10 Dispensing Biotechnology Products: Handling, Professional Education, and Product Information

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INTRODUCTION

Preparation, dispensing, and patient education regarding appropriate use of pharmaceuticals are primarily the responsibility of the pharmacist. Traditionally, parenteral products have been available in ready-to-use containers or required appropriate dilution with sterile water or saline prior to use with no other special handling requirements. Hospital pharmacists, in particular, have prepared and dispensed parenteral products for individual patients for many years. While many pharmacists are skilled in handling parenteral products, biotechnology products present additional challenges since they are proteins subject to physical and chemical denaturation and thus require special handling techniques. These challenges will be explained in greater detail in this chapter. Practice issues with biotechnology products may be handled in slightly different ways depending on laws and pharmacy practice standards in each country. This chapter is written primarily from the view of practice in the United States since that is the primary experience of the original chapter authors.

PHARMACIST READINESS

To be prepared to provide pharmaceutical care services to patients who require therapy with biotechnology drugs, pharmacists must be well versed ands skilled in (1) knowledge about the tools of biotechnology; (2) an understanding of the therapeutic aspects of recombinant protein products; (3) a thorough familiarity with the side effects and patient education considerations; (4) a familiarity with the storage, handling, and reconstitution of proteins; and (5) the difficulty of handling expensive biotech drug reimbursement issues.

Pharmacists may view biotechnology drugs as quite different from traditional parenteral products and familiar oral dosage forms. However, in most respects, the services offered by pharmacists when preparing and dispensing biotechnology products are the same as those provided for traditional tablets or injectable products. To determine the knowledge and skills a pharmacist requires to work with biotechnology drugs, one must first consider who will be storing, preparing, dispensing, and administering the agent. Many agents will be prepared by a pharmacist or other health-care provider and the drug administered by a nurse, while the patient will prepare others and self-administered. Pharmacists who work in clinics or with home health-care providers need to understand how to store, prepare, and dispense the product to a nurse with instructions to maintain potency and sterility until the biotech drug is administered to the patient. The knowledge and skill set is similar but has some significant differences from the skills required by a community pharmacist who must be able to teach the patient how to store, reconstitute, and self-administer the biotechnology agent.

The decision as to who will store, prepare, and administer the drug is typically determined from a business perspective. For example, in the U.S., in order for a clinic to administer and be paid for a drug, the drug must not be "usually self-administered by the patients who take them" (Department of Health and Human Services 2018). The Medicare Benefit Policy manual, Chap. 13 outlines a process to make this determination. Drugs and biologicals are usually covered by U.S. Centers for Medicare & Medicaid Services (CMS) if they are of the type that cannot be self-administered, they are not excluded (i.e., immunizations), they are reasonable and necessary for the

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diagnosis or treatment of the illness or injury for which they are administered and they have not been determined by the FDA to be less than effective. In addition they must meet all the general requirements for coverage of items as incident to a physician's services. Generally, prescription and non-prescription drugs and biologicals purchased by or dispensed to a patient are not covered.

From a practical standpoint, drugs administered in the clinic are billed using a "J" code. What is a J-Code? J-Codes relate to permanent codes used in the U.S. CMS to report injectable drugs that ordinarily cannot be self-administered by patients such as chemotherapy drugs, immunosuppressive drugs and inhalation solutions as well as some orally administered drugs. Based on logistics, it is relatively safe to say that a drug that does not have a "J code" will be prepared and administered by the patient (see Table 10.3 for examples of biotechnology drugs with and without a J code). It is important, regardless of the product being dispensed, to ensure that the pharmacist and patient understand the use, dosage regimen, and potential adverse effects of the product. Patients who will be preparing and self-administering the drug must know the proper storage and handling instructions as well as receive specific training on the administration of the drug and proper disposal of unused medication. When patients do not understand the administration and monitoring requirements of biotechnology products, training sessions for patients and caregivers should be considered to ensure appropriate patient care.

As more novel protein products, in particular the monoclonal antibody drugs, have come to market and the indications for existing agents have expanded, pharmacists are increasingly required to deal with these protein pharmaceuticals. While the first protein/peptide recombinant products were used primarily in hospital settings, many of these agents are now commonplace in ambulatory settings. The traditional community pharmacy may now dispense products like colony-stimulating factors, growth hormone, and interferons to name a just a few.

Traditional routes of delivery for pharmaceuticals have been challenged by the unique characteristics of biotech product delivery. Community pharmacies may struggle to maintain sufficient inventory of high-cost products, with in-depth knowledge of the products and its characteristics and with product administration. Assisting patients with reimbursement issues is very important, but is also a time-consuming, complicated process. Physicians also have difficulty with inventory and with slow reimbursement. Managed care organizations may have difficulty tracking claims for these products. As a result, the majority of patients receiving biotech drugs are now managed by home health, home infusion, or specialty pharmacy services (Managed Care 2014). Specialty pharmacies have evolved to manage outpatient biotechnology therapies for patients (National Association of Specialty Pharmacy 2018; https://naspnet.org/). Specialty pharmacy, which once occupied only a small niche in the marketplace, has become a burgeoning industry. Pharmacists, regardless of their area of practice, should understand the place of specialty pharmacy within the industry, even though the field may be difficult to define. Collaborations between specialty pharmacies, retail settings, hospitals, and manufacturers are becoming increasingly commonplace. These collaborations can enhance patient access to specialty pharmaceuticals and the high-touch services a specialty pharmacy can provide, thereby improving patient care.

Specialty pharmacies are growing in size and scope, in part because an aging population requires more specialty drugs such as the biotech-produced protein pharmaceuticals and also infusion therapies for cancer treatment. These drugs are expensive and often require special training to be administered and to be used by the patient home. Often the medications also need to be stored under specific conditions. Because misuse can be costly, many insurers pay for the high-touch service via a specialty pharmacy to assure so that costly medication errors are minimized. Specialty pharmacists practicing within academic health systems are uniquely positioned to overcome restrictions to medication access, financial constraints, and provider burdens that often lead to obstacles for patients to start and maintain necessary treatments (Bagwell et al. 2017).

The services offered by these pharmacies go far beyond dispensing biotech products. These pharmacies have expertise in the following areas:

- Insurance coverage and drug costs
- Pipeline monitoring and management
- Utilization management
- Promoting adherence to drug regimen
- Disease state management
- One-on-one counseling
- Risk Evaluation and Mitigation Strategies (REMS) requirements

Payers, particularly managed care organizations, now contract with specialty pharmacies to provide biotech and other expensive agents to solve many of the problems these products pose for the payer. The specialty pharmacy market is expected to continue to grow within the overall pharmaceutical market, according to a report from the Healthcare Distribution Alliance Research Foundation (HDA Research Foundation 2018). In 2016, specialty pharmacy was 40% of the $450 billion pharmaceutical market, compared to 30% of the $318 billion market in 2012.

Specialty sales in 2016 rose 11% over 2015 sales, to $181 billion. Of the $181 billion in 2016 sales of specialty drugs, $45 billion in sales was in the oncology market, the largest single therapeutic category. Medications for autoimmune issues came in second at $37 billion. Both of these categories of medicines have a large number of biotech drugs. In 2016, the top three specialty drugs by plan cost cross medical and pharmacy claims were Humira®, Enbrel®, and Remicade® (Artemetrix 2017). The introduction of new gene therapy and CAR-T therapies will likely accelerate the growth in specialty pharmacies.

■ Types of Information Needed by Pharmacists

What types of information do pharmacists require to be confident providers of biotech drugs and services? For pharmacists who have been out of school for many years, a contemporary understanding of the immune system, autoimmune diseases, and mechanisms by which drugs modify the immune system is essential. Several appropriate books that can provide a basic background in immunology are listed in Table 10.1. Additionally, practitioners may enroll in organized courses or continuing education programs that can provide up-to-date information in the discipline of immunology. Current pharmacy students and recent graduates should be sufficiently trained in basic immunology as part of their professional curriculum.

Pharmacists dispensing and counseling on biotech drugs must recognize that biotechnology primarily refers to a set of tools that has allowed great strides to be made in basic research, the understanding of disease and development of new therapeutic agents. It is essential for pharmacists to have a basic understanding of recombinant DNA technology and monoclonal antibody technology. However, it is not necessary that pharmacy practitioners know how to use these tools in the laboratory but rather how the use of these tools provides new therapeutic agents and a greater understanding of disease processes.

Pharmacists may need to review or learn anew about protein chemistry and those characteristics that affect therapeutic activity, product storage, and routes of administration of these drugs. Apart from this textbook, several publications, videotapes, and continuing professional education programs from industry and academic institutions are available to pharmacists for learning about the technical aspects of product storage and handling. Pharmacists also need to become familiar with the drug delivery systems currently in use for biotech drugs as well as those that are in development (see Chap. 5).

■ Sources of Information for Pharmacists

Many pharmacists do not know where to obtain the information that will allow them to be good providers of products of biotechnology. This textbook provides much of the essential background information in one source.

An excellent source of information on biotechnology in general, and specific products in particular, is the biotech drug industry. Many manufacturer-sponsored programs describe approved biotech products and those likely to come to market in the near future. Manufacturer programs provide extensive information about the disease states for which their products are indicated as well as product-specific information. Manufacturers are prepared to help pharmacists in the most effective provision of products and services to hospital-based and ambulatory patients.

Cellular and Molecular Immunology. 9th ed.
Abbas AK, Lichtman AH, Pillai S. Philadelphia: Elsevier, 2017: 565 pp.
Softbound book providing basic immunology concepts and clinical issues. Includes access to online edition
Immunology: A Short Course. 7th ed.
Coico R, Sunshine G. New Jersey: John Wiley and Sons, Inc., 2015: 406 pp
Softbound elementary text with review questions for each chapter *Clinical Immunology, Principles and Practice.* 5th ed. Rich RR, Fleisher TA, Shearer WT, Schroeder, Jr. HW, Frew AJ, Weyand CM. Philadelphia: Elsevier, 2018: 1392 pp. Hardbound book based on evidence-based practices that result in improved patient care
Cancer Immunotherapy Principles and Practice
Butterfield LH, Kaufman HL, Marincola FM. New York: Demos Medical, Springer Publishing, 2017: 920 pp.
Hardbound, detailed overview of immunology and immunobiotechnology from the perspective of Immunotherapy advances.
Roitt's Essential immunology. 13th ed.
Delves, PJ, Martin, SJ, Burton, DR, Roitt, IM. Oxford; Boston: Wiley-Blackwell Publishing, 2017: 576 pp.
Softbound basic immunology textbook
Janeway's Immunobiology. 9th ed.
Murphy K, Weaver C. New York: Garland Science, 2016: 924 pp.
Softback text that presents immunology at the introductory level. Also available in e-book format

Table 10.1 ■ Selected texts to enhance immunology knowledge

Manufacturer	Professional services	Reimbursement hotline/ indigent patient programs	Manufacturer website
Amgen	1-800-772-6436	1-800-272-9376	www.amgen.com
Astellas Pharma	1-800-727-7003	1-800-477-6472	www.astellas.us
Baxter Healthcare	1-800-422-9837	1-800-548-4448	www.baxter.com
Bayer Healthcare	1-888-765-3846	1-800-288-8374	www.bayerhealthcare.com
Biogen Idec	1-800-456-2255	1-800-456-2255	www.biogenidec.com
BioMarin	1-800-983-4587	1-866-906-6100	www.bmrn.com
Bristol-Myers Squibb	1-800-332-2056	1-800-736-0003	www.bms.com
CSL Behring	1-800-504-5434		www.cslbehring.com
Eli Lilly	1-877-237-8197	1-800-545-5979	www.lilly.com
Genentech	1-800-821-8590	1-800-530-3083	www.gene.com
Genentech	1-800-821-8590	1-866-422-2377	www.genentechaccesssolutions.com
Genzyme	1-800-745-4447	1-800-745-4447	www.genzyme.com
GlaxoSmithKline	1-888-825-5249	1-888-825-5249	www.gsk.com
Janssen Biotech	1-800-526-7736	1-800-652-6227	www.janssenbiotech.com
Kite Pharma	1-844-454-KITE	1-844-454-KITE	www.kitepharma.com
Merck	1-800-444-2080	1-800-727-5400	www.merck.com
Novartis	1-888-669-6682	1-800-257-3273	www.novartis.com
Novo Nordisk	1-800-727-6500	1-877-668-6777	www.novomedlink.com
Pfizer	1-800-505-4426	1-866-706-2400	www.pfizer.com
Pfizer	1-800-505-4426	1-866-706-2400	www.pfizerhelpfulanswers.com
Roche	1-800-821-8590	1-800-285-2484	www.roche.com
Sanofi	1-800-981-2491	1-800-221-4025	www.sanofi.us
Sun Pharmaceuticals	1-877-208-3015		www.sunpharma.com

Table 10.2 Toll-free assistance numbers and websites for selected biopharmaceutical manufacturers in the USA and Canada

However, many pharmacists are unaware of these services and how to obtain them. A web search of specific products will lead to the product and manufacturer's websites where this information can be accessed.

The information provided by manufacturers can help pharmacists to confidently provide biotechnology products to their patients. The services provided generally fall into three categories: customer/medical services and support, educational materials, and reimbursement information. Manufacturers may have a separate number for reimbursement questions. Table 10.2 lists the manufacturer's toll-free assistance numbers and web addresses for obtaining product and reimbursement information in North America. Vaccines and insulin products are not included in this table since these products were previously available in a nonrecombinant form and pharmacists are generally well familiar with these products. Moreover, the recombinant forms of these products are generally not as costly as other types of biologic agents.

The Pharmacist and Handling of Biotech Drugs

The pharmacist is responsible for the storage, preparation, and dispensing of biotechnology drugs as well as patient education regarding the use of these products. In many cases, pharmacists must have additional training in order to be prepared for this role. This is especially true for pharmacists who practice in the ambulatory setting since these products are increasingly available for self-administration in the home. Pharmacies of the future may stock pumps, patches, timed-release tablets, liposomes, implants, and vials of tailored monoclonal antibodies. With advances in gene therapy and pharmacogenomics, it is possible that the pharmacist may eventually prepare and dispense precision medicine products tailored for specific patients.

This chapter discusses the general principles that pharmacists need to understand about storage, handling, preparation, administration of biotech products, and issues related to outpatient/home care. Specific examples will be discussed for illustrative purposes. Table 10.3 lists selected products along with

Generic name	Brand name	Storage temperature	Reconstitution solution	Stability after reconstitution		Dilution/stability	J code[a]
				RT	Ref		
Abatacept	Orencia®	2–8 °C	SWFI	24 h	24 h	24 h (further diluted in NS)	Yes
Adalimumab	Humira®	2–8 °C	RTU	NA	NA	NA	Yes
Alteplase	Activase®	2–25 °C	Dil	8 h	8 h	NA	Yes
Alteplase	Cathflo® Activase®	2–8 °C	SWFI	8 h	8 h	NA	Yes
Bevacizumab	Avastin®	2–8 °C	NS	NA	8 h	NA	Yes
Canakinumab	Ilaris®	2–8 °C	SWFI	24 h	24 h	NA	Yes
Cetuximab	Erbitux®	2–8 °C	RTU	NA	NA	NA	Yes
Darbepoetin alfa	Aranesp®	2–8 °C	RTU	NA	NA	NA	Yes
Denosumab	Prolia® Xgeva®	2–8 °C	RTU	NA	NA	NA	Yes
Dornase alfa	Pulmozyme®	2–8 °C	RTU	NA	NA	NA	Yes
Epoetin alfa SDV	Epogen® Procrit®	2–8 °C	SBWFI containing benzyl alcohol 0.9% in a 1:1 ratio	14 d (except for 40,000 units/mL vials which are stable for 7 d)	NA	Dilutions of 1:10 and 1:20 (1 part epoetin:19 parts sodium chloride): 18 h	Yes
Epoetin alfa MDV	Epogen® Procrit®	2–8 °C aie and between doses	RTU	NA	NA	Dilutions of 1:10 in $D_{10}W$ with human albumin 0.05 or 0.1%: 24 h	Yes
Erenumab-aooc	Aimovigv	2–8 °C	RTU	NA	NA	NA	No
Etanercept	Enbrel®	2–8 °C	SBWFI	NA	14 d	NA	Yes
Evolocumab	Rapatha®	2–8 °C	RTU	NA	NA	NA	Yes
Factor VIIa recombinant	NovoSeven® RT	2–25 °C	Histidine diluent	3 h	3 h	NA	No
Filgrastim	Neupogen®	2–8 °C	D_5W	24 h	14 d	24 h	Yes
Golimumab	Kinevet®	2–8 °C	RTU	NA	NA	NA	No
Infliximab	Remicade®	2–8 °C	SWFI	NA	NA	3 h	Yes
Interferon alfa- 2b	Intron®A	2–8 °C	SWFI		24 h	24 h (further diluted in NS)	Yes
Interferon-β1a prefilled syringe	Avonex®, Rebif®	2–8 °C	RTU	NA	NA	NA	Yes
Interferon-β1a reconstitutable vial	Avonex®, Rebif	2–8 °C	SWFI	NA	6 h	NA	Yes
Interferon-β1b	Betaseron®	25 °C	NaCl 0.54%	NA	3 h	NA	Yes
Ipilimumab	Yervoy®	2–8 °C	NS or D_5W	24 h	24 h	NA	Yes
Ixekizumab	Taltz®	2–8 °C	RTU	NA	5 d	NA	Yes
Ocrelizumab	Ocrevus®	2–8 °C	NaCl 0.9%	NA	NA	NA	No
Paclitaxel (protein bound)	Abraxane®	25 °C	NS	8 h	8 h	NA	Yes
Palivizumab	Synagis®	2–8 °C	RTU	NA	NA	NA	No
Peginterferon alfa-2a	Pegasys® Convenience Pack	2–8 °C	RTU	NA	NA	NA	No

Table 10.3 ■ Storage, stability, and reconstitution of selected biotechnology products

Generic name	Brand name	Storage temperature	Reconstitution solution	Stability after reconstitution		Dilution/stability	J code[a]
				RT	Ref		
Peginterferon alfa-2b	PegIntron®	25 °C	SWFI	NA	24 h	NA	No
Peginterferon alfa-2b	Sylatron®	25 °C	SWFI	NA	24 h	NA	No
Peginterferon alfa-2b	Redipen®	2–8 °C	RTU	NA	24 h	NA	No
Pegfilgrastim	Neulasta®	2–8 °C	RTU	NA	NA	NA	Yes
Ramucirumab	Cyramza®	2–8 °C	NaCl 0.9%	4 h	24 h	24 h	Yes
Ranibizumab	Lucentis®	2–8 °C	RTU	NA	NA	NA	Yes
Redolizumab	Entyvio®	2–8 °C	NaCl 0.9%	12 h	24 h	12 h	Yes
Rituximab	Rituxan®	2–8 °C	NS or D_5W	24 h	24 h	NA	No
Secukinumab	Cosentyx®	2–8 °C	RTU	NA	NA	NA	No
Teriparatide	Forteo®	2–8 °C	RTU	NA	NA	NA	No
Tisagenlecleucel	Kymriah®	NA	In clinic	NA	NA	NA	No
Trastuzumab	Herceptin®	2–8 °C	SBWFI	NA	28 d	24 h (further diluted in NS)	Yes

Biologic products listed in the top 200 drugs in the US market by sales, 2017
Table key: *aie* after initial entry into vial, *d* days; *dil* supplied diluent, *h* hours, *mdv* applies only to multidose vials, *NA* not applicable/not available, *NS* normal saline, *Ref* under refrigeration, *RT* room temperature, *RTU* ready to use, *SBWFI* sterile bacterial water for injection, *SDV* applies only to single-dose vials, *SWFI* sterile water for injection
[a]Products have a J code for the first quarter of 2018 according to the document, 2018 ASP Drug Pricing Files Medicare Part B Drug Average Sales Price, listed on cms.gov (https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2018ASPFiles.html)

Table 10.3 ■ (continued)

specific handling requirements for each. For specific products or recent updates to these requirements, contact the manufacturer. For additional information regarding drug handling and preparation, the pharmacist may consult publications such as the American Hospital Formulary Service (AHFS) Drug Information ONLINE (http://www.ahfsdruginformation.com/ahfs-clinical-drug-information/; and in print each year annually by the Association of Health-Systems Pharmacists) (AHFS 2018) or the *King Guide to Parenteral Admixture* (https://kingguide.net/collections/internet-edition) (King Guide 2018), an updated online guide to IV drug compatibility and stability (there are also print versions available for purchase). Pharmacy benefits management companies (PBMs) usually own specialty pharmacy companies and provide valuable information via their websites. The three largest specialty pharmacy companies in 2016 were CVS Specialty (CVS Health), Accredo/Freedom Fertility owned by Express Scripts, and Alliance Rx Walgreens Prime/Walgreens stores (Walgreens Boots Alliance) (Drug Channels 2018).

STORAGE

Biotech products have unique storage requirements when compared to the majority of products that pharmacists dispense. The shelf-life of these products is often considerably shorter than for traditional compounds (Cf. Chap. 5). For example, interferon-α2a (Roferon-A®, Roche Laboratories 2018) is only stable in a refrigerator in the ready-to-use solution for 2 years. After the first dose, cartridges may be stored at less than 25 °C for *up to* 28 days although refrigeration is recommended. Since most biologic products need to be kept at refrigerated temperatures (as discussed below), some pharmacies may need to increase cold storage space in order to accommodate the storage needs.

■ Temperature Requirements

Since biotech products are primarily proteins, they are subject to denaturation when exposed to extreme temperatures. In general, most biotech products are shipped by the manufacturer in gel ice containers and need to be stored at 2–8 °C (Banga and Reddy 1994; Rayfield et al. 2017). Once reconstituted, they should be stored under refrigeration until just prior to use. There are a few exceptions to this rule. For example, alteplase (tissue plasminogen activator, Activase®) lyophilized powder is stable at room temperature for several years at temperatures not to exceed 30 °C (86 °F). However, after reconstitution, the product should be used within 8 h (Genentech 2018b). For individual product temperature requirements, the product insert, product website, or the manufacturer should be

contacted. Table 10.3 lists temperature requirements for selected frequently prescribed products.

The variability between products with respect to temperature is exemplified by granulocyte colony-stimulating factor (G-CSF, filgrastim, Neupogen®) (Amgen Inc 2018b) and erythropoietin (Epogen®) (Amgen Inc 2018a), which are stable in ready-to-use form at room temperature for 24 h and 14 days, respectively. Granulocyte macrophage colony-stimulating factor (GM-CSF, sargramostim, Leukine®) (Sanofi-Aventis 2018) is packaged as a lyophilized powder but still requires refrigeration and once reconstituted is stable at room temperature for 30 days or in the refrigerator for 2 years. Aldesleukin (interleukin-2, Proleukin®) is stable for 48 h at room temperature or under refrigeration (Prometheus Therapeutics and Diagnostics 2018). Interferon-β1b (Betaseron®) must be stored in a refrigerator and should be used within 3 h after reconstitution (Bayer HealthCare 2018). While most products require refrigeration to maintain stability due to denaturation by elevated temperatures, extreme cold such as freezing may be just as harmful to most products. The key is to avoid extremes in temperature whether it is heat or cold (Banga and Reddy 1994).

■ Storage in Dosing and Administration Devices

Many biotech products can adhere to either plastic or glass containers such as syringes, polyvinyl chloride (PVC) intravenous bags, infusion equipment, and glass intravenous bottles. The effectiveness of the product may be reduced by three- or fourfold due to adherence. In order to decrease the amount of adherence human serum albumin, (HSA) is usually added to the solutions. The relative loss through adherence is concentration dependent, i.e., the more concentrated the final solution, the less significant the adherence becomes. The amount of HSA added varies with the product (Banga and Reddy 1994; Finn et al. 2012). Some products that require the addition of HSA include filgrastim, sargramostim, aldesleukin, erythropoietin, and interferon-α. In the case of filgrastim, the addition of 2 mg/mL of HSA to the final solution is required for concentrations of 5–15 μg/mL (Amgen Inc 2018c). One milligram of HSA per 1 mL 0.9% sodium chloride injection is added to achieve a final concentration of 0.1% HSA for sargramostim concentrations of <10 μg/mL (Sanofi-Aventis 2018). For aldesleukin 0.1%, HSA is required for all concentrations (Prometheus Therapeutics and Diagnostics 2018). For erythropoietin, 2.5 mg HSA is present per mL in each single-dose and multidose vial (Amgen Inc 2018d). One milligram per milliliter of HSA is added to interferon-α-2b (Intron-A®) in single-dose and multidose vials and pens (RxList 2018).

For additional information or to find information for other products, check the current product information or contact the manufacturer.

■ Storage in IV Solutions

Biotech product stability may vary when stored in different types of containers and syringes. Some products are only stable in plastic syringes, e.g., somatropin and erythropoietin, while others are stable in glass, polyvinyl chloride, and polypropylene, e.g., aldesleukin. Batch prefilling of syringes is possible. However, it is important to make sure that the product you wish to provide in prefilled syringes is stable in the type of syringe you wish to use. This may present a challenge to specialty pharmacy programs. Determining how far in advance doses may be prepared is also an important consideration. G-CSF is stable in Becton Dickinson (B-D) disposable plastic syringes for up to 7 days (Amgen Inc 2018c), while erythropoietin is stable for up to 14 days (Amgen Inc 2018d). Aldesleukin is recommended to be administered in PVC although glass has been used in clinical trials with comparable results (Prometheus Therapeutics and Diagnostics 2018). Solutions are stable for 48 h when refrigerated. GM-CSF and G-CSF can be administered in either PVC or polypropylene (Sanofi-Aventis 2018).

■ Light Protection

Many biotech products are sensitive to light. Manufacturer's information usually suggests that products be protected from strong light until the product is used. Dornase-α (Pulmozyme®) is packaged in protective foil pouches by the manufacturer to protect it from light degradation and should be stored in these original light protective containers until use. For patients who travel, the manufacturer will provide special travel pouches on request (Genentech 2018a). Alteplase in the lyophilized form also needs to be protected from light but is not light sensitive when in solution (Genentech 2018b). Pharmacists must be aware of the specific storage requirements with respect to light for each of the products stocked in the pharmacy.

HANDLING

■ Mixing and Shaking

Improper handling of protein products can lead to denaturation. Shaking and severe agitation of most of these products will result in degradation (cf. Chap. 5). Therefore, special techniques must be observed in preparing biotech products for use. Biotech products should not be shaken when adding any diluent as this may cause the product to breakdown. Once the diluent is added to the container, the vial should be swirled rather than vigorously shaken. Some shaking during transport may be unavoidable and proper inspection of products should occur to make sure the products have not been damaged during transit. When a product is affected by excessive shaking, physical separation or frothing within the vial of liquid products can usually

be observed. For lyophilized products, agitation is not harmful until the product has been or is reconstituted. In distributing individual products to patient or ward areas, pneumatic tubes should be avoided.

■ Travel Requirements

When patients travel with these products, certain precautions should be observed. The drugs should be stored in insulated, cool containers. This can be accomplished by using ice packs to keep the biotech drug at the proper temperature in warmer climates, whereas the insulated container in colder climates may be all that is required. When traveling in subfreezing weather, the products should be protected from freezing (temperatures below 2 °C). Keeping biotech drugs at proper temperature during automobile travel may present a problem with temperatures inside a parked car often exceeding 37 °C (100 °F) on a warm day. Patients and delivery personnel must take care not to leave products that are not in insulated containers inside the car, trunk, or glove compartment while shopping or making deliveries. When ice is used, care should be taken not to place the product directly on the ice. Dry ice should be avoided since it has the potential for freezing the product. When traveling by air, biotech products should be taken onto the plane in insulated packages and not placed in a cargo container. Airplane cargo containers may be cold enough to cause freezing (Banga and Reddy 1994).

PREPARATION

When preparing biotech products, aseptic technique must be employed as it is with traditional parenteral products. Sterile compounding procedures require clean facilities, specific training for operators, air quality evaluations, and a sound knowledge of sterilization and stability principles. USP 797 provides guidelines, procedures and compliance requirements for compounding sterile preparations. The product should be prepared in a clean room designed for this purpose with laminar airflow hoods, and other practices consistent with USP 797. Most of the products require reconstitution with sterile water or bacteriostatic water for injection depending on stability data. The compatibility of individual products varies and limited data is available. As mentioned previously, when adding diluent to these products, care should be taken not to shake them, but to swirl the container or roll it between the palms of the hands. In the case of lyophilized products, introduction of the diluent should be directed down the side of the vial and not directly on the powder to avoid denaturing the protein. It is important to mention that stability does not mean sterility. Biotech products require the same precautions as any other parenteral product. Sterility is particularly important when prefilling and premixing various doses for administration at home. Once the manufacturer's sterile packaging is entered, sterility can no longer be assured nor will the manufacturer be responsible for any subsequent related problems. Many biotech drugs are not compatible with preservative agents, and single-use vials do not contain a preservative. Individual manufacturers have not addressed the issue of sterility and each institution or organization must determine its own policy on this issue. Many of the currently available biotechnology-produced products are provided as single-dose vials and should not be reused. This does not, however, prevent preparing batches ("batching") of unit-of-use doses in order to be efficient. Many of the patients receiving these agents are likely to have suppressed immune systems and are vulnerable to infection. Therefore, a policy involving the maintenance of sterility of biotech products should be developed by each health-care organization, especially hospitals and specialty pharmacies. When products are made in a sterile environment under aseptic procedures, they should remain sterile until used and thus could be stored for as long as physical compatibility data dictates. However, most institutions have shorter expiration dates, which are generally 72 h or less, on reconstituted products. These expiration dates have been conservatively set due to lack of good sterility data to the contrary. Sterility studies should be performed in order to determine if reconstituted products could be stored for a longer period of time and still maintain sterility. For products reconstituted for home use, in the pharmacy sterile products area, a 7-day expiration date is used provided the product is stable and can be stored in the refrigerator. The American Society of Health-System Pharmacists has published a technical assistance bulletin on sterile products, which should be consulted for developing policies on storage of reconstituted parenteral products (American Society of Health-System Pharmacists 2017). Patients need to be informed about specific storage requirements and expiration dates to assure sterility and stability.

ADMINISTRATION

Prior to administering these products, pharmacists will need to use caution in reviewing dosing regimens. A potential source of medication error is the variation in units of measure for the various products. Some products are dosed in micrograms/kilogram (μg/kg) rather than milligrams/kilogram (mg/kg). Dosage calculations need to be carefully checked to avoid potential errors. Biotech products frequently receive approval for new indications after they have been on the market

for a few years. The dosing regimen for these indications may be different than the original indication. Therefore, it is important to confirm the diagnosis and indication for products with multiple indications and dosing regimens. For example, adalimumab (Humira®) is dosed at 40 mg subcutaneously every other week to treat rheumatoid arthritis. The initial dose for plaque psoriasis is 80 mg subcutaneously, followed by a weekly dose of 40 mg. The initial dose for Crohn's disease is 160 mg subcutaneously, given as 4 injections on day 1 or 2 injections/day over 2 consecutive days, followed by an 80 mg dose 2 weeks later and a weekly maintenance dose of 40 mg every other week beginning on day 29 (AbbVie Inc 2018).

Another example of variations in dosing regimen is for the monoclonal antibody denosumab from Amgen Inc. For treatment of osteoporosis in postmenopausal females, the dose of denosumab (Prolia®; Amgen Inc 2018c) is 60 mg every month. For prevention of skeletal-related events in bone metastases from solid tumors, denosumab is administered 120 mg every 4 weeks (Xgeva®; Amgen Inc 2018d). The manufacturer recognizes the risk of errors in dosing and has given the product different names to help prevent mistakes in dosing regimens.

■ Routes of Administration

Biotech products are primarily administered parenterally although routes of administration may be used. For example, dornase alfa is administered by inhalation (Genentech 2018b). Some products may be given by either the intravenous or subcutaneous route, while others are restricted to the subcutaneous or intramuscular routes. In some cases, manufacturers have information on unapproved routes of administration or other unpublished information that may be available by contacting the individual manufacturer. In any case, the manufacturer should always be consulted in order to obtain supporting evidence for a particular route that is not approved, but may be more convenient for the patient. For example, G-CSF should be administered by the subcutaneous or intravenous route only, while GM-CSF is given by intravenous infusion, over a 2 h period (AHFS 2018). Aldesleukin is approved for intravenous administration only. However, subcutaneous administration has been used by some as an unlabeled route of administration (McDermott et al. 2005). Erythropoietin should only be administered by the intravenous or subcutaneous routes (Amgen Inc 2018d), while alteplase is only approved for the intravenous route (AHFS 2018; Genentech 2018a) Alteplase has also been administered by the intracoronary, intra-arterial, and intraorbital routes as well (AHFS 2018).

■ Filtration

Filtering biotech products is not generally recommended since most of these proteins will adhere to the filter. Some hospitals and home infusion companies routinely use in-line filters for all intravenous solutions to minimize the introduction of particulate matter into the patient. In the case of biotech products, they should be infused below the filter to avoid a potential decrease in the amount of drug delivered to the patient (Banga and Reddy 1994). Some manufacturers recommend infusing products using an in-line low protein-binding filter (≤1.2 μm).

■ Flushing Solutions

Biotechnology products are usually flushed with either saline or dextrose 5% in water. The product literature should be consulted and care should be taken to assure that the proper solution is used with each agent. In general, biotech drugs should not be administered with other drugs since, in most cases, data does not exist that demonstrates whether biotech products are compatible with other drugs or fluids.

■ Prophylaxis to Prevent Infusion Reactions

Some products have protocols to treat and/or prevent infusion reactions for repeat infusions. For example, the infliximab protocol to treat an infusion reaction includes reducing the infusion rate, initiating a normal saline infusion, use of symptomatic treatment (normally consisting of acetaminophen and diphenhydramine), and vital sign monitoring every 10 min until resolution of the reaction. For subsequent infusions, pretreatment with acetaminophen and diphenhydramine 90 min prior to the infusion is standard procedure. Patients who had severe reactions may receive corticosteroids (AbbVie Inc 2018).

BIOSIMILARS

The present state of the regulatory aspects of biosimilars (through FDA and EMA) is dealt with in Chap. 12. Making choices for health-care professionals is not new in the biotech market as it already contains several types of insulins, growth hormones, and second-generation products such as darbepoetin alfa (Aranesp®) and pegfilgrastim (Neulasta®). Pharmacists and formulary committees need to choose between a variety of biotech drugs produced in different cell lines with differences in physical properties but intended to produce the same therapeutic effect. The ability to achieve a similar therapeutic effect for patients with a particular chronic disease using a biosimilar product is only one important consideration of comparing biosimilar products to the innovator drug. Biosimilars will also differ from the innovator drug in the manufacturing process.

For example, a different cell line may be used to produce the recombinant protein. It is possible that the innovator and biosimilar drug may therefore differ in the immunogenicity of the product. Patients may be more or less likely to develop an immune response to the biosimilar agent. Health professionals will need to be involved in the clinical trials, patient monitoring, and postmarketing surveillance of biosimilars to determine the interchangeability of products and the patient care considerations that may be involved in using biosimilar agents.

OUTPATIENT/HOME CARE ISSUES

As mentioned previously, the management of patients in the outpatient and home settings is now an accepted aspect of health-care delivery. Home infusion and specialty pharmacy services dispense all forms of parenteral and enteral products including biotech drugs. These pharmacies have grown exponentially in the last 25 years due to cost savings for third-party payers, technological advances that allow these services to occur in the home, and patient preference to be treated at home rather than an in-patient setting.

■ Patient Assessment and Education

Before a patient can be a candidate for home therapy, an assessment of the patient's capabilities must occur. The patient, family member, or caregiver will need to be able to administer the medication and comply with all of the storage, handling, and preparation requirements. If the patient is incapable, then a caregiver (usually a relative, spouse, or friend) needs to be recruited to assist the patient. The pharmacy staff or other health professional may also make home visits to assist the patient in these tasks. The use of aseptic technique is usually new to the patients and in some cases may be overwhelming. The health-care provider must be sure that the patient or caregiver is competent and willing to follow these procedures. Self-instructional guides on specific products may be available from the manufacturer and, if so, should be provided to the patient providing they have the proper equipment for viewing.

Proper storage facilities will need to be available in the patient's home as well as a clean area for preparation and administration. Ideally, the patient will be able to prepare each dose immediately prior to the time of administration. If this is not possible, the pharmacy will have to prepare prefilled syringes and provide appropriate storage and handling requirements to the patient. The patient will also need to be educated regarding the proper handling of the syringes as well as other required supplies and materials such as needles, syringes, and alcohol wipes. Proper disposal of these hazardous wastes must also be reviewed. Specific issues related to patient teaching include rotating injection sites, product handling, drug storage including transporting and traveling with biotech drugs, expiration dates, refrigeration, cleansing the injection site with alcohol, disposal of needles and syringes, potential adverse effects, and expected therapeutic outcomes.

■ Monitoring

For patients who receive biotech drug therapy in the home, it is particularly important that close patient monitoring occurs. This will require frequent phone calls to the patient and periodic home visits. Monitoring parameters should include adverse events, progress to expected outcomes, assessment of administration technique, review of storage and handling procedures, and adherence to aseptic technique.

REIMBURSEMENT

Reimbursement issues include third-party billing information and availability of forms, cost-sharing programs that limit the annual cost of therapy, financial assistance programs for patients who would otherwise have difficulty paying for therapy, and reimbursement assurance programs that are designed to remove reimbursement barriers when reimbursement has been denied. Any detailed discussion of reimbursement issues is beyond the scope of this book and is subject to practice location. This discussion will deal only with the availability of information to pharmacists to appropriately handle reimbursement for products and services in the United States.

Pharmacists need to know current third-party payment policies including those conditions under which insurance companies will disallow claims. Some examples include off-label prescribing or administration of the product in the home rather than administration in a hospital or physician's office. Prior authorization is usually required particularly with managed care or prepaid plans. Manufacturers will often assist the patient by contacting the carrier to verify coverage, providing sample prior-approval letters, and following up on claims to determine the claim's status, and continuing to follow the case until it is resolved.

Manufacturers can also provide information that may convince the third-party payer to reconsider a denied claim. Some companies will intervene with the third-party payer to evaluate the case for denial and provide additional clinical documentation or coding information and will follow the appeal to conclusion. Pharmacists can act as facilitators to get qualified patients enrolled in programs to provide free medication to those who have insufficient insurance coverage or are otherwise unable to purchase the therapy.

Manufacturers' websites and toll-free numbers for reimbursement issues are provided in Table 10.2. Websites, toll-free numbers and email addresses can be found for a wide range of assistance programs on the WebMD site including programs run by pharmaceutical companies, by states and by non-profit groups (https://www.webmd.com/healthy-aging/patient-assistance-programs-for-prescription-drugs#1). A major program is the Partnership for Prescription Assistance website (https://www.pparx.org/) which provides information on a variety of patient assistance programs as well as the requirements to qualify for various programs. They are a program sponsored by drug companies, doctors, patient advocacy organizations, and civic groups.

EDUCATIONAL MATERIALS

Therapy with biotech drugs is a rapidly growing, ever-changing area of therapeutics, particularly as cell and gene therapy approaches enter the market. Pharmacists need to keep abreast of current information about existing agents such as new indications, management of adverse effects, results of studies describing drug interactions, or changes in information regarding product stability and reconstitution. Pharmacists will also be interested in the status of new agents as they move through the FDA approval process. Some good periodical sources of practical information about products of biotechnology are listed in Table 10.4. The Internet is a valuable site rich in up-to-date information concerning all aspects of pharmaceutical biotechnology. Sites include virtual libraries/catalogs, online journals (usually requiring a subscription), biomedical newsletters, and biotechnology-specific home pages. Since the number of biotech-related sites is constantly increasing, readers are encouraged to explore the web for useful options.

■ Educational Materials for Health Professionals

Manufacturer and specific product websites provide a variety of educational materials including continuing education programs for physicians, pharmacists, and nurses. These programs often focus on specific disease states as well as drug therapy. The programs sometimes include slides, videos, and brochures. Since most biotechnology products are parenteral products, several manufacturers have produced videotapes that show the proper procedure for product administration, storage, and handling. These instructional tapes are beneficial not just for patients but also for health professionals who may not be skilled in injection techniques.

■ Educational Materials for Patients

Detailed patient information booklets exist for many of the products both in print and by downloading from the Internet. Patient education materials can assist the patient and family members in learning more about his or her disease and how it will be treated. Education allows the patient to participate more actively in the therapy and to feel a greater level of control over the process. By contacting the manufacturer and acquiring patient educational materials, pharmacists can offer support to the patient in learning to use a new product. Dealing with a diagnosis of serious or chronic disease already overwhelms many patients. Learning about a new therapy, especially if it involves the necessity of self-injection, can cause additional stress for the patient and family.

Most commercially available biotech drugs now have individual websites to provide updated information to patients. These sites usually contain the following types of information: disease background, reimbursement information, dosing information, references, frequently asked questions, administration and storage information, and information specifically for health professionals. These websites also offer tools such as journals for patients to record administration of doses and monitoring information to assist health professionals in following the patient's progress. The websites also refer patients to disease-related associations and organizations whose services include a link to local chapters, meetings, and support groups. These groups may provide support to the patient while he or she adjusts to the diagnosis and treatment of a potentially serious disease.

2017 State of the Industry; PhRMA; http://phrma.org/industryprofile/
An *Introduction to Biotechnology*—Amgen; http://www.biotechnology.amgen.com/index.html
BioCentury News, BioCentury, Inc., San Carlos, CA; https://www.biocentury.com/
Bio/Technology, New York, nature Publishing Company; www.nature.com/nbt
BiotechNow Blog, Biotechnology Innovation Organization (BIO), Washington, D.C., https://www.bio.org/
BioWorld *Today*, Atlanta, Bioworld Publishing Group, newspaper; http://www.bioworld.com/
Genetic Engineering News, New York, GEN Publishing, bimonthly publication; https://www.genengnews.com/
"*The Pink Sheet*" Bridgewater, NJ, published weekly; https://pink.pharmaintelligence.informa.com/

Table 10.4 ■ Information sources for current trends in biotechnology

CONCLUDING REMARKS

The handling of biotechnology products requires similar skills and techniques as required for the preparation of other parenteral drugs, but there are often different nuances to the handling, preparation, and administration of biotechnology-produced pharmaceuticals. The pharmacist can become an educator regarding the pharmaceutical aspects of biotechnology products and can serve as a valuable resource to other health-care professionals. In addition, biotech products give the pharmacist the opportunity to provide enhanced patient care services since patient education and monitoring is required. To carry out this role successfully, the pharmacist will need to keep abreast of new developments as new literature and products become available.

SELF-ASSESSMENT QUESTIONS

■ Questions

1. What are some of the causes of pharmacist reluctance to handling biotech products?
2. In what areas of study do pharmacists and pharmacy students need to engage to be best prepared to provide pharmaceutical care services to patients receiving biotechnology therapeutic agents?
3. What resources are available to pharmacy practitioners to learn more about biotechnology and the drug products of biotechnology?
4. How do the storage requirements of biotech products differ from the majority of products pharmacists normally dispense?
5. What is the most common temperature for the storage of biotech pharmaceuticals?
6. Why is human serum albumin added to the solution of many biotech drugs?
7. Why should biotech products not be shaken when adding any diluent?
8. During travel, what precautions should also be observed with biotech products?
9. Should biotech products be filtered prior to administration?
10. What assessments must be done by the pharmacist before a patient can be considered a candidate for home therapy with a biotech product?
11. What types of professional services information are provided by manufacturers of biotech drugs?
12. What issues will the pharmacist need to consider when comparing innovator drugs to biosimilars?

■ Answers

1. Lack of understanding of the basics of biotechnology; lack of understanding of the therapeutics of recombinant protein products; unfamiliarity with the side effects and patient counseling information; lack of familiarity with the storage, handling, and reconstitution of proteins; and the difficulty of handling reimbursement issues.
2. Basic biotechnology/immunological methods; protein chemistry; therapeutics of biotechnology agents; and storage, handling, reconstitution, and administration of biotechnology products.
3. Biotechnology/immunology texts, continuing education programs, manufacturers' information and toll-free assistance, biotechnology-oriented journals, and the Internet.
4. The shelf-life of these products is often considerably shorter than has been the case with more traditional compounds. These products need to be kept at refrigerated temperatures. There are, of course, exceptions to this rule.
5. In general, most biotech products are shipped by the manufacturer in gel ice containers and need to be stored at 2–8 °C. Once reconstituted, they should be kept under refrigeration until just prior to use.
6. Most biotech products may adhere to either plastic or glass containers such as syringes and polyvinyl chloride (PVC) intravenous bags reducing effectiveness of the product. Human serum albumin is usually added to the solutions to prevent adherence.
7. Shaking may cause the product to breakdown (aggregation). Usually when this happens one can observe physical separation or frothing within the vial of liquid products.
8. They should be stored in insulated, cool containers. This can be accomplished by using ice packs to keep the biotech drug at the proper temperature in warmer climates, whereas the insulated container in colder climates may be all that is required. In fact, when traveling in subfreezing weather, the products should be protected from freezing.
9. Filtering biotech products is not generally recommended since most of the proteins will adhere to the filter.
10. Before a patient can be a candidate for home therapy, an assessment of the patient's capabilities must occur. The patient, family member, or caregiver will need to be able to inject the medication and comply with all of the storage, handling, and preparation requirements.
11. Medical information services provided by manufacturers of biotech drugs are similar to the product, medical and patient management services provided by drug companies for traditional drug products. Information provided via this service generally includes appropriate indications, side effects, contraindications to use, results of clinical trials, and investigational uses. Upon request, manufacturers can supply a product monograph

and selected research articles that provide valuable information about each product.

12. In addition to ensuring that the biosimilar drug produces the same therapeutic effect, differences in manufacturing that may affect the patient will need to be considered. The most significant of these is potential immunogenicity of the product.

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SUGGESTED READING

See Tables 10.1, 10.2, and 10.4 for suggested readings