

4 Key Regulatory Guidelines for the Development of Biologics in the United States and Europe¹

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4.1 INTRODUCTION

The United States and the European Union have distinct but overlapping schemes for the regulation of biologics, ranging from the definition of a biologic itself to the technical requirements for approval. In the United States, the definition of “biological product” was developed over time, and historical context continues to inform its interpretation. In the European Union, biologics are largely defined in terms of their active substances and methods of manufacture. Despite these differences, both jurisdictions recognize that biologics warrant special treatment because of their distinct characteristics, such as their complex structures and susceptibility to variation during manufacturing. Whereas in the United States, Congress enacted a separate statute for biologics, in the EU, the general approval scheme and certain specific requirements apply to biologics. Nevertheless, US and EU authorities have undertaken harmonization efforts with respect to some technical requirements for biologics applications; thus, there is significant overlap in requirements imposed by both regions. This chapter provides an overview of the US and EU regulatory schemes, from nonclinical trials through clinical trials to approval. It then discusses considerations for global development of biologics, and it ends by discussing special issues for developing vaccines.

¹ The chapter uses both the terms “drug” and “medicine” as they are used in the US and EU regulatory schemes, respectively.

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4.2 GENERAL UNITED STATES REGULATORY SCHEME

4.2.1 The Definition of “Biological Product” and Its Significance

In the United States, “biological products” are subject to a different premarket pathway and differing intellectual property protections than products regulated only as “drugs.”³ Whereas a biological product must be licensed pursuant to a biologics license application (BLA) showing it is “safe, pure, and potent,” the sponsor of a nonbiologic drug must submit a New Drug Application (NDA) showing the drug is safe and effective.⁴ Certain new biological products receive 12 years of data protection, but new drugs receive up to 5 years of this protection.⁵ Biologic and drug legislation also provide different schemes for resolving patent issues regarding entry of follow-on products.⁶ Thus, determining whether a product meets the definition of “biological product” is enormously important.

Unfortunately, this inquiry is not straightforward. Drug and biologic legislation developed separately, and Congress did not provide detailed guidance for distinguishing biologics from other drugs. As a result, the Food and Drug Administration (FDA) and other agencies administering the biologics law over time have made these distinctions mostly on an *ad hoc* basis based on history and relevant precedents.⁷ The FDA has recently proposed a bright-line rule for distinguishing “proteins” that qualify for treatment as biologics from certain other products that do not. This approach remains in the proposal stages, however, and history and precedent continue to play important roles in product jurisdiction determinations. This section outlines that relevant history.

In 1902, Congress passed the Biologics Control Act, which applied to “any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention and cure of diseases of man” and required licensure of facilities making these products.⁸ Over the next hundred-plus years, Congress expanded this list of covered products to include, among other things, the following products and those “analogous” to them: vaccines, blood, blood products, allergenic products, and proteins (except chemically synthesized polypeptides).⁹ Despite all of these

³ Products meeting the “biological product” definition also meet either the definition of “drug” or “device” under the Federal Food, Drug, and Cosmetic Act (FDCA). Intercenter Agreement Between CDER and CBER (effective October 31, 1991) [hereinafter ICA], § II.

⁴ Public Health Service Act (PHSA) § 351(a)(2)(C)(i)(I); FDCA § 505(b) & (d).

⁵ PHSA § 351(k)(7); FDCA §§ 505(c)(3)(E), 505(j)(5)(F).

⁶ PHSA § 351(l); see, e.g., FDCA §§ 505(b)(1), 505(c)(2), 505(c)(3)(A)-(D), 505(j)(2)(A)(vii) and (B), 505(j)(5).

⁷ Michael S. Labson, Krista Hessler Carver, and Marie C. Boyd, *FDA Regulation of Biological Products*, in *THE PHARM. REGULATORY PROCESS* 103, 110 (Ira R. Berry & Robert P. Martin, eds., 2008).

⁸ Pub. L. No. 57-244, 32 Stat. 728, 728 (1902). Congress added a product licensure requirement in 1944 and then replaced the dual license requirement with a single requirement for a BLA in 1997. Pub. L. No. 78-410, § 351, 58 Stat. 682, 702 (1944); Pub. L. No. 105-115, § 123(a), 111 Stat. 2296, 2323 (1997).

⁹ Pub. L. No. 111-148, Title VII, Subtitle A, § 7002 (b)(2), 124 Stat. 119, 814 (2010); Pub. L. No. 105-115, § 123(d), 111 Stat. 2296, 2324 (1997); Pub. L. No. 91-515, § 291, 84 Stat. 1297, 1308 (1970); Pub. L. No. 78-410, 58 Stat. 682, 702 (1944).

amendments, Congress never defined the listed terms and, in particular, never defined “analogous,” so the scope of the biological product definition remained unclear.

The overlapping definition of “drug” added to this complexity. The Food and Drugs Act of 1906 and the Federal Food, Drug, and Cosmetic Act of 1938 (FDCA) defined “drug” broadly to include, among other things, substances intended for use in the cure, mitigation, or prevention of disease, and the latter statute mandated submission of an NDA before marketing of a drug.¹⁰ Although these “drug” definitions encompassed many biologics, the statutes did not provide concrete parameters for distinguishing nonbiological drugs from biological products. In 1944, when Congress revised and recodified the 1902 Act in the Public Health Service Act (PHSA), it clarified that the NDA requirement did not apply to biologics, but it did not elucidate the scope of the biological product definition.¹¹

Regulators attempted to fill this gap by promulgating regulatory definitions of virus, therapeutic serum, toxin, antitoxin, and analogous product.¹² For example, the 1947 regulations, which are essentially similar to the current regulations,¹³ defined products “analogous” to a toxin or antitoxin as those intended for preventing, treating, or curing diseases or injuries “through specific immunization.”¹⁴ The 1947 definition of products analogous to therapeutic serums excluded hormones.¹⁵ Hormones such as insulin and human growth hormone were approved under the FDCA, not the PHSA.¹⁶ Despite the 1947 regulations, differentiating biologics from drugs remained challenging at the margins.

¹⁰ Pub. L. No. 59-384 § 6, 34 Stat 768 (1906); Pub. L. No. 75-717 §§ 201(g)(2), 52 Stat. 1040, 1041, 1052-53 (1938).

¹¹ See Pub. L. No. 78-410 § 351(g), 58 Stat. 682, 703 (1944) (“Nothing contained in this Act shall be construed as in any way affecting, modifying, repealing, or superseding the provisions of the [FDCA]”); H. R. Rep. No. 1364, 78th Cong., at 23 (1944) (“Subsection (g) is an explicit statement, confirming the present legal situation, that products subject to this section are not exempted from the [FDCA], except for the provision of that act relating to the licensing of new drugs”).

¹² 42 C.F.R. § 73.1(g) (1949); see, e.g., Treasury Dep’t, U.S. Pub. Health & Marine-Hospital Serv., Regulations for the Sale of Viruses, Serums, Toxins, and Analogous Products, Miscellaneous Publication No. 20, ¶ 16 (1909).

¹³ 21 C.F.R. § 600.3(h) (2012). The FDA has not updated 21 C.F.R. § 600.3(h) to reflect that the statutory definition of biological product now includes products applicable to the prevention, treatment, or cure of “condition[s]” of human beings. For this reason, one court has concluded that the regulation is invalid “to the extent that [it] purports to eliminate the application... to ‘conditions.’” *United States v. Livdahl*, 459 F. Supp. 2d. 1255, 1261 (S.D. Fla. 2005).

¹⁴ 42 C.F.R. § 73.1(g)(5)(iii) (1949).

¹⁵ *Id.* § 73.1(g)(5)(ii) (defining a product as analogous to a serum if it was “composed of whole blood or plasma or containing some organic constituent or product *other than a hormone* or an amino acid, derived from whole blood, plasma, or serum and intended for administration by a route other than ingestion”) (emphasis added).

¹⁶ Letter of Steven K. Galson, M.D., M.P.H., Director, CDER, to Kathleen M. Sanzo, Esq., Morgan, Lewis & Bockius LLP; Stephan E. Lawton, Esq., BIO; and Stephen J. Juelsgaard, Esq., Genentech, Docket No. 2004P-0231, PDN1 (May 30, 2006) (2006 Consolidated Response), at 44 & n.82; FDA, Ever Approved Drug Products Listed by Active Ingredient, at 2291 (printout dated August 2, 1989) (obtained via FOIA request) (listing NDA 1-754 for Sterling Drug Inc.’s insulin suspension product, approved November 27, 1939).

The advent of biotechnology, along with agency organizational disputes, brought this issue to the forefront of FDA's focus. In 1986, the FDA issued a policy statement stating that it would determine whether biotechnology products constituted biologics "based on the intended use of each product on a case-by-case basis."¹⁷ Thus, the FDA continued to make product-specific determinations informed by history and precedent, and different units of the FDA had to agree on the approval pathway for a given product. This proved to be difficult, with press reports of "turf battles" between the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) for jurisdiction over blockbuster biotechnology products¹⁸ and claims that the decisions were "inconsisten[t]."¹⁹ For example, epidermal growth factors were regulated as drugs because their first approved indications were traditionally drug indications.²⁰ Most monoclonal antibodies (mAbs) were licensed as biologics because of their biological source material and immunologic function.²¹ Recombinant insulin and human growth hormone, similar to their naturally derived counterparts, were approved pursuant to NDAs.²²

CDER and CBER subsequently executed an Intercenter Agreement (ICA) that attempted to clarify the governing authorities for products derived from living material. The agreement provided that the following products, among others, were subject to licensure under the PHSA: vaccines; proteins, peptides, and carbohydrates produced by cell culture (other than hormones and products previously derived from human or animal tissue and approved as drugs); proteins made in transgenic animals; blood and blood products; and allergenic products.²³ NDAs were required for, among other things, hormones (regardless of method of manufacture), synthetic mononucleotide and polynucleotide products, and naturally derived products other than vaccines or allergenics.²⁴ Twelve years later, the FDA consolidated review of most therapeutic proteins in CDER, but this transfer did not modify the governing statutory scheme for any ICA product, and the FDA continued to decide whether new products were biological products or nonbiologic drugs on a case-by-case basis using the principles of the ICA and historical precedent.²⁵

In February 2012, the FDA issued draft guidance aimed at implementing recent legislation that added "protein (except any chemically synthesized polypeptide)" to the biological product definition.²⁶ In this draft guidance, the FDA proposed a

¹⁷ 51 Fed. Reg. 23309, 23310 (June 26, 1986).

¹⁸ *FDA Triage System for Drugs/Biologics Questioned*, U.S. REGULATORY REPORTER (November 1990), at 3.

¹⁹ *FDA's Handling of Biotech Approvals*, SCRIP (August 26, 1988), at 14.

²⁰ *The FDA and Drug-Biologic Classifications*, U.S. REGULATORY REPORTER (August 1988), at 6.

²¹ *Id.*

²² Suzanne White Junod, Ph.D., FDA Historian, *Celebrating a Milestone: FDA's Approval of First Genetically-Engineered Product*, UPDATE, September/October 2007, at 43, 44; 2006 Consolidated Response, at 44 and n.82.

²³ ICA, § III(B)(1).

²⁴ *Id.* § III(A).

²⁵ 68 Fed. Reg. 38067, 38068 (June 26, 2003).

²⁶ Patient Protection and Affordable Care Act (PPACA), Pub. L. No. 111-148 § 7002(b)(2), 124 Stat 119, 814 (2010) (amending section 351(i) of the PHSA).

bright-line rule distinguishing proteins from “peptides” and “chemically synthesized polypeptide[s]” that the FDA proposes to approve under the FDCA.²⁷ The agency proposed to define “protein” as “any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size.”²⁸ According to the draft guidance, “peptides” have 40 or fewer amino acids and are not “proteins.”²⁹ The agency also proposed to define “chemically synthesized polypeptide” as an alpha amino acid polymer that is made entirely by chemical synthesis and that has fewer than 100 amino acids.³⁰ Until the draft guidance is finalized, these definitions must be considered proposals. Nevertheless, they signal that the FDA might be shifting from its traditional, ad hoc approach to jurisdictional decisions to a new approach guided by bright-line rules.³¹

4.2.2 Nonclinical Studies for Biologics

Similar to other drugs, biologics must undergo laboratory and animal testing to define their pharmacologic and toxicologic effects before they can be studied in humans.³² The legal framework for preclinical testing of biologics is essentially similar to that for drugs; for example, the FDA’s good laboratory practice (GLP) regulations typically apply.³³ Nevertheless, biologics present special issues, necessitating a “flexible, case-by-case, science-based approach” to preclinical testing.³⁴

For biotechnology-derived pharmaceuticals, the FDA has adopted the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) S6 guidance, which describes the unique

²⁷ FDA, *Draft Guidance for Industry: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* 13 (February 2012) (Q&A Draft Guidance). Sponsors of certain transitional proteins will remain eligible to submit their applications as NDAs during a transition period that ends on March 23, 2020. PPACA § 7002(e), 124 Stat. at 817. This option is available if a protein is the same “product class” as a biological product that was approved under the FDCA on or before March 23, 2010. *Id.* § 7002(e)(2). In the draft guidance, the FDA proposes to consider two products to be in the same product class if they “are homologous to the same gene-coded sequence,” with allowances “for additional novel flanking sequences.” Q&A Draft Guidance, at 14. Under the draft guidance, two products may be in the same product class even if their differences result in changes in pharmacokinetics, but not if the changes “alter[] a biological target or effect.” *Id.* at 14–15.

²⁸ Q&A Draft Guidance, at 13.

²⁹ *Id.*

³⁰ *Id.*

³¹ The FDA also has special rules for determining the regulatory status of tissue engineering and cell processing products. See 21 C.F.R. Parts 1270 & 1271. Detailed discussion of these rules is beyond the scope of this chapter.

³² FDA, *Guidance for Industry: S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* 3 (July 1997) (S6 Guidance).

³³ 21 C.F.R. Part 58. For some studies using specialized test systems, it may be impossible to fully comply with GLP, but this might not preclude use of the studies to support clinical trial initiation and marketing authorization. S6 Guidance, at 3.

³⁴ S6 Guidance, at 1.

approach needed to selection of animal species and immunogenicity testing as overarching considerations and outlines typical preclinical testing.³⁵ Also, in May 2012, the FDA adopted the addendum to that ICH guidance.³⁶ Because Europe's Committee for Medicinal Products for Human Use (CHMP) approved that guidance nearly a year earlier, in July 2011, the addendum is discussed in Section 3.1, *infra*, but it is now equally applicable in the United States. Therefore, for a full understanding of nonclinical testing standards in the United States, readers should also review Section 3.1 of this chapter.

4.2.2.1 Relevant Species Many biologics cannot be tested in commonly used animal species, such as rats and dogs, because of their biological activity and species- or tissue-specific activity.³⁷ Instead, sponsors must use a variety of tests, such as *in vitro* binding assays and functional tests, to identify a “relevant species,” that is, “one in which the test material is pharmacologically active due to the expression of the receptor or an epitope (in the case of monoclonal antibodies).”³⁸ Generally, a sponsor should identify two relevant species, although one species may suffice when the product's biological activity is well understood or only one relevant species exists.³⁹

In some cases, the chimpanzee—which cannot be sacrificed at the end of the study—is the only relevant species, and in other cases, identifying a relevant species might be impossible.⁴⁰ In these situations, the sponsor might need to consider alternative approaches to gathering animal data, such as the use of homologous proteins (which recognize the target protein or epitope in the animal),⁴¹ transgenic animals that express the human receptor, or other animal models.⁴²

4.2.2.2 Immunogenicity Many biologics elicit immune responses, which can affect preclinical study results.⁴³ In some cases, these effects are desired (e.g., with a vaccine), but unwanted immunogenicity might be harmful. Potential undesired effects include neutralizing or prolonging the biologic's activity, forming immune complexes, or cross-reacting with endogenous substances.⁴⁴ As a result, sponsors

³⁵ *Id.* at 1 n.1. This guidance applies to biotechnology-derived proteins and peptides, their derivatives, and products of which they are components. It may also apply to recombinant DNA protein vaccines, chemically synthesized peptides, and plasma-derived products, among other things. It does not apply to allergenic extracts, cellular blood components, conventional bacterial or viral vaccines, DNA vaccines, or cellular and gene therapies. *Id.* at 2.

³⁶ FDA, *Guidance for Industry S6 Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (May 2012) as adopted by FDA at 77 Fed. Reg. 29665, 29666 (May 18, 2012).

³⁷ S6 Guidance, at 4.

³⁸ *Id.*

³⁹ *Id.*

⁴⁰ Andrea B. Weir, Ph.D., DABT, Pharmacologist/Toxicologist, Office of Drug Evaluation VI, CDER, FDA, *Preclinical Safety Assessment of Therapeutic Proteins and Monoclonal Antibodies*, in *BIOLOGICS DEVELOPMENT: A REGULATORY OVERVIEW* 17, 19 (Mark Mathieu, ed., 3rd ed., 2004).

⁴¹ *Id.*

⁴² S6 Guidance, at 4–5.

⁴³ Weir, *supra* note 40, at 19.

⁴⁴ *Id.* at 20.

should obtain necessary samples for antibody testing during repeat-dose toxicity studies and, when interpreting the data, should consider the effects of antibody formation on pharmacokinetics (PK), pharmacodynamics (PD), and adverse events.⁴⁵ Detection of antibodies should not prompt termination of a preclinical study unless the immune response neutralizes the biologic's effects in "a large proportion" of the test animals.⁴⁶ Finally, sponsors should be aware that animals' immune responses are not indicative of those in humans.⁴⁷

4.2.2.3 Typical Preclinical Testing Sponsors usually must conduct PD studies, such as *in vitro* binding assays and *in vivo* studies that assess the product's pharmacologic activity and define its mechanism of action.⁴⁸ Biologics typically undergo single- and repeat-dose toxicity studies using relevant species, as noted earlier.⁴⁹ Safety pharmacology studies, which evaluate the product's functional effects on major body systems and specific organs, and local tolerance testing can be done separately or subsumed in toxicity testing.⁵⁰

Sponsors also usually conduct single- and multiple-dose PK and/or toxicokinetic studies to assess absorption, disposition, exposure, and clearance (in particular, antibody-mediated clearance) and explore dose-response relationships.⁵¹ This information is used to predict margins of safety for human studies. Immunogenicity testing might include screening and mechanistic studies, but animal models are not highly predictive of human immunogenicity.⁵²

Typical carcinogenicity bioassays are "generally inappropriate" for biologics, although the S6 guidance calls for assessment of carcinogenicity when warranted based on the "duration of clinical dosing, patient population, and/or biological activity."⁵³ If concern exists regarding carcinogenic potential, the sponsor can consider several approaches to assess risk, including testing in a variety of malignant and normal human cells and further testing in relevant species.⁵⁴ According to ICH S6, reproductive and developmental toxicity studies may or may not be recommended, depending on "the product, clinical indication, and intended patient population."⁵⁵ Such studies using primate species pose challenges because of these animals' heterogeneous drug responses, high background abortion rate, and low number of offspring.⁵⁶

⁴⁵ S6 Guidance, at 6.

⁴⁶ *Id.*

⁴⁷ *Id.*

⁴⁸ Weir, *supra* note 40, at 20; S6 guidance, at 4.

⁴⁹ Weir, *supra* note 40, at 21.

⁵⁰ S6 guidance, at 7, 10.

⁵¹ *Id.* at 7-8; Weir, *supra* note 40, at 21.

⁵² Weir, *supra* note 40, at 22; S6 guidance, at 9.

⁵³ S6 guidance, at 10.

⁵⁴ *Id.*

⁵⁵ *Id.* at 9.

⁵⁶ Weir, *supra* note 40, at 22.

Because biologics generally degrade into peptides and amino acids, classic biotransformation studies are unnecessary.⁵⁷ Genotoxicity studies also usually are not applicable to biotechnology-derived drugs because they are not expected to interact with DNA or chromosomes.⁵⁸

4.2.3 Clinical Studies for Biologics

4.2.3.1 The Investigational New Drug Application If a sponsor plans to perform clinical testing of a biologic in the United States, it must first have an investigational new drug application (IND) in effect.⁵⁹ An IND generally goes into effect 30 days after the FDA receives it.⁶⁰ During this 30-day time period, the FDA reviews the IND for any safety issues and may place a clinical hold on the study if, among other things, it presents an “unreasonable” risk to patients.⁶¹ The IND must contain “[a]dequate” information from preclinical studies, on which the sponsor bases its conclusion that clinical trials are reasonably safe.⁶² For well-characterized therapeutic biotechnology products, the IND should describe the product’s pharmacologic effects and mechanism of action and provide information on its absorption, distribution, metabolism, and excretion.⁶³ Sponsors must include a description of the overall investigational plan and a protocol for each planned study; protocols not submitted in the initial IND should be submitted as protocol amendments.⁶⁴ The IND also must contain chemistry, manufacturing, and controls information sufficient to allow evaluation of safety.⁶⁵ This information is particularly important for many biologics, which may raise concerns because of their impurity profiles or the use of materials with unknown components in their manufacture.⁶⁶ The FDA recognizes that sponsors likely will change their manufacturing processes as development progresses. Section 2.3.4, *infra*, discusses the effects of these changes on product development.

4.2.3.2 Good Clinical Practices Traditionally, the FDA used the phrase “good clinical practices” (GCP) to collectively describe a number of regulations and guidance documents with two overarching goals: (1) to ensure the integrity of data collected in clinical trials and (2) to protect clinical trial subjects.⁶⁷ In the mid

⁵⁷ S6 guidance, at 8.

⁵⁸ *Id.* at 9–10.

⁵⁹ 21 C.F.R. § 312.20(a) & (b); 21 C.F.R. § 312.40(b)(1); FDA, *Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products 2* (November 1995) (Phase 1 Guidance).

⁶⁰ 21 C.F.R. § 312.40(b)(1).

⁶¹ 21 C.F.R. § 312.42(b)(i).

⁶² 21 C.F.R. § 312.23(a)(8).

⁶³ Phase 1 Guidance, at 10.

⁶⁴ 21 C.F.R. § 312.23(a)(3)(iv) & (6).

⁶⁵ 21 C.F.R. § 312.23(a)(7); Phase 1 Guidance, at 4.

⁶⁶ Phase 1 Guidance, at 4–5. This Guidance applies only to well-characterized therapeutic biotech products. *Id.* at 2.

⁶⁷ *Good Clinical Practices (GCP)*, in *BIOLOGICS DEVELOPMENT: A REGULATORY OVERVIEW* 115, 115 (Mark Mathieu, ed., 3rd ed., 2004); see also 62 Fed. Reg. 25691, 25692 (May 9, 1997).

1990s, however, the ICH developed a consolidated GCP guideline, known as the E6 guidance, to harmonize standards for clinical study design, conduct, reporting, and recordkeeping.⁶⁸ The FDA has adopted this guidance. The agency recommends that sponsors use it when generating data for submission to the agency⁶⁹ and has stated that it will deem studies complying with ICH GCP as meeting the FDA's GCP standards.⁷⁰ This guidance supplements and clarifies FDA regulations on institutional review boards (IRBs) (21 C.F.R. Part 56), informed consent (Part 50), and clinical studies for drugs and biologics (Part 312). It describes the overarching principles for conducting clinical trials, the responsibilities of various parties involved with the clinical trial (IRB, sponsor, investigator), and the necessary documents for conducting a clinical study (e.g., the study protocol and investigator's brochure).⁷¹ Sponsors should consider it in combination with the above-cited regulations, more recent FDA regulations (such as Part 54 on financial disclosures for clinical investigators), and more recently released FDA guidance on specific GCP topics.

4.2.3.3 Study Design Considerations As with new drugs, clinical development of biologics typically involves three phases, which may or may not overlap. Biologics present several unique clinical considerations, however. Often, their clinical development programs must include an assessment of immunogenicity, which is typically not an issue for small molecule drugs. Also, because many biologics treat serious or life-threatening illnesses, their development may be compressed.⁷²

Phase 1 studies involve the "initial introduction" of the biologic into a small number of humans to assess the product's metabolism, pharmacology, and safety at escalating doses.⁷³ Unlike phase 1 trials for nonbiologic drugs, phase 1 studies of biologics frequently involve administration to patients rather than healthy volunteers who will not derive benefit from them to ensure the risk-benefit profile of the product is acceptable for ethical purposes.⁷⁴ For example, studies may enroll patients when the biologic is known or suspected to be "unavoidably toxic," when there is a risk of antibody development to a native protein or mAb, or when the product's bioactivity is disease specific.⁷⁵ Phase 1 studies should determine the maximum tolerated dose and assess the product's bioactivity and PK to determine the optimum biological dose.⁷⁶ With respect to immunogenicity, these studies should assess subjects' antibody

⁶⁸ 62 Fed. Reg. at 25692.

⁶⁹ *Id.*; FDA, *Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance* (E6 Guidance) 1 (April 1996).

⁷⁰ *Good Clinical Practices (GCP)*, *supra* note 67, at 118.

⁷¹ See generally E6 Guidance.

⁷² See Barbara G. Matthews, M.D., M.P.H., *Clinical Testing of Biologically Derived Therapeutics*, in *BIOLOGICS DEVELOPMENT: A REGULATORY OVERVIEW* 79, 84 (Mark Mathieu, ed., 3rd ed., 2004).

⁷³ 21 C.F.R. § 312.21(a)(1) & (2).

⁷⁴ FDA, *Guidance for Industry, Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers* 3 (July 2005) (MRSD Guidance); Matthews, *supra* note 72, at 83.

⁷⁵ MRSD Guidance, at 3; Matthews, *supra* note 72, at 83.

⁷⁶ Matthews, *supra* note 72, at 81-82, 83.

development, both directly after administration and at least 28 days thereafter, and determine whether these results are linked to adverse events, PK, or PD.⁷⁷

Phase 2 trials are controlled studies that evaluate short-term adverse events and effectiveness for a specific use in several hundred patients.⁷⁸ These studies further explore exposure–response relationships and the biologic’s PK, PD, and immunogenicity, and they provide information to help refine the phase 3 protocol, including with respect to size, population, and endpoints.⁷⁹ Biologics sponsors often combine phase 2 studies with phase 1 or phase 3 studies.⁸⁰

Phase 3 studies enroll patients and provide primary evidence for labeling claims and risk–benefit assessment.⁸¹ They are larger than phase 2 studies, but their size ranges considerably depending on the patient population and the availability of alternative therapies.⁸² They typically are randomized, double blinded, controlled, and performed at multiple study centers.⁸³ Placebo controls are used when ethical considerations permit, but in some cases (e.g., when effective treatment is already available and withholding treatment would expose subjects to unreasonable risks), active controls are used.⁸⁴ The studied patient population, as defined in the protocol’s exclusion and inclusion criteria, should be representative of the population for which the sponsor seeks approval.⁸⁵

Endpoint selection is critical to a successful phase 3 trial. The endpoint must demonstrate clinical benefit in the intended patient population.⁸⁶ Ideally, the endpoint is an established clinical outcome measure, although validated surrogate endpoints may be used in some cases.⁸⁷ If the endpoint is not well defined, the sponsor might have to combine use of several effectiveness outcomes.⁸⁸

Several alternatives to traditional endpoints are available. Under the accelerated approval scheme, eligible sponsors may obtain approval based on either (1) a surrogate endpoint that is “reasonably likely to predict clinical benefit” or (2) a clinical endpoint that is measurable earlier than irreversible morbidity or mortality and that is “reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit.”⁸⁹ The evidence supporting an endpoint’s

⁷⁷ *Id.*

⁷⁸ 21 C.F.R. § 312.21(b).

⁷⁹ Matthews, *supra* note 72, at 84–85, 90–92.

⁸⁰ *Id.* at 84.

⁸¹ 21 C.F.R. § 312.21(c).

⁸² See *id.*; Matthews, *supra* note 72, at 80.

⁸³ Matthews, *supra* note 72, at 85–86.

⁸⁴ *Id.*; FDA, Inside Clinical Trials: Testing Medical Products in People, <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143531.htm> (last accessed November 29, 2012).

⁸⁵ Matthews, *supra* note 72, at 85.

⁸⁶ *Id.*

⁸⁷ *Id.* at 85–86.

⁸⁸ *Id.* at 85.

⁸⁹ FDCA § 506(c)(1)(A). In July 2012, Congress amended the criteria for accelerated approval as part of the Food and Drug Administration Safety and Innovation Act (FDASIA). Pub. L. No. 112-144 §§ 901-902, 126 Stat. 993, 1082-1088 (2012). The amended statutory provisions are discussed here. The FDA has not yet updated its accelerated approval regulations to reflect these statutory changes. See 21 C.F.R. Part 601, Subpart E.

likelihood of predicting clinical benefit may include epidemiologic, patho-physiologic, therapeutic, pharmacologic, or other evidence developed using biomarkers or other scientific tools.⁹⁰ To be eligible for accelerated approval, a medicine must be intended for a serious or life-threatening disease or condition.⁹¹ The FDA may require that the sponsor of an accelerated approval product conduct post-approval studies to “verify and describe the predicated effect on irreversible morbidity or mortality or other clinical benefit.”⁹²

Another alternative, the “animal rule,” applies only to biologics that address serious or life-threatening conditions caused by “exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances” and for which human efficacy studies are unethical and infeasible.⁹³ Under the animal rule, a sponsor may obtain approval based on human safety data and adequate and well-controlled animal studies show the product is “reasonably likely to produce clinical benefit in humans” if, among other things, available data allow selection of an effective human dose.⁹⁴ Sponsors obtaining approval under the animal rule must commit to conduct postmarket clinical studies to confirm clinical benefit.⁹⁵

4.2.3.4 Manufacturing Process Changes During Development Sponsors often change the manufacturing process of biologics before approval (e.g., to scale up from pilot production to full-scale manufacturing, to improve manufacturing efficiency, or to change the production facility).⁹⁶ Biologics are much more sensitive to process changes than chemically synthesized drugs, and process changes have the potential to adversely affect a biological product. As a result, the FDA will determine whether the sponsor must conduct additional studies to support licensure of the postchange biological product. The FDA has issued guidance that describes this inquiry.⁹⁷

According to this guidance, the FDA deems pre- and postchange products to be “comparable” when testing shows that “the manufacturing change does not affect safety, identity, purity, or potency.”⁹⁸ The FDA may require that the sponsor perform some combination of analytical testing, *in vitro* and *in vivo* biological assays, animal

⁹⁰ FDCA § 506(c)(1)(B).

⁹¹ FDCA § 506(c)(1)(A).

⁹² FDCA § 506(c)(2)(A).

⁹³ 21 C.F.R. § 601.90.

⁹⁴ 21 C.F.R. § 601.91; see also FDA, *Draft Guidance for Industry: Animal Models—Essential Elements to Address Efficacy Under the Animal Rule* 16 (January 2009).

⁹⁵ 21 C.F.R. § 601.91(b)(1).

⁹⁶ FDA, *Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products* § II (April 1996) (Comparability Guidance). The FDA has also adopted ICH guidance regarding quality issues in comparability determinations. FDA, *Q5E Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process* (June 2005).

⁹⁷ Comparability Guidance § II.

⁹⁸ *Id.*

tests (PK, PD, and/or toxicity), and clinical testing (pharmacology, immunogenicity, safety, and/or efficacy studies) to make this showing.⁹⁹ In determining the type and amount of data necessary to support a specific change, the FDA will consider the extent of manufacturing changes, the stages of manufacturing at which they occur, the profile of the prechange product, the ease of characterizing the product, and the results of the necessary tests.¹⁰⁰ Data from in-process assays at the affected phase of manufacture can be particularly important to this determination.¹⁰¹

For example, the FDA might require human pharmacology tests to assess changes—such as those in product formulation—that could affect PK or PD. If the change results in differences in structure, bioactivity, or PK that “are meaningful with respect to potential impact on the product’s safety, purity, or potency,” the FDA generally requires additional clinical study of the product’s safety, effectiveness, or both.¹⁰² The same is true when “analytical and other preclinical testing is not sufficiently sensitive or broad enough to detect such meaningful differences.”¹⁰³ In contrast, changes in filling site might only require comparative data as to final release specifications and stability.¹⁰⁴ Because the FDA has broad discretion in formulating the testing requirements for a comparability showing, the agency encourages sponsors to consult with it before implementing the proposed process change.¹⁰⁵ In any event, the sponsor must fully describe the change in the IND or BLA.¹⁰⁶

4.2.3.5 Meetings with the Food and Drug Administration Before and During the Clinical Trial Period Sponsor meetings with the FDA are often critical to successful, streamlined clinical development. They can help sponsors avoid conducting expensive clinical studies that the agency would ultimately reject. The FDA has promulgated regulations and issued guidance on FDA–sponsor meetings. Except when otherwise noted, agreements reached at these meetings do not bind the agency; the FDA’s regulations provide that action on meetings does not constitute final agency action.¹⁰⁷

Sponsors can obtain several types of pre-approval meetings with the FDA. 21 C.F.R. § 312.82 describes two types of such meetings. First, under this regulation, the sponsor can seek a pre-IND meeting to reach agreement with the FDA on the design of preclinical studies needed to commence human testing.¹⁰⁸ Although the regulation notes that these meetings are available to sponsors of therapies for life-threatening or

⁹⁹ *Id.* § III.

¹⁰⁰ *Id.*

¹⁰¹ *Id.*

¹⁰² *Id.*

¹⁰³ *Id.*

¹⁰⁴ *Id.*

¹⁰⁵ *Id.* § IV.

¹⁰⁶ *Id.* § III.

¹⁰⁷ 21 C.F.R. § 10.65(a).

¹⁰⁸ 21 C.F.R. § 312.82(a).

severely debilitating illnesses,¹⁰⁹ other sponsors can also obtain them. For example, the FDA has indicated that pre-IND meetings can be useful in various challenging development scenarios (e.g., when the sponsor has identified a concerning safety signal).¹¹⁰ Second, after phase 1 data are available for a therapy intended for life-threatening or severely debilitating illnesses, the sponsor may meet with the FDA to reach agreement on phase 2 study design, “with the goal that such testing will . . . provide sufficient data . . . to support a decision on its approvability for marketing.”¹¹¹

Sponsors also may request End of Phase 2 (EOP2) meetings and pre-BLA meetings.¹¹² At EOP2 meetings, the FDA aims to evaluate whether proceeding to phase 3 is safe, assess the protocols for phase 3, and determine whether any other information will be needed to approve the product.¹¹³ The FDA will record any agreements reached in minutes and transmit them to the sponsor, and studies conducted in accordance with an agreement will be “presumed sufficient” for approval unless a “significant scientific development . . . requires otherwise.”¹¹⁴ Pre-BLA meetings are intended to identify “any major unresolved problems,” discuss analysis of the data, and agree on the approach to formatting the BLA.¹¹⁵

The FDA classifies its meetings with sponsors into three categories. Type A meetings relate to “an otherwise stalled product development plan.”¹¹⁶ These include certain meetings to discuss clinical holds, meetings to resolve disputes with the FDA, and meetings to discuss the FDA’s evaluation of Special Protocol Assessments (SPAs), described later.¹¹⁷ Pre-IND, EOP1, EOP2, and pre-BLA meetings typically are Type B meetings.¹¹⁸ All other meetings are Type C meetings.¹¹⁹ Type A and Type C meetings have the shortest and longest time lead times to meeting dates, respectively.¹²⁰ FDA guidance and regulations describe the recommended content of the meeting request and pre-meeting briefing package, procedures for pre-meeting communication to narrow the topics for discussion (if possible), and the FDA’s

¹⁰⁹ 21 C.F.R. § 312.82.

¹¹⁰ FDA, *Small Business Assistance: Frequently Asked Questions on the Pre-Investigational New Drug (IND) Meeting*, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069906.htm> (last accessed November 29, 2012).

¹¹¹ 21 C.F.R. § 312.82(b).

¹¹² 21 C.F.R. § 312.47(b).

¹¹³ 21 C.F.R. § 312.47(b)(1)(i).

¹¹⁴ 21 C.F.R. § 312.47(b)(1)(v). The FDA also holds End of Phase 2A (EOP2A) meetings, which occur after completion of phase 1 trials and the first set of clinical exposure-response studies, to discuss dose selection for later trials and methods (e.g., trial design, modeling, or simulation) for improving quantification of exposure-response data from early trials. FDA, *Guidance for Industry: End-of-Phase 2A Meetings* 1, 4 (September 2009).

¹¹⁵ 21 C.F.R. § 312.47(b)(2).

¹¹⁶ FDA, *Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants* 2 (May 2009).

¹¹⁷ *Id.*

¹¹⁸ *Id.* at 3.

¹¹⁹ *Id.*; FDA, *Guidance for Industry: End-of-Phase 2A Meetings*, at 5.

¹²⁰ FDA, *Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants*, at 3.

practices for documenting the substance of the meeting in official meeting minutes and for resolving disputes concerning these minutes.¹²¹

Sponsors also may request an SPA and accompanying meeting. Pursuant to Section 505(b)(5) of the FDCA and FDA guidance, the FDA must grant “reasonable written request[s]” to meet with BLA sponsors to achieve agreement on the design and size of the following kinds of trials: (1) clinical trials intended to form the primary basis of an efficacy claim, (2) animal carcinogenicity protocols, and (3) final product stability protocols.¹²² The agency must reduce to writing any agreements made through this SPA process and make them part of the administrative record.¹²³ The FDA cannot deviate from any such agreement unless the sponsor consents or the FDA identifies a significant scientific issue essential to determine the drug’s safety or efficacy.¹²⁴

4.2.4 The Biologics License Application

4.2.4.1 Contents of the Biologics License Application Unlike the drug regulations, which specify the required contents of an NDA in great detail, the regulation on BLA content is quite brief. Under 21 C.F.R. § 601.2, the BLA must contain, among other things, nonclinical and clinical data showing the biologic’s safety, purity, and potency; a “full description of manufacturing methods” for the product; stability data substantiating the expiration date; product samples and a summary of test results for the lot from which they derived; proposed labeling, enclosures, and containers; and the addresses of manufacturing facilities.¹²⁵ Although this regulation is far less prescriptive than its counterpart in the NDA regulations,¹²⁶ the FDA expects BLAs to contain essentially the same information and data as NDAs, and the electronic Common Technical Document (eCTD) format is the FDA’s standard format for both.¹²⁷ The FDA’s approach thus accords with Congress’ 1997 directive that the agency “shall take measures to minimize differences in the review and approval of products required to have approved [BLAs and NDAs].”¹²⁸

4.2.4.2 Food and Drug Administration Review The Prescription Drug User Fee Act (PDUFA), which applies to most innovative biologics,¹²⁹ and the FDA’s good

¹²¹ *Id.* at 4–5, 7–10; see also 21 C.F.R. § 10.65(e).

¹²² FDCA § 505(b)(5)(B); FDA, *Guidance for Industry: Special Protocol Assessment 2* (May 2002).

¹²³ FDCA § 505(b)(5)(C).

¹²⁴ *Id.*

¹²⁵ 21 C.F.R. § 601.2(a).

¹²⁶ 21 C.F.R. § 314.50.

¹²⁷ See, e.g., FDA, Electronic Common Technical Document (eCTD), <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm> (last accessed December 9, 2012).

¹²⁸ Pub. L. No. 105–115, § 123(f), 111 Stat. at 2324.

¹²⁹ FDCA § 735(1) (excluding whole blood, blood components for transfusion, allergenic extracts, and certain other biologics from the definition of “human drug application” for purposes of PDUFA).

review management principles and practices (GRMPs) govern agency review of BLAs.¹³⁰ Pursuant to PDUFA, the FDA levies “user fees” to defray part of its costs from reviewing applications and commits to performance goals for its review of those applications through a letter to Congress.¹³¹ PDUFA sunsets every 5 years and was reauthorized for the fifth time in July 2012 (PDUFA V).¹³²

After a sponsor submits a BLA, the agency assembles a review team comprising reviewers focusing on varying disciplines, such as clinical and toxicology issues.¹³³ The FDA then decides, within the first 60 days after submission, whether it can “file” the application (i.e., whether the BLA contains all information needed to permit a substantive review).¹³⁴ The FDA may issue a refuse-to-file decision if the BLA does not meet this threshold. During the filing period, the FDA will also decide whether to designate the BLA as a “priority” or “standard” application. For CBER-regulated applications, “priority” means that the biologic would constitute a significant improvement in the safety or effectiveness of treatment, diagnosis, or prevention of a serious or life-threatening disease.¹³⁵ In CDER, the same basic standard applies except that treatments for nonserious diseases also are eligible.¹³⁶

In connection with PDUFA V, the FDA committed to “review and act on”—that is, issue an action letter for—90% of priority, original BLAs within 6 months of the 60-day filing date; the goal date for standard BLAs is 10 months from the 60-day filing date.¹³⁷ In the past, the FDA’s actual performance has varied, with the agency meeting its PDUFA performance goals in some years but not others.¹³⁸ As part of its PDUFA V performance goals, the FDA committed to establish a new review model, known as “the Program,” for original BLAs and certain NDAs. The Program offers

¹³⁰ FDA, *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products 2* (April 2005) (GRMP Guidance) (“The principles of this guidance also pertain, in general, to all preapproval reviews of NDAs, BLAs, and efficacy supplements”).

¹³¹ See generally FDCA §§ 735, 736, 736B; FDA, *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017*, available at: <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm270412.pdf> (last accessed November 28, 2012) (PDUFA V Performance Goals).

¹³² FDASIA, Pub. L. No. 112–144, Title I, 126 Stat. at 996–1002.

¹³³ GRMP Guidance, at 11.

¹³⁴ 21 C.F.R. § 601.2(a); CBER, SOPP 8404: *Refusal to File Procedures for Biologic License Applications* (Version #3) (August 27, 2007); see also CDER, *New Drug Evaluation Guidance Document: Refusal to File* (1993); CDER, *21st Century Review Process Desk Reference Guide* 16–20 (Version September 2012) (Desk Reference Guide).

¹³⁵ CBER, SOPP 8405: *Complete Review and Issuance of Action Letters* (Version #4) (September 20, 2004).

¹³⁶ *Id.*; CDER MaPP 6020.3: *Review Classification Policy: Priority (P) and Standard (S) 2* (February 2012).

¹³⁷ PDUFA V Performance Goals, § I(E).

¹³⁸ Compare, e.g., FDA, *FY 2005 Performance Report to the President and Congress for the Prescription Drug User Fee Act* 11 (indicating that, during fiscal year 2004, the FDA reviewed and acted on 97% of priority and standard applications within the specified time frames) with FDA, *FY 2009 Performance Report to the President and Congress for the Prescription Drug User Fee Act* 19 (indicating that, during fiscal year 2008, the FDA reviewed and acted on 85% of standard applications and 68% of priority applications within the specified time frames).

the opportunity for additional communication with the agency, including in a new “late-cycle” meeting.¹³⁹

After FDA has begun substantive review of the BLA, reviewers may issue information request (IR) and discipline review (DR) letters to the applicant.¹⁴⁰ IR letters ask for specific information while review is in progress.¹⁴¹ Reviewers issue DR letters at the end of a particular discipline review “to convey early thoughts on possible deficiencies.” These letters do not necessarily reflect the input of their supervisors.¹⁴² IR and DR letters do not stop the review clock.¹⁴³ Applicants may respond to IR and DR letters with additional information. This type of submission might constitute a “major amendment” to the application; if so, the FDA might extend the PDUFA goal date.¹⁴⁴

Next, the FDA might seek an advisory committee’s (AC’s) advice on the application. By statute, the FDA must refer an original BLA to an AC or explain, in the action letter for the application, why that step was not taken.¹⁴⁵ The FDA typically requests that the AC address particular questions and vote on the answers, but the AC’s advice does not bind the FDA.¹⁴⁶

After the agency completes its review of the BLA, it will issue an approval letter, or a complete response letter (CRL), which states that the agency cannot approve the BLA in its current form.¹⁴⁷ A CRL lists identified deficiencies and, when possible, recommends sponsor actions to place the BLA in a position for approval.¹⁴⁸ An applicant may file a “resubmission” to address the deficiencies.¹⁴⁹ The review timeline for a resubmission depends on its content but is either 2 or 6 months from receipt.¹⁵⁰ An applicant also can request resolution of any dispute concerning the CRL.¹⁵¹ If the FDA denies approval of the application, the applicant may request, and the Commissioner must issue, a notice of opportunity for hearing.¹⁵²

4.2.4.3 Approval Standard The FDA must approve a BLA if it shows that the proposed product is “safe, pure, and potent” and the facilities where the product

¹³⁹ PDUFA V Performance Goals, § II.

¹⁴⁰ See generally FDA, *Guidance for Industry: Information Request and Discipline Review Letters Under the Prescription Drug User Fee Act* (November 2001).

¹⁴¹ *Id.* at 2.

¹⁴² *Id.* at 2–3.

¹⁴³ *Id.* at 3.

¹⁴⁴ CDER, MaPP 6010.8: *NDA and BLAs: Communication to Applicants of Planned Review Timelines 3* (June 2008); CBER, SOPP 8402: *Designation of Amendments as Major* (Version #4) (October 2012).

¹⁴⁵ FDCA § 505(s); Desk Reference Guide 22.

¹⁴⁶ 21 C.F.R. § 14.5(b).

¹⁴⁷ 21 C.F.R. §§ 601.3(a), 601.4(a).

¹⁴⁸ 21 C.F.R. § 601.3(a)(1) & (3).

¹⁴⁹ 21 C.F.R. § 601.3(b)(1).

¹⁵⁰ See generally CDER and CBER, *Guidance for Industry: Classifying Resubmissions in Response to Action Letters* (April 1998); see also PDUFA V Performance Goals, §§ I(E), XVI(D)&(E).

¹⁵¹ FDA, *Guidance for Industry: Formal Dispute Resolution: Appeals Above the Division Level* (February 2000). Dispute resolution can occur at any time in the BLA review process, GRMP Guidance, at 26, but typically occurs after receipt of a CRL.

¹⁵² 21 C.F.R. § 601.4(b).

made, processed, packed, or held comply with good manufacturing practice (GMP).¹⁵³ Two FDA regulations define “safety” to mean “relative freedom from harmful effect” in light of the patient’s underlying condition, assuming that the biologic is “prudently administered.”¹⁵⁴ In determining whether this standard is met, the FDA must consider the risks of the product against its benefits.¹⁵⁵ Proof of safety comprises “adequate tests by methods reasonably applicable,” including reports of “significant human experience” with the product.¹⁵⁶ “Purity” means that the finished product is “relative[ly] free[]” from “extraneous matter,” including moisture and pyrogens.¹⁵⁷

“Potency” means the product’s “specific ability or capacity . . . to effect a given result” based on laboratory testing or controlled clinical data.¹⁵⁸ Thus, the FDA has interpreted “potency” to include effectiveness.¹⁵⁹ Nevertheless, the FDCA’s requirement for “adequate and well-controlled trials,” which typically means at least two pivotal clinical studies, does not apply to biologics in all circumstances.¹⁶⁰ Instead, this is a default requirement for biologics. Proof of efficacy must comprise adequate and well-controlled trials unless the sponsor shows that this requirement (1) “is not reasonably applicable” to the biologic or “essential to the validity” of the trial and (2) an alternative method is “adequate to substantiate effectiveness.”¹⁶¹ For example, serologic response evaluations may be sufficient when the correlation between the marker and clinical effectiveness has been established.¹⁶²

4.3 EUROPEAN UNION GUIDELINES

In the European Union, biological medicinal product is an umbrella term covering a broad spectrum of medicinal products, all of which are larger and more complex than chemically synthesized products. Biological medicines are defined as “product[s], the active substance of which is a biological substance.”¹⁶³ A “biological substance,”

¹⁵³ PHSA § 351(a)(2)(C); 21 C.F.R. § 601.3(a).

¹⁵⁴ 21 C.F.R. §§ 600.3(p), 601.25(d)(1).

¹⁵⁵ 21 C.F.R. § 601.25(d)(3).

¹⁵⁶ 21 C.F.R. § 601.25(d)(1).

¹⁵⁷ 21 C.F.R. § 600.3(r).

¹⁵⁸ 21 C.F.R. § 600.3(s).

¹⁵⁹ FDA, *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* 3–4 (May 1998) (Effectiveness Guidance).

¹⁶⁰ 46 Fed. Reg. 4634, 4635 (January 16, 1981) (“While it is clear that... the applicable statutory requirement for potency in the [PHSA] has been interpreted as requiring that a [biological] product be effective, the specific statutory criteria governing new drugs, ‘adequate and well-controlled clinical studies,’ have not been applied to biological drugs”); see also 21 C.F.R. § 201.57(c)(2)(F)(iv) and (v) (noting that “substantial evidence of effectiveness based on adequate and well-controlled studies” must support indications labeling for non-biologic drugs, whereas “[f]or biological products, all indications listed in this section must be supported by substantial evidence of effectiveness”).

¹⁶¹ 21 C.F.R. § 601.25(d)(2); see also Effectiveness Guidance, at 4.

¹⁶² 21 C.F.R. § 601.25(d)(2).

¹⁶³ Section 3.2.1.1. Module 3, Part I, Annex I to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (as amended by Directive 2009/120/EC of 14 September 2009).

in turn, 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.”¹⁶⁴ Annex II to the EU GMP guidelines notes that biologics “can be defined... largely by reference to their method of manufacture.”¹⁶⁵ Examples of biological medicines include immunologic medicines; medicines derived from human blood and plasma; medicines developed by means of recombinant DNA technology, “controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells,”¹⁶⁶ or hybridoma and mAb methods; and advanced therapy medicinal products.¹⁶⁷

4.3.1 Nonclinical Studies

Similar to the FDA,¹⁶⁸ the CHMP has adopted ICH S6 as a guideline governing preclinical testing of biologics.¹⁶⁹ In July 2011, the CHMP adopted the addendum to this guideline, and the addendum came into effect in Europe in December 2011. The addendum complements, clarifies, and updates ICH S6 and is intended to further harmonize the standards for nonclinical studies. As explained in Section 2.2, we discuss the addendum here in light of the CHMP’s earlier approval of it. The addendum and ICH S6 are applicable in both the United States and EU, however, and readers interested in understanding the nonclinical standards in either jurisdiction should review both sections.

4.3.1.1 General Principles Although the addendum does not alter the scope of the ICH S6, it prevails whenever there are differences between the two.¹⁷⁰ The

¹⁶⁴ *Id.*

¹⁶⁵ Annex 2 on the Manufacture of Biological Medicinal Products for Human Use, Eudralex Volume 4—Guidelines for Good Manufacturing Practices for Medicinal Products for Human and Veterinary Use. The same is confirmed in the revised EU guidelines on the manufacture of biological active substances and medicinal products for human use (deadline for coming into operation is January 31, 2013) [Annex 2 on the Manufacture of Biological active substances and Medicinal Products for Human Use, Eudralex Volume 4—Guidelines for good manufacturing practices for medicinal products for human and veterinary use].

¹⁶⁶ Section 1 of the Annex to Regulation 726/2004/EC of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (as amended by Regulation (EC) No. 1394/2007 of 13 November 2007).

¹⁶⁷ Section 3.2.1.1. Module 3, Part I, Annex I to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (as amended by Directive 2009/120/EC of 14 September 2009).

¹⁶⁸ See *supra* Section 4.2.2.

¹⁶⁹ Guideline on pre-clinical safety evaluation of biotechnology-derived pharmaceuticals (ICH S6) (CPMP/ICH/302/95) (in operation from March 1998).

¹⁷⁰ See generally Addendum to Guideline on pre-clinical safety evaluation of biotechnology-derived pharmaceuticals (ICH S6), EMA/CHMP/ICH/731268/1998 (July 2011) (ICH S6 Addendum). Unlike ICH S6, the addendum advises that sponsors of nonclinical trials for biologics used in cancer treatment should consult the ICH S9 guideline. ICH S6 Addendum, at Section 1.3; Note for guidance on nonclinical evaluation for anticancer pharmaceuticals, EMEA/CHMP/ICH/646107/2008 (November 2009).

addendum covers the following five topics: species selection, study design, immunogenicity, reproductive and developmental toxicity, and carcinogenicity.¹⁷¹

4.3.1.2 Species Selection The addendum discusses the factors that sponsors should consider in selecting relevant species for nonclinical testing.¹⁷² According to the addendum, initial testing should compare target sequence homology between species, with subsequent *in vitro* assays making qualitative and quantitative cross-species comparisons of relative target binding affinities, receptor–ligand occupancy, and kinetics. Sponsors also should assess functional activity. This testing should permit identification of a species model that can demonstrate potentially adverse consequences of target modulation.

When the preceding approaches cannot be used to determine relevant species, the sponsor may conduct tissue cross-reactivity studies. If no relevant species exists, the sponsor may consider homologous molecules or transgenic models, as noted in ICH S6.¹⁷³ Specific instructions are provided for mAbs, for which a short-term safety study in one species—and no additional toxicity studies—are recommended.¹⁷⁴

If there are two relevant species (one rodent and one nonrodent), the sponsor should conduct short-term studies in both. If the toxicologic findings from these studies are similar for both species, long-term studies may involve one of those species, usually the rodent species.¹⁷⁵

4.3.1.3 Study Design Sponsors should consider PK–PD approaches—such as exposure–response relationships, modeling, or simulation approaches—when selecting the high dose for toxicity testing. The high dose should be the higher of (1) the dose providing the maximum intended pharmacologic effect in the preclinical species and (2) the dose providing “an approximately 10-fold exposure multiple over the maximum exposure to be achieved in the clinic.”¹⁷⁶ When no PD endpoint is available, the sponsor should select the high dose based on PK data, as well as available *in vitro* binding and/or pharmacology data. Generally, repeat-dose toxicity tests should have a duration of 6 months; studies of longer duration are not considered valuable.¹⁷⁷

Finally, the sponsor may need to assess subject recovery from the medicine’s pharmacologic and toxicologic effects when these effects occur at clinically relevant exposures. One approach is to include, in at least one study, a nondosing period assessing the reversibility of the toxic effects.¹⁷⁸

¹⁷¹ ICH S6 Addendum, at Section 1.1.

¹⁷² *Id.* at Section 2.1.

¹⁷³ See *supra* notes 40–42 and accompanying text.

¹⁷⁴ ICH S6 Addendum, at Section 2.1.

¹⁷⁵ *Id.* at Section 2.2.

¹⁷⁶ *Id.* at Section 3.1.

¹⁷⁷ *Id.* at Section 3.2.

¹⁷⁸ *Id.* at Section 3.3.

4.3.1.4 Immunogenicity As noted in ICH S6, nonclinical studies are not useful in predicting potential immunogenicity of human or humanized proteins in humans.¹⁷⁹ The addendum provides more detail than ICH S6 regarding situations when the sponsor should measure antidrug antibodies (ADAs), namely when (1) there is evidence of altered PD activity, (2) there are unexpected changes in exposure in the absence of a PD marker, or (3) there is evidence of immune-mediated reactions. Collection of appropriate samples during the study is recommended, as noted in Section 2.2, because it is hard to predict the need for ADA measurement before the completion of the in-life phase of the study.¹⁸⁰

4.3.1.5 Reproductive and Developmental Toxicity The addendum first provides general advice on reproductive and developmental testing and then discusses more specific recommendations for fertility studies, embryo–fetal development (EFD) studies and pre- and postnatal development (PPND) studies, and the timing of studies in nonhuman primates (NHPs).¹⁸¹

The addendum first discusses appropriate species for testing.¹⁸² Reproductive studies should occur in a relevant species, but no such studies are required for products directed at foreign targets, such as bacteria and viruses. If the product is pharmacologically active in both rodents and rabbits, EFD studies should occur in both species unless teratogenicity or embryo–fetal lethality is identified in one of them. Sponsors should not use NHPs in developmental testing unless they are the only relevant species, and even then, the sponsor can provide scientific justification to use an alternative model. If no relevant species exists, the sponsor may consider using transgenic mice or homologous proteins. If the weight of the evidence (e.g., information regarding the mechanism of action, phenotypic data from genetically modified animals, or class effects) suggests an adverse effect on fertility or pregnancy, this information may permit communication of the risks, and additional studies might not be warranted.

Fertility studies should occur in mice or rats when either is a relevant species. Mating studies are impractical for NHPs, but sponsors can evaluate the reproductive tract in repeat-dose toxicity studies of sexually mature NHPs that last at least 3 months.¹⁸³ Concerns about effects on conception or implantation should be addressed through studies of NHPs, a transgenic model, or a homologous protein or through risk management, informed consent, and labeling. With respect to EFD and PPND, the sponsor may conduct separate studies or may consider one study that covers day 20 of gestation to birth (an enhanced PPND or ePPND).¹⁸⁴

¹⁷⁹ See *supra* note 47 and accompanying text.

¹⁸⁰ ICH S6 Addendum, at Section 4.

¹⁸¹ *Id.* at Section 5.

¹⁸² *Id.* at Section 5.1.

¹⁸³ *Id.* at Section 5.2.

¹⁸⁴ *Id.* at Section 5.3.

If the candidate enters clinical trials before completion of EFD studies, appropriate risk management techniques (e.g., contraception) should be used in any clinical trial involving women of childbearing potential.¹⁸⁵ If these precautions are in place and NHPs are the only relevant species, the sponsor can conduct EFD and ePPND studies during phase III. When these precautions are not possible, the sponsor should submit the complete EFD report or interim ePPND study before beginning phase III.¹⁸⁶ When the product's mechanism of action raises serious developmental toxicity concerns and NHPs are the only relevant species, no study is necessary; instead, the labeling should disclose the concern, and the sponsor should avoid administering the candidate to women of childbearing potential.

4.3.1.6 Carcinogenicity As noted, carcinogenicity assessments of biologics are not always warranted, but the addendum provides advice for use in situations when they are appropriate.¹⁸⁷ According to the addendum, the sponsor may design a strategy addressing potential carcinogenicity based on a weight of evidence approach, including a review of relevant information, such as literature; information on class effects, target biology, and mechanisms of action; *in vitro* data; clinical data; and data from chronic toxicity studies.¹⁸⁸ In some cases, this review will be sufficient to address the carcinogenic potential.¹⁸⁹

In situations when the mechanism of action raises concerns and the weight of the evidence supports them, the hazard should be addressed through product labeling and risk management practices.¹⁹⁰ If the weight of the evidence regarding a mechanism-based concern is instead unclear, the sponsor can propose additional studies to address it.¹⁹¹

When insufficient information exists on product characteristics and mechanism of action, a more extensive assessment might be appropriate, including, for example, additional endpoints in toxicity studies.¹⁹² If this assessment suggests a carcinogenicity concern, sponsors may propose additional studies or labeling to address the concern.¹⁹³ If this assessment instead suggests no carcinogenicity concern, additional nonclinical testing is not recommended.¹⁹⁴

4.3.2 Clinical Studies in Compliance with the Clinical Trials Directive

After complying with the preclinical testing requirements, biologics also need to undergo clinical trials before a marketing authorization application (MAA) can be

¹⁸⁵ *Id.* at Section 5.4.

¹⁸⁶ *Id.* at Section 5.4.

¹⁸⁷ See *supra* Section 4.2.2.3.

¹⁸⁸ ICH S6 Addendum, at Section 6.

¹⁸⁹ *Id.*

¹⁹⁰ *Id.*

¹⁹¹ *Id.*

¹⁹² *Id.*

¹⁹³ *Id.*

¹⁹⁴ *Id.*

submitted. The Clinical Trials Directive sets forth the general requirements for clinical trials of medicinal products, including biologics.¹⁹⁵ Because some general standards may not be relevant or appropriate for biologics, however, regulators must take a flexible approach to trials of these products. This section summarizes the requirements of the Clinical Trials Directive, noting special considerations for biologics when necessary.

4.3.2.1 Clinical Trial Authorization The Clinical Trials Directive and European Commission guidance¹⁹⁶ describe the steps that a sponsor must take before commencing a clinical trial. According to these documents, a clinical trial may commence only if (1) the anticipated therapeutic and public health benefits outweigh any foreseeable risks and inconveniences to the subjects; (2) the trial subjects understand the objectives and risks of the trial and give informed, written consent to participate; (3) the trial safeguards the physical and mental integrity of the subjects; and (4) insurance covers the liability of the sponsor and investigator.

To comply with these requirements, the trial sponsor must take certain steps. In general, the sponsor must take responsibility for the following: trial conduct, appointment of an appropriate investigator, selection of the institution that will conduct the trial, quality control, data collection standards, protocol drafting, and creation of the investigator's brochure.¹⁹⁷ The sponsor then must apply for approval from both the ethics committee in the country where the trial will be conducted and competent authorities of the Member States. Written authorization may be required for all biologics trials and is required for trials involving medicines containing genetically modified organisms, medicines for gene therapy, and medicines for somatic cell therapy (including xenogenic cell therapy).¹⁹⁸ The opinion of the ethics committee should be issued within 60 days. A review period of 30 days can be added for medicines requiring written authorization noted earlier, and for xenogenic cell therapy, there are no time limits for authorization. This time frame can be extended by an additional 90 days (in addition to the original 90 days) if the ethics committee consults a national group or committee. The trial may begin only if (1) the ethics committee has issued a favorable opinion

¹⁹⁵ Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (as amended by Regulation (EC) No. 596/2009 of 18 June 2009).

¹⁹⁶ Communication from the Commission—Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1), 2010 O.J. (C 82), 1.

¹⁹⁷ S. Shorthose, "Guide to EU pharmaceutical regulatory law," Alphen aan den Rijn: Kluwer Law International, 2011, p. 139.

¹⁹⁸ Article 9(5) and (6), Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (as amended by Regulation (EC) No. 596/2009 of 18 June 2009).

and (2) no competent authority has informed the applicant of grounds for non-acceptance.¹⁹⁹

4.3.2.2 *Good Clinical Practices and Other Considerations for Clinical Trials*

Clinical trials of biologics must comply with GCP, as described in Directive 2005/28/EC on Good Clinical Practice²⁰⁰ and the ICH E6 guideline, which the CHMP has adopted.²⁰¹ The directive and guideline describe general governing principles for clinical trials. The rights, safety, and well-being of trial subjects must prevail over the interests of science and society. Investigators must obtain freely given informed consent from every trial subject before each subject is enrolled. Clinical trial information must be handled, recorded, and stored with respect for relevant confidentiality and privacy rules. Trials must comply with the ethical principles of the World Medical Association's Declaration of Helsinki. Specific GCP guidelines apply to trials of advanced therapy medicinal products.²⁰² These guidelines regulate issues such as the donation, procurement, and testing of human tissues and cells; the implementation of a traceability system; and specific rules on safety reporting and long-term follow-up.

Under the Clinical Trials Directive, special requirements apply to clinical trials conducted on minors and other persons not able to give informed legal consent.²⁰³ These requirements are intended to preserve the dignity of the trial subjects, confirm that the benefits of the trial outweigh the risks, and ensure that subjects' representatives give consent with as much involvement of the subject as possible. Competent authorities must record information regarding trials in the European database of clinical trials (EudraCT), which is accessible only to other competent authorities, the European Medicines Agency (EMA), and the European Commission.²⁰⁴

CHMP has issued a guideline on quality requirements during the clinical trial period for investigational medicinal products (IMPs) containing biological or biotechnology-derived substances.²⁰⁵ The guideline describes quality documentation that should be submitted to the competent authority as part of the sponsor's investigational medicinal product dossier (IMPD). Given the importance of the production process for a biologic's properties, as described in Section 3, the

¹⁹⁹ *Id.* Article 9(1).

²⁰⁰ Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products, 2005 O.J. (L 91) 13.

²⁰¹ Note for guidance on good clinical practice, CPMP/ICH/135/95 (1997; revised July 2002) (ICH E6 Guideline).

²⁰² Detailed guidelines on good clinical practice specific to advanced therapy medicinal products, ENTR/F/2/SF/dn D(2009) 35810 (December 3, 2009).

²⁰³ Article 4 and Article 5, Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (as amended by Regulation (EC) No. 596/2009 of 18 June 2009).

²⁰⁴ *Id.* Article 11.

²⁰⁵ Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials, EMA/CHMP/BWP/534898/2008 (March 15, 2012).

guideline states that the IMPD should include, among other things (1) an adequate description of the process and process controls, including a flow chart of all successive steps and details of in-process testing, and (2) a description and justification of “any reprocessing during manufacture of the drug substance.”²⁰⁶

The guideline also recognizes that sponsors will improve and optimize their manufacturing processes during clinical development and describes the steps sponsors should take following these changes.²⁰⁷ Specifically, the sponsor must compare the quality attributes of the pre- and postchange biological active substances and relevant intermediates, and “[d]epending on the consequences of the change introduced and the stage of development, a comparability exercise may be necessary.”²⁰⁸ For first-in-human (FIH) clinical trials, sponsors should use product representative of the material used during the nonclinical testing phase.²⁰⁹ Finally, with regard to characterization, the guideline requires details on the biological activity to be provided, recognizing that the extent of characterization data will further increase in later phases.²¹⁰

4.3.2.3 Study Design Considerations General guidance on study design applies to biologics as well as small molecule medicines.²¹¹ According to the guidance, there is a “close, but variable correlation” between phase of development and type of study, but one type of trial can occur in several different phases.²¹² The guidance therefore identifies the “[m]ost typical kind of study for each phase.”²¹³

Phase I usually involves the initial introduction of the investigational product into human subjects, and studies in this phase usually have nontherapeutic objectives. Specifically, phase I studies typically investigate one or more of the following: (1) initial safety and tolerability; (2) PK, which are “particularly important to assess the clearance of the drug and to anticipate possible accumulation of parent drug or metabolites and potential drug-drug interactions”; (3) PD; and (4) drug activity, to preliminarily determine the potential therapeutic benefit of a medicine.²¹⁴ The most typical phase I study is the human pharmacology study. According to the guidance, phase I studies may be conducted in healthy volunteers or certain types of patients (e.g., patients with mild hypertension). If the medicine has significant potential toxicity (e.g., cytotoxic products), the trial will usually be conducted in patients.

The CHMP introduced new guidelines on FIH studies after the 2006 TeGenero incident. That case involved a FIH clinical trial of a novel mAb, during which

²⁰⁶ *Id.* at S.2.2.

²⁰⁷ *Id.* at S.2.6.

²⁰⁸ *Id.*

²⁰⁹ *Id.*

²¹⁰ *Id.* at S.3.1.

²¹¹ Note for guidance on general considerations for clinical trials, CPMP/ICH/291/95 (March 1998) (ICH E8 Guideline).

²¹² *Id.* at 3.1.3.

²¹³ *Id.* at 3.1.3.1, 3.1.3.2, 3.1.3.3.

²¹⁴ *Id.* at 3.1.3.1.

subjects experienced severe adverse events, including multiorgan failure.²¹⁵ The new guideline describes risk factors helpful in identifying potential severe adverse reactions, including concerns derived from knowledge or lack thereof regarding (1) the product's mode of action, (2) the nature of the target, or (3) the relevance of animal models.²¹⁶ The guideline also discusses quality, nonclinical, and clinical study design considerations for minimizing risk to human subjects.²¹⁷

The most typical phase II study is a therapeutic exploratory study that explores efficacy in narrowly defined, relatively homogenous groups of patients. Initially, studies may use a variety of designs (e.g., concurrent controls and comparisons with baseline status). Subsequent phase II trials usually are randomized and concurrently controlled, allowing for evaluation of the medicine's safety and efficacy for a particular indication. A major goal of this phase is to determine the dose(s) for phase III trials.²¹⁸

Phase III typically involves therapeutic confirmatory studies that are designed to verify the preliminary evidence obtained in phase II and to provide a sufficient basis for marketing authorization. Phase III studies "may also further explore the dose-response relationship, or explore the drug's use in wider populations, in different stages of disease, or in combination with another [medicine]."²¹⁹ With regard to medicines administered for long periods, extended exposure trials ordinarily occur during phase III, although the sponsor may start them in phase II.²²⁰

To ensure that clinical trials in all three phases of development will be adequate to support an MAA, sponsors should design these trials with the MAA requirements in mind. Biologics in general need to comply with the requirements set out in Part III of the CTD, and advanced therapy medicinal products need to comply with the requirements described in Part IV of the CTD. Section 3.3, *infra*, provides more information regarding the MAA.

4.3.2.4 Consultation with the European Medicines Agency A sponsor may obtain, from the EMA, scientific advice regarding clinical trial protocols.²²¹ Although this advice does not bind the ethics committee and national competent authority and is not binding for purposes of a future MAA, it can be useful to guide revisions to the protocol.²²² The agency's remarks will only address scientific issues

²¹⁵ Ganesh Suntharalingam et al., *Cytokine Storm in a Phase I Trial of the Anti-CD28 Monoclonal Antibody TGN1412*, 355(10) N ENGL. J. MED. 1018, 1018 (2006).

²¹⁶ CHMP Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products, EMEA/CHMP/SWP/28367/07 (July 19, 2007), at Section 4.1.

²¹⁷ *Id.* at Sections 4.2–4.4.

²¹⁸ ICH E8 Guideline, at 3.1.3.2.

²¹⁹ *Id.* at 3.1.3.3.

²²⁰ *Id.*

²²¹ Article 57(1)(n), Regulation 726/2004/EC of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (as amended by Regulation (EU) No. 1235/2010 of 15 December 2010).

²²² EMA, Scientific Advice, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000050.jsp&mid=WC0b01ac05800229bb&jsenabled=true (last accessed December 3, 2012).

and will generally focus on matters such as the selection of endpoints and comparator, the duration of treatment or follow-up, and the design of pivotal studies.²²³ Advice also might address a sponsor's proposal to deviate from a CHMP guideline.²²⁴ If the applicant decides not to follow the EMA's advice, it should justify this decision in its MAA.²²⁵ EMA guidance details the procedures for requesting scientific advice.²²⁶

The fact that an applicant requests advice from EMA does not preclude it from also seeking advice from national competent authorities or from foreign regulators, such as the FDA. The process of obtaining advice from the national competent authorities is often less formal than requesting advice from the EMA, and such advice can prove helpful. Consequently, seeking such advice is a common choice among applicants.²²⁷

Applicants also may seek parallel scientific advice from the EMA and FDA.²²⁸ Generally, the parallel scientific procedure is available for "important breakthrough drugs," products that the EMA and FDA have identified as falling within therapeutic areas of overlapping interest (e.g., oncology products, vaccines, and blood products), and products with "significant clinical safety, animal toxicology, or unique manufacturing concerns that could impede . . . development."²²⁹ The goal of these meetings is to provide clarity regarding the regulatory requirements of each region and the reasons for any differences between them.²³⁰ A sponsor requesting parallel advice should authorize the agencies to exchange all information about the product, including trade secrets.²³¹ After the parallel scientific advice procedure, each agency will provide its own independent advice on the questions at issue.²³² There is no guarantee of harmonized advice or identical regulatory decisions on the approvability of the product.²³³ Nevertheless, sponsors are increasingly requesting parallel scientific advice. For example, in the period ranging from September 2009 to September 2010, the agencies received seven requests for such advice.²³⁴

²²³ See Shorthose, *supra* note 197, at 141.

²²⁴ European Medicines Agency guidance for companies requesting scientific advice and protocol assistance, EMEA-H-4260-01-Rev. 6 (May 21, 2010).

²²⁵ *Id.* Item 20.

²²⁶ See generally *id.*

²²⁷ See Shorthose, *supra* note 197, at 143.

²²⁸ EMA/FDA, General Principles: EMEA-FDA Parallel Scientific Advice, EMEA/24517/2009 (July 2009), at 1.

²²⁹ *Id.* at 2.

²³⁰ *Id.*

²³¹ *Id.*

²³² *Id.* at 3.

²³³ *Id.*

²³⁴ EMA/FDA, Interactions between the European Medicines Agency and U.S. Food and Drug Administration September 2009–September 2010, EMA/705027/2010 (June 2011), Section 6.

4.3.3 The Marketing Authorization Application: Contents and Approval Standard

Many biologics fall under the scope of the centralized marketing authorization procedure, which is mandatory for medicines developed through biotechnological methods (recombinant DNA technology; controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes, including transformed mammalian cells; and hybridoma and mAb methods).²³⁵ For example, the following are subject to the centralized procedure: cell therapy, gene therapy, vaccines from strains developed through recombinant DNA technology (including gene deletion), and “any medicinal product for which a monoclonal antibody is used at any stage in the manufacturing process.”²³⁶

Nonetheless, some biologics are still approved at the Member State level. For example, many vaccines do not fall within the scope of the centralized procedure. The EMA has published a guideline intended to harmonize the summaries of product characteristics and patient information leaflets for human vaccines.²³⁷ This chapter discusses the requirements of the EU centralized procedure.

The approval standards for biotechnology products are the same as for chemically synthesized medicines. Both types of products must be safe and effective and have appropriate quality. Because of their special characteristics, however, biotechnology products must comply with several additional dossier requirements.

The MAA for a biotechnology product must meet the standard dossier submission requirements, as described in Article 8 of the Medicines Directive.²³⁸ Consequently, the MAA must generally comply with the CTD format, including with respect to Module I (administrative information, including labeling and mock-ups), Module 2 (various summaries), Module 3 (chemical, pharmaceutical, and biological information), Module 4 (nonclinical reports), and Module 5 (clinical study reports).²³⁹

MAAs for biologics also must meet special requirements. The applicant must thoroughly describe the manufacturing process and must (1) provide information on the origin and history of the starting materials; (2) demonstrate that the active substance complies with specific measures for preventing the transmission of animal spongiform encephalopathies; (3) if cell banks are used, demonstrate that cell

²³⁵ Article 3(1) and Annex to Regulation 726/2004/EC of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (as amended by Regulation (EC) No. 1394/2007 of 13 November 2007).

²³⁶ European Commission, Notice to Applicants, vol. 2A, ch. 4, of April 2006 (ENTR/F2/BL D(2006)), Section 1.1.

²³⁷ CPMP Guideline on pharmaceutical aspects of the product information for human vaccines, EMEA/CPMP/BWP/2758/02 (November 23, 2003). Revisions to this guideline are under consideration. Concept paper on a revision of the guideline on pharmaceutical aspects of the product information for human vaccines EMEA/CHMP/BWP/290688/2009 (June 17, 2009).

²³⁸ 8, Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (as amended by Directive 2011/62/EU of 8 June 2011).

²³⁹ *Id.* at Annex I, Table of Contents.

characteristics remain unchanged at the passage level for production (and beyond); (4) provide information as to whether there are adventitious agents in seed materials, cell banks, pools of serum or plasma, and all other materials of biological origin, and, if it is not possible to avoid the presence of potentially pathogenic adventitious agents, show that further processing ensures elimination or inactivation of the agents; (5) if possible, base vaccine production on a seed lot system and established cell banks; (6) in case of medicines derived from human blood or plasma, describe the origin, criteria, and procedures for the collection, transportation, and storage of the starting material; and (7) describe the manufacturing facilities and equipment.²⁴⁰

Other special rules apply certain types of biological medicines. For example, for plasma-derived medicinal products, the applicant must provide an information dossier, the Plasma Master File. MAAs for vaccines other than for influenza need to contain a Vaccine Antigen Master File. Special rules also apply to advanced therapy medicinal products, including gene therapies, somatic cell therapies, and tissue-engineered products.²⁴¹

4.4 REGULATORY STRATEGIES FOR WORLDWIDE MARKETING OF BIOLOGICAL PRODUCTS

4.4.1 Acceptance of Foreign Clinical Studies in the United States and Europe

4.4.1.1 United States The FDA has adopted two regulations governing its acceptance of foreign clinical data, one applicable to supportive data and one applicable to data that form the sole basis for approval. Both regulations require the sponsor to meet certain conditions before the FDA will agree to use of the data.

First, the FDA accepts “well-designed and well-conducted” foreign, non-IND studies as “support” for an IND or BLA if two conditions are met.²⁴² The FDA generally must be able to conduct an onsite inspection of the data, if necessary.²⁴³ The sponsor also must have conducted the study using GCP, as defined in 21 C.F.R. § 312.120.²⁴⁴ For purposes of that regulation, GCP means standards that ensure the credibility of the results and the protection of subjects, including independent ethics board approval and documentation of subjects’ informed consent.²⁴⁵ Complying with ICH E6, the GCP guidance, is one way—but not the only way—to meet this requirement.²⁴⁶ The FDA recently issued guidance on

²⁴⁰ *Id.* at Annex I, Section 3.2.1.2.

²⁴¹ Advanced therapy medicinal products are regulated under a separate regime, Regulation 1394/2007 / EC of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No. 726/2004 (as amended by Regulation (EU) No. 1235/2010 of 15 December 2010).

²⁴² 21 C.F.R. § 312.120(a)(1).

²⁴³ 21 C.F.R. § 312.120(a)(1)(ii).

²⁴⁴ 21 C.F.R. § 312.120(a)(1)(i).

²⁴⁵ *Id.*; see also 73 Fed. Reg. 22800, 22807 (April 28, 2008).

²⁴⁶ 73 Fed. Reg. at 22807.

submitting information to demonstrate compliance with 21 C.F.R. § 312.120.²⁴⁷ After these threshold criteria are met, the FDA will use the factors described in ICH E5, *Ethnic Factors in the Acceptability of Foreign Clinical Data*, to determine the scientific relevance of the data with respect to the US population and the need for additional bridging data to confirm their value. This exercise is described in Section 4.2, *infra*.

Second, when foreign data are intended to form the sole basis for United States marketing approval, the sponsor must comply with GCP and meet three other criteria.²⁴⁸ The FDA must deem the foreign data to be “[a]pplicable to the U.S. population and U.S. medical practice” using the criteria described in ICH E5.²⁴⁹ The clinical investigators must have “recognized competence.” Finally, the data must be considered valid without the need for an onsite FDA inspection, or the FDA must be able to validate the data through such an inspection.

4.4.1.2 Europe Directive 2001/83/EC allows for clinical trials conducted outside the European Union to be taken into consideration during the review of an MAA in the European Union if such trials have been designed, implemented, and reported based on principles equivalent to those of the Clinical Trials Directive with regard to good clinical practice and ethical principles. Moreover, they should comply with the ethical principles outlined in the Declaration of Helsinki.²⁵⁰ The applicant must submit a statement declaring such compliance as part of the MAA.²⁵¹

In December 2008, the EMA published a strategy paper on the acceptance of data from foreign clinical trials conducted in “third countries,” particularly those outside the “‘traditional’ Western European and North American research areas.”²⁵² According to this strategy paper, there is a “growing concern both among regulators and in public debate about how well these trials are conducted from an ethical and scientific/organizational standpoint.”²⁵³ The EMA has called for increased cooperation between international regulatory authorities involved in the supervision of clinical trials and has put forth other proposals to address these issues.²⁵⁴

²⁴⁷ FDA, *Guidance for Industry and FDA Staff: FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND Frequently Asked Questions* (March 2012).

²⁴⁸ 21 C.F.R. § 314.106(b); Murray M. Lumpkin, M.D., M.Sc., Deputy Commissioner, Int’l Programs, FDA, *FDA Perspective on Int’l Clinical Trials*, Presentation at FDA Clinical Trials Workshop (November 8, 2011), Slide 7.

²⁴⁹ Lumpkin, *supra* note 248, Slide 14.

²⁵⁰ Recital 8, Annex I to Directive 2001/83/EC of 6 November 2001 on the Community code relating to medicinal products for human use (as amended by Directive 2009/120/EC of 14 September 2009).

²⁵¹ Article 8 of Directive 2001/83/EC of 6 November 2001 on the Community code relating to medicinal products for human use (as amended by Directive 2011/62/EU of 8 June 2011).

²⁵² EMEA strategy paper: Acceptance of clinical trials conducted in third countries, for evaluation in Marketing Authorisation Applications, December 5, 2008, EMEA/228067/2008.

²⁵³ *Id.*

²⁵⁴ See, e.g., *id.*; “Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities,” April 16, 2012, EMA/121340/2011; “International workshop on the ethical and good-clinical-practice aspects of clinical trials conducted in third countries”, held from June 9, 2010, to July 9, 2010, in London, UK.

4.4.2 Foreign and Multinational Clinical Studies: Addressing Ethnic Factors

ICH E5 describes strategies to extrapolate clinical data generated in one region to support approval in another based on an assessment of ethnic factors' impact on the medicine's safety and efficacy.²⁵⁵ "Ethnic factors" include intrinsic factors, such as genetics and age, and extrinsic factors, such as regional clinical trial conduct and medical practice.²⁵⁶

For the ICH E5 framework to apply, the clinical trial must meet the regulatory requirements (e.g., choice of control, trial endpoints, and key design features) of the region where approval is sought.²⁵⁷ Regulators then assess the medicine's sensitivity to ethnic factors using information about its PK and PD and their relationship to safety and efficacy.²⁵⁸ Based on the level of ethnic sensitivity, regulators will then determine whether existing data show the trials' relevance to the new region or whether a bridging study is necessary to confirm their relevance.²⁵⁹ For example, when the medicine is ethnically insensitive and extrinsic factors in the two regions are similar, regulators might not require a bridging study.²⁶⁰ Generally, one bridging study will suffice for extrapolation under ICH E5 unless the bridging study is too small to assess safety or does not confirm the relevance of the foreign data to the new region's population.²⁶¹ In these cases, regulators in the new region likely will require additional data. Depending on the circumstances, a bridging study might use pharmacologic endpoints or might constitute a controlled clinical trial.²⁶² Separate safety data might be needed when the sponsor does not need to perform a bridging efficacy study or when the efficacy study is not powered for safety.²⁶³

ICH E5 and its companion Q&A guidance also discuss strategies for a multinational trial to support simultaneous registration applications in multiple countries.²⁶⁴ The trial's goals would be to show efficacy in each region and to compare regional results to show insensitivity to ethnic factors.²⁶⁵ In designing these types of studies, sponsors should choose a primary endpoint that is acceptable to all regional regulatory authorities (or when this is impossible, collect data on all primary endpoints in all regions for comparison).²⁶⁶ The sponsor should use a common

²⁵⁵ FDA, *ICH E5: Ethnic Factors in the Acceptability of Foreign Clinical Data*, as adopted by FDA at 63 Fed. Reg. 31790, 31791 (June 10, 1998).

²⁵⁶ *Id.* at 31791, 31793–31794.

²⁵⁷ *Id.* at 31791–31792; FDA/ICH, *Guidance for Industry: E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data: Questions & Answers 4* (September 2006) (ICH E5 Q&A).

²⁵⁸ 63 Fed. Reg. at 31792.

²⁵⁹ *Id.*

²⁶⁰ *Id.*

²⁶¹ *Id.*

²⁶² *Id.* at 31792–31793.

²⁶³ *Id.* at 31793.

²⁶⁴ See *id.* at 31793; ICH E5 Q&A, at 6.

²⁶⁵ ICH E5 Q&A, at 6.

²⁶⁶ *Id.*

protocol to collect endpoint data and should power the study to permit an efficacy showing in each region.²⁶⁷ Collection of safety data should be as uniform as possible across regions, and the study should meet all regional requirements for design and analysis.²⁶⁸ Other factors relevant to study design, such as definition of disease and choice of control group, should be discussed with regional regulatory authorities.²⁶⁹ The sponsor should provide the results by region and assess the consistency of the product's effect across regions.²⁷⁰ When the regional results are persuasive, this showing can confirm the relevancy of the foreign results as further support for the regional marketing application.²⁷¹

4.5 PREVENTIVE VACCINE DEVELOPMENT: SPECIAL CONSIDERATIONS

4.5.1 General Considerations for Vaccine Development in the United States

Development of a vaccine for FDA approval presents special issues. For example, vaccines are often intended for use in healthy populations; thus, they present distinct risk–benefit issues from therapeutic products.²⁷² As another example, data regarding concomitant use of other vaccinations are important to licensure.²⁷³ Section 5.1 provides an overview of vaccine development issues in the United States, including necessary studies by phase of development, study endpoints, and the possible need for bridging studies.

4.5.1.1 Types of Studies by Phase of Development For vaccines, phase 1 studies involve an initial assessment of safety and immunogenicity in a small number of healthy adult volunteers, ordinarily individuals at low risk of contracting the disease of interest.²⁷⁴ The phase 1 study primarily assesses safety. Investigators should monitor patients for local and systemic adverse events at specified times in the week after administration and in the months that follow (including an assessment at 6 months after the last dose).²⁷⁵ The protocol should include a toxicity grading scale for these events.²⁷⁶ The stopping criteria generally must be more conservative than in therapeutic settings because vaccine trials enroll healthy individuals.²⁷⁷ When the

²⁶⁷ *Id.* at 6–7.

²⁶⁸ *Id.* at 7.

²⁶⁹ *Id.* at 2.

²⁷⁰ *Id.* at 7.

²⁷¹ *Id.* at 6.

²⁷² Karen L. Goldenthal, M.D., Loris D. McVittie, Ph.D., Cynthia Kleppinger, M.D., and Antonia Gerber, M.D., Div. of Vaccines and Related Products Applications, CBER, FDA, in *BIOLOGICS DEVELOPMENT: A REGULATORY OVERVIEW* 99, 100 (Mark Mathieu, ed., 3rd ed., 2004).

²⁷³ *Id.* at 101.

²⁷⁴ *Id.*

²⁷⁵ *Id.* at 102.

²⁷⁶ See generally FDA, *Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* (September 2007).

²⁷⁷ See *id.* at 1; Goldenthal et al., *supra* note 272, at 102–103.

sponsor studies a live vaccine, the phase 1 study should assess the “shedding” of live vaccine organisms in bodily substances, and investigators might need to isolate vaccinated individuals to evaluate shedding and any reversion of the vaccine strain to wild type.²⁷⁸ The sponsor also might need to conduct additional studies assessing secondary transmission of the disease to third parties coming into contact with the vaccinated individual.²⁷⁹

Phase 2 studies should enroll individuals “at clear risk” for the disease.²⁸⁰ These studies should produce “more definitive” immunogenicity data that allow the sponsor to determine whether an adjuvant is needed and to select the vaccine formulation, dose, dosing schedule, and route of administration for phase 3 trials.²⁸¹ Phase 2 studies also should evaluate the immune response to the vaccine upon administration with likely concomitant vaccines.²⁸² In addition to assessing the vaccine’s effects, these studies also should assess the disease that it is intended to prevent, to allow refinement of one or more “case definitions” of the disease or infection to be prevented.²⁸³ For example, the sponsor should gather epidemiologic data on the disease, including seroincidence data when applicable, in at-risk individuals and should determine geographic strain specificity.²⁸⁴ By the end of phase 2, the sponsor should have developed and validated laboratory assays that will be used for the case definition for the efficacy trials (e.g., those used to distinguish wild-type immune responses from those that the vaccine elicits).²⁸⁵

Phase 3 studies should be controlled, randomized, and double blinded.²⁸⁶ In formulating sample size calculations, sponsors should consider that multiple immunizations might be needed to achieve maximum efficacy.²⁸⁷ When appropriate, however, sponsors may conduct a detailed safety assessment in only a subset of subjects as long as active monitoring for serious adverse events is in place for all subjects.²⁸⁸ The FDA typically requires long-term follow-up, which might take the form of a postmarket commitment, to assess the duration of immunogenicity and efficacy, long-term safety, and the need for different doses.²⁸⁹ “Ideally,” the sponsor will evaluate the correlation of protection with immune response at specific time points after immunization as part of the phase 3 program.²⁹⁰

Sponsors should consider use of a Data Safety Monitoring Board (DSMB), which may conduct an interim review of the data, for the phase 3 vaccine trials.²⁹¹ The

²⁷⁸ Goldenthal et al., *supra* note 272, at 103.

²⁷⁹ *Id.*

²⁸⁰ *Id.* at 104.

²⁸¹ *Id.*

²⁸² *Id.*

²⁸³ *Id.*

²⁸⁴ *Id.*

²⁸⁵ *Id.*

²⁸⁶ *Id.* at 105.

²⁸⁷ *Id.*

²⁸⁸ *Id.*

²⁸⁹ *Id.*

²⁹⁰ *Id.* at 107.

²⁹¹ *Id.*

protocol should specify the conditions that trigger any planned interim review, the statistical analysis plan for the interim analysis, and specific early termination criteria (e.g., criteria based on a toxicity grading scale).²⁹²

4.5.1.2 Endpoints in Vaccine Studies The FDA accepts three types of endpoints for showing vaccine efficacy: (1) clinical endpoints (i.e., prevention of the disease in question); (2) immune response endpoints; and (3) pursuant to the animal rule described earlier in Section 2.3.3, animal study endpoints that are “clearly related” to the desired benefit in humans, such as survival or prevention of major morbidity.²⁹³ First, the FDA generally mandates use of a clinical endpoint for vaccines that are novel or the first of their kind for the population, among other things.²⁹⁴ Second, as noted earlier, the FDA will accept a serologic endpoint “where a previously accepted correlation between [this endpoint] and clinical effectiveness already exists”²⁹⁵ (e.g., based on prior successful clinical studies using clinical endpoints or population-based studies of immunized individuals).²⁹⁶ Because serologic endpoints may allow for smaller efficacy trials, however, their use in pivotal efficacy studies might result in a need for additional safety studies.²⁹⁷ Third, sponsors can use the animal rule only when studies using clinical or serologic endpoints are unethical or infeasible; this might be the case for vaccines to address smallpox or anthrax, for example.²⁹⁸

4.5.1.3 Necessary Bridging Studies Bridging data might be needed in several circumstances. For example, these data might be needed when the sponsor conducts efficacy studies abroad. In this case, the frameworks described in Sections 4.1.1 and 4.2 will govern the acceptability of the foreign data and the type of bridging studies needed to assess ethnic factors, respectively.²⁹⁹ For vaccines studied in foreign efficacy trials, the FDA typically requires bridging data regarding safety and immunogenicity.³⁰⁰ Similarly, when the manufacturer implements process changes after the pivotal study for a vaccine, the FDA may require clinical bridging studies between the pre- and postchange vaccines to assess whether the immune responses to both are equivalent and to evaluate safety.³⁰¹ If no immune correlate of protection has been identified and the new product elicits a decreased immune response, a comparability showing might not be possible.³⁰²

²⁹² *Id.*; Rosemary Tiernan, M.D., M.P.H., FDA, Div. of Vaccines and Related Products Applications, CBER, FDA, Regulatory Perspective on Development of Preventive Vaccines for Global Infectious Diseases: Presentation at the Nat’l Institute for Allergy & Infectious Diseases (October 30, 2007), Slide 24.

²⁹³ Tiernan, *supra* note 292, Slide 11; 21 C.F.R. § 601.91(a)(3).

²⁹⁴ Tiernan, *supra* note 292, Slide 12.

²⁹⁵ 21 C.F.R. § 601.25(d)(2).

²⁹⁶ Goldenthal et al., *supra* note 272, at 107–108.

²⁹⁷ *Id.* at 109.

²⁹⁸ 21 C.F.R. § 601.90; Tiernan, *supra* note 292, Slide 21.

²⁹⁹ See Goldenthal et al., *supra* note 272, at 107.

³⁰⁰ *Id.*

³⁰¹ *Id.* at 108.

³⁰² *Id.* at 109.

4.5.2 Special Procedures for Centralized Review of Vaccine Dossiers in the European Union

Under EU law, a fast track authorization procedure is available for pandemic influenza vaccines. The sponsor may submit, and obtain approval of, the core pandemic dossier during the interpandemic period³⁰³ based on a “mock-up” vaccine (i.e., a vaccine containing an active ingredient that mimics the novelty of a pandemic virus).³⁰⁴ After a pandemic is declared, the special procedure allows for fast track approval of a pandemic variation.³⁰⁵ The manufacturers of influenza vaccines may submit the core pandemic dossier and the subsequent pandemic variation either to the EMA for a centralized approval or to the national authorities for a national or mutual recognition procedure approval.³⁰⁶ The centralized procedure is obligatory for certain techniques of vaccine preparation, such as reverse genetics.³⁰⁷

4.5.3 Development of Vaccines to Protect Against Global Infectious Diseases

4.5.3.1 United States The FDA reviews and approves vaccines for infectious diseases that are not endemic or have not been reported to occur in the United States, such as cholera, malaria, and tuberculosis.³⁰⁸ The regulatory pathway, approval standard, and required level of evidence are no different for these vaccines and those intended to prevent diseases endemic in the United States.³⁰⁹ For example, review under the animal rule is available under the same conditions for both types of vaccines.³¹⁰ The FDA has licensed several vaccines, including ones for Japanese encephalitis and typhoid, based on efficacy trials performed solely in disease-endemic regions.³¹¹

Because foreign efficacy trials likely will be necessary when the disease has a low incidence in the United States, the FDA’s regulations governing acceptability of foreign data and ICH guidance on ethnic factors again are likely to apply.³¹² In these situations, the “bridge” might comprise data from a single-arm safety and

³⁰³ For a detailed explanation of the procedure, see CHMP Guideline on the submission of marketing authorization applications for pandemic influenza vaccines through the centralized procedure of 5 April 2004, EMEA/CHMP/VEG/4986/03.

³⁰⁴ WHO, Safety of pandemic vaccines, http://www.who.int/csr/disease/swineflu/notes/h1n1_safety_vaccines_20090805/en/index.html (last accessed December 3, 2012).

³⁰⁵ CPMP Guideline on Dossier Structure and Content for Pandemic Influenza Vaccine Marketing Authorization Application of 18 December 2008, EMEA/CPMP/VEG/4717/2003.

³⁰⁶ CHMP Guideline on the submission of marketing authorization applications for pandemic influenza vaccines through the centralized procedure of 5 April 2004, EMEA/CHMP/VEG/4986/03.

³⁰⁷ Part 1 of Annex to Regulation 726/2004/EC of 31 March 2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency” (as amended by Regulation (EC) No. 1394/2007 of 13 November 2007).

³⁰⁸ FDA, *Guidance for Industry: General Principles for the Development of Vaccines to Protect Against Global Infectious Diseases 3* (December 2011) (Global Infectious Disease Guidance).

³⁰⁹ *Id.* at 3, 7.

³¹⁰ See *id.* at 4, 6–7.

³¹¹ *Id.* at 5, 8.

³¹² See *supra* Sections 4.4.1.1 and 4.4.2.

immunogenicity study in the United States, from which comparisons can be drawn to pivotal foreign data.³¹³ Sponsors should discuss with FDA their plans for development of global infectious disease vaccines, including bridging study design and special issues for concomitant vaccines in this context.³¹⁴

4.5.3.2 Europe The CHMP may “give a scientific opinion, in the context of cooperation with the World Health Organization” regarding medicines that are intended exclusively for markets outside the Community and “used to prevent or treat diseases of major public health interest.”³¹⁵ Eligible medicines include vaccines used in the World Health Organization Expanded Program on Immunization or vaccines for protection against a public health priority disease.³¹⁶

4.6 CONCLUSION

Despite clear differences in the US and EU regulatory regimes for biologics—for example, with respect to the definitional frameworks for biologics—the systems share a number of similarities. Both regimes use certain harmonized scientific testing standards, and one can safely conclude that both regimes clearly recognize the specific nature of biologics and take appropriate measures to address the possible issues resulting from it. The regions have distinct regulatory approval procedures because of the general structural differences in their medicine authorization regimes, as well as different historical developments in both systems. Overall, the US and EU regulatory regimes for biologics are more similar than they are different.

³¹³ Tiernan, *supra* note 292, Slides 48–49.

³¹⁴ *Id.*, Slide 52; Global Infectious Disease Guidance, at 5.

³¹⁵ Article 58 of Regulation 726/2004/EC of 31 March 2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (as amended by Regulation (EU) No. 1235/2010 of 15 December 2010); EMA, Opinions on medicines for use outside the European Union, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000312.jsp&mid=WC0b01ac058001d12c&jsetEnabled=true.

³¹⁶ EMA, Opinions on medicines for use outside the European Union, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000312.jsp&mid=WC0b01ac058001d12c&jsetEnabled=true.