

BACKGROUND

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Biopharmaceuticals: Definition and Regulation

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1.1 INTRODUCTION

Compared with other types of pharmaceutical products, products derived from a biological source or a biotechnological process are structurally complex and involve manufacturing processes that require tight control to ensure their safety, quality, and efficacy. Biological products, because of their sheer size, are orders of magnitude more complicated than small-molecule drugs. This can be seen by a comparison of molecular weight, which can be used as a measure of the size of a given product. Moreover the product arising from the manufacturing process is often not a pure, homogeneous mixture. Rather, various forms of these molecules are usually present in the final product.

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In scientific terms, conventional biological products such as blood-derived clotting products, vaccines, and those derived from high technology such as those employing a recombinant DNA technology are characterized as biological products. Because of these differences in respect of the product characteristics and manufacturing process, the regulatory oversight of biological products is distinguishable from conventional pharmaceutical products based on small molecules. This chapter addresses legal framework governing biological products principally in the United States and in the European Union. The regulatory landscape in Japan is briefly described particularly in relation to the recent changes to Japan's Pharmaceutical Affairs Law.

1.2 UNITED STATES

The United States has one of the most active and sophisticated systems in the world for ensuring the safety and effectiveness of biopharmaceuticals. To understand this system, it is important to understand (1) how the United States defines biopharmaceuticals and biologics, (2) the legal foundations for regulating these products, and (3) the rules that apply during various stages, including research, development, approval, and marketing. This section also highlights how the United States regulates biologics in relation to drugs.

1.2.1 How the United States Defines Biologics and Biopharmaceuticals

US law does not have a single, simple definition for *biologics* or *biopharmaceuticals*. The Food and Drug Administration (FDA) recognizes that most biologic products “are complex mixtures that are not easily identified or characterized” [1]. Traditionally *biologics* are substances that are derived from living organisms, such as humans, animals, plants, and microorganisms [2]. Today *biologics* include these substances as well as those produced by biotechnology [2]. A federal statute defines *biological product* as a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound) that is “applicable to the prevention, treatment, or cure of a disease or condition of human beings” [3]. The corresponding federal regulation uses similar language, but clarifies several key terms [4]:

1. A *virus* is interpreted to be a product containing the minute living cause of an infectious disease and includes filterable viruses, bacteria, rickettsia, fungi, and protozoa, among other things.
2. A *therapeutic serum* is a product obtained from blood by removing the clot or clot components and the blood cells.

3. A *toxin* is a product containing a soluble substance poisonous to laboratory animals or to human in doses of one milliliter or less (or equivalent in weight) of the product, and having the property, following the injection of nonfatal doses into an animal, of causing to be produced therein another soluble substance that specifically neutralizes the poisonous substance and that is demonstrable in the serum of the animal thus immunized.
4. An *antitoxin* is a product containing the soluble substance in serum or other body fluid of an immunized animal that specifically neutralizes the toxin against which the animal is immune.

The regulation also clarifies how additional products may be biologics if they are “analogous” to certain categories of products listed in the definition. A product is a biologic if it is analogous to the following [5]:

1. A *virus*, if prepared from or with a virus or agent actually or potentially infectious, without regard to the degree of virulence or toxicogenicity of the specific strain used.
2. A *therapeutic serum*, if 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 a serum.
3. A *toxin* or *antitoxin*, if intended, regardless of its source of origin, to be applicable to the prevention, treatment, or cure of diseases or injuries of human through a specific immune process.

Although these definitions seem to be relatively concrete, biological products come in many forms, including drugs, devices, and “combination” products [6]. The FDA regulates biopharmaceuticals as both drugs and biologics because they meet both definitions. US law, as described above, defines *biological products* by referring to several categories of tangible products. In contrast, the law defines *drugs* by their functions [7]. The term *drug* means “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man” and “articles (other than food) intended to affect the structure or any function of the body of man” [8]. Thus the definitions of *drugs* and *biologics* are not mutually exclusive, which allows the FDA to regulate some products as both.

1.2.2 Legal Foundations for Regulating US Biopharmaceuticals

To understand how biopharmaceuticals are regulated in the United States, it is helpful to understand the underlying legal bases for regulation, how these laws have evolved, and how regulatory responsibility for biologics has shifted. Currently the Public Health Service Act authorizes the FDA to ensure the safety, purity, and potency of biologics. The FDA approves biologics for mar-

keting under section 351 of the Act [9]. The FDA also regulates biopharmaceuticals as drugs under the Federal Food, Drug, and Cosmetic Act. Thus the FDA now delegates responsibility for regulating biopharmaceuticals to two centers within the agency: the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). Regulation under the Public Health Service Act precludes the manufacture of generic, or “follow-on” biologics and “biosimilars.”

The foundations for this regulatory system were set in 1902 with the Biologics Control Act, the first legislation to regulate a specific class of drugs [7]. The Biologics Control Act was a response to tragedies in St. Louis, Missouri, and Camden, New Jersey, in which several people died after taking diphtheria and small pox vaccines [10]. The purpose of the Act was to authorize the regulation of certain biologics, require manufacturers to obtain licensing, and authorize the government to inspect manufacturing facilities [7]. The Act prohibited companies from selling or transporting biologics that were either not manufactured at facilities licensed and inspected by the government or not labeled with the manufacturer’s name and an expiration date [7].

Since the 1902 Act, the laws and regulations for biologics have steadily evolved, and responsibility for regulating biological products has shifted several times. In 1903, the federal government issued the first biologics regulations, administered by the Hygienic Laboratory in the Public Health and Marine Hospital Service. The regulations required manufacturers to annually renew their licenses and make their facilities available for unannounced inspections. In 1919, the regulations were amended to require manufacturers to report changes in manufacturing methods, equipment, and personnel. The regulations also required manufacturers to maintain manufacturing records and submit certain product samples for government inspection and approval [7].

These initial laws and regulations laid the foundation for the current biologics regulatory scheme. From the beginning the United States regulated biologics and drugs differently. The government did not regulate nonbiologic drugs until it passed the Pure Food and Drugs Act in 1906, which did not address biologics or the 1902 Biologics Control Act [7]. In fact Congress did not formally recognize the difference between drugs and biologics until after it passed the 1938 Federal Food, Drug, and Cosmetic Act (FDCA) [12]. In 1944, Congress reenacted the 1902 Biologics Control Act and recodified the Public Health Service Act. A major issue was the definitional overlap between drugs and biologics [12].

Between 1902 and 1972, regulatory responsibility for biologics transferred several times, ultimately settling with FDA, as shown by this brief timeline of the relevant transfers:

- 1930 The Hygienic Laboratory within the Public Health and Marine Hospital Service is redesignated as the National Institutes of Health (NIH).

- 1937 The NIH is reorganized, and responsibility for biologics is transferred to the Division of Biologics Control. In 1944 it is renamed the Laboratory of Biologics Control.
- 1948 The Laboratory of Biologics Control is integrated into the NIH's National Microbiological Institute, which later becomes the Institute of Allergy and Infectious Diseases.
- 1955 Responsibility for biologics is transferred to the new Division of Biologics Standards, a new independent entity within the NIH.
- 1972 The Division of Biologics Standards is transferred from the NIH to the FDA, becoming the Bureau of Biologics.
- 1982 The Bureau of Biologics is merged with the Bureau of Drugs to form the National Center for Drugs and Biologics (NCDB).
- 1983 The biologics component of the NCDB is renamed the Office of Biologics Research and Review, within the Center for Drugs and Biologics (CDB).
- 1988 CDB split into two centers, the Center for Biologics Evaluation and Research (CBER), and the Center for Drug Evaluation and Research (CDER).
- 2003 Transfer of therapeutic biological products from CBER to CDER.

The steady stream of reorganizations in many ways reflects the difficulty of both categorizing and regulating biologics. The FDA continues to struggle with these responsibilities. For instance, since the FDA created CBER in 1988, the agency has both overhauled the way it approves biologics, and once again shifted responsibility for certain biologics. First, the FDA established a single approval application, the Biological License Application (BLA) through the Food and Drug Modernization Act of 1997 (FDAMA), the most comprehensive rewrite of food and drug laws since 1938. Second, in 2003, the FDA shifted responsibility for therapeutic biologics from CBER to CDER, given CDER's role in regulating therapeutic drugs. CDER's new responsibilities include a wide array of biological products, including monoclonal antibodies for in vivo use, therapeutic proteins, and immunomodulators [10]. CBER retained authority over traditional biologic products such as vaccines, allergenic extracts, antitoxins, blood, and blood products, as well as products composed of human, bacterial, or animal cells [10].

1.2.3 Legal Requirements for US Biopharmaceuticals

The regulation of biologics continues to evolve. The transcendent growth of biotechnology research, spurred by the Human Genome Project, almost ensures that biologic regulations will require further tinkering to accommodate new products. The following is a brief synopsis of relevant US laws and regulations at various stages, including research, development, approval, and

marketing. Where relevant, we highlight where the rules for biologics differ from drugs.

Research and Development The United States heavily regulates the research and development of biologics. At the preclinical stage, FDA requires companies to comply with regulations on good laboratory practices (GLPs) at 21 CFR part 58. The GLP regulations seek to ensure the quality and integrity of preclinical safety data submitted to the FDA. GLPs apply to nonclinical (preclinical) laboratory studies intended to support research or marketing applications, and address a broad range of topics, including personnel, facilities, and equipment. Ideally preclinical studies to support safety are subject to GLPs and should be supported by a statement that the study was conducted in compliance with the good laboratory practice regulations in 21 CFR part 58, or if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance (21 CFR 312.23 (8) (iii)).

At the clinical stage, FDA sets minimum standards for clinical trials through several regulations and guidance documents, collectively known as good clinical practices (GCPs). GCPs are designed to ensure the quality and integrity of data submitted to FDA and protect the rights of human subjects. GCPs govern key personnel involved in clinical trials—particularly sponsors, and investigators—and address several important areas, including informed consent, institutional review boards (IRBs), and investigational new drug (IND) requirements.

Informed consent is governed by both federal and state law [14]. These laws generally require that before participating in clinical trials, human research subjects state in writing that they understand the risks of the trial and are participating voluntarily. Each informed consent document must contain several elements required by FDA regulations [15].

IRBs are also governed by federal and state law. FDA regulations require IRBs to provide initial and continuing review of clinical trials [16]. IRBs must ensure that investigators and sponsors protect the study subjects, obtain adequate informed consent, and adhere to other safeguards and reporting requirements [16]. Moreover FDA regulations require IRBs members to meet specific membership criteria [17].

Investigational biologics are subject to the FDA's investigational new drug (IND) requirements [18]. The IND application is the first formal submission to FDA, and the application must be submitted before initiating any clinical studies [7]. It is not a request for commercial marketing approval; rather, it is a request to be exempt from the federal statute that prohibits shipping "unapproved" drugs across state lines. Thus an IND permit allows the product to be shipped during investigational studies. The purpose of the IND requirement is to assure the FDA that the safety and rights of subjects will be protected in all phases of the investigation, and that the quality of the studies are adequate to permit the FDA to evaluate the product's safety and effectiveness [13].

Approval The FDA approves biologics for marketing through the biological license application (BLA), which requires the applicant to show that the product is safe, pure, and potent [19]. The BLA submission is typically the culmination of years of research and development, through which the company submits preclinical and clinical data, physiochemical information, biological activity results, and manufacturing information [7]. Previously the FDA approved biologics through two license applications, the product license application (PLA) and the establishment license application (ELA). In 1996, CBER consolidated these applications into a single BLA for certain products, and in 1997, Congress extended the BLA to all biological products.

Although the BLA process differs in some ways from the new drug approval (NDA) application process for nonbiologic drugs, the required showing of safety and efficacy is similar, if not identical, between drugs and biologics [20]. While the FDA requires biologics to be “safe, pure, and potent,” the agency interprets this language as requiring the same type of evidence in NDAs for nonbiologic drugs [20]. Nevertheless, there are differences between the BLA and NDA that reflect CBER’s historical emphasis on manufacturing and process control. For instance, the FDA requires BLA applicants to submit detailed information on manufacturing processes so that the FDA can determine whether the manufacturer can produce a product consistent with current good manufacturing practices (cGMPs) and the manufacturing specifications listed in the BLA. The manufacturer’s facility is also a major factor—its construction, design, layout, validation processes, and environmental monitoring must meet FDA standards.

After approval, biologics manufacturers must comply with the FDA’s cGMP regulations [21]. These regulations govern the manufacturer’s use of raw materials, buildings and facilities, production and process controls, packaging and labeling, laboratory controls, stability testing, expiration dates, production records, and the company’s overall quality system. Although the same cGMP regulations apply to drugs and biologics, manufacturing biologics can be quite different. Physically and chemically, biologics act differently than drugs [11]. They are less defined, less pure, less stable, and degrade in more complex ways than most drugs [11]. Their potency also depends greatly on the underlying organisms from which they are produced [11]. Thus, if a manufacturer makes relatively minor changes to the manufacturing process of a biologic, the FDA may require the manufacture to demonstrate through new clinical studies that the process produces the same results as the original clinical studies [11].

Marketing and Postapproval Requirements Once the FDA approves a biopharmaceutical for marketing, the agency applies a different set of regulatory standards. The main postapproval requirements govern: (1) adverse event reporting, (2) manufacturing under cGMPs, (3) lot release testing, (4) general reporting, and (5) postmarketing studies.

- The FDA's adverse event reporting system does not differ significantly between drugs and biologics. However, the FDA did not have a comprehensive adverse event reporting system for biologics until 1994 [22]. Biologics manufacturers can use two reporting systems: MedWatch and the Vaccine Adverse Event Reporting System (VAERS). MedWatch is administered by the FDA and covers drugs, biologics, medical devices, and special nutritional products. VAERS is jointly administered by the FDA and the Centers for Disease Control and Prevention (CDC), and covers adverse events following immunizations. FDA regulations require manufacturers to report serious, unexpected adverse events within 15 days. Less serious reports can be submitted in periodic follow-up, or distribution reports.
- The FDA's cGMP regulations specify minimum standards for manufacturing facilities and their production controls. These regulations generally apply to both drugs and biologics, but the FDA has additional cGMP-related regulations that focus on biologics [23]. CBER has also tailored cGMP requirements for "specified biotechnology and synthetic biological products" to be as similar to drug requirements as possible.
- The FDA's lot release regulations allow the agency to require manufacturers to submit samples of any licensed biological products for testing [24]. Manufacturers must submit to CBER representative samples of each lot, a lot release protocol, and a summary of the test results. Lots may not be released until CBER authorizes an "official release." However, CBER does not require lot release in all circumstances.
- The FDA requires manufacturers to report certain changes in the product, production process, quality controls, equipment, facilities, personnel, or labeling that are established in the approved license application [25]. The manufacturer must demonstrate that the change does not adversely affect the identity, strength, quality, purity, or potency of the product that may affect the product's safety or effectiveness. FDA regulations and guidance categorize each change as "minor," "moderate," or "major" based on the risk to the product's quality, safety, and effectiveness. The FDA must give prior approval before the manufacturer can implement "major" changes. "Moderate" changes must be reported to the FDA within 30 days. Minor changes must be reported annually.
- The FDA may require, at the time of product approval, that the manufacture agree to conduct additional testing on its biological product, called phase 4 studies. These postmarketing studies may further evaluate the product's safety, efficacy, or manufacturing methods. Sponsors that agreed to conduct phase 4 studies as part of their BLA approval must update the FDA annually.

1.3 EUROPEAN UNION

1.3.1 How EU Law Defines a Biological Medicinal Product

In the European Union the regulation of biological products is subject to continuing review taking account of the evolving science and technology. Directive 87/22/EEC (now repealed) provided the first time in EU law the legal definition of a medicinal product developed by a biotechnological process. The following processes were considered as biotechnological: recombinant DNA technology, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells, hybridoma, and monoclonal antibody methods. This definition remains unchanged since 1987, and it is now used for defining a biotechnological medicinal product as set out in the Annex to Regulation (EC) 726/2004 [26], which repealed Regulation (EC) 2309/93 [27] governing the European centralized procedure.

The definition of a process based on biotechnology is sufficiently broad to capture a wide arrange of medicinal products, such as recombinant proteins and gene-based therapeutics, and prophylactics, such as gene transfer medicinal products and DNA vaccines. Medicinal products manufactured by biotechnological processes as defined in the Annex to Regulation (EC) 726/2004 must be authorized centrally pursuant to article 3 of the Regulation.

In June 2003 the European Commission adopted a new Annex I to Directive 2001/83/EC [28] on the EU code relating to medicinal products for human use. This new Annex was adopted in the form of Commission Directive 2003/63/EC [29]. The new Annex was adopted for implementation of the International Conference on Harmonization (ICH) Common Technical Document (CTD) format. Annex I sets out the particulars and documents accompanying an application for marketing authorization irrespective of the EU procedure used for obtaining a marketing authorization. Directive 2003/63/EC defines a biological medicinal product, and this definition consists of two essential elements. First, the active substance is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source. Any one of the following source is considered as a biological source: microorganisms, organs and tissues of either plant or animal origin, cells or fluids (including blood or plasma) of human or animal origin, and biotechnological cell constructs utilizing cell substrates. If the product is produced from primary cells such as certain prophylactic vaccines, the product is considered a biological medicinal product. Second, the product requires for its characterization and the determination of its quality a combination of physicochemical-biological testing together with the production process and its control.

The Commission has indicated that the following are considered as biological medicinal products: immunological medicinal products and medicinal

products derived from human blood and human plasma. EU law defines an immunological medicinal product as any medicinal product consisting of vaccines, toxins, serums, or allergen products. Vaccines, toxins, and serums cover, in particular, agents used to produce active or passive immunity, and to diagnose the state of immunity. An allergen product means any medicinal product that is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent.

Medicinal products derived from human blood or human plasma means those based on blood constituents that are prepared industrially by public or private establishments, such as albumin, coagulation factors, and immunoglobulins of human origin. This definition reflects the way plasma derived medicinal products are manufactured in the European Union. This class of products may be produced by privately owned industry or by public organizations that are owned by the member state.

1.3.2 Legal Foundation for Regulation of Biological Medicinal Product

The regulatory framework governing biological medicinal products is based on the European Community Treaty, which aims at the free movement of goods within the European Union. Although the legal base is built on the principle of free trade of medicinal products within the European Union, the essential aim of any rules governing the production, distribution, and use of medicinal products must be firmly based on protection of public health. Recital 3 of Directive 2001/83/EC notes that the objective of public health protection must be attained by means that do not hinder the development of the pharmaceutical industry or trade in medicinal products within the European Union.

The EU regulatory system is based on cooperation among the competent authorities of the member states (including the member states of the European Economic Area, e.g., Norway, Liechtenstein, and Iceland) and various relevant European institutions such as the European Commission and the European Medicines Agency (formerly called the European Agency for the Evaluation of Medicinal Products). The European Medicines Agency (EMA) was formally established in 1995 by virtue of Regulation (EC) 2309/93, which is now replaced by Regulation (EC) 726/2004. The EMA's role is narrowly defined in the Regulation as a body responsible for coordinating the existing scientific resources put at its disposal by member states for the evaluation, supervision, and pharmacovigilance of medicinal products. In practice, the scientific work is carried out by the member states through the EMA's advisory committees and working parties.

The Committee for Medicinal Products for Human Use (CHMP) is one of the main committees responsible for preparing the opinion of the EMA on any question relating to the assessment of medicinal products for human use. Pursuant to Regulation (EC) 141/2000 [30] the Committee for Orphan Medici-

nal Products (COMP) was established to provide scientific opinion on whether a medicinal product meets the criteria under EU law for it to be designated as an orphan medicinal product.

The sector-specific rules governing medicinal products are set out in various legal instruments and administrative guidance which follow the following hierarchy [31].

- A Regulation is directly applicable and binding in its entirety on in all member states. Therefore it does not require a period of transposition into the domestic laws of the member states.
- A Directive is directly effective that requires it to be transposed into domestic laws in order to give effect to the Directive. Under EU law, member states are only required to implement the Directive with respect to its objectives and EU law does not control the manner and form of how a Directive is transposed into the national laws.
- A Decision is binding in its entirety upon persons to whom it is addressed.
- Opinion is not legally binding.

In addition the Commission has issued a number of technical and administrative guidelines such as those set out in various volumes of the Notice to Applicants in order to explain how EU law can workably put into practice. The EMEA has developed a body of scientific guidelines regarding the technical requirements for addressing issues relating to safety, quality and efficacy. Although guidelines are not legally binding, the European Courts have increasingly relied on such documents as an aid in interpretation of the legal requirements.

Research and Development Clinical development in the European Union is regulated by Directive 2001/20/EC [32], which is commonly known as the Clinical Trials Directive. This Directive regulates all stages of clinical development in the European Union, including Phase I clinical studies involving healthy volunteers. The competent authorities of the member states are responsible for assessing the applications for clinical trial authorization. In assessing whether an approval should be granted, the competent authorities are required to ensure that conduct of the clinical trials comply with the principles of good clinical practice and the relevant ethical principles. Reference is made to the principles set out in the ICH E6 Guideline on Clinical Practice and the applicable version of the Declaration of Helsinki. Under the Clinical Trials Directive, competent authorities are required to make a determination of an application for clinical trial authorisation within 60 days from the date of submission. However, the Directive permits the member states to extend the statutory time limit for certain investigational medicinal products such as gene therapy, xenotransplantation, and products that are derived from biological source.

Compliance with the requirements of Directive 2001/20/EC is important. This is because Annex I to Directive 2001/83/EC (as amended) expressly requires that for the purpose of obtaining a marketing authorization, all clinical trials conducted within the European Union to comply with Directive 2001/20/EC. For clinical trials conducted outside the European Union and the data of which are used in support of an application for a marketing authorization, such clinical trials must be designed, implemented, and reported on the basis of principles that are equivalent to the provisions of Directive 2001/20/EC and carried out in accordance with the ethical principles that are reflected in the Declaration of Helsinki.

EU law expressly requires nonclinical (pharmacotoxicological) studies to be carried out in conformity with the provisions related to good laboratory practice set out in Directive 2004/10/EC [33] and Directive 2004/9/EC [34] on the inspection and verification of laboratory practice.

Approval Approval process for biological medicinal products is the same as other chemically synthesized small molecules. The legal test is firmly based upon an assessment of risk–benefit balance. However, in assessing risk–benefit balance of a biological medicinal product, EU law requires the applicant to provide certain additional information. If the medicinal product contains a new biological active substance, the applicant must comply with the requirements set out in article 8(3) of Directive 2001/83/EC by providing results of the pharmaceutical and nonclinical testing, and clinical trials.

Given the safety and efficacy of a biological medicinal product is determined largely by the starting material used and the process, EU law requires applicants to describe and document the origin and history of starting materials. Starting materials mean any substance of biological origin such as micro-organism, organs, and tissues of either plant or animal origin; cells or fluids of human or animal origin; and biotechnological cell constructs, including the cell substrates whether or not they are recombinant. Moreover, for medicinal products that are manufactured based on a cell bank system, the cell characteristics must be shown to have remained unchanged at the passage level used for the production and beyond. It is also a requirement to test all materials used in the process for adventitious agents, including animal spongiform encephalopathy agents. If the presence of potentially pathogenic adventitious agents is inevitable, the corresponding material must only be used when further processing is demonstrated to be capable of eliminating and/or inactivating such adventitious agents. The capability of the process must be validated. In comparison with chemically synthesized products, greater emphasis is placed on the in-process controls to ensure batch to batch consistency.

With respect to preclinical testing, EU law expressly states the testing program must be adapted for individual products. It is for the applicant for a marketing authorization to justify the testing program to elucidate the pre-clinical safety and biological activity of the product. EU law states that in establishing the testing program, the following must be taken into account:

- All tests requiring repeated administration of the product must be designed to take account of the possible induction of, and interference by antibodies.
- Examination of reproductive function, of embryo-fetal and perinatal toxicity of mutagenic potential and of carcinogenic potential must be considered. However, constituents other than the active substance(s) are incriminated, validation of their removal may replace the study.
- The toxicology and pharmacokinetics of an excipient used for the first time in the pharmaceutical field must be investigated.
- Where there is a possibility of significant degradation during storage of the medicinal product, the toxicology of degradation products must be considered.

In general, according to EU law, applicants are expected to carry out controlled clinical trials, randomized and as appropriate against a placebo and an established medicinal product (an active comparator) of proved therapeutic value. However, applicants may justify use of other trial design. The treatment of the control groups will vary from case to case and also will depend on ethical consideration and therapeutic area. In some cases it may be more justified to compare the efficacy of a new medicinal product with that of an established medicinal product of proved therapeutic value rather than with a placebo.

In the new European pharmaceutical legislation, a new regulatory path has been created for approval of a similar biological medicinal product, which is commonly known as a biosimilar medicinal product. The definition of a similar biological medicinal product as set out in article 10(4) of Directive 2001/83 (as amended by Directive 2004/27/EC) [35] to mean a biological medicinal product that is similar to a reference product does not mean the conditions in the definition of generic medicinal products owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product. In such cases the results of appropriate nonclinical tests and/or clinical trials relating to these conditions must be provided. The EMEA has developed has now developed a series of technical guidelines to address the type and quantity of supplementary data to be provided [36].

Marketing and Postapproval Requirements Regardless of whether a medicinal product is considered a conventional pharmaceutical product or a biological product, after grant of an approval, the holder of the marketing authorization is required to monitor the continuing risk–benefit balance of the product. In relation to the method of manufacture, in addition to ensuring compliance with good manufacturing practice in accordance with Directive 2003/94/EC [37] the authorization holder must take account of scientific and technical progress and introduce any changes that may be required to enable

the product to be manufactured and controlled by means of generally accepted scientific methods. Immunological products such as vaccines and products derived from human blood or plasma may be subject to official batch release testing at the request of a competent authority.

In the new pharmaceutical legislation, greater emphasis is placed on pharmacovigilance and risk management. Indeed, at pre-approval, applicants are required to submit to the competent authority a detailed description of the pharmacovigilance and of the risk management system that the applicant will introduce. In general, it is a requirement for the marketing authorization holder to record all suspected serious adverse reactions and to report them promptly to the competent authority within a defined time frame as set out in EU law. For new products, the marketing authorization holder is required to provide periodic, updated safety report at least every six months during the first two years following the initial placing on the market and once a year for the following two years. Thereafter the reports must be submitted at three yearly intervals or immediately on request by the competent authority. The Commission has developed a guidance document published in volume 9 of the Rules governing medicinal products in the European Union, which is currently being revised. This guidance takes account of various guidelines promulgated under the International Conference on Harmonization.

In order to establish and maintain a pharmacovigilance system, the holder of the marketing authorization is required to have permanently and continuously at his or her disposal an appropriately qualified person. This qualified person is personally responsible for ensuring that information about all adverse reactions that are reported to the personnel of the company and to medical representatives is collected and collated. This qualified person is also responsible for ensuring that all suspected serious adverse reactions are reported to the competent authority concerned.

1.4 JAPAN

On 25 July 2002, the Japanese House of Representatives passed the revised Pharmaceutical Affairs Law (PAL), which dates back to 1943. Although amendments have been made in the 1940s, 1960s, and 1970s, certain parts of the legislation required updating to take account of changes in science and technology, and the need for the liberalization of the Japanese market. Companies can now outsource the manufacturing process, allowing pharmaceutical companies to market their products in Japan without operating their own production facilities. Changes made to the PAL have also fueled growth in the clinical trial sector in Japan. Notwithstanding the revision of the PAL, the basic purpose of the law remains intact in that it is designed to protect public health by ensuring the safety, quality, and efficacy of medical products in Japan.

The revised PAL of 2002 aims at addressing the following challenges:

- The need to strengthen the safety measures related to medical devices
- The need to strengthen regulatory control over products based on biotechnology and genomic technology
- The need to strengthen the postmarketing safety monitoring and take account of the efforts in international harmonization for the technical assessment of pharmaceutical products

A new regulatory agency, the Pharmaceuticals and Medical Devices Agency (PMDA), has been created with the executive function of overseeing regulation of pharmaceutical products and medical devices. Similar to the system adopted by the United States and the European Union, the regulatory control of medicinal products in Japan is through a system of approval/licensing for certain regulated activities such as conduct of clinical trials, manufacture, marketing, distribution, sale, and supply of specific pharmaceutical products. The Japanese Pharmacopoeia is an integral part of the regulatory framework as it sets out the quality standards for certain pharmaceutical products or substances.

Japan is a party to the tripartite ICH process. Therefore all the adopted guidelines have been implemented as the basic technical standards for the evaluation of safety, quality, and efficacy for pharmaceutical and biotechnological products. In addition the requirements for good laboratory practices for conducting nonclinical safety testing of pharmaceutical products have been applied since the 1980s in the form of administrative instruction. The requirements for conducting clinical trials in accordance with good clinical practice have been implemented since 1990. Such standards have now been enforced through various ministerial ordinances.

The PAL sets out the broad legislative framework for regulating medical products. However, the Ministry for Health, Labor, and Welfare (MHLW) has the authority to issue ordinances and notifications setting out the details for regulating certain product types, such as pharmaceutical products, medical devices, in vitro diagnostic reagents, cosmetic and quasi-drugs. For example, Ministerial Ordinance No. 136, 2004 sets out standards for quality assurance for drugs, quasi-drugs, cosmetics, and medical devices. This Ordinance seemingly applies to drugs based on cells or tissues. The basic structure of this ordinance reflects the principles of good manufacturing practice where a focus is placed on the quality management system, quality control, personnel, training, documentation, and self-inspection.

Given that global trade and international harmonization are key to the development of a sustainable life sciences industry, closer international cooperation is key to tackling technical barriers to trade in medicines. In addition to the ICH process, increasingly regulatory authorities have entered into agreements to enable them to exchange confidential information about approval and safety of medicines.

In February 2007 the European Commission and the EMEA signed a confidentiality agreement with the MHLW and PMDA to enable both parties to

exchange confidential information relating to all legislation and guidance documents, postapproval pharmacovigilance, scientific advice, orphan designation, good clinical practices inspections, and so forth [39]. The US FDA has established a similar confidentiality arrangement with the European Commission and the EMEA.

1.5 CONCLUSION

This chapter introduces the legal and regulatory aspects pertaining to biological products in the United States and in the European Union. The regulatory laws in these two jurisdictions distinguish between conventional pharmaceutical products based on small molecules and biological products. While the legal test for regulatory approval is firmly based on an assessment of risk–benefit balance, the approach to such an assessment is distinctly different with respect to biological products. This is exemplified by the publication of a recent scientific review commissioned by the health ministers following serious adverse reactions that occurred in a first-in-human clinical trial involving a monoclonal antibody TGN 1412 at Northwick Park Hospital in London (March 2006). Six healthy volunteers experienced severe systemic adverse reactions after administration with the biological product. The adverse reactions were characterized as associated with cytokine release. The report emphasizes the importance of performing appropriately conducted preclinical studies in identifying the safe starting dose in humans. The report appears to accept that the conventional approach based upon NOAEL (no observed adverse effect level), a concept that is generally applicable to chemically synthesized small molecules, may not be appropriate. Instead, the principle based on minimal anticipated biological effect level (MABEL) is a good model for defining the safe starting dose, taking account of the novelty of the agent, its biological potency, its mechanism of action, the degree of species-specificity of the agent, the dose–response curves *in vitro* and *in vivo*. This concept is also articulated in the FDA guidance in consideration of lowering the starting dose based on a variety of factors that include the pharmacologically active dose (PAD) [38].

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