User's Guide

Quick Start – This book is rather simply laid out, with product-specific and, where needed, product class monographs followed at the end by multiple indexes. Most casual users will be able to instinctually use this book without referring to the information below (or the more extensive information online at www.biopharma.com).

Coverage includes all currently approved biopharmaceuticals (in the U.S. and European Union), those with pending applications, and many others, including products formerly approved, approved in other countries, approvals rejected, etc. Monographs concentrate on scientific, technological, commercial, regulatory and other product information. Coverage is fully inclusive, including approvals and commercial news, past September 1, 2007.

Monographs are arranged in sections by basic product class. Accession (entry) numbers, not page numbers, are used to order and index the monographs.

Multiple indexes are provided, e.g., Product/Active Agents, Approval Date, Regulatory/Status, Biological, Chemical, Medical, Company, and Company Roles. Some of these are rather specific in coverage (see the indexes at the back of volume 2).

Monograph Record Structure

Information is presented in fields or sections. Information may be reported in each field on an arbitrary basis, wherever it best served to describe the product. Few records contain all of the fields listed below. Monograph fields/sections include:

a) **Entry number and title** – The monograph's title (*Biopharmaceutical Products in the U.S. and European Markets'* name) is a completely arbitrary product name selected to be a simple, short, unique, yet descriptive.

b) **Main names** – Major product names are presented in bold; usually FDA proper names, followed by trade names and descriptive synonyms.

c) **Status** – Regulatory and marketing status is briefly summarized.

d) **Organizations involved** – Organizations are listed along with role indicators characterizing their involvement with the product. See the Company Roles Index for further information.

e) **Cross ref.** – references to related entries.

f) **Description** – This is the main field used to describe the product (what it is). This may include information also handled by other fields.

g) **Nomenclature** – Product and active agent names are provided with a notation as to their source/

This book attempts to answer the following questions for each product:

- What is it? What basic terms apply? What names and identifiers apply—FDA, trade names, chemical, biological and other nomenclature (for products, sources, cell lines, genes, etc.)?
- Whose product is it? Who discovered it, developed it, patented it, conducted clinical trials, markets it in the U.S. and internationally?
- How is it made? Where does it come from? Who makes it and where? What processing steps and tests assure that it's a safe and consistent product?
- What patents cover the product, its manufacture and use? What licensing is involved, related patent disputes, etc.
- What is the product's biological activity? How is it assayed?
- What is the rationale for therapeutic use? What place/role has the product assumed?
- When was the original approval date and review time? What about supplemental approvals for new indications and manufacturing changes?
- What is the product's regulatory history—current status; biologic, drug or medical device; orphan designation; priority review; foreign filings?
- What is the product's cost, e.g., per unit, for course of treatment or annually?
- What is the disease, particularly epidemiology, in relation to the product?
- What are the reported U.S. and worldwide sales and market shares?
- What is the product's main competition, current and upcoming?
- What is happening with the product—controversies, trials, pending filings, follow-on R&D, etc.?

type:
[BIO] = short unique *Biopharmaceutical Products in the U.S. and European Markets* name;
[TR] = trade names, almost always trademarks;
[FDA] = FDA proper and other names used by FDA;
[USAN] = U.S. Adopted Names;
[CAS] = Chemical Abstracts Service names and other systematic nomenclature;
[CAS RN] = CAS Registry Numbers;
[SY] = synonyms and other names;
[NDC] = National Drug Codes;

CAS names and numbers have been extracted from diverse sources, and many are of suspect quality. Synonyms can include names/terms that others have used to refer to the product, but which may be imprecise or even wrong.

h) **Biological** – Biological and other scientific background and descriptive information.

i) **History** – Historical aspects of the product.

j) **Companies** – Organizations and their involvement in product development, manufacture, and marketing are described in detail.

k) **Manufacture** – manufacturing and quality control descriptions, to the extent available (highly variable).

l) **FDA class**: Brief notation of how the product was regulated upon submission to FDA, ie., as a biologic, drug or medical device, and the original approval type, e.g., [Biologic PLA], [Biologic BLA], [Drug NDA], and [Device PMA]. Note, all biologics approvals have been converted to BLAs in recent years, and many biologics regulated by the Center for Biologics Research and Evaluation (CBER), have been transferred to the Center for Drug Evaluation and Research (CDER).

m) **CBER class** – terms used by CBER/FDA, often indicative of the division within CBER and/or advisory committee that evaluated the product.

n) **CBER to CDER** – identifies products, generally those currently approved, for which juridiction with FDA was transferred in mid-2003 from the Center for Biologics Evaluation and Research (CBER) to the Center for Drug Evaluation and Research (CDER). The underlying regulation, e.g., BLA vs. NDA, for these products was not changed.

0) **Approvals** – Approval dates and information.

p) **Indications** – The current U.S. approved indications are described. This usually involves presentation of the full text or portions of the "Indications and Usage" section of official product insert/labeling.

q) **Status** – Product regulatory and marketing status and activities, foreign approvals, controversies, trends, and other topical information.

r) **Tech. transfer** – Discussion of patents and technology transfers, licensing, patent disputes, etc.

s) **Trials** – Information about clinical trials, particularly for newer and pending products.

t) **Medical** – Information about the product's medical usage, e.g., typical treatment regimens. For further medical/use information, consider starting with the product insert, product-specific Web sites and other references, many of which are on the Internet.

u) **Disease** – Information about diseases and indications, including epidemiological and other information, to put product use and marketing in context.

v) **Market** – Information about marketing and sales, U.S. and worldwide market size, market share, etc., where available.

w) **R&D** – Ongoing R&D and clinical trials related to the product (may not be comprehensive).

x) **Competition** – Notes about competing products and technologies (may not be comprehensive).

y) **Ref**. – Selected unique references may be listed. Those included in prior editions may not be included in this edition.

What is a biopharmaceutical?

This book assumes biopharmaceuticals are pharmaceuticals manufactured using biotechnology (living organisms; bioprocesssing). See the "Coverage" section below and the later articles on this topic.

Coverage

Biopharmaceutical Products in the U.S. and European Markets includes all products generally considered to be human biopharmaceuticals, plus some borderline and other products. Simply defined, 'biopharmaceuticals' refers to therapeutics and other pharmaceuticals manufactured by biotechnology methods/processes (generally involving live organisms or derived components). Like 'biotechnology,' 'biopharmaceutical' is much easier to identify on a case-by-case basis than to define. 'Biopharmaceuticals' is used much as the term 'drugs' may be used to refer to therapeutic agents manufactured by chemical methods. Caution! Some use the term to solely refer to recombinant proteins and monoclonal antibody-based products, ignoring vaccines blood-derived and other products. *Biopharmaceutical Products in the U.S. and European Markets* takes a broad approach, and even includes monographs (at the end) for some

clearly drug (synthetic) products.

Coverage includes all biotechnology-derived products currently approved by FDA and the European Union (or with filings pending or expected within a year) for therapeutic indications or used in vivo, e.g., radiolabeled antibody diagnostics. This includes microorganism and animal-derived proteins, antibodies, vaccines, blood products, enzymes, toxins, radioimmune conjugates and engineered cells/tissues. Products are included irrespective of whether they involve old (e.g., fermentation) or newer (e.g., rDNA, monoclonal antibody) biotechnologies.

Coverage includes biopharmaceuticals with therapeutic or in vivo indications, irrespective of their FDA regulation as biologics, drugs or medical devices. Coverage does not include products generally considered to be chemical substances, e.g, antibiotics (secondary metabolites; including those produced by biotechnology methods), botanicals, and other natural products. Please inform us of any products that should be included in *Biopharmaceutical Products in the U.S. and European Markets*.

Many other products are also included, e.g., previously approved products, those with applications rejected, controversial products, biodefense products, and some products in foreign markets.

Information Sources Used

Biopharmaceutical Products in the U.S. and European Markets represents an effort to provide detailed, coherent information about very complex commercial products – what they are, how they are made/defined, companies involved, patents/technology transfer, regulatory status, marketing aspects, etc. Emphasis is on biotechnology and commercial information. Much of this information comes from unpublished, "fugitive" or "grey area" sources (e.g., FDA documents, information from companies, Web sites), and from various news and competitive intelligence sources. Some of the major information sources used include:

- Information from companies: Information was requested from all relevant companies. Contacts are limited to going through designated channels, usually the medical information and press/public relations departments (both of which are often unresponsive to requests for product/technology vs. medical/use or company information).
- Summary Basis of Approval (SBAs): Freedom of Information (FOI) requests were filed with FDA for SBAs and approval letters for over 200 products. Recent approval information is obtained from FDA Web sites. Other regulatory sources are used, e.g., European Product Assessment Reports (EPARs).
- Industry news sources: The author continually examines a large number pharmaceutical and biotechnology newsletters, press releases, databases, Web sites, newsgroups, blogs, etc. Much of the information presented comes from these sources and has been collected over years. Monographs are up-to-date to August 2007.
- Patents - Patent searches are primarily confined to U.S. patents. Thousand of patents were examined in full text.
- Approval lists, letters, etc. - In many respects, the FDA approvals information in *Biopharmaceutical Products in the U.S. and European Markets* far surpasses that available from FDA. Approval information was collated from approval letters, multiple FDA approval lists, and other sources. Note, there are many errors, inconsistencies, and other problems with FDA's public data, particularly for biologics approved prior to the early/mid-1970s, when biologics regulation was transferred from NIH to FDA (with FDA having corrupted or lost much of this legacy approvals data).
- Product inserts/labeling - All available product inserts/labeling were examined. Monographs for approved products generally include the full text or portion(s) of the "Indications and Usage" section of these documents.
- Reference sources: Standard pharmaceutical and other references were examined in libraries and online.
- Business information sources: SEC filings (10Ks) and annual reports were examined, but not every year. Press releases are received from companies and multiple reporting services.
- Internet sources: Google® and other Internet search engines were used.
- Networking: The author spoke and corresponded with hundreds of persons seeking information. This included FDA officials; product specialists in companies; major pharmaceutical libraries; trade associations; etc.

Information Sources Not Used

The economics of publishing this book, covering over 400 products, requires limiting information acquisition costs, e.g., spending just $100/product, which is very easy with fee-based databases and inter-library loans, requires >$40,000 (wiping out all income for the author). Similarly, the time and effort expended on each product must, by necessity, be limited.

Many high quality pharmaceutical, biotechnology, bibliographic, patent and other databases, publications and services were not used. If there is a significant expense involved in using an information resource, it likely was not used! This includes many high quality, fee-based bibliographic and other databases, e.g., Derwent patent databases, and many specialized pharmaceutical information services, e.g., from IMS, ADIS and PJB/Informa. Also, some information was not systematically extracted from various sources due to copyright violation concerns.

Bibliographic database searching was largely restricted to PUBMED/MEDLINE; and, sometimes, databases accessible at local university libraries. Generally, the scientific and medical literatures, e.g., peer-reviewed articles, were not sufficiently productive and often too off-target to warrant the time and expense required to search, procure and examine articles in full text, particularly considering that this book's primary interests are in product-specific biotechnology and commercial information, much of which rarely ever appears in these sources.

Further Background Information

Articles following this section include two 2-part series – "What is a Biopharmaceutical?..." and "What is a Generic Biopharmaceutical?..."

References*:* some books and articles:

a) Advances in Large-scale Biopharmaceutical Manufacturing and Scale-up Production, 2nd Ed., E. Langer Editor, September 2007, BioPlan Associates, Inc., and ASM Press.

b) *Directory of Approved Biopharmaceutical Products*, by S. Spada and G. Walsh, CRC Press, July 2004, 317 pages [This "directory," unlike this book, has a small-sized format, no indexes, provides only a "brief overview" for each product, and includes only recombinant proteins and monoclonal antibodies].

c) *Biopharmaceuticals: Biochemistry and Biotechnology*, 2nd edition, by Walsh, G., Wiley, 2003, 551 pages [small size format].

d) *Biophamaceuticals, an Industrial Perspective*, edited by Walsh, G. and Murphy, B., Kluwer, 1999, 514 pages [small size format]

d) "New Biopharmaceuticals in the USA: Trends in Development and Marketing Approvals 1995-1999," J.M. Reichert, *Trends in Biotechnology*, 18 (9) 364-369, Sept. 2000.

e) "First Biopharmaceuticals Approved in the U.S.: 1980-1994," by M.E. Goss and M. Manocchia, *Drug. Info. Journal*, vol. 30, p. 991-1001, 1996.

Bibliographic and other fee-based databases are good places to look for further information after using this book. Web and news search engines, SEC filings, company sites and other Internet sources may be searched for the most recent information. Medical and treatment-related information is readily available at a large number of Web sites; and from the product inserts, now almost always available online, either at product-specific or company Web sites.

Use the Web database at www.biopharma.com!

The free online database is designed to be used along with this book. Search the database and, using the entry numbers provided, open directly to the full monographs in this book. The Web site also has more background information, news, etc. [password = sixth]