International Journal of Chemistry and Pharmaceutical Sciences
ISSN: 2321-3132 | CODEN (USA): IJCPNH
Available online at:http://www.pharmaresearchlibrary.com/ijcps

Regulations and Management of Biological Products

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ABSTRACT

The regulation of the biological and biotechnological products constitutes a significant challenge, since they are part of a sector of the pharmaceutical industry that is currently experiencing rapid growth. Unlike conventional medicines, the manufacture of these products involves the use of living organisms and processes that impede manufacturing consistency. Even though there are numerous international reference documents related to biotechnological product regulation, there is no consensus by official entities that are considered reference institutions, with regard to the most important definitions used and the mechanisms for product regulation. The Pan-American Health Organization (PAHO), through the Technology, Health Care and Research Area, has developed a series of activities that are described in this document. The objective of this publication is to present the current picture of biotechnological and biological product regulation in the Latin American and Caribbean Region, in order to offer guidance that will facilitate the regulation of these products in a harmonized manner among the countries of the Member States, as well as responding to the request from some regulatory agencies to address the growing demand for licensing applications of these products.

Keywords: Biotechnological products, Regulation, Biosimilars, Biotech products, Biological products

ARTICLE HISTORY: Received 20 January 2020, **Accepted** 29 March 2020, **Available Online** 27April 2020

Citation: B. Abhirami, *et al.* Regulations and Management of Biological Products. .*International Journal of Chemistry and Pharmaceutical Sciences,* 8(4), 2020: 79-85.

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JOURNAL QR-CODE

1. Introduction

Biological products, as defined by the World Health Organization (WHO) [1], are medicines obtained from microorganisms, blood or other living tissues whose manufacturing procedures may include one or more of the following elements: growth of microorganism, strains in different types of substrate, use of eukaryotic cells, biological substances extracted from tissues, including human, animal and plant tissues, and also products obtained

by recombinant DNA or hybridoma technology, and the propagation of microorganisms in embryos or animals, among others In its most recent definitions, the WHO includes the following medicines as biological products: vaccines, allergens, antigens, hormones, cytokines, enzymes, derivatives of human blood and plasma, immunological sera, monoclonal immunoglobulin antibodies, fermentation products (including products made by recombinant DNA technology) and reagents employed for in vitro diagnosis.

Biological and biotechnological product regulation in Latin American and Caribbean countries:

The Pan-American Health Organization (PAHO), with the aim of giving technical support to the National Regulatory Authorities (NRAs) of the Member States, in view of the urgent necessity to rationalize and to harmonize biotechnological and biological product regulation, has begun to develop a series of activities with the countries of the Region, including the meeting on the Biological and Biotechnological Regulation Challenges, held in Montevideo, Uruguay, in November of 2007. This meeting focused especially on the regulation and similarity conditions of these products. At the same time the update on regulation at world-wide level of ‘‘biosimilar’’ products was presented.

Simultaneously and as part of the activities established by the PAHO, the following challenges were established:

- ✓ Evaluating the needs and/or strengths of NRAs of the Region in the matter of biotechnological and biological product regulation in general, including ‘‘biosimilars’’ and therapeutic biological medicines.
- ✓ Identifying the existing regulatory differences among the Latin America and Caribbean countries for the above products.
- ✓ Providing technical support to the NRAs in required areas, as well as to motivate harmonization in the regulation of biological and biotechnological products in the Region of the Americas.

The PAHO, through the Essential Medicines and Vaccines Project, part of the Technology, Health Care and Research Area, has developed a survey to evaluate the needs of NRAs of Latin America and the Caribbean Region in biological and biotechnological product regulation, which was sent to a total of 27 countries: Republic of Argentina, Bahamas, Barbados, Belize, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Ecuador, El Salvador, Guatemala, Guyana, Haiti, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, Dominican Republic, Surinam, Trinidad and Tobago, Uruguay, and Bolivarian Republic of Venezuela.

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.

General United States Regulatory Scheme

In the United States, “biological products” are subject to a different premarket path way and differing ntellectual property rotectionsthanproductsregulatedonly 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 non-biologic 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. Regulators attempted to fill this gap by promulgating regulatory definitions of virus, therapeutic serum, toxin, antitoxin, and analogous product. For example, the 1947 regulations, which are essentially similar to the current regulations, defined products “analogous” to a toxin or antitoxin as those intended for preventing, treating, or curing diseases or injuries “through specific immunization.”The 1947 definition of products analogous to therapeutic serums excluded hormones.

Nonclinical Studies for Biologics:

Similar to other drugs, biologics must undergo laboratory and animal testing to define their pharmacologic and toxicological 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. Nevertheless, biologics present special issues, necessitating a “flexible, case-by-case, science-based approach” to preclinical testing. 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 approach needed to selection of animal species and immunogenicity testing as overarching considerations and outlines typical preclinical testing. Also, in May 2012, the FDA adopted the addendum to that ICH guidance. 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.

2. Clinical Studies for Biologics

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. An IND generally goes into effect 30 days after the FDA receives it. 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. The IND must contain "adequate" information from preclinical studies, on which the sponsor bases its conclusion that clinical trials are reasonably safe. 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. 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. The IND also must contain chemistry, manufacturing, and controls information sufficient to allow evaluation of safety. 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. 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.

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. In the mid 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. The FDA has adopted this guidance. The agency recommends that sponsors use it when generating data for submission to the agency and has stated that it will deem studies complying with ICH GCP as meeting the FDA's GCP standards. 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). 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.

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). 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.

The Biologics License Application:

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. Although this regulation is far less prescriptive than its counterpart in the NDA regulations, 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. 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]." Food and Drug Administration Review The Prescription Drug User Fee Act (PDUFA), which applies to most innovative biologics, and the FDA's good review management principles and practices (GRMPs) govern agency review of BLAs. 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. PDUFA sunsets every 5 years and was reauthorized for the fifth time in July 2012 (PDUFA V).

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 made, processed, packed, or held comply with good manufacturing practice (GMP).

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." In determining whether this standard is met, the FDA must consider the risks of the product against its benefits. Proof of safety comprises "adequate tests by methods reasonably applicable," including reports of "significant human experience" with the product. "Purity" means that the finished product is "relatively free" from "extraneous matter," including moisture and pyrogens."Potency" means the product's

"specific ability or capacity to effect a given result" based on laboratory testing or controlled clinical data. Thus, the FDA has interpreted "potency" to include effectiveness. 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. 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." For example, serologic response evaluations may be sufficient when the correlation between the marker and clinical effectiveness has been established.

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."A "biological substance," 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." Annex II to the EU GMP guidelines notes that biologics "can be defined . . . largely by reference to their method of manufacture." 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" or hybridoma and mAb methods; and advanced therapy medicinal products.

Nonclinical Studies:

Similar to the FDA, the CHMP has adopted ICH S6 as a guideline governing preclinical testing of biologics. 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.

General Principles

Although the addendum does not alter the scope of the ICH S6, it prevails whenever there are differences between the two. The addendum covers the following five topics: species selection, study design, immunogenicity, reproductive and developmental toxicity, and carcinogenicity.

Species Selection:

The addendum discusses the factors that sponsors should consider in selecting relevant species for nonclinical testing. 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.

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." 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.

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).

Carcinogenicity:

As noted, carcinogenicity assessments of biologics are not always warranted, but the addendum provides advice for use in situations when they are appropriate. 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. In some cases, this review will be sufficient to address the carcinogenic potential.

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 submitted. The Clinical Trials Directive sets forth the general requirements for clinical trials of medicinal products, including biologics. 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.

Clinical Trial Authorization:

The Clinical Trials Directive and European Commission guidance 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.

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 Practice and the ICH E6 guideline, which the CHMP has adopted. 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. 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.

Consultation with the European Medicines Agency:

A sponsor may obtain, from the EMA, scientific advice regarding clinical trial protocols.

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. The agency's remarks will only address scientific issues 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. Advice also might address a sponsor's proposal to deviate from a CHMP guideline. If the applicant decides not to follow the EMA's advice, it should justify this decision in its MAA. EMA guidance details the procedures for requesting scientific advice. 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.

The Marketing Authorization Application:

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). 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."

3. Regulatory Strategies for Worldwide Marketing of Biological Products

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

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. The FDA generally must be able to conduct an onsite inspection of the data, if necessary. The sponsor also must have conducted the study using GCP, as defined in 21 C.F.R. § 312.120. 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. Complying with ICH E6, the GCP guidance, is one way but not the only way to meet this requirement.

Preventive Vaccine Development: Special Considerations

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. As another example, data regarding concomitant use of other vaccinations are important to licensure.

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. 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). The protocol should include a toxicity grading scale for these events. The stopping criteria generally must be more conservative than in therapeutic settings because vaccine trials enroll healthy individuals. When the 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. 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.

Phase 2 studies should enroll individuals "at clear risk" for the disease. 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.

Phase 2 studies also should evaluate the immune response to the vaccine upon administration with likely concomitant vaccines. 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. 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. 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).
Phase 3 studies should be controlled, randomized, and double blinded. In formulating sample size calculations, sponsors should consider that multiple immunizations might be needed to achieve maximum efficacy. 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. The FDA typically requires long-term follow-up, which might take the form of a post market commitment, to assess the duration of immunogenicity and efficacy, long-term safety, and the need for different doses. "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.
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. The 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).

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 previous Section, animal study endpoints that are "clearly related" to the desired benefit in humans, such as survival or prevention of major morbidity.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. Second, as noted earlier, the FDA will accept a serologic endpoint "where a previously accepted correlation between [this endpoint] and clinical effectiveness already exists" (e.g., based on prior successful clinical studies using clinical endpoints or population- based studies of immunized individuals). 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. 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.

Pharmaceutical quality system and quality risk management

Biological products, like any pharmaceutical product, should be manufactured in accordance with the requirements of a pharmaceutical quality system (PQS) based on a life-cycle approach as defined in WHO good manufacturing practices for pharmaceutical products: main principles (2). This approach facilitates innovation and continual improvement, and also strengthens the link between pharmaceutical development and manufacturing activities.

QRM principles should be used to develop the control strategy across all manufacturing and control stages – including materials sourcing and storage, personnel and materials flow, manufacture and packaging, quality control, quality assurance, storage and distribution activities, as described in relevant WHO guidelines (14) and other documents (22). Due to the inherent variability of biological processes and starting materials, ongoing trend analysis and periodic review are particularly important elements of PQS. Thus, special attention should be paid to starting material controls, change control, trend analysis and deviation management in order to ensure production consistency. Monitoring systems should be designed so as to provide early detection of any unwanted or unanticipated factors that may affect the quality, safety and efficacy of the product. The effectiveness of the control strategy in monitoring, reducing and managing such risks should be regularly reviewed and the systems updated as required taking into account scientific and technical progress.

Quality control

As part of quality control sampling and testing procedures for biological materials and products, special consideration should be given to the nature of the materials being sampled (for example, the need to avoid contamination, ensure biocontainment and/or cold chain requirements) in order to ensure that the testing carried out is representative.Samples for post-release use typically fall into one of two categories – reference samples or retention samples – for the purposes of analytical testing and identification respectively. For finished products the reference and retention samples will in many instances be presented identically as fully packaged units. In such circumstances, reference and retention samples may be regarded as interchangeable.

4. Conclusion

The regulation of biological/biotechnological products is facing new challenges in comparison with conventional pharmaceutical products. Strong pressure from pharmaceutical companies who recently have incorporated these products into their portfolios, looking for innovation and favorable economic consequences, is making regulators seek for easier and not always adequate pathways to face the new challenges. Main regulatory agencies are aware that they are not prepared to regulate properly these products which are invading markets all around the world with a major impact and consequences which could affect negatively mainly developing countries. With the intention

to give the first steps for supporting countries in the Pan American Region, the PAHO has conducted a survey to make a review of the current situation for the regulation of these products. This overview indicates that there are preliminary regulatory activities in the Region which can be used as a platform for the establishment of harmonized documents, harmonized procedures and guidelines relating to this subject, which will support the improvement of existing regulatory mechanisms and facilitate the information exchange among the regulators of the Americas. Despite the existing strengths in some countries of the Region regarding regulatory matters, there are also shortcomings, some of which are related to a lack of definitions for each type of product, and/or specific training, not allowing the establishment of harmonized procedures, and also enabling evaluators at the regulatory level to face the specific challenges of biotechnological and biological product regulation.

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