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Safety of Biologics Therapy

Monoclonal Antibodies, Cytokines, Fusion Proteins, Hormones, Enzymes, Coagulation Proteins, Vaccines, Botulinum Toxins

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ISBN 978-3-319-30470-0 ISBN 978-3-319-30472-4 (eBook)
DOI 10.1007/978-3-319-30472-4

Library of Congress Control Number: 2016943849

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland

Dedicated to the memories of my mother and father and to Gail MacDiarmid for the cherished years of support, partnership, and mutual devotion

Preface

In writing this book, the author's primary intention was to produce an up-to-date text book on approved biologic therapies as far as that is possible in this time of rapidly evolving and seemingly ever-expanding developments in biotherapeutic research and the introduction of new and novel biopharmaceuticals. Emergence of the disciplines of genomics and proteomics, together with molecular biological approaches to elucidate the functions of single genes, continues to reveal the complexities and multifaceted nature of diseases such as cancer, autoimmunity, and metabolic disorders and to identify potential targets for the development of new drug therapies. Targeted approaches, long practiced in relation to peptide hormones and enzymes, now so often drive the extraordinary interest in, and development of, monoclonal antibody, fusion protein, and cytokine therapies. Added stimulus has been provided by regulatory authorities in efforts to encourage the development of diagnostic agents and treatments for rare diseases previously neglected because of inadequate financial returns from very small markets. In particular, The US Food and Drug Authority (FDA) Office of Orphan Products Development provides incentives for the study and development of products for so-called orphan diseases, that is, diseases with fewer than 200,000 patients in the USA. This initiative has, for example, transformed the extent and nature of the research and development of enzymes as replacement therapies for lysosomal storage diseases and led to the introduction of monoclonal antibody therapy for the rare paroxymal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome by targeting complement C5. These advances, among many others presented in this monograph, would almost certainly not have been made in the absence of recombinant DNA technology, today's sequencing methods, application of modern bioinformatics, and parallel proteome analyses by application of techniques such as mass spectroscopy.

An attempt has been made to cover those biologics that are currently the main product classes with regulatory approval in the USA and/or European Union and which show every indication of remaining important therapies over at least the next decade and beyond. Due to considerations of established therapeutic relevance and space constraints, coverage has been almost totally restricted to products given regulatory approval. This is reflected in the three chapters devoted to monoclonal

antibodies, the dominant biotherapeutic agents in terms of diversity of target recognition and approved indications, and the products with the highest global sales revenue in today's biopharmaceutical market. Although there are well over 300 monoclonal antibodies in development, coverage here at June 2016 is restricted to the 50 (counting alemtuzumab [MabCampath® and Lemtrada®] and Denosumab [Prolia® and Xgeva®] as two not four antibodies) currently approved by the FDA or European Medicines Agency or both. Unsurprisingly, recombinant preparations dominate the different categories of approved biologics, and because of their inherent advantages including production of large quantities of pure human materials without the need to purify crude extracts, their ease of genetic and chemical manipulation to reduce side effects and accentuate or reduce selected properties, consistency of supply, minimal batch-to-batch variation, reduced cost of production, and their safety of manufacture, this is certain to continue. Coverage is extended to the relatively small number of cytokines approved for therapy out of more than 130 of these known pleiotropic immune modulators of immune and inflammatory responses and to the growing list of approved fusion proteins most of which are made up of an effector peptide (such as a cytokine, growth factor, etc.) linked to an antibody Fc fusion partner or human albumin. Known, studied, and used as therapies for many years, peptide and glycoprotein hormones, now mainly as recombinant products, are examined in some detail together with other related and/or modified hormone products produced to effect therapeutic improvements, alter pharmacokinetic and pharmacodynamic properties, or reduce adverse effects. In addition to enzymes as replacement therapies for lysosomal storage diseases, a number of other enzymes indicated for disorders as diverse as cystic fibrosis, Dupuytren's contracture, vitreomacular adhesion, myocardial infarction, and acute lymphocytic leukemia are examined. Descriptions, approved indications, and usage, of 22 approved coagulation or clotting factor preparations, essential for maintaining homeostasis, are reviewed together with the clotting cascade, an emphasis on safety aspects, and new product developments. Vaccination, an indispensable public health measure described as "the greatest triumph of modern immunology and the most successful exploitation of our knowledge of the workings of the immune response," has nevertheless not always been afforded the respect it deserves in modern medical practice. While vaccines are not free of associated adverse events, those that have been recorded together with the known and suspected effects induced by additives and possible contaminants are examined for all 46 approved vaccine preparations presented. Botulinum neurotoxins, surprising in their sheer number of clinical applications (a few approved, many not), which now include muscular, neurologic, gastrointestinal, urologic, ophthalmic, and oropharyngeal disorders, have exceeded the most optimistic early estimates of their usage. This already large list of approved and potential indications is currently being further enlarged by evaluations in off-label treatments outside controlled clinical trials. Such relatively uncontrolled activity is a reminder of the need to remain aware of the potentially extreme toxicity of the botulinum neurotoxins and to record and report adverse events when they occur. In the light of the seemingly exorbitant costs associated with many of today's biologic therapies, follow-on biologics or biosimilars offer the promise of fostering

competition, allowing the treatment of more patients at lower cost, and helping to lower ever-increasing government health costs. Difficulties in achieving the required comparability or similarity, safety evaluations, and eventual regulatory approval are considered in the book's final chapter.

While efforts have been made to unify the text by cross-referencing and interconnecting common or related subjects, no comprehensive and scrupulous referencing to the original literature that is standard for scientific papers has been undertaken since this would have considerably increased the size of the book and been at odds with its intended organization and textbook style. As a reasonable compromise and with the aim of assisting the reader to locate original sources and extend understanding, carefully selected suggestions for Further Reading have been included at the end of each chapter. The chapters on cytokines, fusion proteins, and enzymes are based on the author's previous publications for Springer. These publications, quoted in the Further Reading lists, provide a comprehensive reference list for Chaps. 5, 6, and 9. Further Reading selections for these and other chapters have been selected to guide the interested reader to the most significant studies in the original literature and preview potentially important future developments.

It is with sincere appreciation and thanks that the author acknowledges the skills, dedication, cooperation, and help, given by long-standing collaborator Dr. Nghia H. Pham in the joint preparation of numerous tables and a widely diverse range of figures, many of the latter demonstrating individuality and produced with some artistry as well as relevance, scientific accuracy, and dedication to detail.

In conclusion, with biologic therapies continuing to demonstrate extraordinary growth in the origin and nature of the agents employed, the introduction of new disease targets, the enlarging range of approved indications, and the increasing understanding of each agent's spectrum of associated risks and adverse events, the continued development and innovation seen in biologic therapies over the last few years seem certain to be sustained. Given this ongoing expansion of new knowledge, research, and development in therapeutic biologics, the author remains open and ready to consider all comments in an ongoing effort to remain abreast of new developments, improve the book, and correct any errors.

Sydney, Australia Brian A. Baldo

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Chapter 1
Approved Biologics Used for Therapy and Their Adverse Effects

Biologics

"Biologics" in this book refer to therapies that are prepared from materials made or expressed in living organisms. They may simply be isolated proteins such as enzymes and blood products or, as is increasingly the case, preparations produced by recombinant DNA technology. Biologics, sometimes also referred to as "biotherapeutics" or "biopharmaceuticals," are covered by a number of different definitions depending on the perspective of the interested party, with researchers from different disciplines, biotechnologists, chemists, clinicians, legislators, and regulatory agencies, to name only a few, requiring or excluding aspects that reflect their interest and involvement. Whereas a biologist, chemist, or clinician may see a biologic used for therapy as material derived from, or related to, a living organism, for example, cells, cell extracts, or molecules composed of protein, peptide, complex carbohydrate, lipid, or nucleic acid, a regulatory authority will also consider how such agents are to be classified and assessed for characterization, manufacturing, and control; product development; identity, purity, and potency; and so on. In other words, in a regulatory context, "biologics" does not necessarily correspond to common usage or usage in everyday medical research and likewise for the terms "biotechnology medicine/drug," "biological medical product/drug," and "biopharmaceuticals," used outside the regulatory environment.

US Guidelines

In 1902, in the Biologics Control Act passed by the US Congress, biologics and biologic products were defined as "any virus, therapeutic serum, toxin, antitoxin or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man." Although this definition has changed over time, uncertainties, difficulties, and impreciseness have remained for agencies, many groups, and individuals

B.A. Baldo, *Safety of Biologics Therapy*, DOI 10.1007/978-3-319-30472-4_1

concerned and/or working with biologic therapeutics. In particular, the term "analogous" has remained undefined and open to varying degrees of relatedness. Since 1902, the Congress has expanded the list of biologics to include other products including vaccines, blood products, and some other proteins, but polypeptides prepared by chemical synthesis remained excluded. In the 1938 Federal Food, Drug, and Cosmetic Act, "drug" was defined as a substance for the investigation, prevention, or cure of disease, but no guidance was forthcoming to distinguish biologic and non-biologic drugs. However, in 1944, the Congress did declare that a requirement for a new drug application (NDA) did not apply to biologics. The latter are now marketed under the provisions of the Public Health Service Act requiring a Biologics License Application (BLA) showing the agent is "safe, pure, and potent." By 1947, hormones had been excluded from the list of biologics, and with the arrival of the new age of biotechnology in the mid- to late 1980s, US Food and Drug Administration (FDA) issued a policy statement saying that agents would be regarded as biologics "based on the intended use of each product on a case-by-case basis." Following an Intercenter Agreement, in June 2003, the FDA transferred some of the therapeutic biologic products that had formerly been reviewed and regulated by the Center for Biologics Evaluation and Research (CBER) to the Center for Drug Evaluation and Research (CDER). Therapeutic biological products transferred to the CDER include monoclonal antibodies (mAbs), cytokines, fusion proteins, some enzymes, growth factors, non-vaccine immunomodulators, and therapeutic proteins derived from animals, plants, and microorganisms and recombinant versions of these products. Remaining with the CBER are cellular products of human, animal, or bacterial origin; gene therapy products such as nucleic acids, viruses and genetically engineered microorganisms; vaccines; allergenic extracts; antitoxins, antivenins, and venoms; and blood, blood components, and plasma-derived products. The approved biologics covered in this monograph are comprised of therapeutic biological products from both the CDER and CBER lists. In 2012, the FDA issued a draft guidance addressing and distinguishing the long-standing proposed differences between proteins, peptides, and chemically synthesized polypeptides. A protein was defined as any alfa amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size. From this definition, it followed that peptides have fewer than 40 amino acids and are therefore not proteins. A chemically synthesized polypeptide was defined as an alfa amino acid polymer that is made entirely by chemical synthesis and has fewer than 100 amino acids. Until the draft guidance is finalized, these definitions can be seen as proposals, but regardless of the definitions finally declared and adopted and for the coverage of biologics in this volume, peptides with less than 40 amino acids and chemically synthesized polypeptides (whether they contain fewer or more than 100 amino acids) with regulatory approval for therapeutic use in humans will be considered first and foremost as biologics regardless of size or method of preparation. In keeping with this approach, peptide hormones (Chap. 7) and glycoprotein hormones (Chap. 8) are logically included in the coverage of biologics licensed for marketing as approved therapeutic agents. Note that regardless of the method of manufacture, hormones require a NDA. In summary, in the US, distinguishing a product from other drugs and classifying it as a biologic on the basis of existing

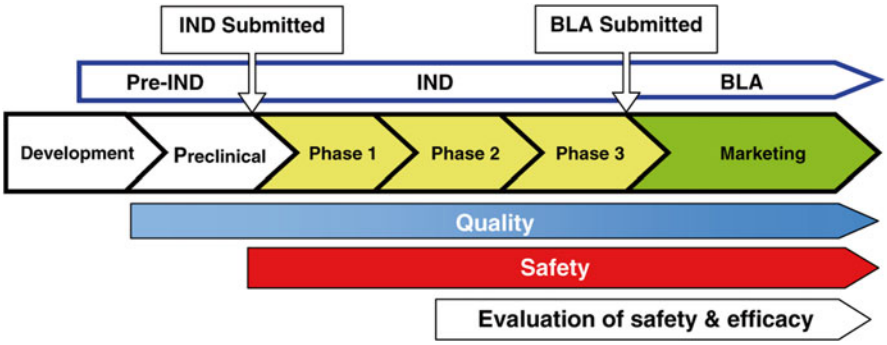

Fig. 1.1 Phases in biological product development under an investigational new drug (ING) application leading to clinical trials with evaluations for safety and efficacy, a Biologics License Application (BLA) and ultimately licensing and marketing. Reproduced from Vatsan RS, Bross PF, Liu K, et al. J Immunother Cancer 2013;1:5. http://www.immunotherapyofcancer.org/content/1/1/5, an open access article distributed under the terms of the Creative Commons Attribution License

definitions is not straightforward since detailed legislated guidance has never been provided. Recently, the FDA has mentioned the application of a so-called bright-line rule for distinguishing proteins suggesting a much-needed shift from ad hoc to jurisdictional decision-making.

From the early preliminary specifications for product characterization, Fig. 1.1 summarizes the phases in biological product development under an investigational new drug (IND) application leading on to clinical trials with evaluations for safety and efficacy, a BLA, and ultimately licensing and marketing.

European Guidelines

From a 2001 Directive of the European Parliament and the Council of Six on the community code relating to medicinal products for human use, "biological medicines" are defined as "products, the active substance of which is a biological substance." In turn, a "biological substance" is defined as "a substance that is produced by or extracted from a biological source and that needs for its characterization and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control." In the European Union, the European Medicines Agency (EMA) defines a "biological medicinal product" as "a protein or nucleic acid-based pharmaceutical substance used for therapeutic or in vivo diagnostic purposes, which is produced by means other than direct extraction from a native (nonengineered) biological source." This definition essentially appears to restrict "biological medicinal products" to recombinant preparations including mAbs, cytokines, fusion proteins, some hormones (such as insulin, glucagon, growth hormone), enzymes (e.g., alteplase and enzymes used for enzyme replacement therapy), and coagulation proteins (factors VIIa, VIII, IX, XIII, and antithrombin).