing safe and effective products to meet "unmet" medical need despite the high development costs and risk of failure. The expanded use of biotechnology in a broader range of diseases and conditions has opened a public debate about societal issues surrounding the expanded use of biotechnology, such as broadening the use of genetic testing to predict an individual's susceptibility to a particular disease, the use of stem cells for tissue regeneration, the implications of genomic and potentially transmissible changes produced by gene

therapy, and the availability of allograft or xenograft organs and tissues for transplantation.

Heightened public awareness means industry must initiate interactions with regulators and their scientific and medical advisers and with public interest representatives early in development to select the most promising products, to ensure that the rationale for each project is acceptable, and to obtain agreement that the development and testing strategy will provide valid and appropriate information to justify approval of the product as a prescribable medicine. It is important for industry to understand not only the regulatory review process but also to prepare development plans that comply with the process and address particular requirements. It is equally important for regulators to provide guidance that is consistent to enable strategic planning and yet flexible enough to allow tailored development of individual therapies to meet regulatory expectations for individual companies. Industry as a whole will also have to meet their legal and other official expectations.

Creating a cooperative atmosphere and processes to maintain increased trust and easy communication between "regulators" and "industry," meaning scientists, clinicians, and industrialists, is becoming a key element in the growth and strength of the industry, which sees itself as the originator of life-saving, life-enhancing, and life-extending treatments and therapies. In the same way it is no less necessary to maintain trust and ready communication with academics and the public and their representatives and especially with regulators, whose mandate is to protect and enhance the public health.

The publication of the results of clinical trials and preclinical research has resulted in the general understanding that biopharmaceuticals can be toxic as well as beneficial in humans and animals and that many aspects of their toxicity can be studied with relevance in animals. Toxicology as a science has benefited from this experience in many ways by improved and widely applicable understanding of basic biological mechanisms of health and disease and the introduction of novel methods to detect and assess effects. Case-by-case assessment based on science encourages scientific advancement in toxicology and infuses excitement and quality research into safety assessment.

This book is intended to provide a comprehensive account of the past 20 years of biopharmaceutical preclinical development practices. Although the book was written from the viewpoint of biopharmaceutical research, development, and evaluation, the principles and concepts presented can be used for other stakeholders in the clinical research enterprise, including academic research scientists, clinical investigators, ethics committees, venture capitalists, and consultants to the pharmaceutical industry. The goal is to provide a comprehensive reference book for the preclinical discovery and development scientist whose responsibilities span target identification, lead candidate selection, pharmacokinetics, pharmacology, and toxicology and for the regulatory scientist whose responsibilities include the evaluation of novel therapies.

The scope of this book covers the entire clinical development continuum from selection of lead candidate to first-in-human studies to ultimate product

approval. This book is devoted to the principles and practices of preclinical safety evaluation. It is divided into eight parts including (Part I) background, which provides definitions and methods of production of biopharmaceuticals; (Part II) discussion of the principles of ICHS6 and the global implementation of the principles; (Part III) current practices and comparisons to small molecule development; (Part IV) the importance and criteria for selection of relevant species; (Part V) a consideration of the various toxicity endpoints "icities" as they relate to biopharmaceuticals; (Part VI) specific considerations based on each product class; (Part VII) practical considerations in design, implementation, and analysis of biopharmaceuticals; and finally (Part VIII) the ultimate transition to clinical trials. The parts of the book are self-contained but may be interrelated or cross-referenced for more general or specific details.

Many new challenges in biopharmaceutical clinical development lie ahead. New technologies such as nanotechnology, microelectronics, tissue engineering, and regenerative medicine utilizing stem cells are progressing rapidly. These technologies and potential products not yet envisioned will continue to challenge toxicologists. Additional challenges and advances will come from efforts devoted to site-directed delivery or site-specific expression. Open dialogue among scientists who are regulators, academics, or who work in industry will be critical in ensuring that the new products that are safe and effective are made available without unnecessary delay. A regulatory environment that encourages innovation will make this possible. Society has a large role as a neutral facilitator of ongoing discussions and as the receiver of the benefits and risks of the new developments. The concepts, justified uses, and limitations of the new medicines must be explained and understood at all levels of the community. How toxicologists respond to the challenges ahead will influence whether we will continue to seize the opportunity to advance toxicology and enjoy medical and scientific progress or whether we will lose rigor and default to previous inefficiencies and weaknesses as it is often easier to maintain old habits than to develop and justify new approaches.

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In February of 2005 I received an invitation from Jonathan Rose, then assistant editor for sponsoring and acquisitions with Wiley's Scientific, Technical and Medical Division, to develop a book on the preclinical assessment for biopharmaceuticals. Since that time Jonathan Rose has been promoted to Editor of Wiley-Blackwell, and I have become a bit wiser in accepting such invitations in the future.

This book is a reality today because of the dedication of colleagues who accepted the invitation to participate in this comprehensive "bio-knowledge transfer mission." I thank each of them for their expert contributions and for not blocking my e-mails and phone calls during the editing process; I am much the wiser because of their efforts.

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Most of all I thank my husband, Dr. Richard Lewis, and our daughters Sara, Adrianne, and Jacqueline for their unconditional love and support. I dedicate this work to them.

jc

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PART I

BACKGROUND

CHAPTER 1

Biopharmaceuticals: Definition and Regulation

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1.1 INTRODUCTION

Compared with other types of pharmaceutical products, products derived from a biological source or a biotechnological process are structurally complex and involve manufacturing processes that require tight control to ensure their safety, quality, and efficacy. Biological products, because of their sheer size, are orders of magnitude more complicated than small-molecule drugs. This can be seen by a comparison of molecular weight, which can be used as a measure of the size of a given product. Moreover the product arising from the manufacturing process is often not a pure, homogeneous mixture. Rather, various forms of these molecules are usually present in the final product.

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In scientific terms, conventional biological products such as blood-derived clotting products, vaccines, and those derived from high technology such as those employing a recombinant DNA technology are characterized as biological products. Because of these differences in respect of the product characteristics and manufacturing process, the regulatory oversight of biological products is distinguishable from conventional pharmaceutical products based on small molecules. This chapter addresses legal framework governing biological products principally in the United States and in the European Union. The regulatory landscape in Japan is briefly described particularly in relation to the recent changes to Japan's Pharmaceutical Affairs Law.

1.2 UNITED STATES

The United States has one of the most active and sophisticated systems in the world for ensuring the safety and effectiveness of biopharmaceuticals. To understand this system, it is important to understand (1) how the United States defines biopharmaceuticals and biologics, (2) the legal foundations for regulating these products, and (3) the rules that apply during various stages, including research, development, approval, and marketing. This section also highlights how the United States regulates biologics in relation to drugs.

1.2.1 How the United States Defines Biologics and Biopharmaceuticals

US law does not have a single, simple definition for *biologics* or *biopharmaceuticals*. The Food and Drug Administration (FDA) recognizes that most biologic products "are complex mixtures that are not easily identified or characterized" [1]. Traditionally *biologics* are substances that are derived from living organisms, such as humans, animals, plants, and microorganisms [2]. Today *biologics* include these substances as well as those produced by biotechnology [2]. A federal statute defines *biological product* as a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound) that is "applicable to the prevention, treatment, or cure of a disease or condition of human beings" [3]. The corresponding federal regulation uses similar language, but clarifies several key terms [4]:

1. A *virus* is interpreted to be a product containing the minute living cause of an infectious disease and includes filterable viruses, bacteria, rickettsia, fungi, and protozoa, among other things.
2. A *therapeutic serum* is a product obtained from blood by removing the clot or clot components and the blood cells.

3. A *toxin* is a product containing a soluble substance poisonous to laboratory animals or to human in doses of one milliliter or less (or equivalent in weight) of the product, and having the property, following the injection of nonfatal doses into an animal, of causing to be produced therein another soluble substance that specifically neutralizes the poisonous substance and that is demonstrable in the serum of the animal thus immunized.
4. An *antitoxin* is a product containing the soluble substance in serum or other body fluid of an immunized animal that specifically neutralizes the toxin against which the animal is immune.

The regulation also clarifies how additional products may be biologics if they are "analogous" to certain categories of products listed in the definition. A product is a biologic if it is analogous to the following [5]:

1. A *virus*, if prepared from or with a virus or agent actually or potentially infectious, without regard to the degree of virulence or toxicogenicity of the specific strain used.
2. A *therapeutic serum*, if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or a serum.
3. A *toxin* or *antitoxin*, if intended, regardless of its source of origin, to be applicable to the prevention, treatment, or cure of diseases or injuries of human through a specific immune process.

Although these definitions seem to be relatively concrete, biological products come in many forms, including drugs, devices, and "combination" products [6]. The FDA regulates biopharmaceuticals as both drugs and biologics because they meet both definitions. US law, as described above, defines *biological products* by referring to several categories of tangible products. In contrast, the law defines *drugs* by their functions [7]. The term *drug* means "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man" and "articles (other than food) intended to affect the structure or any function of the body of man" [8]. Thus the definitions of *drugs* and *biologics* are not mutually exclusive, which allows the FDA to regulate some products as both.

1.2.2 Legal Foundations for Regulating US Biopharmaceuticals

To understand how biopharmaceuticals are regulated in the United States, it is helpful to understand the underlying legal bases for regulation, how these laws have evolved, and how regulatory responsibility for biologics has shifted. Currently the Public Health Service Act authorizes the FDA to ensure the safety, purity, and potency of biologics. The FDA approves biologics for mar-

keting under section 351 of the Act [9]. The FDA also regulates biopharmaceuticals as drugs under the Federal Food, Drug, and Cosmetic Act. Thus the FDA now delegates responsibility for regulating biopharmaceuticals to two centers within the agency: the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). Regulation under the Public Health Service Act precludes the manufacture of generic, or "follow-on" biologicals and "biosimilars."

The foundations for this regulatory system were set in 1902 with the Biologics Control Act, the first legislation to regulate a specific class of drugs [7]. The Biologics Control Act was a response to tragedies in St. Louis, Missouri, and Camden, New Jersey, in which several people died after taking diphtheria and small pox vaccines [10]. The purpose of the Act was to authorize the regulation of certain biologics, require manufacturers to obtain licensing, and authorize the government to inspect manufacturing facilities [7]. The Act prohibited companies from selling or transporting biologics that were either not manufactured at facilities licensed and inspected by the government or not labeled with the manufacturer's name and an expiration date [7].

Since the 1902 Act, the laws and regulations for biologics have steadily evolved, and responsibility for regulating biological products has shifted several times. In 1903, the federal government issued the first biologics regulations, administered by the Hygienic Laboratory in the Public Health and Marine Hospital Service. The regulations required manufacturers to annually renew their licenses and make their facilities available for unannounced inspections. In 1919, the regulations were amended to require manufacturers to report changes in manufacturing methods, equipment, and personnel. The regulations also required manufacturers to maintain manufacturing records and submit certain product samples for government inspection and approval [7].

These initial laws and regulations laid the foundation for the current biologics regulatory scheme. From the beginning the United States regulated biologics and drugs differently. The government did not regulate nonbiologic drugs until it passed the Pure Food and Drugs Act in 1906, which did not address biologics or the 1902 Biologics Control Act [7]. In fact Congress did not formally recognize the difference between drugs and biologics until after it passed the 1938 Federal Food, Drug, and Cosmetic Act (FDCA) [12]. In 1944, Congress reenacted the 1902 Biologics Control Act and recodified the Public Health Service Act. A major issue was the definitional overlap between drugs and biologics [12].

Between 1902 and 1972, regulatory responsibility for biologics transferred several times, ultimately settling with FDA, as shown by this brief timeline of the relevant transfers:

1930 The Hygienic Laboratory within the Public Health and Marine Hospital Service is redesignated as the National Institutes of Health (NIH).

1937	The NIH is reorganized, and responsibility for biologics is transferred to the Division of Biologics Control. In 1944 it is renamed the Laboratory of Biologics Control.
1948	The Laboratory of Biologics Control is integrated into the NIH's National Microbiological Institute, which later becomes the Institute of Allergy and Infectious Diseases.
1955	Responsibility for biologics is transferred to the new Division of Biologics Standards, a new independent entity within the NIH.
1972	The Division of Biologics Standards is transferred from the NIH to the FDA, becoming the Bureau of Biologics.
1982	The Bureau of Biologics is merged with the Bureau of Drugs to form the National Center for Drugs and Biologics (NCDB).
1983	The biologics component of the NCDB is renamed the Office of Biologics Research and Review, within the Center for Drugs and Biologics (CDB).
1988	CDB split into two centers, the Center for Biologics Evaluation and Research (CBER), and the Center for Drug Evaluation and Research (CDER).
2003	Transfer of therapeutic biological products from CBER to CDER.

The steady stream of reorganizations in many ways reflects the difficulty of both categorizing and regulating biologics. The FDA continues to struggle with these responsibilities. For instance, since the FDA created CBER in 1988, the agency has both overhauled the way it approves biologics, and once again shifted responsibility for certain biologics. First, the FDA established a single approval application, the Biological License Application (BLA) through the Food and Drug Modernization Act of 1997 (FDAMA), the most comprehensive rewrite of food and drug laws since 1938. Second, in 2003, the FDA shifted responsibility for therapeutic biologics from CBER to CDER, given CDER's role in regulating therapeutic drugs. CDER's new responsibilities include a wide array of biological products, including monoclonal antibodies for in vivo use, therapeutic proteins, and immunomodulators [10]. CBER retained authority over traditional biologic products such as vaccines, allergenic extracts, antitoxins, blood, and blood products, as well as products composed of human, bacterial, or animal cells [10].

1.2.3 Legal Requirements for US Biopharmaceuticals

The regulation of biologics continues to evolve. The transcendent growth of biotechnology research, spurred by the Human Genome Project, almost ensures that biologic regulations will require further tinkering to accommodate new products. The following is a brief synopsis of relevant US laws and regulations at various stages, including research, development, approval, and

marketing. Where relevant, we highlight where the rules for biologics differ from drugs.

Research and Development The United States heavily regulates the research and development of biologics. At the preclinical stage, FDA requires companies to comply with regulations on good laboratory practices (GLPs) at 21 CFR part 58. The GLP regulations seek to ensure the quality and integrity of preclinical safety data submitted to the FDA. GLPs apply to nonclinical (preclinical) laboratory studies intended to support research or marketing applications, and address a broad range of topics, including personnel, facilities, and equipment. Ideally preclinical studies to support safety are subject to GLPs and should be supported by a statement that the study was conducted in compliance with the good laboratory practice regulations in 21 CFR part 58, or if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance (21 CFR 312.23 (8) (iii)).

At the clinical stage, FDA sets minimum standards for clinical trials through several regulations and guidance documents, collectively known as good clinical practices (GCPs). GCPs are designed to ensure the quality and integrity of data submitted to FDA and protect the rights of human subjects. GCPs govern key personnel involved in clinical trials—particularly sponsors, and investigators—and address several important areas, including informed consent, institutional review boards (IRBs), and investigational new drug (IND) requirements.

Informed consent is governed by both federal and state law [14]. These laws generally require that before participating in clinical trials, human research subjects state in writing that they understand the risks of the trial and are participating voluntarily. Each informed consent document must contain several elements required by FDA regulations [15].

IRBs are also governed by federal and state law. FDA regulations require IRBs to provide initial and continuing review of clinical trials [16]. IRBs must ensure that investigators and sponsors protect the study subjects, obtain adequate informed consent, and adhere to other safeguards and reporting requirements [16]. Moreover FDA regulations require IRBs members to meet specific membership criteria [17].

Investigational biologics are subject to the FDA's investigational new drug (IND) requirements [18]. The IND application is the first formal submission to FDA, and the application must be submitted before initiating any clinical studies [7]. It is not a request for commercial marketing approval; rather, it is a request to be exempt from the federal statute that prohibits shipping "unapproved" drugs across state lines. Thus an IND permit allows the product to be shipped during investigational studies. The purpose of the IND requirement is to assure the FDA that the safety and rights of subjects will be protected in all phases of the investigation, and that the quality of the studies are adequate to permit the FDA to evaluate the product's safety and effectiveness [13].

Approval The FDA approves biologics for marketing through the biological license application (BLA), which requires the applicant to show that the product is safe, pure, and potent [19]. The BLA submission is typically the culmination of years of research and development, through which the company submits preclinical and clinical data, physiochemical information, biological activity results, and manufacturing information [7]. Previously the FDA approved biologics through two license applications, the product license application (PLA) and the establishment license application (ELA). In 1996, CBER consolidated these applications into a single BLA for certain products, and in 1997, Congress extended the BLA to all biological products.

Although the BLA process differs in some ways from the new drug approval (NDA) application process for nonbiologic drugs, the required showing of safety and efficacy is similar, if not identical, between drugs and biologics [20]. While the FDA requires biologics to be "safe, pure, and potent," the agency interprets this language as requiring the same type of evidence in NDAs for nonbiologic drugs [20]. Nevertheless, there are differences between the BLA and NDA that reflect CBER's historical emphasis on manufacturing and process control. For instance, the FDA requires BLA applicants to submit detailed information on manufacturing processes so that the FDA can determine whether the manufacturer can produce a product consistent with current good manufacturing practices (cGMPs) and the manufacturing specifications listed in the BLA. The manufacturer's facility is also a major factor—its construction, design, layout, validation processes, and environmental monitoring must meet FDA standards.

After approval, biologics manufacturers must comply with the FDA's cGMP regulations [21]. These regulations govern the manufacturer's use of raw materials, buildings and facilities, production and process controls, packaging and labeling, laboratory controls, stability testing, expiration dates, production records, and the company's overall quality system. Although the same cGMP regulations apply to drugs and biologics, manufacturing biologics can be quite different. Physically and chemically, biologics act differently than drugs [11]. They are less defined, less pure, less stable, and degrade in more complex ways than most drugs [11]. Their potency also depends greatly on the underlying organisms from which they are produced [11]. Thus, if a manufacturer makes relatively minor changes to the manufacturing process of a biologic, the FDA may require the manufacture to demonstrate through new clinical studies that the process produces the same results as the original clinical studies [11].

Marketing and Postapproval Requirements Once the FDA approves a biopharmaceutical for marketing, the agency applies a different set of regulatory standards. The main postapproval requirements govern: (1) adverse event reporting, (2) manufacturing under cGMPs, (3) lot release testing, (4) general reporting, and (5) postmarketing studies.

- The FDA's adverse event reporting system does not differ significantly between drugs and biologics. However, the FDA did not have a comprehensive adverse event reporting system for biologics until 1994 [22]. Biologics manufacturers can use two reporting systems: MedWatch and the Vaccine Adverse Event Reporting System (VAERS). MedWatch is administered by the FDA and covers drugs, biologics, medical devices, and special nutritional products. VAERS is jointly administered by the FDA and the Centers for Disease Control and Prevention (CDC), and covers adverse events following immunizations. FDA regulations require manufacturers to report serious, unexpected adverse events within 15 days. Less serious reports can be submitted in periodic follow-up, or distribution reports.
- The FDA's cGMP regulations specify minimum standards for manufacturing facilities and their production controls. These regulations generally apply to both drugs and biologics, but the FDA has additional cGMP-related regulations that focus on biologics [23]. CBER has also tailored cGMP requirements for "specified biotechnology and synthetic biological products" to be as similar to drug requirements as possible.
- The FDA's lot release regulations allow the agency to require manufacturers to submit samples of any licensed biological products for testing [24]. Manufacturers must submit to CBER representative samples of each lot, a lot release protocol, and a summary of the test results. Lots may not be released until CBER authorizes an "official release." However, CBER does not require lot release in all circumstances.
- The FDA requires manufacturers to report certain changes in the product, production process, quality controls, equipment, facilities, personnel, or labeling that are established in the approved license application [25]. The manufacturer must demonstrate that the change does not adversely affect the identity, strength, quality, purity, or potency of the product that may affect the product's safety or effectiveness. FDA regulations and guidance categorize each change as "minor," "moderate," or "major" based on the risk to the product's quality, safety, and effectiveness. The FDA must give prior approval before the manufacturer can implement "major" changes. "Moderate" changes must be reported to the FDA within 30 days. Minor changes must be reported annually.
- The FDA may require, at the time of product approval, that the manufacture agree to conduct additional testing on its biological product, called phase 4 studies. These postmarketing studies may further evaluate the product's safety, efficacy, or manufacturing methods. Sponsors that agreed to conduct phase 4 studies as part of their BLA approval must update the FDA annually.

1.3 EUROPEAN UNION

1.3.1 How EU Law Defines a Biological Medicinal Product

In the European Union the regulation of biological products is subject to continuing review taking account of the evolving science and technology. Directive 87/22/EEC (now repealed) provided the first time in EU law the legal definition of a medicinal product developed by a biotechnological process. The following processes were considered as biotechnological: recombinant DNA technology, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells, hybridoma, and monoclonal antibody methods. This definition remains unchanged since 1987, and it is now used for defining a biotechnological medicinal product as set out in the Annex to Regulation (EC) 726/2004 [26], which repealed Regulation (EC) 2309/93 [27] governing the European centralized procedure.

The definition of a process based on biotechnology is sufficiently broad to capture a wide arrange of medicinal products, such as recombinant proteins and gene-based therapeutics, and prophylactics, such as gene transfer medicinal products and DNA vaccines. Medicinal products manufactured by biotechnological processes as defined in the Annex to Regulation (EC) 726/2004 must be authorized centrally pursuant to article 3 of the Regulation.

In June 2003 the European Commission adopted a new Annex I to Directive 2001/83/EC [28] on the EU code relating to medicinal products for human use. This new Annex was adopted in the form of Commission Directive 2003/63/EC [29]. The new Annex was adopted for implementation of the International Conference on Harmonization (ICH) Common Technical Document (CTD) format. Annex I sets out the particulars and documents accompanying an application for marketing authorization irrespective of the EU procedure used for obtaining a marketing authorization. Directive 2003/63/EC defines a biological medicinal product, and this definition consists of two essential elements. First, the active substance is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source. Any one of the following source is considered as a biological source: microorganisms, organs and tissues of either plant or animal origin, cells or fluids (including blood or plasma) of human or animal origin, and biotechnological cell constructs utilizing cell substrates. If the product is produced from primary cells such as certain prophylactic vaccines, the product is considered a biological medicinal product. Second, the product requires for its characterization and the determination of its quality a combination of physicochemical-biological testing together with the production process and its control.

The Commission has indicated that the following are considered as biological medicinal products: immunological medicinal products and medicinal

products derived from human blood and human plasma. EU law defines an immunological medicinal product as any medicinal product consisting of vaccines, toxins, serums, or allergen products. Vaccines, toxins, and serums cover, in particular, agents used to produce active or passive immunity, and to diagnose the state of immunity. An allergen product means any medicinal product that is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent.

Medicinal products derived from human blood or human plasma means those based on blood constituents that are prepared industrially by public or private establishments, such as albumin, coagulation factors, and immunoglobulins of human origin. This definition reflects the way plasma derived medicinal products are manufactured in the European Union. This class of products may be produced by privately owned industry or by public organizations that are owned by the member state.

1.3.2 Legal Foundation for Regulation of Biological Medicinal Product

The regulatory framework governing biological medicinal products is based on the European Community Treaty, which aims at the free movement of goods within the European Union. Although the legal base is built on the principle of free trade of medicinal products within the European Union, the essential aim of any rules governing the production, distribution, and use of medicinal products must be firmly based on protection of public health. Recital 3 of Directive 2001/83/EC notes that the objective of public health protection must be attained by means that do not hinder the development of the pharmaceutical industry or trade in medicinal products within the European Union.

The EU regulatory system is based on cooperation among the competent authorities of the member states (including the member states of the European Economic Area, e.g., Norway, Liechtenstein, and Iceland) and various relevant European institutions such as the European Commission and the European Medicines Agency (formerly called the European Agency for the Evaluation of Medicinal Products). The European Medicines Agency (EMEA) was formally established in 1995 by virtue of Regulation (EC) 2309/93, which is now replaced by Regulation (EC) 726/2004. The EMEA's role is narrowly defined in the Regulation as a body responsible for coordinating the existing scientific resources put at its disposal by member states for the evaluation, supervision, and pharmacovigilance of medicinal products. In practice, the scientific work is carried out by the member states through the EMEA's advisory committees and working parties.

The Committee for Medicinal Products for Human Use (CHMP) is one of the main committees responsible for preparing the opinion of the EMEA on any question relating to the assessment of medicinal products for human use. Pursuant to Regulation (EC) 141/2000 [30] the Committee for Orphan Medici-