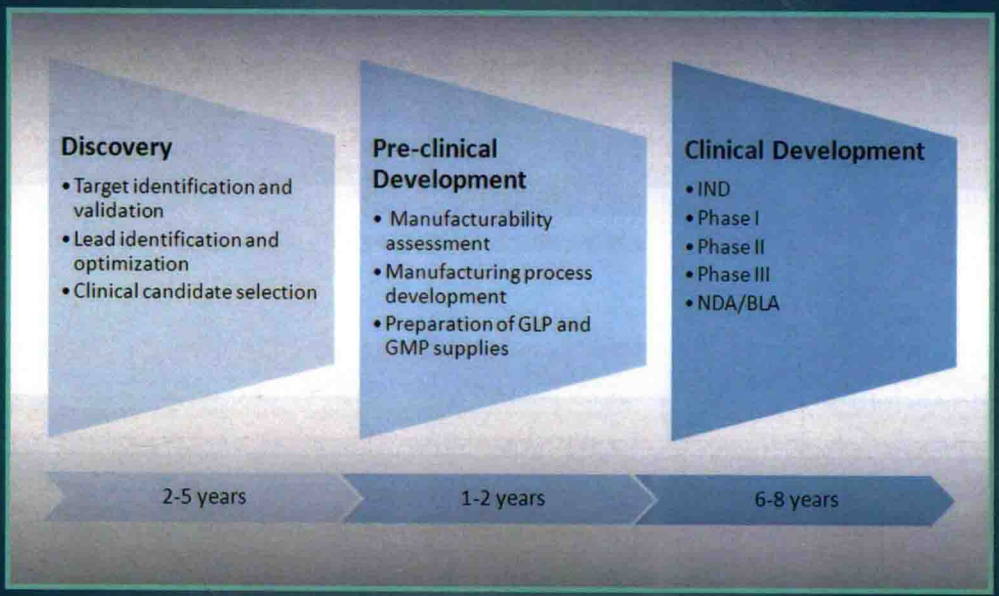
Biological Drug Products

Development and Strategies



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BIOLOGICAL DRUG PRODUCTS

Development and Strategies

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BIOLOGICAL DRUG PRODUCTS

To my wife, Linlin Wang, for her unconditional support and love.
—Wei Wang

I dedicate this work to my family for their lifetime of support.
—Manmohan Singh

PREFACE

Biological drug products have been playing a key role in combating human diseases. The growth of biologics has clearly outpaced that for small molecule drugs in the past decade, and the trend is expected to continue for the next one. However, successful development of biological drug products has not been straightforward because of both the labor-extensive production processes and the rather limited process and storage stabilities of biologics. On top of these are additional challenges, including stringent requirements of good manufacturing process (GMP) compliances, ever-increasing regulatory scrutiny, and intense market competition (e.g., biosimilars).

This book is intended to summarize the recent progress in the development of different types of biologics, to describe the development challenges and more importantly, to discuss the development strategies. It is divided into five parts, covering general aspects in the development of biologics (Part 1) and challenges and strategies in the development of specific types of biologics (Parts 2 to 5). The general topics include overall product development process (Chapter 1), preclinical and clinical assessment (Chapter 2 and 3), key regulatory guidelines (Chapter 4), intellectual property considerations (Chapter 5), and GMP issues (Chapter 6). Development of specific types of biologics are discussed, covering proteins and peptides (Chapters 7 to 11), biosimilars (Chapter 12), vaccines (Chapters 13 to 15), gene medicines (Chapter 16), nucleic acid vaccines (Chapter 17), oligonucleotides (Chapter 18), and regenerative medicines (Chapter 19) along with product administration and delivery-related issues (Chapters 20 to 22).

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Part 1
General Aspects

1 An Overview of the Discovery and Development Process for Biologics

HEATHER H. SHIH, PAULA MILLER, and DOUGLAS C. HARNISH

1.1 INTRODUCTION

Biologics, also called biotherapeutics or biopharmaceuticals, are drug substances derived from living organisms or produced using biotechnology that are composed of biological entities such as proteins, peptides, nucleic acids, or cells [1]. They differ from small molecule (SM) drugs that are chemically synthesized and have low molecular weights. Some biologics, such as antibody–drug conjugates, consist of both a protein moiety and an SM component, both of which are required for the therapeutic action of the drug. Traditional biologics that have reached the market include vaccines and blood-derived factors. The advancement in modern biotechnology has brought forth new classes of biologics as exemplified by monoclonal antibodies (mAbs), Fc fusion proteins, recombinant proteins, and peptide drugs. Some early clinical success is now seen in several novel classes of biologics, which include antibody variants, novel protein scaffolds, RNA therapeutics, and cell-based therapies [2–5]. This chapter focuses on protein-based biologics, particularly mAbs because they represent the largest class of biologic drugs. By the end of 2011, the US Food and Drug Administration (FDA) had approved close to 40 mAbs and antibody variants as summarized in Table 1.1. Details on other forms of biologics such as vaccines and RNA drugs can be found in later chapters.

The first protein-based biologic drug, recombinant insulin Humulin, was approved in the United States in 1982 [6]. Since then the field of biologics grew steadily, with the biotechnology sector laying the foundation for both the drug discovery process and technology innovation. Around late 1990s, the pharmaceutical industry started to invest more in the development of biologics. This shift from a primary focus on SM drugs was largely due to patent expiration on these drugs and the concurrent fierce competition from generic SM drugs. In addition, the increasing difficulty to bring new drugs to the market because of tightened regulations and a lack of breakthroughs in the drug discovery process has also contributed to this shift.

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TABLE 1.1 List of Food and Drug Administration–Approved Antibody-Based Therapeutics Up to 2011 as Categorized by Types

Type of Ab-Based Therapeutics	Nonproprietary/ Trade Name	Ab Target or Fc Fusion Partner	Company
Human antibodies	Ipilimumab/Yervoy	CTLA4	Bristol-Myers Squibb
	Belimumab/Benlysta	B-lymphocyte stimulator	Human Genome Sciences
	Ustekinumab/Stelara	p40 subunit of IL-12 and IL-23	Johnson & Johnson
	Canakinumab/Ilaris	IL-1β	Novartis
	Denosumab/Prolia/Xgeva	RANKL	Amgen
	Ofatumumab/Arzerra	CD20	Genmab
	Golimumab/Simponi	TNF	Centocor
	Panitumumab/Vectibix	EGFR	Amgen
	Adalimumab/Humira	TNF	Abbott
Humanized antibodies	Tocilizumab/Actemra	IL-6R	Roche
	Eculizumab/Soliris	C5	Alexion
	Natalizumab/Tysabri	Alpha4 integrin	Biogen/Elan
	Bevacizumab/Avastin	VEGFa	Genentech
	Efalizumab/Raptiva	CD11a	Genentech
	Omalizumab/Xolair	Human IgE Fc	Genentech
	Alemtuzumab/ Campath-IH	CD52	Genzyme
	Trastuzumab/Herceptin	Her2	Genentech
	Palivizumab/Synagis	RSV protein F	MedImmune
	Daclizumab	CD25	Roche
Chimeric antibodies	Cetuximab/Erbitux	EGFR	Imclone
	Infliximab/Remicade	TNFα	Centocor
	Basiliximab/Simulect	CD25	Novartis
	Rituximab/Rituxan	CD20	IDEC
Murine antibody	Muromonab-CD3/Orthoclone OKT3	CD3	Janssen-Cilag
Fab fragment	Abciximab/Reopro	CD43	Centocor
	Ranibizumab/Lucentis	VEGFa	Genentech
	Certolizumab pegol/Cimzia	TNFα	UCB
Antibody conjugates	Brentuximab vedotin/Adcetris	CD30	Seattle Genetics
	Tositumomab-I131/Bexxar	CD20	GlaxoSmithKline
	Ibritumomab tiuxetan/Zevalin	CD20	IDEC
	Gemtuzumab ozogamicin/Mylotarg	CD33	Wyeth

TABLE 1.1 (*Continued*)

Type of Ab-Based Therapeutics	Nonproprietary/ Trade Name	Ab Target or Fc Fusion Partner	Company
Fc fusions	Afilibercept/Eylea	VEGFR1 and 2 ECD	Regeneron, Bayer
	Belatacept/Nulojix	CTLA4 ECD	Bristol-Myers Squibb
	Romiplostim/Nplate	Peptide thrombopoietin mimetic	Amgen
	Rilonacept/Arcalyst	IL-1R ECD	Regeneron
	Abatacept/Orencia	CTLA4 ECD	Bristol-Myers Squibb
	Alefacept/Amevive	LFA-3 ECD	Biogen IDEC
	Etanercept/Enbrel	TNFRII ECD	Wyeth/Amgen

Presently, the number of biologics on the market has reached more than 200, and the sales of biologics in 2009 reached $93 billion, with approximately one third of current pharmaceutical pipelines consisting of biologics [7]. Given that almost all of the large pharmaceutical companies have acquired infrastructures and committed resources to develop biologics, we will continue to see a robust growth in this sector in the coming years.

Compared with SM drugs, protein-based biologics have unique therapeutic features. A therapeutic protein usually exhibits exquisite specificity when binding to and modulating its molecular target, which often translates into low off-target toxicity and clinical safety. For example, therapeutic mAbs bind to their target molecules with affinities in the picomolar to low nanomolar range (e.g., [8]). Furthermore, the interaction occurs over a broad interface with multiple physical and chemical bonds formed between an antibody and its cognate antigen, resulting in an extraordinary binding specificity that allows the differentiation of binding partners that differ by as few as one amino acid or subtle conformational difference. On the contrary, the small size of an SM drug makes it prone to off-target binding to proteins other than its intended target, which may result in unacceptable levels of toxicities. A potentially short development cycle is another advantage for the development of biologics, particularly mAbs and recombinant proteins. A clinical candidate for mAb or recombinant protein can be generated and selected in as short as 3 to 5 years compared with typically 7 to 8 years for SMs.

Protein-based biologics have their own limitations. Presently, almost all protein-based drugs must be administered as intravenous or subcutaneous injections because oral delivery is not yet a viable route of administration. Furthermore, protein drugs do not readily penetrate cell membrane and blood–brain barrier (BBB) and therefore are limited to the modulation of peripherally located extracellular targets. The cost of goods to manufacture protein drugs is significantly higher than for SM drugs, which translates into a high drug price that exacerbates health management cost issues [9].