

**Diversity of regulatory requirements for the approval of biosimilars in the
LATAM region: Comparison of the WHO guidance with the available
guidelines/regulations in Brazil, Chile and Colombia**

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Abbreviations

Abbreviation	Explanation
ANAMED	Agencia Nacional de Medicamentos
ANMAT	Administración Nacional de Medicamentos, Alimentos y Tecnología Médica
ANVISA	Agência Nacional de Vigilância Sanitária
API	active pharmaceutical ingredient
AUC	Area under blood-concentration curve
BP	Biological product
CBP	Comparer biological product
CP 49/10	Public Consultation 49/2010
cf.	conferre / compare
DAB	Deutsches Arzneibuch
DNA	Desoxyribonukleinsäure
E.coli	Escherichia coli
e.g.	exempli gratia / for example
EMA	European Medicines Agency
HPLS	Hydroperoxid lyase
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
i.e.	id est / that is
incl.	inclusive
INVIMA	Instituto Nacional de Vigilancia de Medicamentos y Alimentos
LATAM	Latin America
MINSAL	Ministerio de Salud
NRA	National Regulatory Authorities
GMP	Good Manufacturing Practice
OECD	Organization for Economic Cooperation and Development
OMS	WHO Pharmacopeia
PAHO	Pan American Health Organisation
PBR	Producto Biotecnológico de Referencia
PBS	Producto Biotecnológico Biosimilar
PD	Pharmacodynamic
Ph. Eur.	Pharmacopoea Europaea
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/Pharmacodynamic
RBP	Reference Biotherapeutic Product
SBP	Similar Biotherapeutic Product
U.S.A.	United States of America
USP	U.S. Pharmacopeial Convention
WHO	World Health Organization

1 Introduction and Background

During the past decades the marketing and use of biotechnological products has grown enormously, as these products provide revolutionary options for the treatment of many diseases such as diabetes, inflammatory diseases and cancer ([1]; [2]; [3]). However, biotechnology-derived medicines are extremely expensive - because of their cost-intensive development and production - and are thus accessible for only a limited number of patients ([4]; [5]; [6]). Due to the fact that the patents of many of these biological medicinal products have recently expired or will expire in the near future, the world health market has been opening itself for the development of “biosimilars” – as a cost-saving measure ([1]; [3]; [7]; [8]; [9]; [10]; [11]; [12]; [13]; [14]).

Biopharmaceuticals are medicinal products, including “proteins, antibodies, hormones, vaccines, blood products, gene therapies, etc.”, produced by biotechnological processes ([10] in [1]: page 1334). A biosimilar is a copy version of an approved biological medicinal product, demonstrated to be similar in terms of quality, efficacy and safety based on comprehensive comparability studies. Thus, a biosimilar is expected to have the same therapeutic effect as the innovator product and is therefore accepted as an appropriate substitute medication ([1]; [3]; [15]; [16]). However, unlike small molecule generic drugs, a biosimilar is not identical to its reference product: it is a large molecule with a highly ordered complex structure that is strongly influenced by its manufacturing process. This process may differ slightly from that of the originator product, which inevitably results in slight molecular differences between the two products. These differences may have a significant impact on safety and efficacy of a biosimilar product that may become apparent only after market authorization – in a greater patient population ([1]; [3]; [7] [7] [8]; [17]).

Despite these potential safety, efficacy, or quality concerns, governments have worldwide implemented or are currently implementing specific abbreviated licensing pathways to enable biosimilars to gain market access. In 2005, the first regulatory pathway and guidelines for biosimilars were adopted by the European Union. Subsequently, in 2009, the WHO finalised the “Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)”, which aims to globally harmonise the requirements and to provide guidance to the different national regulatory authorities (NRAs) for the evaluation and licensing of safe, high-quality and efficacious biosimilars. NRAs may adopt the WHO requirements as a whole, or only partially, or as a basis for national regulatory frameworks, considering particular national aspects ([1]; [2]; [8]; [18]; [19]; [20]; [21]; [22]).

In recent years, many Latin American (LATAM) countries have published specific regulations or guidance documents for the approval of biosimilars – in order to serve the growing need of cost-effective medical products in the LATAM region [23]. An overview of biosimilar regulations/guidelines in the LATAM countries is shown in Table 1.

Table 1. Biosimilar regulations/guidelines in Latin America ([24]; [25]; [26]; [19])

Country	Regulatory Authority	Relevant law / guideline	Year of publication
Argentina	Administración Nacional de Medicamentos, Alimentos y Tecnología (ANMAT)	Disposición 3397/2012 for biological products; Disposición 7729/2011 for biosimilar products	2011/ 2012
Bolivia	Ministerio de Salud y Deportes	*regulation / guideline in work*	2016
Brazil	Agência Nacional de Vigilância Sanitária (ANVISA)	RDC 55/2010 Guia para Realização do Exercício de Comparabilidade para Registro de Produtos Biológicos	2010 / 2011
Chile	Agencia Nacional de Medicamentos (ANAMED)	D.S. 3/2010 Norma Técnica No. 170 / 2014	2010 / 2014
Colombia	Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA)	Ministerial Decree 677/1995 Biological Medicine Decree 1782/2014	1995 / 2014
Costa Rica	Ministerio de Salud	Reglamento Técnico RTCR 440:2010	2012
Cuba	Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos (CECMED)	Resolution no. 56/2011	2011
Dominican Republic	La Secretaría de Salud Pública / Cámara de Diputados De La República Dominicana	Proyecto de Ley que Regula el Registro de Medicamentos Biológicos, Biotecnológicos y Biosimilares para uso Humano en la República Dominicana *regulation in work*	2013/2014
Ecuador	LA MINISTRA DE SALUD PÚBLICA	vigilancia de medicamentos biológicos para uso y consumo humano (Acuerdo No. 00003344) Formulario de requisitos que se deben adjuntar para el registro sanitario de medicamentos biológicos extranjeros en general y por homologación *no specific regulation for biosimilars*	2013
Guatemala	Ministerio de Salud Pública y Asistencia Social	Norma Técnica 67-2015 / 2010 Ley 4245 /2011	2010/2011
Guyana		*No biosimilars regulation*	
Honduras		*No biosimilars regulation*	
Jamaica		*No biosimilars regulation*	
Mexico	Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS)	NOM-257 NOM 177	2014
Nicaragua		*No biosimilars regulation*	
Panama	Ministerio de Salud Panama (MINSa)	Decreto Ejecutivo 340/2007;	2007
Paraguay	Ministerio de Salud Pública y Bienestar Social	*no specific regulation for biosimilars* Resolución S.G. 003	2015
Peru	Ministerio de Salud Peru (MINSA)	Decreto 011-2016-SA Decreto 013-2016-SA	2016
Suriname		*No biosimilars regulation*	
Uruguay	El Ministerio de Salud Pública (MSP)	Registro de Medicamentos Biotecnológicos / Decreto N° 38/015 N-PERC-003;	2015
Venezuela	Instituto Nacional de Higiene 'Rafael Rangel' (INHRR)	*review process ongoing / new guideline in work*	2012

According to a study conducted by Pan American Health Organisation (PAHO) in 2013, some of the LATAM countries fully adopt the international WHO standards, other countries consider the WHO standards only partly (approx. 39% of the participating countries), while more than half of the participating LATAM countries do not incorporate the WHO guidelines at all. As a consequence, one of the main challenges regarding the licensing of biosimilars in the LATAM region remain the different regulatory standards regarding quality, safety and efficacy across the LATAM countries ([13]; [25]; [23]; [27]; [28]; [29]; [30]).

The aim of this master thesis is to describe and discuss the diversity of regulatory requirements for the licensure of biosimilars in the LATAM region by comparing the established regulations/guidelines in Brazil, Chile and Colombia with the internationally accepted “WHO standards for biosimilar products”. Therefore, the development of the WHO guideline and the regulations/guidelines in the selected countries (Section 2) as well as the requirements for abbreviated licensing of biosimilar products are described (Section 3). Subsequently, the difference and similarities of the requirements are analysed (Section 4). Finally, the main aspects and findings of this master thesis are summarized in the conclusion of this thesis (Section 5).

The scope of this thesis does not include a detailed description and comparison of country-specific intellectual property rights and pharmacovigilance systems. However, the importance of an effective pharmacovigilance system for tracking adverse events that may be associated with the use of biosimilar products after their approval is considered in the conclusion of this thesis.

2 Regulations and Guidance Documents

2.1 WHO: Guidelines on evaluation of similar biotherapeutic products (SBPs)

During an informal consultation held in April 2007 at the World Health Organization (WHO), the WHO and a variety of international drug regulatory agencies as well as industry associations acknowledged the need for a worldwide-harmonised regulatory framework for the market authorisation of biosimilar products, termed “Similar Biotherapeutic Products” (SBP). The aim of this initiative was to establish a set of globally acceptable principles and regulatory standards for the evaluation and licensing of SBPs. It gave answer to the growing number of SBPs under development or already licensed worldwide, with the prospect of an improved and regulated accreditation and access to safe, high-quality and efficacious SPBs ([20]; [31]; [32]).

In 2010, the Expert Committee on Biological Standardization of the WHO published the “Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)”. Key principle of the WHO guidelines is the licensing of a SBP on basis of proven similarity to a “Reference Biotherapeutic Product” (RBP) licensed on basis of a full dossier, which consists of a complete quality, non-clinical and clinical data package. It has been recognized that the extent of the adoption of these guidelines can vary, implying that national regulatory authorities can add national requirements due to the specific country needs ([20]; [31]; [32]; [33]).

The WHO guidelines form the global framework for health authorities for the adoption of national regulatory principles for the licensure of “well-established and well-characterised biotherapeutic products such as recombinant DNA-derived therapeutic proteins” ([20]: page 54). Vaccines and plasma-derived products and their recombinant analogues are not in the focus of the WHO guidelines.

2.2 Chile: Technical norms for biotechnological pharmaceutical products derived from recombinant DNA techniques

Before 2011, biotechnological products in Chile were licensed either (1) as a new product based on a full (or partially reduced) dossier or (2) as biogenerics to an originator product (termed „Producto Biotecnológico de Referencia“, PBR) ([34], [35]). Biogenerics (or copies of biological products) were referenced to as „any active ingredient that is described within the official pharmacopeia recognized in the country (as established under Art. 42o of D.S. (Supreme Decree) No. 1876/95 of the Chilean Ministry of Health (MINSAL))“ [35]. Otherwise the copies were considered as new biological products. Thus, no specific regulatory pathway existed for biosimilars in Chile for many years ([36]; [37]).

On December 26th 2011, the legal basis for the development of regulations for biosimilar products in Chile was established with D.S. 3/2010 of the MINSAL. According to this decree, biological products are specified as an individual pharmaceutical subject area, including all therapeutic proteins „whose procurement and production involves living organisms, as well as their fluids or tissues (...), (...) such as vaccines, serums, blood products, hormones, recombinant or biotechnological drugs, antibiotics, allergens and gene therapies“ [35]: page 5). Moreover, as recommended under Article 42 letter i) of D.S. 3/2010, a specific biotechnological guideline for the processing and assessment of licensure of „Producto

Biotechnológico Biosimilar“ (PBS) in Chile was introduced by Chile’s Agencia Nacional de Medicamentos (ANAMED) ([34]; [35]).

In August 2014, the final Chilean guideline for the processing and assessment of PBSs (termed „Norma Técnica No. 170“) was adopted by MINSAL. This guideline is based on the international recommendations of the WHO and the national particulars introduced in D.S. 3/2010 with the aim to open the Chilean health market for safe, high-quality and efficacious biosimilar products. It includes the general requirements on quality, safety and efficacy that have to be fulfilled for PBSs in order to obtain market authorisation ([35]; [38]). According to this guideline, the licensing of PBSs is based on a reduced dossier as well as the proven similarity of the PBS to a PBR. Both products shall own “the same active ingredients, unit doses, pharmaceutical form and administration route”, the reference product being licensed with a full dossier in order to evidence quality, safety and efficacy ([35]: page 7).

The technical regulations included in the guideline form the national framework for licensure of PBSs containing active substances fully characterized and developed by means of the use of modern biotechnological procedures, such as the use of recombinant DNA [35]. It thus refers to products that can gain market authorization based on a shortened dossier of clinical and preclinical data; provided, there exists an adequate reference product with a full dossier in order to exercise comparability studies. They are not applicable to vaccines, human plasma-derived products and heparins [35].

2.3 Brazil: Regulation RDC 55/2010 for new biological products and copies of biological products

In 2002, the Brazilian Health Surveillance Agency (Agência Nacional de Vigilância Sanitária, ANVISA) adopted the first regulation RDC 80/2002 referring to biological products in Brazil. This regulation required a full dossier to be submitted by the applicant, i.e. a complete set of quality, non-clinical and clinical data (phase I, II and III studies). Furthermore, it defined exactly the same regulatory pathway for new and copies of biological products. An update of this regulation in 2005 (RDC 315/05) did not alter these regulatory standards and the pathway for new and copies of biological products remained unchanged ([39]; [40]).

However, in 2010 ANVISA specified different regulatory pathways for new biological products and copies of already licensed biological products. This was first drafted in the Public Consultation 49/2010 (CP 49/10) and, later on, adopted in form of the new regulation RDC 55/2010, based on existing international guidelines, such as the WHO Similar Biological Product guidelines. This new regulation aimed to facilitate the registration of safe, high-quality and efficacious biological products and establish the national minimum standards for the market authorization for biological products in Brazil ([36]; [40]; [39]).

The regulation RDC 55/2010 differentiates between “new biological products” and “biological products”. The term “new biological products” refers to biological products containing a *still not registered* molecule with a known biological activity ([41]: Chapter I, Section II, Article 2, Paragraph XX). The term “biological products” includes biological drugs that are either *known* or *not new* containing an *already registered* molecule with a known biological activity. Both types of products should already have passed all relevant steps of the manufacturing process ([41]: Chapter I, Section II, Article 2, Paragraph XV).

For the licensure of new biological products, it is necessary to submit a full dossier, in order to demonstrate its quality, safety and efficacy on basis of a full characterization of the product, an elaborate documentation of production and manufacturing processes as well as the comprehensive proof of clinical safety and efficacy in form of non-clinical and clinical studies (phase I, II, III) ([41]: Section II, Article 25).

Regarding the biological products, marketing authorization can be obtained either through the “route of development by comparability” or the “route of individual development” ([41]: Section II, Article 26). The “route of development by comparability” is based on comparability studies between a biological product (BP) and a reference product (termed comparer biological product, CBP) in terms of quality, safety and efficacy ([41]: Chapter I, Section II, Article 2, Paragraph XVI, XXV). The individual development pathway requires the presentation of full data with regard to the development, production, quality control as well as non-clinical and clinical data in order to evidence the quality, efficacy and safety of the product ([41]: Chapter I, Section II, Article 2, Paragraph XXVI).

In 2011, the Brazilian Health Surveillance Agency adopted a separate guideline especially for the comparability pathway defining regulatory requirements regarding quality criteria of the product. These requirements incorporate established analytical methods, biochemical characterization, physicochemical and immunochemical characteristics, biological effects, and impurities. Furthermore, non-clinical and clinical studies are required, the complexity of these studies being dependent on the individual product class (e.g. level of characterisation for

modern analytical techniques, differences observed on the reference product, and clinical experience with the product class) ([36]: page 95; [42]).

The RDC 55/2010 applies to new biological products and biological products that aim to obtain market authorization [41]. Within the scope of the regulation RDC 55/2010, biological products are: “vaccines, hyperimmune serums and hemoderivates, biomedicines gained from biological fluids or animal origin, biomedicines gained by biotechnological procedures, monoclonal antibodies, biomedicines consisting of living, fermented or dead microorganisms“ ([41]: Chapter I, Section II, Article 4).

The RDC 55/2010 does not refer to antibiotics, and anovulatories (semi-synthetic conjugated oestrogens), probiotics and allergens ([41]: Chapter I, Section II, Article 5).

2.4 Colombia: Decree 1782/2014 establishing the requirements and procedures for pharmaceutical and pharmacological evaluations of biological medicines

In 1995, the Colombian Ministry of Health and Social Protection (*Ministerio de Salud y Protección Social de Colombia*) released the Decree 677 which defines the technical requirements for the assessment of quality, safety and efficacy of all „pharmaceutical preparations produced from natural resources“, including biological drugs ([43]: page 1; [44]; [45]). In September 2014, the new Colombian Biological Medicine Decree 1782 was finalized, introducing the „requirements and procedure for pharmaceutical and pharmacological assessment of biological drugs in the process of health registration“ ([46]: page 1) for INVIMA (*Instituto Nacional de Vigilancia de Medicamentos y Alimentos*). INVIMA is the responsible institute for the scientific evaluation of quality, safety and efficacy of biological products as well as their approval in Colombia [45].

The Decree 1782 implements three specific regulatory pathways for the registration of biological products: a „full dossier pathway“ for new or innovator biotherapeutic products and a „comparability pathway“ as well as a „comparability abbreviated pathway“ for biosimilar products ([37]; [45]; [46]: Title II, Article 5). While the comparability pathway requires a comparison between the biosimilar product (termed biological drug under evaluation) and the reference product (termed „reference biological drug“), for the abbreviated pathway the biosimilar product can be compared to a pharmacopeia standard or a reference standard established by the applicant ([46]: Title II, Article 8/9; [47]).

According to Article 2, the Decree 1782 applies to all “natural or legal entities carrying out manufacturing activities, import and marketing of biologic drugs” as well as “all biological products, whether or not included in pharmacological standards”([16]: Title 1, Article 2). The Decree hereby defines biological products as “drugs derived from living organisms or cells, or their parts (...) obtained from sources such as tissues or cells, components of human or animal blood (such as antitoxins and other antibodies, cytokines, growth factors, hormones and clotting factors), viruses, micro-organisms and products derived from them such as toxins. These products are obtained through methods including, but not limited to, cell cultures of human or animal origin, culture and propagation of microorganisms and viruses, processing from human or animal tissues or biological fluids, transgenesis, techniques of recombinant deoxyribonucleic acid (DNA), and hybridoma techniques. Drugs that result from these last three methods are called biotechnological ” ([46]: Title I, Article 3).

The Decree 1782 of 2014 does not apply to “allergens, masterful medicinal products derived from living organisms or their tissues and products that contain or consist exclusively of cells

and/or non-viable human or animal tissue and do not have an effect mainly pharmacological, immunological or metabolic, as well as the homeopathic preparations obtained from biological fluids, microorganisms and other substances of biological origin” ([46]: Title 1, Article 2).

3 Requirements for abbreviated licensing of biosimilar products according to the WHO guideline and the legislation in the LATAM countries Brazil, Chile and Colombia

3.1 Choice of the reference product

3.1.1 WHO

According to the WHO guidelines, the RBP plays a key role for evaluation of the SBP licensing process. The RBP is used as a basis of comparison to demonstrate similarity between the SBP and the RBP in terms of quality, safety and efficacy. Comprehensive information about the RBP has to be delivered by the individual applicant to the NRA. A high degree of similarity between the two products at the quality level is a prerequisite for a shortened non-clinical and clinical program, thereby facilitating market authorization of the SBP. In general, the NRA may request a nationally licensed reference product to accept the submission of a SBP for marketing authorization. According to the WHO guideline, the choice of a reference product should be based on the following requirements [48]:

- **Originator product based on a full registration dossier**
The licensing of the RBP should be based on a full registration dossier, including comprehensive data on quality, safety, and efficacy. A RBP should therefore be an originator product and *not* a SBP.
- **Appropriate time of market authorisation and volume of market usage**
The RBP should be on the market for an appropriate period of time. The usage of the licensed product should be of a crucial volume in order to provide reasonable data regarding safety and efficacy.
- **Identical dosage form and route of administration, similar drug substance**
The SBP and the RBP should own the identical dosage form and route of administration. Additionally, the drug substance of the RBP and the SBP has to be similar.
- **No substitution of the RBP during the development and comparability process**
In the course of the development process of the SBP (i.e., quality/comparability exercise, non-clinical and clinical studies), the same RBP has to be used and may not be substituted.
- **Proof of similarity based on a head-to-head comparability exercise**
The similarity between the SBP and the RBP in terms of quality, safety and efficacy should be proven by head-to-head comparability studies. A comparison of SBP data to historical data of the originator product should not be included in the comparability exercise.

Some countries do not own an appropriate nationally licensed RBP that serves as a comparator for the SBP. In this case, the applicant may have to refer to a RBP licensed or utilised in other countries and/or regions. Moreover, the selected RBP should assist the application for marketing authorization of the SBP. The NRA needs to develop supplementary criteria, based on the following factors:

- **Clinical use, duration and volume of marketed use of the RBP**
The RBP should be in clinical use for an appropriate period of time. The usage of the

licensed product should be of a crucial volume in order to provide reasonable data regarding safety and efficacy in a given population.

- **Licensed within a well-established regulatory legal framework**
The RBP should be licensed and used within a country that provides a well-established regulatory framework and jurisdiction, as well as profound knowledge of the development and evaluation of biotherapeutic products and post-marketing monitoring activities.
- **No approval of the RBP included**
If the NRA of one country accepts a RBP licensed or utilised in another country as a reasonable comparator of a SBP, this does not automatically include the approval of the RBP for use in this country.

3.1.2 Chile

The Chilean guideline defines the PBR as “the basis for establishing the quality, safety, efficacy and immunogenicity as well as the dose and administration route” for the proposed biosimilar product ([35]: Chapter IV, Section 2). Furthermore, the choice of the PBR is considered to be crucial for the comparability exercise between the PBR and the PBS.

The selection of the PBR should be based on the following requirements [35]:

- **Originator product based on comprehensive studies regarding quality, safety and efficacy**
A PBR has to be an originator product and *not* a registered biosimilar product. The licensing of the PBR should be based on its own comprehensive studies regarding quality, safety, and efficacy for each of the approved indications.
- **National accepted PBR**
The chosen PBR has to be accepted by the national health authority in the field of pharmaceutical products.
- **Similar pharmaceutical form, active ingredient, unit dose, indication(s), concentration and route of administration**
The PBS and the PBR should own the similar „pharmaceutical form, active ingredient, unit dose, indication(s), concentration and route of administration“.
- **No substitution of the PBR during the comparability process**
In the course of the comparability exercise, the same PBR has to be used and should not be substituted to achieve a consistent set of data set and argumentation.

3.1.3 Brazil

The Brazilian national regulatory authority ANVISA requests a nationally licensed reference product as a suitable comparer biological product.

The requirements for the choice of a comparer biological product for biological products registered under the comparability and individual development pathway are described in Article 27 of the Brazilian regulation RDC 55/2010 ([41]: page 6, Article 27, Paragraph 1; page 2, XVI):

- **Comparer biological product with market authorization based on a full registration dossier**
The licensing and market authorization of the comparer product should be based on a

full registration dossier, including comprehensive data on its quality, safety and efficacy.

- **No substitution of the comparer product during the comparability process**
In the course of the comparability exercise the same comparer product should be used and should not be substituted.

If it is evidenced that no appropriate nationally or internationally licensed comparer biological product is commercially available, the choice of the comparer product has to be previously reviewed and approved by ANVISA. In this case, the following factors should be considered ([41]: page 6, Article 27, Paragraph 2/3).

- **Similar technical-scientific framework regarding the licensing process**
The comparer product should be licensed and used within a country that provides comparable scientific and technical criteria to ANVISA's criteria.
- **Accessibility of registration information of the comparer product**
There should be complete and unlimited access regarding the registration information of the comparer biological product for ANVISA.

3.1.4 Colombia

Article 3 of the Colombian Decree 1782 requires a biological drug as reference medicine, which is nationally licensed by INVIMA. The choice of an adequate reference product should fulfill the following requirements ([46]: page 3):

- **Full registration dossier**
The licensing of the reference product should be based on a full registration dossier, containing comprehensive data on quality, safety, and efficacy.
- **Comparability studies**
The reference medicine should be used as a comparator in the comparability exercise.

If there exists no suitable reference medicine product licensed by INVIMA, the applicant may refer to a comparer product licensed or utilised by other health authorities, provided that it comes from the following countries / regions / authorities ([46]: page 4, Article 8):

- „United States of America, Canada, Germany, Switzerland, France, England, Denmark, The Netherlands, Sweden, Japan and Norway“ ([43]: page 7).
- The EMA (European Medicines Agency), ANVISA, ANMAT (Administración Nacional de Medicamentos, Alimentos y Tecnología Médica).
- Countries of high health monitoring, members of the Organization for Economic Cooperation and Development (OECD). “

In this case, the following factor should be considered for the selection of an appropriate comparer product ([46]: page 4, Article 8):

- **Distinct pharmacological assessment regarding quality, safety and efficacy**
The reference product is considered acceptable by the Specialized Branch of INVIMA if the pharmacological assessment delivers unambiguous results and provides evidence of its quality, safety and efficacy.

3.2 Quality data

3.2.1 WHO

Generally, an SBP is derived from a separate and independent master cell bank using manufacturing processes and control independent from the RBP. Therefore, a full quality dossier (CTD module 3) for both drug substance and drug product is always required which must meet the same standards as required by National Regulatory Authorities (NRAs) for originator products.

In addition, to evaluate comparability with the reference product, the manufacturer should perform a comprehensive physicochemical and biological characterization of the SBP in head-to-head comparison with the RBP assessing all aspects of product quality and heterogeneity.

3.2.1.1 Quality Requirements

3.2.1.1.1 Manufacturing Process

The manufacturer of an SBP must demonstrate consistency and robustness of the manufacturing process independent from the RBP using state-of-the-art science and technology to achieve a high-quality product. In this respect the manufacturing process should meet the same standards as required by NRAs for originator products, applying good manufacturing practices (GMP), modern quality control and assurance procedures, in-process controls, and process validation. A complete description of the manufacturing process and development studies conducted to establish and validate the dosage form, formulation and container closure system should be provided according to relevant guidelines (e.g. the ICH guidance documents) [49].

Since the manufacturer developing an SBP usually has no access to confidential details of the RBP manufacturing process, it is expected that the production process of the SBP will differ from the licensed process of the RBP. However, the manufacturing process of the SBP should be designed and optimized to achieve an SBP that is as similar as possible to the RBP. To minimize differences between the SBP and the RBP, the manufacturer of the SBP should collect all available information of the RBP regarding the type of host cell, the formulation and the container closure system used for marketing of the RBP and apply this knowledge to the design of the SBP manufacturing process. It is explicitly stated that the SBP should be expressed and produced in the same type of host cell as the RBP (e.g. *E.coli* or CHO cells) to avoid possible changes in critical quality attributes of the protein and/or introduction of process-related impurities (e.g. host cell proteins, endotoxins etc.) that might potentially impact clinical safety, efficacy and immunogenicity. However, in case a different host cell type is used, the manufacturer of the SBP has to demonstrate that the structure of the molecule or the clinical profile of the product will not be affected by this difference.

3.2.1.1.2 Quality Characterization

Specifications

As required for any biotherapeutic product, specifications for SBPs should be set as described in established guidelines and pharmacopeia monographs, where they exist. However, monographs may only provide a minimum set of requirements for a particular product, therefore additional test parameters and specifications may be needed. For each test

parameter, reference to the applied analytical methods should be provided. Specifications, analytical methods and acceptance limits should be justified. In addition, all analytical methods referenced in the specification should be validated and the corresponding validation should be documented.

Since different manufacturing processes and analytical procedures will usually be established for an SBP when compared to the RBP, it is not expected that the same specifications are applied for both products. Nevertheless, the specifications should include important known product quality attributes for the RBP (e.g. identity, purity, potency etc.). In addition, specifications should be determined and set upon the manufacturer's experience with the SBP as well as the experimental results obtained by comparing the SBP and the RBP. Unless justified, the limits set for a given specification should not be significantly wider than the range of tested variability of the RBP over the shelf life of the product.

Analytical techniques

A battery of state-of-the-art analytical methods should be employed to determine structure, function, purity and heterogeneity of the SBP and the RBP. The applied methods should be capable to separate and analyse product variants based upon different chemical, physical and biological properties. Whereas analytical methods used for batch release of the SBP need to be validated (in accordance with relevant guidelines, if appropriate), the assays used in characterization studies do not need formal validation but should be scientifically sound and qualified to achieve results that are meaningful and reliable. Complete description of the analytical techniques for both release and characterization should be provided in the dossier.

To detect any differences between the RBP and the SBP that may affect clinical activity, the investigation of analytical comparability should be as comprehensive as possible. Limitations of each analytical technique (e.g. limits of sensitivity or resolving power) should be considered when determining the similarity between the SBP and RBP (cf. Section 3.2.1.2).

Stability

Stability studies should be conducted in compliance with relevant guidance recommended by the NRA. The studies should demonstrate which release and characterization methods are stability indicating for the product and should include results from accelerated degradation and different stress testing conditions (e.g. temperature, light, humidity and mechanical agitation).

The stability data should support the recommended storage and shipping conditions as well as the shelf life of drug substance, drug product, and process intermediates. Stability studies on drug substance should be performed with containers and conditions that are representative of the actual storage containers and conditions. Stability studies on drug product should be carried out in the intended drug product container-closure system. Independently from the shelf life of the RBP, real-time/real-temperature stability studies will need to determine the storage conditions and expiry date of the SBP.

Head-to-head accelerated and stress stability studies comparing the SBP and the RBP are considered as an important part of the comparability exercise since they may reveal otherwise hidden properties and establish degradation profiles for both products (cf. Section 3.2.1.2).

3.2.1.2 Comparability Exercise at the Quality Level

3.2.1.2.1 Product Characterization

To evaluate comparability at the quality level, the SBP manufacturer should perform a comprehensive characterization of the SBP in head-to-head comparisons with the RBP.

For the comparability exercise, the SBP and the RBP should be used in its final dosage form (containing drug substance formulated with excipients). It should be demonstrated that the excipients do not interfere with the applied analytical methods. In case only the drug substance but not the finally formulated RBP is suitable for characterization, additional studies are required to prove that all relevant quality attributes of the drug substance are not influenced by the purification process.

Characterization of the RBP and the SBP should also include stability studies under intended, accelerated and stress testing conditions.

Following properties should be assessed in the comparability exercise:

Physicochemical properties

Primary and higher order structure (secondary, tertiary and quaternary) as well as other biophysical properties should be assessed with appropriate analytical methods. Since the SBP and the RBP likely consist of different post-translationally modified forms, efforts should be made to investigate, identify and quantify these variants.

Biological activity

Relevant biological assay(s) with appropriate precision and accuracy should be applied to demonstrate that there are no significant functional differences between the SBP and the RBP. For a product with multiple biological activities, the SBP manufacturer should include a set of relevant functional assays to determine and compare the range of all relevant functional activities of the SBP and the RBP. The biological assay(s) should also complement the physicochemical characterization and confirm the correct higher-order structure of the SBP. If possible, the applied bioassay(s) should reflect the understood mechanism of action of the protein and provide a link to clinical activity. Bioassays used to determine and compare the potency of the SBP and the RBP should (if available) be calibrated against an international or national reference standard. It is recommended that biological activity in potency assays should also be provided and expressed in international units (IU) or units (U) or as specific activity (e.g. units/mg protein).

Immunochemical properties

For SBPs with immunochemical properties (e.g. antibodies or antibody-based products) data should be provided to demonstrate that the SBP is comparable to the RBP in terms of specificity, affinity, binding kinetics, and Fc functional activity, if applicable.

Impurities

Process- and product-related impurities should be identified, quantified and compared between the SBP and the RBP. Due to the fact that different manufacturing processes usually produce both products, some differences in the impurity profile can be expected. However, significant differences should be evaluated with respect to their potential impact on efficacy, safety and immunogenicity. Regarding process-related impurities, the WHO guideline

explicitly states that it is important to establish suitable assays specific to the cell line used to manufacture the SBP.

3.2.1.2.2 Comparability Assessment

Quality comparison showing a high degree of similarity between the SBP and the RBP is a prerequisite for reducing the nonclinical and clinical data package for abbreviated licensing. However, it has been recognized by the WHO that some differences in quality attributes (e.g. regarding impurities or excipients) between the SBP and the RBP may exist. If differences are found, their potential impact on safety and efficacy of the SBP needs to be evaluated and justification for allowing these differences should be provided. In case the comparability exercise reveals differences of unknown clinical relevance, particularly regarding safety, additional non-clinical and/or clinical studies may be required. Differences in quality attributes known to have a potential impact on clinical activity will impact the decision on whether the product is regarded as an SBP. In this context the WHO guideline states that, for example, a product cannot be considered an SBP if the quality comparison shows differences in glycosylation patterns that influence the biodistribution and require a change of the dosing scheme of the product. Other differences between the SBP and the RBP (e.g. lower levels of protein aggregates or heterogeneity in the terminal amino acids of the RBP) are considered acceptable and would not require additional nonclinical and/or clinical evaluation, if it is known that such differences do not affect bioactivity, distribution or immunogenicity of the RBP or similar products in its class.

For evaluation of comparability results, predefined acceptable limits need to be set up before conducting the comparability exercise. The determination of the acceptable limits of quality attributes should take into account i) knowledge of the relationship between quality attributes (e.g. composition, glycosylation profile and bioactivity) and clinical activity of the RBP and related products, ii) the clinical history of the RBP, iii) lot-to-lot differences between commercial lots of the RBP and iv) knowledge of the analytical limitations of techniques (e.g. limits of sensitivity and resolving power) used to characterize the RBP and the SBP.

3.2.2 Chile

In alignment with the requirements for originator products (PBR), the Chilean guideline states that a complete quality dossier is also required for biosimilar products (PBS). In addition, a comparability study comparing the PBS and the PBR must be submitted with the quality dossier ([35]: Chapter III, Section 2).

3.2.2.1 Quality Requirements

3.2.2.1.1 Manufacturing Process

The PBS manufacturer must submit a complete description of the manufacturing process and methods at all critical steps of the process.

The description of the manufacturing process must at least include following information:

- Description of production and packaging/bottling processes, including process controls and reference to the applied analytical methods
- Type of host cell
- Information on expression vectors, cell banks and cell line fermentation

- Detection and control of adventitious agents (if applicable)
- Information on purification and formulation methods
- Storage of bulk and final drug product
- Development studies performed to establish and to validate the dosage form, formulation and the container closure system (integrity to prevent microbial contamination)
- Description and background information on the manufacturing process validation

The manufacturer must show consistency and stability of the manufacturing process. Manufacturing and quality control need to comply with GMP and GLP standards to guarantee validated procedures and processes.

To obtain a high-quality PBS as close as possible to the PBR, state-of-the-art scientific knowledge and technology must be employed for the manufacture of the PBS. It is generally expected that the production process of the PBS will differ to some extent from that developed for the RBP. However, in case the manufacturing process differs substantially it will not be possible to demonstrate comparability and thus the product cannot be considered as “biocomparable” to the RBP. In this context the Chilean guideline explicitly states that for example the same type of host cell must be used for the production of the PBS and the PBR.

3.2.2.1.2 Quality Characterization

Both the drug substance and the final drug product of the PBS must be completely characterized using appropriate analytical techniques. In particular, primary and higher order structures (secondary, tertiary and quaternary), posttranslational modifications, biological activity, purity and impurities (product- and process-related) and (if applicable) immunochemical properties need to be thoroughly investigated.

The information on quality properties to be submitted with the dossier is summarized in the Sections below.

Physicochemical properties

The manufacturer must determine and quantify all relevant physicochemical parameters (e.g. isoform distribution) of the PBS both of the active ingredient and the finished product. For this purpose, state of the art analytical methods need to be employed.

Biological activity

All relevant biological activities of the PBS must be determined preferably using *in-vitro* methods (e.g. cell-based or immunological bioassays). The applied methods must be capable to differentiate between active variants and (biologically inactive) product- or process-related impurities. Whenever possible, the applied bioassays should be calibrated against a working or international reference standard and the results from should be reported in activity units.

Immunochemical properties

In case the PBS has immunochemical properties, the corresponding characterization data (e.g. specificity, affinity, binding kinetics or Fc functional activity) have to be provided in the dossier.

Impurities

Impurities in the PBS need to be determined and quantified with appropriate analytical methods to evaluate the impurity profile for product- and process-related impurities in the final product. The limits of impurities need to be justified and their potential effect on the products efficacy, safety and immunogenicity needs to be assessed.

Specifications

Specifications for PBSs must be defined in accordance with official pharmacopoeia (e.g. USP and Ph. Eur.). It is not expected that a PBS and a PBR will have exactly the same specifications due to differences in the manufacturing processes and analytical procedures. In addition, the methods described in the monographs are not sufficient for complete characterization and represent only the minimal requirements to confirm the quality of a particular product. The applied methods and specifications must control the most relevant quality attributes of the product (e.g. identity, purity, potency, molecular size, hydrophobicity charge, silylation degrees, amount of peptide chains, glycation, impurities such as the host cells proteins and DNA) and must include acceptable limits for each specification. All analytical methods referred to in the specifications must be validated. In case a method is not validated, a justification needs to be provided.

Analytical techniques

State-of-the art techniques must be employed to determine the structure, function, purity and heterogeneity of the PBS. The active ingredient should also be characterized with powerful analytical techniques (e.g. mass spectrometry/HPLS, capillary electrophoresis, sequencing etc.) that allow for a comprehensive analysis of the molecule using orthogonal methods. Different methods may detect different variants, but all in all are complementary and therefore the analytical limitations (e.g. sensitivity limits and resolving power) of each method must be determined.

All analytical methods employed for product release must be validated and the information must be included in the dossier.

Stability

The stability studies for a PBS must be carried out according to the approved regulations and must be performed with the final drug product filled into the container closure system intended for commercial use.

To investigate the stability and stability-indicating parameters of the product, stability studies under long-term, accelerated and temperature stress storage conditions should be performed. The results of stability studies performed under long-term storage conditions must comply with the shelf-life specifications of the product. In addition, the results from the stability studies should reveal whether additional controls are needed during manufacturing, transportation and storage to guarantee integrity of the product until the end of shelf life.

In case the manufacture of the product involves transportation processes (e.g. of bulk product between different packaging sites), stability data and information about the applied materials and controls should be submitted showing that the product is kept under optimal conditions during the transportation.

3.2.2.2 Comparability Exercise at the Quality Level

3.2.2.2.1 Product Characterization

The PBS manufacturer must submit a comparability exercise including a direct comparison of quality attributes of the PBS and the PBR with the quality part of the dossier. In order to obtain consistent results and conclusions, the same PBR shall be used for the complete comparability study ([35]: Chapter IV, Section 2.1).

The same biotechnological product of reference shall be used for the whole comparability study, in order to obtain consistent data and conclusions.

Physicochemical properties, biological activity, immunochemical properties (if applies) and **impurities** shall be characterized and compared between both products using an established set of modern analytical methods. The quality attributes and criteria tested and applied in the comparability exercise should depend on the complexity of the molecule and should already be considered at the time of planning the comparability studies.

The characterization of the drug substance must include a comparison of primary, secondary, tertiary and quaternary structures, posttranslational modifications, biological activities, purity, impurities, related substances and immunochemical properties. The primary structure of the active pharmaceutical ingredient (API) must always be identical between the PBS and the PBR.

To identify potential differences in the degradation pathways and the impurity profile of the PBS and the PBR, comparative stability studies must be performed under accelerated and different stress testing conditions (e.g. moisture, temperature, light and mechanical agitation). If differences are observed under accelerated storage conditions, the stability of both products should be compared based on real-time data generated at long-term storage conditions.

3.2.2.2.2 Comparability Assessment

The comparison of the PBS and the PBR on the quality level is the first step to enable the submission of a reduced non-clinical and clinical package for a PBS for abbreviated licensing. The extent of comparative characterization data requested by the authorities will depend on the complexity and physicochemical properties of the molecule. If the comparability exercise reveals substantial differences between both products or if the characterization is regarded as incomplete, the product cannot be considered a PBS and thus the applicant must submit a comprehensive non-clinical and clinical dossier following the requirements established for originator products. In case the provided information is regarded as insufficient, the authorities will notify the applicant and a deadline for the submission of further information will be granted.

3.2.3 Brazil

According to the Brazilian regulation RDC 55/2010 related to biological products, the same general quality requirements apply for new biological products as well as for copies of biological products (developed either under the comparability or the individual development pathway) [41]. Articles 30, 31 and 34 of the regulation provide a detailed list of quality documentation to be submitted for all biotechnological products independent of the regulatory pathway pursued by the applicant. The quality requirements for copies of biological products developed under the individual and comparability pathway are described in Articles 37/38 and 43, respectively. Under the individual development pathway the applicant needs to present

complete quality data in the application (cf. Section 3.2.3.1), however no comparability exercise at the quality level is required. In contrast, for biological products developed under the comparability pathway, a quality comparison between the biological product (BP) to be comparable and the comparer biological product (CBP) must in addition be submitted with the quality part of the application (cf. Section 3.2.3.2). To clarify the regulatory requirements for registration of BPs through the comparability pathway in more detail, ANVISA published an additional guideline, which specifies the requirements for the comparability exercise with regards to quality attributes of the product ([42]).

3.2.3.1 Quality Requirements

The sections below provide a summary of the quality documentation required for the submission of new biological products and copies of biological products (registered either by the comparability or the individual development pathway) as outlined in detail in the Brazilian regulation in Articles 30 and 31. Although hemoderivative products (Article 32) and vaccines (Article 33) are also in the scope of the Brazilian regulation (c.f. Section 2.3), the following sections focus on requirements for biotechnological products (Article 34) to facilitate a direct comparison with the requirements in the WHO guidelines referring to well-characterized biotherapeutic products such as recombinant DNA-derived proteins (c.f. Section 2.1). In addition, the specific quality requirements for the comparability pathway as outlined in the respective quality guideline are presented ([42]).

3.2.3.1.1 Manufacturing Process

Regarding the manufacturing process, the applicant must submit a technical report containing the following information:

- Description of the manufacturing process, incl. production scale and identification of critical process steps
- Description of process controls and justification of acceptable ranges
- Information on expression vectors, cell banks and cell line fermentation
- Description of solutions, components and culture media used for manufacture of the product
- Description of processes involved in reducing/removing impurities originating from the manufacturing process or from product breakdown
- Information on excipients (functions, physicochemical and microbiological properties, specifications, compatibility with the active ingredient, efficacy of the preservative, if applicable)
- Information on main process equipment
- Information on manufacturing process validation of critical process steps, validation of reprocesses, viral removal and/or elimination (if applicable), transport chain validation
- Development studies performed to establish and to validate the dosage form, formulation and the container closure system (integrity to prevent microbial contamination)
- Storage and storage conditions for the active ingredient, intermediate products, bulk and final drug product, diluent and adjuvant

- History of product development with description and justifications for changes made during development of the manufacturing process and the finished dosage form

To ensure that the manufacturing process and quality control complies with GMP standards, the applicant must submit a copy of the Good Manufacturing Practices Certificate (GMPs) for all manufacturers of the active ingredient, intermediate products, bulk and final drug product, diluent and adjuvant (either issued by ANVISA or the competent authority of the country where the manufacturer is located). In case more than one manufacturing site is used for the production of the above mentioned products, a comparability report needs to be submitted demonstrating that the physicochemical and biological properties of the material produced at different sites is comparable.

For BPs developed under the comparability pathway, it is expected that the BP manufacturing process will differ from the licensed process of the CBP due to the fact that the details of the manufacturing process of the CBP is confidential information. Nevertheless, the manufacturing process of the BP should be optimized to minimize the differences between the BP and the CBP. Some differences between BP and CBP are expected and would be acceptable, provided that an appropriate justification regarding the adverse impact to the clinical performance is given. To achieve a high quality BP as similar as possible to the CBP, the BP manufacturing process for the BP should employ state-of-the-art science and technology. Prior to the development and design of the manufacturing process, the BP manufacturer must gather all available knowledge on the CBP (e.g. the type of host cell, the formulation and the container closure system) and use this information to design the BP manufacturing process. The BP must be expressed and produced in same type of host cell as the CBP to minimize potential changes to critical quality attributes of the protein and to avoid the introduction of process-related impurities that could impact safety and immunogenicity of the product. In case a different host cell type is used for the manufacture of the BP, the product must be registered via the individual development pathway and it needs to be demonstrated that the clinical profile of the product will not be changed.

3.2.3.1.2 Quality Characterization

Impurities

Impurities and contaminants in biological products need to be characterized and the specifications established to routinely control impurities in the final product must be justified. In addition, for starting materials from biological origin a safety evaluation for adventitious agents needs to be provided with the application.

Specifications

The application for a biological product must contain a description of all performed quality control tests. Reference and justification must be provided for the specifications determined with the quality control methods. The manufacturer must confirm that the selected specifications ensure the quality of the product. According to the Brazilian regulation it is required to submit a copy of the compendium (referring to national or international pharmacopeia or to the companies internal test methods and specifications) applied for the finished biological product. It needs to be considered that the pharmacopoeia monographs may contain only a minimal set of requirements for a particular biological product and additional testing parameters may be required. All analytical methods used in the specifications must be validated and documented according to the health legislation in effect. Reference to the analytical methods used and to the limits of acceptance for each testing parameter must be provided and justified. In addition, all reference standards used for calibration of the assays must be described. Whenever possible, an international reference standard must be used and quantities or biological activity must be expressed in international units as defined by the WHO. Finally, a description of the primary and secondary packaging material together with the specifications must be submitted with the application.

For BPs developed under the comparability pathway, it is acknowledged by ANVISA that the specifications for a BP may be different from those of the CBP, since different manufacturing processes, analytical procedures and laboratories will be used. However, the specifications should capture and control important known product quality attributes for the CBP (e.g. identity, purity, potency etc.). Furthermore, specifications should be based upon the manufacturer's experience with the product and the experimental results comparing the BP and the CBP. If not justified otherwise, the manufacturer must demonstrate that the limits fixed for a given specification are not significantly higher than those for the reach of the variability of the CBP during the maximal period of storage of the product [42].

Stability

For all BPs stability studies need to be performed according to the requirements laid out in the health legislation in effect.

For products produced at different manufacturing sites, stability studies comparing the material each manufacturing site needs to be provided in a comparability study (cf. Section 3.2.3.2)

For BPs developed under the comparability pathway, head-to-head accelerated and stress stability studies comparing the BP and the CBP should be performed to establish degradation profiles and to detect differences between both products. Comparative stability studies performed at long-term/intended storage conditions are usually not required and will only be necessary in exceptional cases, e.g. if other characterization studies do not allow for this evaluation. Nevertheless, stability studies at long-term conditions performed only with the BP to be registered will always be necessary. The stability studies performed during the comparability exercise must be performed in accordance with RDC # 50/11 and its updates ([41]; [42]).

3.2.3.2 Comparability Exercise at the Quality Level - Requirements for the Comparability Pathway

3.2.3.2.1 Product Characterization

When filing a biological product registration application through the route of development by comparability, the applicant must submit a comparability exercise comparing the quality properties of the BP and the CBP as a supplement to the general quality documentation required as described in Section 3.2.3.1. According to Article 43 of the Brazilian regulation and the guideline for performance of the comparability exercise, the following information must be provided ([41]; [42]):

- Results of comparative physicochemical and biological characterization related to the quality attributes of the product
- Comparison of the (main) active ingredient(s) and the structure of the biological product and comparer biological product
- Description of differences observed in the purity and impurity profile between the biological product and comparer biological product
- Comparative stability studies performed under accelerated and stress testing conditions, according to the legislation in effect
- Description of the comparability exercise stages, with indication of the capacity to detect differences in the quality attributes between the biological product and comparer biological product
- Description of the analytical techniques used to detect potential differences between the biological product and the comparer biological product

All studies of the biological product's development program must be of comparative in nature. For this purpose, the applicant must specify the comparer biological product and must provide evidence that the same CBP was used in the development studies. Furthermore, information on the expression system used to manufacture the BP and the CBP must be provided with the application.

Detailed requirements for product characterization with regard to the applied analytical techniques, physicochemical properties, biological activity, immunochemical properties, impurities and stability are provided in the guideline for performance of the comparability exercise and are shortly summarized below ([41]; [42]).

Analytical techniques

In order to maximize the detection of differences between the BP and CBP that could affect clinical efficacy and safety, critical quality attributes of the product should be analysed with several techniques taking into account different physico-chemical and biological properties. The analytical limitations of each technique must be considered to determine similarity between the BP and the CBP. For methods used for batch release testing and product in the comparability exercise validation is required and full method description must be submitted with the application.

Physicochemical properties

The BP manufacturer must demonstrate that higher order structures (secondary, tertiary, and quaternary, when applicable) are comparable between the BP and CBP using appropriate analytical methods. Potential differences in post-translationally modified forms and variants must be investigated, identified, characterized and quantified and their impact analysed.

Biological activity

The evaluation of biological activity should i) reflect the mechanism of action and should ideally provide a link to clinical activity of the product, ii) determine if product variant(s) have the appropriate level of activity, and iii) should complement the physicochemical characterization by confirming the correct higher order structure of the molecule. For this purpose, relevant biological assay(s) with appropriate precision and accuracy should be used to demonstrate that there are no significant functional differences between the BP and the CBP.

In case the product has multiple biological activities, the applicant must perform numerous relevant functional tests to evaluate the range of functional activities of the BP and the CBP within the scope of the comparability exercise.

Since potency is a quantitative measure of biological activity, a validated potency assay must be part of the specification of the active ingredient and/or of the finished product, as well as of the comparability study. If appropriate, bioassays should be calibrated against an international or national reference standard, and the results should be expressed in international units (IU) or units (U) or as specific activity (e.g. unit/mg of the protein).

Immunochemical properties

In case the BP is an antibody or an antibody-based product, immunochemical properties (i.e., specificity, affinity, binding kinetics and Fc functional activity) must be compared to the CBP and equivalence of both products needs to be demonstrated with respect to these properties.

Impurities

Process- and product-related impurities must be identified, quantified and compared between the BP and the CBP. Various analytical techniques and cutting edge technology must be applied to establish data that allow for the evaluation of relevant differences in the purity profiles of both products. Some differences in impurities are expected due to different manufacturing processes. Appropriate tests specific for the production cell line must be performed to analyse process-related impurities. If significant differences in the impurity profile are detected, such impurities must be identified and characterized and the potential impact on efficacy, safety and immunogenicity must be evaluated and justified. According to the type and quantity of impurities, it needs to be confirmed in non-clinical and clinical studies that these impurities do not have an adverse effect on efficacy and safety of the BP.

3.2.3.2.2 Comparability Assessment

For a given product to be considered a BP liable for registration via comparability, it is necessary that most of the data resulting from the analytical and biological characterization are similar to the CBP. The demonstration of comparability must comprise sufficient information to predict if differences in quality attributes may have an adverse impact on the safety and efficacy of the BP. For instance, comparability between the BP and the CBP must

be evaluated with regards to contaminants and impurities with discussion of the potential impact on quality, safety and efficacy.

In situations where i) the applied analytical procedures are not capable to reveal relevant differences that may impact the safety and efficacy of the product, or ii) the relation between specific quality attributes and safety and efficacy could not be established, the BP may not be regarded as comparable to the CBP and may therefore not be appropriate for registration by means of development by comparability. In such cases, the individual development pathway must be used for registration of the product, performing all necessary stages for confirmation of its quality, efficacy and safety as per the norms in force (cf. Sections 3.3.3 and 3.4.3).

3.2.4 Colombia

According to the Colombian Decree 1782 of 2014, the same general quality requirements apply for all biotherapeutic products, independent on whether these products are developed via the full dossier pathway (applicable for new biological products), the comparability pathway or the comparability abbreviated pathway (both applicable for a proposed biosimilar product). The information requirements in common to all three regulatory pathways are briefly described in Article 6, Article 11 and Article 12 of decree 1782 [46]. For detailed description of general quality requirements for pharmaceutical evaluation, GMP standards and stability testing for biological products, reference is made to Article 22 of the decree 677 of 1995 [43] and the Colombian draft GMP and stability guidelines of 2015 ([50], [51]). For biological products developed under the comparability route, the applicant shall in addition submit the results of an exercise of comparability between the biological drug under evaluation and the biological reference drug as described in Article 8 of decree 1782 [46].

3.2.4.1 Quality Requirements

The sections below provide a summary of the general quality documentation required for a biological product application as detailed in the already mentioned Articles of the Colombian decrees 1782 and 677. To facilitate comparison with the WHO guidelines (c.f. Section 2.1), the following sections focus on the requirements for biotechnological products and do not describe specific requirements for other biological products also in the scope of the Colombian decree 1782 such as plasma-derived products, toxins etc. (c.f. Section 2.4).

3.2.4.1.1 Manufacturing Process

Regarding the manufacturing process, the applicant shall provide the following information regarding the biological product under evaluation:

- Description of the manufacturing process, incl. the stages of production, purification, characterization and in-process control
- Description of the site(s) of manufacture
- Information on the expression system, incl. origin and process of selection
- Documentation of the quality and control of raw materials, excipients, intermediates and other inputs of the production process

To demonstrate consistency of the production process, the applicant has to provide certificates of analysis of at least three production batches issued by the manufacturer of the biological product. In addition, manufacturing and quality control need to comply with GMP and GLP standards to guarantee validated procedures and processes. Therefore, the applicant shall

provide GMP certificates for the different manufacturing site(s) (of API, bulk and finished product) and quality control laboratories. In addition, GMP standards as recommended by the latest version of the GMP guideline for biological products issued by WHO [22] shall apply for production cells and master working cell banks (incl. conditions, controls and fermentations of the API, bulk and finished product).

3.2.4.1.2 Quality Characterization

The sections below provide a short summary of the essential information on quality properties to be submitted in the dossier for a biological product according to Article 6 of decree 1782 [46] and Article 22 of the decree 677 [43].

Physicochemical properties

The manufacturer must determine the physicochemical properties of the product under evaluation (incl. testing of biological identity).

Biological activity

Information on the assessment of the biological activity of the product must be provided.

Immunochemical properties

In Article 6 of decree 1782 it is stated that immunogenicity testing has to be performed with the biological product under evaluation. However, it is not further specified in this decree whether an evaluation of immunochemical properties at the quality level is required.

Impurities

Impurities and contaminants in the biological product under evaluation need to be assessed. The impurity profile of the product shall be consistent with the manufacture method of the API and the finished product.

Specifications

For the characterization and routine control of quality properties of the biological product under evaluation (i.e., physicochemical parameters, biological activity and impurities), the reference standards, specifications and analytical methods as described in the latest version of pharmacopoeias established in paragraph 1, Article 22 of Decree 677 have to be used. The pharmacopoeias officially accepted in Colombia are the U.S. Pharmacopeial Convention (USP), the British Pharmacopeia (BP), the French-German Codex (Deutsches Arzneibuch, DAB), the WHO Pharmacopeia (OMS) and the European Pharmacopoeia (Ph.Eur.). In case reference standards and specifications of the biological product are not included in monographs of the above-mentioned pharmacopoeia, these should be established using validated analytical techniques and the applicant has to provide this information in the dossier [43].

Stability

As stated in Article 22 of decree 1782, the Colombian Ministry of Health and Social Protection issued a draft guideline for stability testing of biological products [51], which is based on established international standards, e.g. by WHO Expert Committee on Biological Standardization [52] and the ICH expert working group [53].

For biological products, stability studies should be performed under long-term, accelerated

and temperature stress storage conditions to determine the stability and stability-indicating parameters of the product. The shelf life claim of the product must be based on real-time stability data performed under regular storage conditions the product will experience during its sale and commercial use period. Furthermore, the stability studies have to be performed with the final drug product filled into the container closure system as intended for commercial use.

3.2.4.2 Comparability Exercise at the Quality Level - Requirements for the Comparative Pathway

3.2.4.2.1 Product Characterization

In addition to the general quality documentation as described in Section 3.2.4.1.2, the comparability pathway requires the submission of an exercise of comparability at the quality level between the biological product under evaluation and the biological reference product as described in Article 8 of the Colombian decree 1782 [46]. However, the decree provides no further details on how the quality properties of both products should be characterized and compared.

3.2.4.2.2 Comparability Assessment

According to Article 8 of the Colombian decree [46], the comparability exercise must provide evidence that the biological product being evaluated is highly similar to the reference product. The comparability exercise relates to a phased and sequential process of comparing the attributes of quality, safety and efficacy between the two products. In case any differences are found, these must be explained and justified with respect to their clinical relevance (i.e., efficacy and safety as described in Article 4 of the decree [46]). No further details on the evaluation of the comparability exercise are provided in the decree. However, Article 8 contains a “transitional paragraph” stating that for the evaluation of the practice of comparability the specialized branch for drugs and biological products of INVIMA will use the latest version of the technical paper "Recommendations for the evaluation of similar biotherapeutic products" adopted by the committee of experts on biological standardization of WHO [48], unless it is in contradiction to the provisions in decree 1782 or other health regulations in force.

3.2.4.3 Comparability Exercise at the Quality Level - Requirements for the Abbreviated Comparative Pathway

3.2.4.3.1 Product Characterization

As stated in Article 9 of the Colombian decree 1782, for the abbreviated submission pathway the applicant must provide evidence that the API of the proposed biosimilar product is sufficiently characterized in terms of identity, biological activity, physicochemical properties and purity. The characterization of these quality attributes shall also be provided based on the general quality requirements applicable to all three regulatory pathways for biological products as described in Article 6 of this decree.

The characterization of the API must be performed using state-of-the-art analytical methods and must either include a comparison of the product being evaluated with a reference product or, if available, with samples of the reference standard as described in the respective pharmacopoeia.

In addition, for the abbreviated comparability pathway it is not necessarily required to provide own characterization data comparing the biosimilar and the reference product. Instead, the applicant may also refer to information provided by other health authorities for a reference product or even for the whole of products containing an API considered to be highly similar to the drug under evaluation (cf. Section 3.1.4).

3.2.4.3.2 Comparability Assessment

In the comparability assessment, despite minor differences in pharmacologically inactive components, the applicant must provide evidence that the drug under evaluation is either highly similar to the respective reference product or, if appropriate, to the sample of the pharmacopoeia pattern. Taking into account also the results of the general quality characterization as described in Article 6 of decree 1782, the applicant must show that there are no clinically meaningful differences in safety, purity and potency with regard to the whole of drugs containing an API that is considered to be highly similar to the biological product under evaluation.

3.3 Non-clinical data

3.3.1 WHO

3.3.1.1 Design of non-clinical studies

In general, the pharmacotoxicological assessment of a proposed SBP requires the generation of some non-clinical data. While the non-clinical evaluation of a new biotherapeutic compound usually comprises various pharmacodynamic, pharmacokinetic and toxicological studies, the extent and scope of non-clinical data required to establish the safety and efficacy of a SBP has to be defined on a case-by-case basis and depends mostly on different product- and substance class related factors. Factors that trigger the need for additional non-clinical studies for the SBP may be either quality-related (e.g. use of a different expression system compared to the RBP or different purification methods) or related to pharmacotoxicological characteristics of the drug substance (e.g. the mode of action is unknown or poorly understood or the drug substance shows a significant toxicity or narrow therapeutic index).

Since the non-clinical studies are part of the overall comparability exercise, the studies should be set up to detect differences between the SBP and the RBP and should always include a head-to-head comparison of the two products. Furthermore, the design of the studies should be based on the results of the physicochemical and biological characterization of the SBP and the potential impact of product characteristics on efficacy and safety. Existing guidelines for preclinical safety evaluation of biopharmaceuticals (e.g. ICH S6 (R1), „*Preclinical safety evaluation of biotechnology-derived pharmaceuticals*“ [54]) should also be taken into account when planning the non-clinical studies. In addition, the WHO guideline stipulates that the non-clinical studies should be performed with the final formulation of the SBP, if not otherwise justified.

3.3.1.1.1 In vitro studies

Comparability between the SBP and the RBP in terms of pharmacodynamic activity should be demonstrated in in vitro assays (e.g. receptor-binding studies or cell-based assays). Since the results from biological assays are usually already available from the comparability studies

performed at the quality level, reference to these results can be made in the nonclinical part of the dossier (cf. Section 3.2.1),

3.3.1.1.2 In vivo studies

The animal studies performed for the non-clinical evaluation of the SBP should be comparative in nature and should be conducted using state-of-the-art technology. Furthermore, the animal species used must be relevant and should be derived from the species in which the RBP is known to have pharmacodynamic and/or toxicological activity.

The pharmacotoxicological endpoints and parameters that should be taken into consideration for the non-clinical evaluation are described in the Sections below.

Toxicity studies

According to the WHO guidelines, for the non-clinical evaluation of an SBP the conduction of at least one comparative repeat-dose toxicity study with the final formulation represents the minimum requirement to reassure that no unforeseen toxicity will occur during clinical use of the SBP. As part of the toxicokinetic parameters measured in such a study, antibody responses should be determined and characterized (regarding anti-drug antibody titres, product-neutralizing activity and cross-reactivity with homologous proteins). Furthermore, dependent on the route of administration of the SBP local tolerance may also be evaluated as part of the repeat-dose toxicity study. Overall, the duration of the study should allow the determination of potential differences in toxicity and/or antibody responses between the SBP and the RBP.

In general, additional toxicological studies as described in ICH S6 (R1) [54] (such as safety pharmacology, reproductive toxicology, genotoxicity and carcinogenicity studies) are usually not required for the non-clinical evaluation of an SBP. However, such studies may need to be included due to the outcome of the repeat-dose toxicity study or due to other known toxicological properties of the RBP.

Pharmacodynamic studies

The WHO guidelines acknowledge that it is not necessarily required to assess the pharmacodynamic activity of the SBP in an in vivo animal model if validated in vitro assays exist which reliably reflect the clinically relevant pharmacodynamic activity of the RBP. The results from such assays will already be included in the quality part of the dossier and therefore reference to these data can be made in the non-clinical part of the dossier (cf. Section 3.3.1.1.1, Section 3.2.1).

Alternatively, in case no results from validated in vitro assays are available, the pharmacodynamic activity of the SBP may be determined as part of the non-clinical repeat-dose toxicity study (cf. Section above).

3.3.2 Chile

3.3.2.1 Design of non-clinical studies

According to the Chilean biosimilar guideline, comparative non-clinical studies are an essential part of the overall comparability exercise between the PBS and the PBR. The amount of non-clinical data to be provided with a biosimilar application may vary significantly and whether a reduced data package is sufficient must always be decided on a case-by-case basis. For instance, the extent and scope of the non-clinical program largely

depends on the degree of molecular similarity already shown at the quality level by physico-chemical characterization. Therefore, the product characteristics and the results of the comparability exercise at the quality level should be taken into account when designing the non-clinical program.

In the following cases no reduction of the non-clinical data package for an SBP is possible (cf. [35]: Chapter IV, Section 2.2.1):

- If significant differences in the cell expression system exist compared to the PBR,
- If significant differences result from the purification methods used, or
- If the product contains a mixture of not adequately characterized product- and/or process-related impurities.

3.3.2.1.1 In vitro studies

The pharmacodynamic activity of the PBS and the RBP should be compared in vitro bioassays (e.g. in receptor-binding and cell-based proliferation or cytotoxicity assays).

3.3.2.1.2 In vivo studies

The applicant must at least perform a comparative repeat-dose toxicity study using adequate in vivo animal model(s) (i.e., one or several species in which the PBR displays pharmacodynamic and/or toxicological activity). If appropriate, the investigated toxicokinetic parameters should include determination of antibody responses.

Depending on the route of administration of the product, local tolerance should be tested as part of the repeat-dose toxicity studies.

3.3.3 Brazil

3.3.3.1 Non-clinical evaluation - Requirements for the comparability pathway

The requirements for non-clinical studies of biological products developed through the route of comparability are described in Article 44 and 45 of the Brazilian regulation [41].

Article 44 states that the applicant must provide all reports of the performed non-clinical studies when filing the biological product registration application. All non-clinical studies must be comparative in nature and designed to detect significant differences in response between the biological product and comparator biological product.

3.3.3.1.1 In vitro studies

It is not explicitly mentioned in the Brazilian regulation that in vitro studies are required for the non-clinical evaluation of biological products.

3.3.3.1.2 In vivo studies

According to Article 45, in vivo non-clinical studies have to be performed for biological products developed by the comparability pathway. The in-vivo studies must include pharmacodynamic studies relevant for the intended clinical application. In addition, cumulative (repeat-dose) toxicity studies including the characterization of toxicokinetic parameters must be conducted in a relevant animal species.

3.3.3.2 Non-clinical evaluation - Requirements for the individual development pathway

Article 37 and 39 of the Brazilian regulation describe the requirements for non-clinical studies of biological products developed by the individual development pathway [41].

Article 37 refers to Article 35 and 36 (“Technical Experimentation Report”) in which the documentation requirements for filing a new biological product registration application are summarized. Here it is stated that the complete reports of all non-clinical studies have to be submitted with the application. No further details regarding the type and scope of non-clinical studies expected by the Agency can be found in the Brazilian regulation.

However, according to Article 39 the extent of non-clinical studies may be reduced for biological products submitted under the individual development pathway. The reduction of the non-clinical studies depends on factors such as the complexity of the molecule, the extent of physicochemical characterization (e.g. well-known structure or product’s impurities) as well as the knowledge of pharmacological properties, safety and efficacy of the originator product (e.g. mechanism of action, known toxicity or therapeutic index).

3.3.4 Colombia

3.3.4.1 Non-clinical evaluation - Requirements for the comparative pathway

According to Article 8 of the Colombian decree 1782, non-clinical studies are part of a staged comparability exercise to demonstrate comparability in terms of quality, safety and efficacy between the biological drug under evaluation and the reference drug. However, the decree does not provide further details which non-clinical studies are expected or how the studies should be performed. Instead of that, in Article 8 it is stated that the specialized branch of the INVIMA will use the WHO technical paper for the evaluation of similar biotherapeutic products [48] to evaluate the practice of comparability (cf. Section 3.2.4.2).

In addition, according to Article 22 of the decree the Ministry of Health and Social Protection of Colombia plans to issue a separate guideline for the assessment of immunogenicity of biological products. The guideline will also include the required non-clinical studies (incl. in-silico, in-vitro and in-vivo tests) necessary to characterize to the drug under evaluation in terms of immunogenicity, depending on the complexity of the API, formulation, container, packaging, route of administration and clinical application.

3.3.4.2 Non-clinical evaluation - Requirements for the abbreviated comparability pathway

As stated in Article 9 with regard to the abbreviated comparability pathway, the applicant must provide all publicly available non-clinical information demonstrating the safety and efficacy of the drug under evaluation. Such information may come from the whole of drugs containing an active pharmaceutical ingredient that is considered to be highly similar to the drug under evaluation. Based on the information provided by the applicant, the Specialized Branch of the INVIMA will assess if additional non-clinical information resulting from the studies conducted with the drug under evaluation is required. However, the decree does not contain any information which studies are expected and/or how the studies should be performed.

3.4 Clinical data

3.4.1 WHO

3.4.1.1 Design of clinical studies

As part of the comparability exercise clinical studies should be conducted to demonstrate comparable safety and efficacy of the SBP and the RBP. The studies should be designed to allow the detection of any relevant differences between the two products.

The main/pivotal clinical studies should be performed with the product manufactured with the final manufacturing process and containing the same formulation as the product intended to be commercialized. If different formulations have been used in the clinical studies, additional PK bridging studies may be required to compare the PK profiles of the products from the previous and final formulation. For changes in the manufacturing process the direction provided in ICH Q5E should be followed [55].

The clinical comparability exercise should be a stepwise approach, starting with pharmacokinetic and pharmacodynamic studies followed by clinical efficacy and safety studies.

3.4.1.1.1 Pharmacokinetic studies

Comparative pharmacokinetic studies have to be performed to detect potential differences in the PK profiles of the SBP and the chosen RBP.

The design of the PK studies should be justified by the applicant and should consider the following recommendations:

- The PK profile should be investigated for all intended routes of administration using doses that are within the therapeutic dose range of the RBP.
- It is usually considered sufficient and the best option to perform a single-dose, cross-over PK study in a homogenous study population of healthy volunteers using the dose of highest sensitivity to detect PK differences between the SBP and RBP. However, under following circumstances alternative study designs should be taken into account:
 - If the PK profile is dose or time-dependent with higher drug concentrations at steady state level than after single-dose application, it is suggested to perform an additional multi-dose PK study to allow the detection of potential differences in the absorption of the SBP and the RBP.
 - Although the crossover design eliminates inter-subject variability, for products with a long half-life or a risk of inducing anti-drug antibodies the parallel study design may be more suitable. In case a parallel study design is used, variables related the study population (e.g. ethnic background, smoking or metabolizer status) that are known to influence the PK behaviour of the drug substance should be carefully considered.
 - If the risks associated with administration of the drug substance are not acceptable for healthy volunteers, the PK study may also be conducted in the intended patient population.

- Comparison of PK characteristics of the SBP and RBP should include an investigation of both absorption/bioavailability as well as elimination parameters (i.e., clearance and/or elimination half-life).
- The acceptance criteria applied to prove similarity of PK properties should be pre-defined and justified. Based on the absence of established acceptance criteria for biologicals it is accepted to use the traditional 80-125% range established for bioequivalence studies, although this range does not necessarily apply for biological products as it was developed for orally applied small molecule drugs. Thus, even though this criterion may not be met a SBP may still be considered similar to the RBP if the comparison of quality, non-clinical and clinical efficacy and safety data in its totality supports this conclusion.
- The analytical methods used to determine similarity of PK parameters should have adequate specificity and sensitivity and should provide a range of quantification with sufficient accuracy and precision.

3.4.1.1.2 Pharmacodynamic studies

Comparison of the pharmacodynamic profiles of the SBP and the RBP in a combined pharmacokinetic/pharmacodynamic study may provide valuable information on potential differences of dose/exposure and effect, especially if different concentrations of the drug substance are tested.

In general, clinical studies are required to demonstrate similar efficacy of the SBP and the RBP. However, confirmatory pharmacokinetic/pharmacodynamics studies may also be appropriate and, if well designed and executed, even provide higher sensitivity in detecting potential differences in efficacy compared to studies investigating clinical end-points. The design of a confirmatory PK/PD study should meet the following requirements:

- The PK and PD properties of the RBP are well characterized.
- At least one of the investigated PD markers is an accepted surrogate marker for efficacy.
- The correlation between dose/exposure, the relevant PD marker(s) and response/efficacy of the RBP is well-established.
- The confirmatory PK/PD studies should be performed using a population and a dosage at which potential differences between the SBP and the RBP are known to be best detectable.
- Acceptance criteria for demonstration of similarity in confirmatory PK/PD studies have to be pre-defined and should be adequately justified.

3.4.1.1.3 Efficacy studies

As part of the comparability exercise, a confirmatory clinical study is generally required to demonstrate comparability in clinical efficacy of the SBP and the RBP. The confirmatory clinical trial should be carried out in agreement with the principles as defined in relevant ICH guidelines ([56]; [57]).

The WHO advises the applicant to consider the following aspects for the design of the clinical efficacy studies:

- The studies should be adequately powered, randomized and controlled and preferably be double-blind or at a minimum observer-blind. If no blinding is performed at all, very good justification will be needed to show that the study results are not significantly biased.
- To allow the detection of potential differences between the SBP and the RBP, the study should be carried out in a sensitive and, if available, well-established clinical model.
- The same dosage(s) of the SBP and the RBP should be given in head-to-head comparative clinical studies in order to demonstrate that similar efficacy can be achieved upon application of the same dosage(s). If the drug is not administered at fixed dosage(s) but is titrated based on treatment response (e.g. epoetin or insulin), co-primary end-points should be investigated that also include dosage.
- In principle, equivalence or non-inferiority study designs may be used to compare the efficacy and safety of the SBP and the RBP. However, the advantages and disadvantages of both designs should be carefully considered:
 - Equivalence studies are clearly preferred since they are designed to confirm that the SBP is clinically not less or more effective than the RBP when used at the same dosage(s). Therefore, demonstration of equivalence provides a strong argument to allow the extrapolation of efficacy to other indications of the RBP, especially if different dosage(s) are applied as used in the clinical trials. However, the two-sided equivalence design (with an upper and lower comparability margin) in general requires larger sample sizes compared to the one-sided non-inferiority study design (only one lower or upper comparability margin) (cf. Section 3.4.1.2).
 - Non-inferiority studies may also be acceptable for some products with a wide safety margin. Although the non-inferiority design tends to require smaller sample sizes to achieve the same power as the equivalence design, it does per definition not eliminate the risk of a superior efficacy of the SBP compared to the RBP. If superiority in efficacy is found in non-inferiority studies, justification needs to be provided why the observed difference is considered clinically not relevant. The SBP may not be considered similar to the RBP if the superiority in efficacy is considered to be clinically relevant.
 - For both equivalence and non-inferiority designs the comparability margins must be pre-defined and justified statistically and based on the largest difference in efficacy that has no clinical relevance. For setting of comparability margins the effect size of the RBP determined from historical studies should also be considered.

3.4.1.1.4 Safety studies

Pre-authorization clinical safety studies need to be performed to characterize the safety profile of the SBP. For the design of the clinical safety studies the following recommendations should be considered:

- The clinical safety studies should preferentially be comparative in nature. Comparison with the RBP should comprise type, frequency and severity of adverse events and reactions.
- A sufficient number of patients should be investigated to establish an appropriate safety database of the SBP. If feasible, safety data may be obtained in the course of the clinical

efficacy studies. In case confirmatory PK/PD studies are used to demonstrate similarity in efficacy and these studies do not provide relevant safety data, an additional safety study will still need to be conducted.

3.4.1.1.5 Immunogenicity

Immunogenicity is commonly observed in patients treated with biotherapeutic products and the impact of immunogenic reactions on safety and efficacy of the treatment may range from clinically irrelevant to serious or even life-threatening. The formation of anti-drug antibodies depends on several factors related to the product itself (such as the nature of the drug substance, product- and process-related impurities, the excipients or the stability of the product), the administration of the product (such as the route of administration and dosing regimen) or the patient population (e.g. the disease status and therapy/co-medication). Since the SBP and the RBP may be different with respect to immunogenic responses and immune-related adverse events, pre-licensing immunogenicity data should always be obtained for an SBP.

According to the WHO guideline the following aspects should be considered for the evaluation of immunogenicity:

- Immunogenicity studies comparing the SBP and the RBP should always be performed in humans since animal studies are usually not predictive for the immune response in humans.
- Pre-licensing immunogenicity data obtained from the comparative clinical efficacy studies will usually be considered as sufficient to detect a significant increase in immunogenicity of the SBP compared to the RBP. If confirmatory PK/PD studies are used to demonstrate similarity in efficacy, an additional immunogenicity study in the target population still needs to be performed. If it is intended to extrapolate efficacy and safety data to other indications of the RBP, immunogenicity of the SBP should be tested in the patient population with the highest risk of an immune response and immune-related adverse events
- The investigation of immunogenicity should always include a comparison of the type and frequency of induced antibodies. The detected antibodies should also be evaluated with respect to cross-reactivity and neutralizing activity and their potential impact on clinical safety, efficacy and PK of the product.
- Validated assays should be used for antibody testing. Justification should be provided for the testing strategy, including the selection and characterization of antibody assays, the sampling plan (time points, sample volumes and processing/storage) and the statistical methods used for analysis of results.
- The observation period for immunogenicity testing should be justified by the applicant and should be based on the time of clinical application and the expected time of anti-drug antibody development. In cases where rare antibody-related serious adverse events have been observed for the RBP that are not likely to be detected in a pre-licensing immunogenicity study, a post-marketing risk management plan may be required to evaluate this risk for the SBP.

3.4.1.2 Extrapolation of efficacy and safety data to other indications

According to the WHO guideline it may be possible to extrapolate efficacy and safety data to other clinical indications of the RBP provided that similarity between the SBP and the RBP has been demonstrated in one particular indication and all the following requirements are fulfilled:

- Efficacy and safety has been investigated in a sensitive clinical model with the ability to detect potential differences between the SBP and the RBP.
- The SBP has the same clinically relevant mechanism of action and/or the involved receptor(s) are the same in the extrapolated indication(s). If the mechanism of action is different or not known, a strong scientific rationale and additional clinical data will be required.
- The SBP has been thoroughly characterized in terms of safety and immunogenicity and no unique or additional safety issues are anticipated for the extrapolated indication(s). If this is not the case additional clinical data will be required.

If a non-inferiority study design has been employed to demonstrate acceptable safety and efficacy of the SBP compared to the RBP, convincing arguments should be provided that these results can be transferred to the extrapolated indication(s). Otherwise additional clinical safety and efficacy data will need to be submitted by the applicant to support the desired indication(s) (cf. Section 3.4.1.1.3).

3.4.2 Chile

3.4.2.1 Design of clinical studies

According to the Chilean guideline, head-to-head comparative clinical studies are required as part of the comparability exercise for an abbreviated licensing application. The clinical study design should allow the detection of any relevant differences between the PBS and the PBR and should be determined on a case-by-case basis, taking the product class and the results from the quality and non-clinical comparability studies into account. The clinical comparability studies should follow a step-by-step procedure, beginning with the PK and PD studies, followed by comparative clinical efficacy, safety and immunogenicity studies. For the requirements of demonstrating clinical comparability for a specific product-class (i.e., recombinant human insulin, epoetin, recombinant somatotropin, granulocyte-colony stimulating factor, interferon and monoclonal antibodies), reference is made to the product-specific guidelines from EMA in Annex 1 of the Chilean guideline ([35]: Chapter IV, section 2.2.1).

In case the clinical comparability exercise cannot provide sufficient data to properly characterize the PBS or shows that both products are not comparable in terms of efficacy and safety, the applicant must submit a comprehensive clinical data as established for the regulation of originator products.

The pre-licensing clinical data is not considered sufficient to identify all the possible safety differences between the PBS and the PBR, therefore the applicant should submit a post-marketing risk management plan to the Public Health Institute of Chile (“Instituto de Salud Pública”) to evaluate the risk of the PBS.

3.4.2.1.1 Pharmacokinetic studies

PK studies have to be comparative to allow the detection of potential differences between the PK characteristics of the PBS and the PBR.

For the design of the PK studies the following recommendations should be considered:

- PK studies should be performed for all intended routes of administration with doses that are within the therapeutic dose range of the PBR.
- In general, it is considered sufficient to perform a single-dose, crossover PK study in a homogenous study population using the dose of highest sensitivity to detect PK differences between the PBS and PBR. However, under following circumstances alternative study designs should be taken into account:
 - If the PK profile is time-dependent (e.g. in case of controlled release products), additional comparative multi-dose PK studies must be performed.
 - In general, a cross-over study design is recommended since it reduces the number of patients and lowers the inter-subject variability of the study. However, for products with a long half-life or with a risk of inducing anti-drug antibodies the parallel study design is preferable.
 - For abbreviated licensing no additional PK studies (such as interaction or special populations studies) are required as part of the clinical comparability exercise.

3.4.2.1.2 Pharmacodynamic studies

Comparative PD studies have to be performed by determining the most relevant PD marker in an appropriate study population. In this context, it is compulsory to use doses at which potential differences between the PBS and the PBR are known to be best detectable.

Clinical studies are generally requested to show a comparable efficacy profile of the PBS and the PBR. However, according to the Chilean guideline comparative clinical efficacy studies may be omitted if the PK/PD studies meet the following requirements:

- The PK/PD properties of the PBR are well known and characterized.
- The relationship between dose/exposure, relevant PD markers and clinical response/efficacy of the PBR must be well established.
- At least one of the investigated PD marker(s) must be a validated surrogate marker for clinical efficacy.

In case a product meets the above-mentioned requirements and additionally fulfills the criteria outlined in the product-specific guidelines from EMA for demonstration comparability in terms of efficacy and safety as listed in Annex 1 of the Chilean guideline, the applicant may solely provide data from the comparability PK/PD studies and be exceptionally exempted to submit additional clinical data. However, if the PK/PD studies alone cannot provide sufficient data to show clinical comparability between the PBR and the PBS, additional clinical data have to be provided.

3.4.2.1.3 Efficacy studies

A confirmatory clinical efficacy study will generally be required to demonstrate comparability between the PBS and the PBR. In case no comparability exercise with the PBR is performed, the applicant will have to submit a comprehensive clinical data package with the PBS.

The following aspects should be taken into account for the design of the clinical efficacy and safety studies:

- The clinical trial should be comparative, controlled and randomized, double-blind or single-blind, and carried out with sufficient statistical power to detect clinically significant differences between the PBS and the PBR. If, for any reason, blinding of the trial cannot be performed, the applicant must show that the results are not significantly biased.
- The results of the clinical trial must show equivalence regarding efficacy of both products. For this purpose, the clinical comparability parameters and margins must be pre-defined and statistically justified and need to be submitted as part of the evaluation of the clinical efficacy and safety studies.
- Overall, it is required that the design and the accomplishment of the clinical efficacy studies guarantees the scientific validity of the study.

3.4.2.1.4 Safety studies

In case the applicant can demonstrate a comparable PK/PD profile of the PBS and the PBR it will generally still be required to perform a clinical comparability study and compare the safety profile of the two products. For this purpose, the clinical safety data may be acquired in a combined of the clinical safety and efficacy studies. The design of the clinical safety study should consider the aspects as outlined in Section 3.4.2.1.3.

3.4.2.1.5 Immunogenicity

The most important feature in which biotechnology-derived medicinal products differ from small molecule drugs is the ability to induce immunogenicity in the target population resulting in the formation of anti-drug antibodies that may potentially lead to serious complications and adverse events. Immunogenicity represents the most important safety concern related to biological products, and the extent and severity of immunogenic responses is influenced by multiple factors either related to the drug substance (e.g. amino acid sequence, level of glycosylation, purity and stability), the drug product (e.g. formulation, stability and storage conditions) or to the clinical application of the biological product (e.g. route of administration, dose or dosing interval or the immune status of the patient population).

Even though similarity between a PBS and a PBR has been shown in clinical efficacy and safety studies, both products may still differ regarding the extent to induce immunogenicity, ranging from clinically irrelevant to serious reactions in the treated patient population. Therefore immunogenicity of a PBS must always be clinically investigated prior to its market authorization.

The following aspects should be taken into account for the clinical evaluation of immunogenicity:

- Immunogenicity trials comparing the PBS and the PBR should always be performed in humans since data obtained from animal studies are generally not predictive for the immune response in humans.

- Immunogenicity data obtained from the comparative clinical efficacy studies will usually allow the detection of a significant increase in immunogenicity of the PBS in comparison to the PBR and is therefore considered as sufficient to gain marketing authorization. However, in case similarity in efficacy is demonstrated only by comparative PK/PD studies, an additional immunogenicity study in the target population will still be required for marketing authorization.
- The frequency and type of detected anti-drug antibodies should be directly compared between the PBS and the PBR and evaluated with respect to possible clinical consequences of the immune response. It is also not appropriate to use an external control group in the immunogenicity trial since the response is usually influenced by several factors, e.g. the study population, the sampling time, the type of applied assays and the interpretation of study results. The Chilean guideline requests that the observation period for immunogenic responses should be at least one year.
- Due to the limited number of participants in the pivotal clinical trials it will not be possible to finally assess the risk of immunogenicity-related serious adverse event associated with the administration of a PBS prior to its approval. Therefore, a post-marketing pharmacovigilance and risk management plan as described in Annex 2 of the Chilean guideline will need to be submitted by the applicant to evaluate the immunogenicity risk of a PBS.

3.4.2.2 Extrapolation of efficacy and safety data to other indications

As referred to in Annex 1 of the Chilean guideline, the requirements established in the product-class specific guidance documents from EMA should be considered for extrapolation of clinical efficacy and safety data to other indications. Specifically, the following requirements have to be met:

- The PBS has the same mechanism of action and/or the involved pharmacologic receptor(s) are the same in the extrapolated indication(s).
- Safety and immunogenicity has been characterized in a sensitive clinical analysis model and in a sensitive study population in which potential differences between the SBP and the RBP can be detected.
- The investigated PD marker(s) must be a validated surrogate marker for clinical efficacy that allows extrapolation to other indication(s).

3.4.3 Brazil

3.4.3.1 Clinical evaluation - Requirements for the comparability pathway

Article 46 of the Brazilian regulation provides the specific requirements for clinical studies of BPs developed through the route of comparability. The applicant must submit the protocols and reports of following clinical studies [41]:

- PK studies
- PD studies
- Pivotal clinical safety and efficacy studies

3.4.3.1.1 Pharmacokinetic and pharmacodynamic studies

For BPs developed under the comparability pathway, PK and PD clinical studies have to be performed. The PD studies may be combined with PK studies, provided the PK/PD relationship is well known and characterized.

3.4.3.1.2 Efficacy and safety studies

Comparative clinical studies have to be performed to demonstrate a comparable efficacy and safety profiles between the BP and the CBP. The design and the comparability margins of the efficacy and safety studies must be specified and statistically as well as clinically supported by the applicant. If available, phase IV clinical study results (i.e., results from a safety surveillance study in a larger patient population) must also be submitted.

3.4.3.1.3 Immunogenicity

As outlined in Article 28 and 29 and as required independent of the route of development (i.e., also for BPs developed through the comparability pathway), the applicant also has to submit an immunogenicity study report, a pharmacovigilance plan as well as a risk minimization plan according to the health legislation in effect.

3.4.3.1.4 Extrapolation of efficacy and safety data to other indications

According to Article 19 of the Brazilian regulation, specific guidance for extrapolation of safety and efficacy data to other therapeutic indications will be established for BPs registered through the comparability pathway. In general, extrapolation to other indications is possible if following pre-requisites are met [41]:

- Comparability in terms of safety and efficacy between the BP and the CBP has already been demonstrated in one particular indication
- The applied clinical test model is sensitive enough to detect potential differences in safety and efficacy between the two products
- The mechanism of action and involved receptors must be the same in the extrapolated indications
- Safety and immunogenicity of the BP must be sufficiently characterized

3.4.3.2 Clinical evaluation - Requirements for the individual development pathway

The specific requirements for clinical studies of BPs registered through the individual development pathway are described in the Article 40, 41 and 42 of the Brazilian regulation. The applicant must submit the protocols and reports of following clinical studies:

- Phase I and II clinical studies (only if required)
- Phase III clinical studies

3.4.3.2.1 Pharmacokinetic and pharmacodynamic studies

For BPs registered under the individual development pathway, phase I clinical studies (incl. evaluation of PK, PD and safety) and phase II clinical studies (incl. evaluation of efficacy and safety, cf. Section 3.4.3.2.2) may be performed if considered necessary as described in Article 40 of the Brazilian regulation. The necessity of conducting these studies will depend on the

knowledge of pharmacological properties, safety and efficacy of the originator product. However, the phase I and II clinical studies do not mandatorily have to be comparative.

3.4.3.2.2 Efficacy and safety studies

According to Article 41, phase III clinical studies (i.e., confirmatory efficacy and safety studies) will always be required for BPs licensed under the individual development pathway. In addition, with exception of hemoderivatives, vaccines and BPs developed in an oncological indication, the phase III clinical studies must always be comparative to demonstrate a similar efficacy and safety profile between the BP and the CBP. Both equivalence and non-inferiority study designs may be used in the comparative clinical trials. If available, phase IV clinical study results must also be submitted.

3.4.3.2.3 Immunogenicity

As outlined in Article 28 and 29 and as required independent of the route of development (i.e., also for BPs developed through the individual pathway), the applicant also has to submit an immunogenicity study report, a pharmacovigilance plan as well as a risk minimization plan according to the health legislation in effect.

3.4.3.2.4 Extrapolation of efficacy and safety data to other indications

According to Article 20, for BPs registered through the individual route of development extrapolation of clinical safety and efficacy data to other therapeutic indications will not be possible.

3.4.4 Colombia

3.4.4.1 Clinical evaluation - Requirements for the comparative pathway

According to Article 8 of the Colombian decree 1782, the applicant shall present the outcome of clinical efficacy and safety studies as part of the comparability exercise between the biological drug under evaluation and the reference biological drug. The comparability exercise shall prove the attributes described in Article 4 of the decree (“Pharmacological Assessment”), stating that information on efficacy (incl. PK and PD) and safety (incl. adverse effects and immunogenicity) of the biological drug under evaluation must be provided for the intended clinical indications. If the comparability exercise reveals differences between the biological drug under evaluation and the reference biological drug, these must be explained and justified and the specialized branch of INVIMA will assess their clinical relevance. According to Article 10, the pharmacological assessment of INVIMA will also take into account “global evidence” (i.e., information on the assessment of the efficacy and safety profile, clinical trials and pharmacovigilance data from health authorities in countries where the drug under evaluation and/or the whole of drugs containing an active pharmaceutical ingredient considered to be highly similar is already marketed) as well as the complexity of the molecule (i.e., the structure and the level of characterization) (cf. Section 3.1.4).

However, the Colombian decree 1782 does not provide further details which clinical studies are expected or how the studies should be designed. Furthermore, no information on the requirements for extrapolation of efficacy and safety data to other indications is provided. According to Article 8 of the decree, INVIMA will use the WHO technical paper for the evaluation of similar biotherapeutic products [48] to evaluate the practice of comparability (cf. Section 3.2.4.2).

As described in Article 22 of the decree, the Ministry of Health and Social Protection of Colombia plans to issue separate guidelines for setting up risk management plans and the assessment of immunogenicity of biological products. The immunogenicity guideline will include general principles, methods and techniques to characterize the biological drug under evaluation in terms of immunogenicity as well as sources of information related to clinical monitoring or pharmacovigilance processes that enable to determine possible immunotoxic reactions and the potential occurrence of neutralizing antibodies.

3.4.4.2 Clinical evaluation - Requirements for the abbreviated comparative pathway

According to Article 9 of the Colombian decree 1782, the applicant may select the abbreviated comparative pathway in case the API of the drug under evaluation has a well-documented efficacy and safety profile, and extensive clinical experience and pharmacovigilance information is already available. In addition, the applicant may not necessarily provide own clinical data but may provide all available clinical information of all products containing an API considered to be highly similar to the drug under evaluation provided by specified health authorities of other countries (cf. Section 3.1.4). Based on the provided information and the studies conducted with the drug under evaluation, the specialized branch of INVIMA will assess whether additional clinical information is required. However, no information which clinical data are generally expected and/or how the studies should be designed are provided in the Colombian decree.

4 Analysis: Comparison of regulatory requirements for the licensure of biosimilars in the LATAM countries Chile, Brazil and Colombia with the WHO standards for biosimilar products

Analysing the regulatory requirements for the licensure of biosimilars in the LATAM countries Chile, Brazil and Colombia with the WHO standards for biosimilar products, a variety of differences and similarities can be identified. These common and contrarian requirements are presented and discussed in the following Sections.

4.1 Scope of products and regulatory pathways for abbreviated licencing according to WHO, Chile, Brazil and Colombia

The WHO published the “Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)” in 2010. One of the key principles of the WHO guidelines is the proof of similarity of a biosimilar product to a reference product. A biosimilar product can be licensed on basis of a reduced dossier. However, a high degree of similarity between the two products at the quality level is a prerequisite for a shortened non-clinical and clinical program. In addition, the reference product has to be licensed on basis of a full dossier, including a complete quality as well as a non-clinical and clinical data package. The scope of the WHO guidelines is limited to highly purified and well-characterized biotherapeutic products, derived through modern biotechnological methods (i.e., recombinant DNA-derived therapeutic proteins). Vaccines and plasma-derived products and their recombinant analogues are not in the scope of the WHO guidelines (cf. Section 2.1.).

The final Chilean guideline „Norma Technica No. 170“, which specifically outlines the requirements for biosimilar products, was published in 2014. It clearly adopts the WHO standards regarding the proof of similarity of a biosimilar product to a reference product and the prerequisites for the acceptance of a shortened dossier for a biosimilar product. In addition, the same terminology for biosimilar and reference product is used. In line with the WHO guidelines, the Chilean guideline is only applicable to fully characterized active substances, derived from modern biotechnological procedures (e.g. recombinant DNA technology) and does not include less-characterised products such as vaccines, human plasma-derived products and heparins (cf. Section 2.2).

In contrast to WHO and Chile, Brazil issued an overarching regulation, which contains the requirements for the registration of all biological products. Unlike the terminology used by the WHO, the regulation RDC 55/2010 differentiates between “new biological products” (i.e., originator products) and “biological products” (i.e., copies of biological products including biosimilars). The term “biosimilars” is not used in the regulation. For the licensure of new biological products, it is obligatory to submit a full dossier, in order to demonstrate quality, safety and efficacy. Deviating from WHO and Chile, the Brazilian regulation foresees two different regulatory pathways for market authorization of biological products: the “route of development by comparability” and the “route of individual development”. The “route of development by comparability” in general follows the recommendations for biosimilars of the WHO and thus shows a high degree of similarity to the requirements of the Chilean guideline. Accordingly, ANVISA published a guideline specifying regulatory requirements regarding quality criteria of biosimilars, developed through the route of comparability. This guideline fully adopts the WHO Similar Biological Product guidelines. Contrary to the WHO and Chile, the Brazilian regulation describes an alternative abbreviated licensing pathways applicable for

copies of biological products. The “individual development pathway” requires a complete data package for the quality part of the dossier; however, no comparability exercise between the copy and the originator product is required. In addition, non-clinical may be reduced depending on the clinical experience regarding safety and efficacy of the originator product and other products belonging to the same product class but complete clinical data will always be required. The scope of the Brazilian regulation is much broader compared to the WHO and Chile, since it not only applies to highly purified biotechnological products. In general, the regulation applies to any biological medicines, including also vaccines and hemoderivative products (cf. Section 2.3).

Following the example of Brazil, the Colombian Biological Medicine Decree 1782 published in 2014 comprises regulatory requirements for the registration of all biological products. In addition, Colombia differentiates between new biotherapeutic products and copies of biotherapeutic products and their requirements for registration. Unlike to WHO and Chile, the term “biosimilars” is not used in the Colombian decree; instead the copies are summarized under the term “biological drugs under evaluation”. For new biological products the decree defines a „full dossier pathway“, which requires a complete quality, non-clinical and clinical data package in order to verify quality, safety and efficacy of the drug. For copies of biological products, it determines two different pathways: a „comparability pathway“ and a „comparability abbreviated pathway“. The comparability pathway in general follows the WHO recommendations and requires a comparability exercise between the biosimilar and the reference product. For the abbreviated comparability pathway, no comparability exercise is requested in the Colombian Decree 1782. Instead, the applicant may compare the biosimilar product to a pharmacopeia standard or a reference standard established by the applicant. Moreover, the applicant does not necessarily have to provide own non-clinical and clinical data. Thus, in contrast to the requirements established by the WHO, Chile and Brazil, the abbreviated pathway in Colombia allows the registration of a biosimilar product solely based on all available information of APIs of biological products, considered to be highly similar to the API of the biosimilar product. In accordance with the Brazilian regulation RDC 55/2010, the scope of the Colombian Decree 1782 is broader compared to the WHO and Chile. In addition to well-characterized biotechnological products, it comprises any biological product, such as vaccines, hemoderivative products, viruses, microorganisms and toxins (cf. Section 2.4)

4.2 Choice of the reference product

In accordance with the WHO guidelines, Chile as well as the comparability pathways in Brazil and Colombia the reference product plays a key role for the evaluation of the biosimilar product. The reference product is used as a basis of comparison to demonstrate similarity to the biosimilar product in terms of quality, safety and efficacy. In addition, the reference product must be based on a complete registration dossier. However, none of these countries considers the suggestion of the WHO that the chosen reference product should be on the market for an appropriate period of time and constitute a sufficiently large market volume. According to the WHO guidelines, the reference product should own the identical dosage form and route of administration as the biosimilar product, and the drug substance of the two products has to be similar. The Chilean guideline specifies these requirements by adding that the reference product should own the same unit dose, indication and concentration as the biosimilar product. The Brazilian regulation and Colombian decree do not describe these requirements at all (c. f. Section 3.1).

Both Chile and Brazil follow the WHO requirement that the same reference product has to be used during development and in the comparability exercise. This requirement is not explicitly taken into account in the Colombian decree (c. f. Section 3.1), indicating that a substitution of the reference product may be accepted in Colombia. However, the requirements regarding this aspect are not clear and will need to be further clarified, since the decree includes a statement that INVIMA will refer to the WHO guideline for evaluation of the comparability exercise (c.f. Section 3.2.4.2), and according to WHO the same reference product has to be used (see above).

Following the WHO recommendations, the legislations in Chile, Brazil and Colombia in general allow the applicant of a biosimilar application to refer to a reference product licensed in another country or region, in case no appropriate nationally registered reference product is available. However, differences between the different guidelines/regulations exist regarding the prerequisites for acceptance of a foreign reference product in the respective country. The Chilean guideline simply states that the chosen reference product has to be accepted by the national health authority without providing further details. The Brazilian regulation clearly requires a reference product to be licensed in a country that applies comparable scientific and technical standards to ANVISA and that the country provides unlimited access to the full registration dossier of the reference product. Last but not least, the Colombian Decree allows the applicant to refer to a reference product licensed from specific countries, regions and/ or authorities (e.g. U.S.A., Canada, EMA, ANVISA, members of the OECD) (cf. Section 3.1).

4.3 Comparison of quality data required for abbreviated licensing of biosimilar products

Regarding the quality requirements for biosimilar products, the Chilean guideline and the Brazilian regulation together with the supplementary quality guideline for biological products developed under the comparability pathway in Brazil generally implement the recommendations established by the WHO with only very few exceptions. Both jurisdictions acknowledge the fact that the manufacturing process of a biosimilar product will usually differ from that of the originator product and thus a full quality dossier meeting the same quality standards as established for originator products will always be required for both the drug substance and the drug product. In addition, the manufacturing process of the biosimilar product should be designed and optimized to achieve a product as similar as possible to the reference product, including the same host cell type and the same formulation and container closure system as used for the originator product. Differences regarding the selection of the host cell exist between the WHO, Chile and Brazil for biological products developed under the comparability pathway. Whereas the WHO guidelines do not mandatorily require the biosimilar product to be produced in the same type of host cell as used for the reference product provided that the molecular structure and the clinical profile of the product is not affected, it is explicitly stated in the respective guidelines of Chile and Brazil that the same host cell type must be applied. In cases where a different host cell type is used for the manufacture of the biosimilar product in Brazil, the product must be registered via the individual development pathway and it needs be demonstrated that the clinical profile of the product will not be changed using a different host cell type (cf. Section 3.2.3.1.1; [41]; [42]).

In accordance with the WHO, the guidance documents in Chile and Brazil require that quality control and specifications for biosimilar products should be established based on the existing guidelines for biotherapeutics as well as on available pharmacopeia monographs (e.g. in USP and Ph. Eur). Although it is not expected that the same specifications will be established for a

biosimilar and the reference product based on different manufacturing processes and analytical procedures, known important quality attributes of the reference product such as identity, purity and potency should be controlled in specifications for the biosimilar product. Stability studies supporting the shelf life, storage and transportation conditions of the product should be conducted in compliance with the respective national requirements for biotherapeutics in Chile and Brazil.

According to the guidelines/regulations in Chile and Brazil for biological products developed under the comparability pathway, a biosimilar application must contain (in addition to a complete quality dossier) a comprehensive comparability exercise comparing the physicochemical and biological properties of the biosimilar and the reference product. The comparability exercise should be performed in a head-to-head comparison of the biosimilar and the reference product and should employ a battery of state-of-the-art analytical methods to determine physicochemical properties including higher order structures, impurities as well as biological activity to show that there are no relevant functional differences with regard to the mechanism of action between the two products. Furthermore, head-to-head accelerated and stress stability studies should be performed for comparison of the degradation profile. In accordance with the WHO requirements, the Brazilian quality guideline for products developed by the comparability pathway states that the biosimilar and the reference product should be used in its final dosage form for the comparability exercise (i.e., containing the API and excipients in the formulation), or, if only the API can be compared with the available analytical methods, additional studies need to be submitted to prove that all relevant quality attributes of the API are not influenced by the isolation process. In this respect less details are provided in the Chilean guideline since it is not specified whether the final dosage form or only the API should be compared in the comparability exercise.

Consistent with the WHO requirements, a high degree of similarity between the proposed biosimilar and the reference product is a prerequisite for reducing the nonclinical and clinical data package for abbreviated licensing in Chile and under the comparability pathway in Brazil. In case similarity cannot be demonstrated on the quality level, the Chilean guideline requests to submit a comprehensive non-clinical and clinical data package following the requirements established for originator products. The Brazilian guideline for biological products developed under the comparability pathway states that in this case the product must follow the individual route of development and more extensive non-clinical and clinical data will need to be provided for marketing authorization of the biological product (cf. Section 3.3.3.2 and 3.4.3.2).

According to the Brazilian regulation, a full quality dossier is also mandatory for registration of biological products through the individual route of development. However, in contrast to the requirements established by the WHO, Chile and the comparability pathway in Brazil, no comparability exercise comparing the biological product and the reference product in terms of quality is requested.

Following the example of Brazil, in the Colombian decree the same general quality requirements apply for new biological products and similar biological products, independent whether the product is developed via the full dossier pathway, the comparability pathway or the abbreviated comparability pathway. The decree does not include a detailed description of quality requirements, but refers to the older decree 677 of 1995 and the Colombian draft GMP and stability guidelines of 2015 applicable for all biotherapeutic products. According to Colombia's decrees 1782 and 677, the manufacturing process, specifications and characterization of the product in terms of physicochemical properties, biological activity and

stability should be established based on internationally accepted quality guidelines (e.g. ICH, WHO) and pharmacopeia (e.g. OMS, USP, Ph. Eur).

In line with the WHO guidelines and the guidelines/regulations in Chile and in Brazil established for the comparability pathway, the Colombian decree requires an exercise of comparability at the quality level for all biological products developed under the route of comparability. However, in contrast to the WHO, Chile and Brazil, the Colombian decree does not provide any details on how the manufacturing process of the biosimilar should be designed to obtain a product as similar as possible to the reference product. Moreover, the decree does not contain any details on how the quality properties of both products should be characterized and compared and how the result of the comparability exercise should be evaluated. Instead, the decree contains a “transitional paragraph” stating that INVIMA will refer to the WHO guidelines for the evaluation of the comparability exercise, as long as it is not contradicting the requirements of decree 1782 or other health regulations in force.

For biosimilar products developed under the abbreviated comparability pathway, the Colombian decree requests that the API (and not the final drug product) is sufficiently characterized following the general quality requirements established for all biological products. In contrast to the comparability pathway in Colombia and similar to the individual development pathway in Brazil, the abbreviated comparability pathway does not require a comparability exercise on the quality level. Instead, the decree offers several options to characterise the API of a proposed biosimilar product: i) comparison of the API with a reference product, ii) comparison of the API with a pharmacopeial reference standard (if such a standard is available), iii) comparison of the API with the information provided by other health authorities for a reference product and/or iv) comparison of the API to the whole of products containing an API considered to be highly similar to the biosimilar product. The decree requires, despite of minor differences in pharmacologically inactive components, that the biosimilar product is highly similar to the respective reference product or at least to the pharmacopeial pattern of an established pharmacopeia reference standard. In addition, considering the quality characteristics of the biosimilar, global evidence is required that no clinically meaningful differences exist in terms of safety, purity and potency with regard to the whole of drugs containing an API considered to be highly similar to the biosimilar product.

4.4 Comparison of non-clinical data required for abbreviated licensing of biosimilar products

The Chilean guideline and the comparability pathway in the Brazilian regulation generally implement the WHO recommendations with respect to the non-clinical data required for a biosimilar application. The design and extent of non-clinical studies should be based on the outcome of the physicochemical and biological characterization and the potential impact of any detected differences on efficacy and safety of the product. The applicant must at least perform one comparative repeat-dose toxicity study in a relevant animal species. In addition, the non-clinical studies must always include a comparison between the biosimilar and the reference product in terms of pharmacodynamic activity for the intended clinical applications. Differences between the Chilean guideline and the comparability pathway in Brazil exist regarding the design of the PD studies. Whereas the Chilean guideline follows the WHO recommendation stating that the PD properties may alternatively be compared in clinically relevant and validated in vitro bioassays, the Brazilian regulation only mentions that the pharmacodynamic studies must be performed in in vivo animal studies. Further discrepancies

exist between the WHO, Chile and the comparability pathway in Brazil regarding the level of detail on the design of the non-clinical studies and investigated toxicological parameters. Both the Chilean guideline and the Brazilian regulation do not mention that the non-clinical studies should be performed with the final formulation of the product and should always include a head-to-head comparison to the reference product. In addition, it is not mentioned that the ICH S6 (R1) guideline for preclinical safety evaluation of biopharmaceuticals should be taken into account for the study design (e.g. if the reference product has known toxicological properties). Finally, only the Chilean guideline but not the Brazilian regulation refers to the WHO recommendations stating that antibody responses should be determined as part of the toxicity study and that local tolerance should also be evaluated depending on the route of administration of the product (cf. Sections 3.3.2 and 3.3.3.1)

According to the Brazilian regulation, the extent of non-clinical studies may also be reduced for biological products submitted under the individual development pathway in case of less complex molecules with known physicochemical and pharmacological properties or originator products with a well-established efficacy and safety profile. In contrast to the requirements established by the WHO, Chile and the comparability pathway in Brazil, comparative non-clinical studies are not requested for the individual development pathway. However, no further details regarding the type and scope of non-clinical studies are provided in the Brazilian regulation (c.f. Section 3.3.3.2.)

According to the Colombian decree and consistent with the WHO guidelines and the guidelines/regulations in Chile and in Brazil for the comparability pathway, for all biological products developed under the route of comparability non-clinical studies must be submitted as part of the comparability exercise comparing the biosimilar and the reference product. Apart from that the decree does not provide any additional details which non-clinical studies are expected or how the studies should be conducted. Instead, it is only mentioned that INVIMA will currently refer to the WHO guidelines for evaluation of the comparability exercise and that Colombia's Ministry of Health and Social Protection plans to issue a separate immunogenicity guideline with non-clinical requirements for immunogenicity assessment of biological products (cf. Section 3.3.4.1.)

Similar to the individual development pathway in Brazil but not in alignment with the WHO, Chile and the comparability pathways established in Brazil and Colombia, the abbreviated comparability pathway in Colombia does not require any comparative non-clinical data for a biosimilar application. Instead, the applicant may submit the publicly available non-clinical information from products containing an API considered to be highly similar to the proposed biosimilar product. Based on this information INVIMA will then assess if additional non-clinical information or studies need to be provided. Moreover, the decree does not contain any additional information which studies are expected and/or how the studies should be performed, for instance in cases in which the submitted non-clinical data is considered as not sufficient by the authorities (cf. Section 3.3.4.2.)

4.5 Comparison of clinical data required for abbreviated licensing of biosimilar products

Significant differences exist between the WHO guidelines and the established guidelines/regulations in Chile, Brazil and Colombia with respect to the clinical data requirements for a biosimilar application. Whereas the Chilean guideline contains detailed requirements regarding the clinical study design for an abbreviated licensing application, such detailed information is missing in the Brazilian regulation as well as in Colombian decree. In

accordance with the WHO, the Chilean guideline requires head-to-head comparative clinical studies as part of the comparability exercise between the biosimilar and the reference product. The design of the clinical study should allow the detection of any relevant differences between the two products and should be determined on a case-by-case basis, taking into account the product class and the results from the quality and non-clinical comparability studies. Furthermore, the clinical comparability studies should follow a step-by-step procedure, starting with the PK and PD studies, followed by comparative efficacy and safety clinical studies. For the requirements of demonstrating clinical comparability for a specific product-class (i.e., recombinant human insulin, epoetin, recombinant somatotropin, granulocyte-colony stimulating factor, interferon and monoclonal antibodies), the Chilean guideline makes reference to the product-specific guidelines published by EMA (cf. Section 3.4.2.)

The Chilean guideline as well as the comparability pathways of the Brazilian regulation and the Colombian decree request confirmatory PK and PD studies as part of the clinical comparability exercise. However, further details on the clinical study design, regarding e.g. the route of administration, the dosing scheme (single/multiple dose, crossover design) or the study population, are again only provided in the Chilean guideline. In case comparability in efficacy can be demonstrated through the PK/PD studies, the Chilean guideline allows, in line with WHO, to omit additional clinical efficacy studies if following prerequisites are met: i) the PK/PD properties and mode of action of the reference product is known and characterized, ii) the relationship between dose/exposure, PD markers and clinical response of the reference product is well established, iii) at least one of the investigated PD markers is a validated surrogate marker for clinical efficacy, and iv) the criteria for the study design, dose selection and investigation of relevant PK/PD parameters are applied in accordance with the product-class specific guidelines provided by EMA (cf. Section 3.4.2.).

For biological products developed under the individual pathway in Brazil, phase I and II clinical studies including an assessment of PK/PD parameters will need to be conducted. However, in contrast to the comparability pathway and the requirements established by the WHO and the Chilean guideline, for the individual development pathway the Brazilian regulation 55/2010 does not explicitly request that the PK/PD assessment during phase I/II clinical trials has to include a comparison to the reference product (cf. Section 3.4.3.2.).

According to the guidelines/regulations in Chile, for the comparability and individual development pathway in Brazil and for the comparability pathway in Colombia, comparative clinical studies to confirm comparability in terms of efficacy and safety are obligatory required, thereby implementing the requirements of the WHO guidelines. Again, the most detailed description of requirements can be found in the Chilean guideline. Comparative clinical efficacy studies will generally be required for a biosimilar application according to the Chilean guideline, unless, as already outlined above, comparability in efficacy has already been demonstrated by the PK/PD studies. However, the guideline in Chile still requires a clinical comparability study comparing the safety profile of the biosimilar and the reference product, which may also be performed in the course of a combined clinical safety and efficacy study. Furthermore, as recommended by the WHO, the Chilean guideline requires an equivalence study design for the comparison of the efficacy and safety profile and the comparability margins of the clinical trial must be pre-defined and statistically justified (cf. Section 3.4.2.). The Brazilian regulation provides only a very brief description of the requirements for the clinical safety and efficacy studies. While for both the comparability and

the individual pathway in Brazil the clinical safety and efficacy studies have to be comparative in nature (except for blood products, vaccines and biological products developed in an oncological indication under the individual development pathway), equivalence as well as non-inferiority study designs are acceptable for biological products under the individual development pathway (cf. Section 3.4.3.2.). In addition, for biological products registered by the comparability and individual development pathway the Brazilian regulation explicitly requests to submit all results from phase IV clinical safety surveillance studies in case such studies have been conducted (cf. Sections 3.4.3.1 and 3.4.3.2.). In consistence with the requirements in Chile and Brazil, comparative clinical efficacy and safety studies are also requested for biological products developed under the comparability pathway in Colombia. As part of the clinical efficacy and safety studies, a comparative evaluation of PK/PD properties and adverse effects (including immunogenicity) has to be provided with the marketing authorization application. The decree states that the efficacy and safety assessment will also consider the complexity of the molecule and will take into account additional information such as clinical trial and pharmacovigilance data provided from other countries in which the biological product is already marketed. This information may also comprise safety and efficacy data of other drugs containing an API considered to be highly similar to that of the biological product for which marketing authorization is intended. No further details which clinical studies are expected or how the studies should be designed are stated in the Colombian decree; it is only mentioned that for the evaluation of the practice of comparability exercise INVIMA will refer to the WHO guidelines (cf. Section 3.4.4.1). For biological products developed under the abbreviated comparative pathway in Colombia, even less information on the expected clinical data package in terms of efficacy and safety is given in the Colombian decree. The applicant may select the abbreviated comparative pathway in case the API of the biological product under evaluation has a well-documented efficacy and safety profile, and extensive clinical experience and pharmacovigilance information is already available. Strongly deviating from the requirements in Chile and Brazil for the comparability and individual development pathway as well as for the comparability pathway in Colombia, it may not even be necessary to provide own clinical data for the abbreviated comparability pathway in Colombia. Alternatively, the applicant may only submit the available clinical information from the whole of products containing an API considered to be highly similar to the biological product under evaluation provided by health authorities from other countries. Based on this information and the studies that have been conducted with the product under evaluation, INVIMA will assess whether additional clinical information will be required (cf. Section 3.4.4.2).

Pre-licensing immunogenicity data that may be gathered during the comparative clinical efficacy and safety studies are mandatorily required for a biosimilar application according to the WHO guideline. This requirement has also been adopted in the Chilean guideline, in the Brazilian regulation for the comparative and individual pathway and in the Colombian decree for the comparability pathway. However, as for the requirements with regards to the PK/PD, efficacy and safety clinical studies, only the Chilean guideline incorporates more details from the WHO guidelines on how immunogenicity should be evaluated for a biosimilar product. Accordingly, the immunogenicity studies should include a direct comparison of the frequency and type of detected anti-drug antibodies with the reference product and should include an assessment of all possible clinical consequences of the immune response in the respective target population. In addition, the Chilean guideline considers the fact that it will not be feasible to provide a final assessment of the immunogenicity risk of a biosimilar product prior to its approval and thus requires a post-marketing pharmacovigilance and risk management

plan to be submitted with the abbreviated licensing application (cf. Section 3.4.2.1.5.). The requirement for post-marketing immunogenicity evaluation as part of the pharmacovigilance and risk management plan has also been taken up in the Brazilian regulation for biological products developed under the comparative as well as the individual development pathway (cf. Section 3.4.3.). For biological products developed under the comparability pathway in Colombia, the decree only states that information on safety including adverse effects and immunogenicity has to be provided as part of the clinical comparability exercise. However, the Ministry of Health and Social Protection of Colombia plans to provide more detailed guidance for the assessment of immunogenicity, setting up risk management plans and pharmacovigilance processes in a separate immunogenicity guideline. The intended immunogenicity guideline will apply for all biological products developed under the full dossier, the comparability and the abbreviated comparability pathway (cf. Section 3.4.4.).

In accordance with the WHO guidelines, both the Chilean guideline and the comparability pathway in the Brazilian regulation include the option to extrapolate efficacy and safety data demonstrated in one indication to other clinical indications of the reference product. However, extrapolation of indications will only be possible if the product has the same mode of action in the extrapolated indication(s) and the efficacy and safety profile has already been characterized in a sensitive clinical model, allowing to detect potential differences between the biosimilar and the reference product (cf. Sections 3.4.2.2 and 3.4.3.1). For biological products registered under the individual development pathway in Brazil, the regulation explicitly states that extrapolation of safety and efficacy data to additional clinical indications will not be possible (c.f. Section 3.4.3.2). No requirements for extrapolation of indications are provided in the Colombian decree for products developed under the comparative as well as the abbreviated comparative pathway.

5 Summary and Conclusion

In the context of the growing cost pressure on health markets, health agencies all over the world view biosimilars as a means to reduce costs and facilitate the access to affordable efficacious medication. In order to ensure quality, safety and efficacy of these products, health authorities have started to establish regulatory standards, many of them adopting the general principles of the WHO guidelines for biosimilars ([7]; [3]; [1]; [8]). Consequently, biosimilar products have also gained an increasing attractiveness in Latin America. Several governments in Latin America have already implemented specific regulations or guidance documents for the registration of these products ([27]; [18]; [7]; [8]; [3]; [23]; [28]).

This master thesis compares the regulatory requirements for the licensure of biosimilars in the LATAM countries Chile, Brazil and Colombia with the WHO standards for biosimilar products. These three countries are selected to exemplify the diversity of regulatory standards within the LATAM region.

The comparison of regulatory requirements for licensing of biosimilars in Chile, Brazil and Colombia with the WHO standards for biosimilar products reveals a variety of similarities and differences. The main findings of this analysis are summarized in Table 2.

According to the WHO guidelines, the reference product plays a key role for evaluation of a biosimilar product. Regarding the choice of the reference product, most of the key requirements in the WHO guidelines are also considered in the established guidelines/regulations of Chile, Brazil and Colombia. In all three countries the reference product must be approved based on a complete dossier, however it is not necessarily required that a nationally authorized reference product is used for the comparability exercise but also a foreign reference product may be accepted. Of note, none of these countries considers the recommendation of the WHO that the chosen reference product should be on the market for an appropriate period of time and constitute a sufficiently large market volume. This indicates that a reference product with only a small database of post-approval safety and efficacy information may also be acceptable for the regulatory authorities in Chile, Brazil and Colombia.

The Chilean guideline „Norma Technica No. 170“ generally implements the same regulatory principles and requirements for quality, non-clinical and clinical data as stipulated by the WHO guidelines and provides the most detailed information for licensing of a biosimilar product when compared to the guidelines/regulations in Brazil and Colombia. In accordance with the WHO guidelines, a thorough comparability exercise showing a high degree of similarity between the reference and the biosimilar product at the quality level is a prerequisite for abbreviated licensing of the biosimilar product with reduced non-clinical and clinical data including comparative PK/PD, efficacy and safety studies. Furthermore, the Chilean guideline includes the option of extrapolation of results from clinical efficacy and safety studies performed in one indication to additional clinical indications of the reference product. However, extrapolation of indications requires that the reference product has the same mode of action in the extrapolated indication(s) and the efficacy and safety profile has already been characterized in a sensitive clinical model.

In contrast to Chile and deviating from the WHO guidelines, the Brazilian regulation RDC 55/2010 establishes two alternative regulatory pathways for abbreviated licensing of

biological products: the “route of development by comparability” and the “route of individual development”. Both pathways differ with respect to the quality, non-clinical and clinical data requirements: whereas the comparability pathway requires a comparability exercise at the quality level as well as comparative non-clinical and clinical study results as requested by the WHO, at least a comparative head-to-head phase III clinical study is mandatorily required for the individual development pathway. Following this pathway, non-clinical studies do not have to be comparative and can be reduced depending on the molecule’s complexity, the knowledge of impurity levels as well as the safety and efficacy profile of the originator product. Furthermore, phase I/II clinical studies have to be performed but again these studies do not have to be comparative. Not described in the Brazilian regulation but specified by ANVISA in a publication [40], the individual development pathway is thought as a midway between the full dossier pathway for new biological products and the comparability pathway for biosimilar products. The individual development pathway is intended for certain types of less complex biological products and may be selected for those products within the scope of the Brazilian regulation where a comparability approach would not be appropriate, such as hemoderivative products, vaccines and hyperimmune sera [41]. However, ANVISA clearly states that the individual development pathway should not be the first choice for well-characterized biotechnology-derived products [40]. Since the individual development pathway includes comparative clinical efficacy and safety data but omits a complete comparability exercise, this regulatory pathway does not aim to result in a product with a high degree of similarity on the physicochemical and biological level but only in a clinically comparable product. Importantly, only biological products developed by the comparability pathway can be regarded as biosimilars as defined by the WHO guidelines [40]. As a consequence, the Brazilian regulation restricts the possibility for extrapolation of indications to biological products registered through the comparability pathway whereas this option is precluded for the individual development pathway. Concerning the comparability pathway in Brazil, very detailed guidance for the comparability exercise in terms of quality is given in a dedicated quality guideline [42], however, deviating from WHO and Chile, no further details are defined in the Brazilian regulation for the clinical study requirements; the regulation only states that comparative clinical PK/PD, efficacy, safety and immunogenicity studies are required.

Even less information is provided in the Colombian decree 1782 and, in addition to that, the Colombian decree sets the lowest regulatory and scientific standards for abbreviated licensing of biosimilar products in comparison with the guidelines/regulations established in Chile and Brazil. Following the example of Brazil, in Colombia biosimilar products may be evaluated and approved via two different regulatory pathways: the comparability pathway and the abbreviated comparability pathway. The comparability pathway implements some of the main principles of the WHO guidelines, comprising a step-wise comparability assessment and demonstration of similarity at the quality level as well as head-to-head non-clinical and clinical efficacy and safety studies with the biosimilar and the reference product. However, the requirements for evaluation of the comparability exercise, the extent and design of non-clinical and clinical PK/PD, efficacy and safety studies as well as for extrapolation of indications remain undefined in the Colombian decree. Instead, it is only stated that INVIMA will use the WHO guidelines for the assessment of the comparability exercise. In contrast to the comparability pathway, the comparability exercise may be entirely omitted for the abbreviated comparability pathway in Colombia. In fact, the Colombian decree only requests that the API but not the final drug product is sufficiently characterized according to the general quality requirements for biological products and offers several equivalent options for

characterisation of the API: i) comparison of the API with a reference product, ii) comparison of the API with a pharmacopeial reference standard, iii) comparison of the API with the information provided by other health authorities for a reference product and/or iv) comparison of the API to the whole of products containing an API considered to be highly similar to that of the biosimilar product. Moreover, under the abbreviated comparability pathway it is not even required to provide own non-clinical and clinical data; the applicant may only refer to non-clinical and clinical information from other health agencies outside of Colombia including evidence that the product(s) with a claimed identical API has a well-established safety and efficacy profile documented by clinical trials and the available post-marketing safety information. However, since the manufacturing process of the reference product(s) and the biosimilar product will not be the same, it is expected that the quality attribute profile will also be different which may easily result in clinically relevant differences in terms of efficacy, safety and immunogenicity of the products. Based on the fact that a biosimilar product may be approved without confirmed clinical evidence of efficacy and safety and solely based on information derived from other products, the EU and US as well as several Colombian patient organizations raised concerns regarding the abbreviated comparability pathway in the Colombian decree ([26]; [58]); in a letter to the Colombian President Juan Manuel Santos, the US Vice President Joe Biden wrote that the WHO and US experts believe that the Colombian decree 1782 could put health and safety of patients at risk [58].

In conclusion, the comparison of regulatory requirements for licensing of biosimilar products in Chile, Brazil and Colombia with the WHO guidelines reveals significantly different regulatory standards in the three countries and reflects the diversity of standards among the LATAM countries that has previously been described in a study conducted by PAHO in 2013 [28]. Although there is a general tendency to follow and implement the WHO guidelines, different levels of evidence as well as alternative regulatory pathways with less stringent, vague or undefined requirements for the approval of biosimilar products remain a considerable challenge in the LATAM region [26]. Another common issue in many LATAM countries is how to re-assess the large number of “intended copies”, i.e. the biological products that have been registered in the past according to the requirements for small molecule generic drugs and that do no longer meet the recently introduced requirements for biosimilar products based on the WHO standards. Since the efficacy and safety of the intended copies has not been demonstrated yet, these products cannot be considered as biosimilars, however so far none of the LATAM countries requires the approved intended copies to also comply with the current biosimilar regulations in these countries. Against this background, to ensure that all biological products follow same standards in terms of quality, efficacy and safety, big efforts will still be necessary by the regulatory authorities to further harmonize and strengthen the regulatory standards in the LATAM region and by pharmaceutical industry to perform the outstanding studies for intended copies according to the requirements for biosimilar products ([26]; [27]).

Furthermore, although the LATAM countries have begun to introduce post-marketing pharmacovigilance and risk management plans for biosimilar products in their guidelines/regulations (e.g. Chile and Brazil), so far only few regulatory authorities have managed to implement active pharmacovigilance systems to effectively monitor adverse events during clinical application of these products [27]. However, strict post-authorization safety surveillance and analysis of the collected data is a prerequisite for the identification of safety risks such as immunogenic responses associated with the application of a specific biosimilar product and the reference product. Therefore, the implementation of effective

pharmacovigilance systems in the LATAM region will be required to enhance the traceability of adverse events and reactions to biosimilar products, thus contributing to a better protection of public health and patient safety.

Table 2. Regulatory data requirements: WHO, Chile, Brazil and Colombia (c.f. [8]).

	WHO		Chile		Brazil		Colombia	
	Choice of the reference product	Route of development by comparability	Route of individual development	Comparability pathway	Comparability abbreviated pathway			
Choice of the reference product	<ul style="list-style-type: none"> - Reference product authorized with a full dossier - Reference product marketed with an appropriate duration and market volume - Reference product authorized in foreign countries may be accepted - Same reference product must be used during comparability exercise 	<ul style="list-style-type: none"> - Reference product authorized with a full dossier - Reference product authorized in foreign countries may be accepted - Same reference product must be used during comparability exercise 	<ul style="list-style-type: none"> - Reference product authorized with a full dossier - Reference product authorized in foreign countries may be accepted if technical/scientific standards are comparable and full access to registration information is provided - Same reference product must be used during comparability exercise 	<ul style="list-style-type: none"> - Reference product authorized with a full dossier - Reference product authorized in foreign countries may be accepted from specific countries/regions 				
Quality data	Complete quality data with comparability exercise; detailed requirements in the WHO guidelines	Complete quality data with comparability exercise; detailed requirements in the Chilean guideline	Complete quality data, no comparability exercise required	Complete quality data with comparability exercise; no details in the Colombian decree (reference to WHO guidelines)	Complete quality data; no comparability exercise required, but comparison of API against available data or information from reference product or pharmacopoeial standard			
Non-clinical data	Reduced non-clinical data: Comparative repeat-dose toxicity study and comparison of PD activity is minimum requirement	Reduced non-clinical data: Comparative repeat-dose toxicity study and comparison of PD activity is minimum requirement	Reduced non-clinical data possible: No comparative studies required, extent of non-clinical studies depends on complexity of the molecule	Reduced non-clinical data: Comparative studies requested without further details (reference to WHO guidelines)	No own non-clinical data required: Available information on safety/efficacy from products containing an API considered to be highly similar is requested			
Clinical data	Reduced clinical data: Comparative phase I (PK/PD) and phase III (efficacy, safety and immunogenicity) studies with detailed requirements in the WHO guidelines	Reduced clinical data: Comparative phase I (PK/PD) and phase III (efficacy, safety and immunogenicity) studies with detailed requirements provided in the Chilean guideline	Complete clinical data: Phase I/II (PK/PD, safety, efficacy) studies may not be comparative in nature. Comparative phase III (efficacy, safety and analysis of immunogenicity) will always be required; no detailed requirements provided in the Brazilian resolution	Reduced clinical data: Comparative phase I (PK/PD) and phase III (efficacy, safety and immunogenicity) studies; no detailed requirements provided in the Colombian decree (reference to WHO guidelines and planned immunogenicity guideline in Colombia)	No own clinical data required: Available information on safety and efficacy from products containing an API considered to be highly similar is requested			
Extrapolation of indications	Extrapolation of indications possible	Extrapolation of indications possible	Extrapolation of indications not possible	No information on extrapolation of indications provided in the Colombian decree	No information on extrapolation of indications provided in the Colombian decree			

6 References

- [1] Mena-Pérez S. C., Bondani-Guasti A., Garcia.Arrazola R. Ibarra-Cabrera R., "Review on the worldwide regulatory framework for biosimilars focusing on the Mexican case on an emerging market in Latin America," *Biotechnology Advances*, vol. 31, pp. 1333-43, May 2013.
- [2] Niederwieser D., Ludwig H. Mellstedt H., "The challenge of biosimilars," *Annals of Oncology*, vol. 19, no. 3, pp. 411-19, Mar 2008.
- [3] Caballero-Uribe C. V., Gonclaves de Oliveira M., et.al Pineda C., "Recommendations on how to ensure the safety and effectiveness of biosimilars in Latin America: a point of view," *Clin Rheumatol*, vol. 34, pp. 635-40, Feb 2015.
- [4] Rocca L. (2015, Aug) MARKET BRIEF - Latin America Next-Generation Biosimilars Market: Opportunities & Future Grows. [Online]. <http://www.drug-dev.com/Main/Back-Issues/MARKET-BRIEF-Latin-America-NextGeneration-Biosimil-663.aspx>
- [5] Ruiz S., Schneider C. K. Tsiftoglou A. S., "Development and Regulation of Biosimilars: Current Status and Future Challenges," *BioDrugs*, vol. 27, pp. 203-11, Apr 2013.
- [6] Q. F. H. Rosenbluth. (2015, Jan) Biotechnological Regulation in Chile and Biosimilarity. [Online]. http://c.ymcdn.com/sites/www.casss.org/resource/resmgr/WCBP_Speaker_Slides/2014_WCBP_Helen_Rosenbluth.pdf
- [7] Scheinberg M. Mysler E., "Biosimilars in rheumatology: a view from Latin America," *Clin Rheumatol*, vol. 31, no. 9, pp. 1279-80, Aug 2012.
- [8] Sandorff E., Siermak B., Halbert R.J. Azevedo V.F., "Potential regulatory and commercial environment for biosimilars in Latin America," *Value in health regional issues*, vol. 1, no. 2, pp. 228-34, Dec 2012.
- [9] Quinones L. Saavedra I., "Intercambiabilidad de medicamentos de origen biológico (biofármacos): Consideraciones acerca de la aprobación de formulaciones biosimilares (biogénicos) en Chile Interchangeability of biological drugs: Considerations about the approval of biogeneric formulations in Chile," *Rev Méd Chile*, vol. 134, no. 12, pp. 1583-8, Dec 2006.
- [10] Wang S., "Patent search on biologicals as potential biosimilar candidates," *World Patent Inf*, vol. 33, no. 1, pp. 67-71, Mar 2011.
- [11] Oteo L.A. Inesta A., "La industria farmacéutica y la sostenibilidad de los sistemas de salud en países desarrollados y América Latina.[The pharmaceutical industry and the sustainability of the health systems in developed countries and Latin America]," *Ciênc. saúde coletiva*, vol. 16, no. 6, pp. 2713-24, Jun 2011.
- [12] Ugalde A. Homedes N., "Multisource drug policies in Latin America: survey of 10 countries," *Bull World Health Organ.*, vol. 83, no. 1, pp. 64-70, Jan 2005.
- [13] Woollett G. Brockmeyer C., "Developing Quality Biosimilars," *Applied Clinical Trials*, vol. 21, no. 7, Jul 2012.
- [14] Assogenerici. (2012, Jun) Biosimilars - about to leap. [Online]. http://www.assogenerici.org/articolihome/Convegno_2012/PRESENTAZIONE_IERV

[OLINO_IMS.pdf](#)

- [15] Bielsky M.C., De Smet K., Ehmann F., et al Weise M., "Biosimilars - why terminology matters," *Nat Biotechnol*, vol. 29, no. 8, pp. 690-3, Aug 2011.
- [16] Griffiths E. Knezevic I., "Biosimilars - global issues, national solutions," *Biologicals*, vol. 39, no. 5, pp. 252-55, Sep 2011.
- [17] Kresse G.B., "Biosimilars - science, status, and strategic perspective," *Eur J Pharm Biopharm*, vol. 72, no. 3, pp. 479-86, Aug 2009.
- [18] Caro-Moreni J., Enciso-Zuluaga M., Anaya J.M. Desanvicente-Celis Z., "Similar biotherapeutic products in Latin America. Regulation and opportunities for patients with autoimmune diseases," *Biosimilars*, vol. 3, pp. 1-17, Jan 2013.
- [19] Szekanecz Z., Mysler E. et al Castaneda-Hernandez G., "Biopharmaceuticals for rheumatic diseases in Latin America, Europe, Russia, and India: Innovators, biosimilars and intended copies," *Joint Bone Spine*, vol. 81, no. 6, pp. 471-7, Dec 2014.
- [20] WHO Expert Committee on Biological Standardization. (2013) Sixtieth Report - Annex 2. [Online].
http://www.who.int/biologicals/expert_committee/TRS_977_60th_report.pdf
- [21] Kirchlechner T., "Current regulations of biosimilars in the Latin American Region," 3rd Annual Drug Information Association (DIA), April 12-15, Panamy City, Panama, Paper 2011.
- [22] WHO Expert Committee on Biological Standardization. (2015, Feb) WHO GMP for Biological Products. [Online].
http://www.who.int/biologicals/GMP_for_Biologicals_Draft3-V2_20150218.pdf
- [23] Generics and Biosimilars Initiative (GaBi). (2015, Jun) Similar biotherapeutic products approved and marketed in Latin America. [Online].
<http://www.gabionline.net/Biosimilars/General/Similar-biotherapeutic-products-approved-and-marketed-in-Latin-America>
- [24] IHS MarkIt. (2016, Mar) Peruvian president signs biosimilars regulation, MoH forecasts biologic medicine price reductions of up to 60%. [Online].
<https://www.ih.com/country-industry-forecasting.html?ID=10659110149>
- [25] Generics and Biosimilar Initiative (GaBi). (2013, Aug) Regulation of similar biotherapeutic products in Latin America. [Online].
<http://gabionline.net/Biosimilars/Research/Regulation-of-similar-biotherapeutic-products-in-Latin-America>
- [26] R. Garcia and D.V. Araujo, "The Regulation of Biosimilars in Latin America," *Curr Rheumatol Rep.*, vol. 18, no. 3, p. 16, Mar 2016.
- [27] Mysler E., Álvarez A. A., Hughes J., Flores-Murrieta F. J., Ruiz de Castilla E. M. Azevedo V. F., "Recommendations for the regulation of biosimilars and their implementation in Latin America," *Generics and Biosimilars Initiative*, vol. 3, no. 3, pp. 143-68, Jun 2014.
- [28] P. Saidon, Level of adoption and implementation of technical document No 7, Sep 5-7, 2013.
- [29] I. Knezevic, WHO Survey on Biotherapeutic Products (focus on clinical issues), Sep 5-7, 2013.
- [30] Azevedo V. F., "Biosimilars require scientifically reliable comparative clinical data,"

Rev Bras Reumatol, vol. 53, no. 1, pp. 129-31, Feb 2013.

- [31] Gossler U., What are the prospects for a global „biosimilar“ development? Comparison of the regulatory requirements for the marketing authorisation of biosimilar products using the example of implemented or proposed legislation in the EU, Canada, Japan and the proposed WHO guidance, Jan 2010.
- [32] Robertson J. S., Griffiths E., Knezevic I. Joung J. and WHO Informal Consultation Group., "WHO Informal Consultation on Regulatory Evaluation of Therapeutic Biological Medicinal Products," *Biologicals*, vol. 36, no. 4, pp. 269-76, Jul 2008.
- [33] World Health Organisation. (2015) Biological products: general recommendations. [Online]. <http://www.who.int/biologicals/areas/en/>
- [34] Fabiola Muñoz E. Q. F. (2014, August) CMC Strategy Forum LATAM 2014. [Online]. https://c.ymcdn.com/sites/casss.site-ym.com/resource/resmgr/CMC_LATAM_Speaker_Slides/2014_CMCLAT_MunozFabiola.pdf
- [35] Agencia Nacional de Medicamentos (ANAMED). (2014, Aug) Norma Biotecnologicos. [Online]. <http://www.ispch.cl/sites/default/files/Norma%20Biotecnologicos.pdf>
- [36] de Souza Teixeira L., Fernandes de Santana F., Cardoso S., da Costa César I., Pianetti G. A. Chiann Ch., "Biosimilarity in Latin America," *Generics and Biosimilars Initiative Journal (GaBI Journal)*, vol. 2, no. 2, pp. 94-96, Apr 2013.
- [37] Generics and Biosimilars Initiative (GaBi). (2012, Jan) Proposed biosimilar guidelines for Chile. [Online]. <http://www.gabionline.net/Guidelines/Proposed-biosimilars-guidelines-for-Chile>
- [38] Gobierno de Chile /Instituto de Salud Pública. Subdepartamento de Registro: Biotecnológicos. [Online]. http://www.ispch.cl/anamed/subdeptoregistro/seccion_productos_nuevos/biotecnologicos
- [39] Generics and Biosimilar Initiatives (GaBi). (2012, Aug) Building trust in cost-effective treatments. [Online]. <http://www.gabionline.net/Guidelines/Brazilian-guidelines-for-follow-on-biological-products>
- [40] Barbano D. B., Rech N. Castanheira L. G., "Current development in regulation of similar biotherapeutic products in Brazil," *Biologicals*, vol. 39, no. 5, pp. 308-11, Aug 2011.
- [41] Agência Nacional de Vigilância Sanitária, Anvisa. (2010, Dec) Resolução RDC nº 55 de 16 de dezembro de 2010. Dispões sobre o registro de produtos biológicos novos e produtos biológicos e da outras providências. [Online]. http://www.desenvolvimento.gov.br/arquivos/dwnl_1307385325.pdf
- [42] Agência Nacional de Vigilância Sanitária, Ministério da Saúde. (2011, Dec) Guia para Realização do Exercício de Comparabilidade para Registro de Produtos Biológicos. [Online]. <http://portal.anvisa.gov.br>
- [43] República de Colombia, Health Ministry. (1995, Apr) Decreto 677 de 1995. [Online]. <http://www.alcaldiabogota.gov.co/sisjur/normas/Norma1.jsp?i=9751>
- [44] Generics and Biosimilar Initiative (GaBi). (2013, Mar) Colombia issues draft decree for registration of biologicals. [Online]. <http://www.gabionline.net/Guidelines/Colombia-issues-draft-decree-for-registration-of->

biologicals

- [45] Generics and Biosimilars Initiative (GaBi). (2015, Jun) Colombian guidelines for productos bioterapéuticos similares. [Online].
<http://gabionline.net/Guidelines/Colombian-guidelines-for-productos-bioterapeuticos-similares>
- [46] República de Colombia, Health Ministry. (2014, Sep) Decree 1782/2014. [Online].
https://www.minsalud.gov.co/Normatividad_Nuevo/Decreto%201782%20de%202014.pdf
- [47] Universidad Externado de Colombia. (2014, Oct) The Colombian Biological Medicines Decree. [Online].
<http://propintel.uexternado.edu.co/?s=colombian+biological+medicines+decree>
- [48] World Health Organization. (2009, Oct) Guidelines on evaluation of similar Biotherapeutic Products (SBPs), Annex 2, Technical Report Series No. 977, 2009. [Online].
http://www.who.int/entity/biologicals/publications/trs/areas/biological_therapeutics/TRS_977_Annex_2.pdf?ua=1
- [49] World Health Organisation, "Good manufacturing practices for biological products," in *WHO Expert Committee on Biological Standardization. Forty-second report.*, Geneva, 1992, p. Annex 1.
- [50] República de Colombia, Health Ministry. (2015, April) Draft GMP guideline for biological products. [Online].
<https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/VS/MET/BP-biologicos.pdf>
- [51] República de Colombia, Health Ministry. (2015, May) Draft stability guideline for biological drugs. [Online].
<https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/VS/MET/Guia-estabilidad-medicamentos-biologicos.pdf>
- [52] WHO Expert Committee on Biological Standardization. (2011, Aug) Guidelines on stability evaluation of vaccines (WHO Technical Report Series No. 962) - Annex 3. [Online]. http://www.who.int/biologicals/vaccines/Annex_3_WHO_TRS_962-3.pdf
- [53] ICH Expert Working Group. (1995, Nov) ICH Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products. [Online].
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5C/Step4/Q5C_Guideline.pdf
- [54] ICH Expert Working Group. (1997, Jul) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6(R1). [Online].
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S6_R1/Step4/S6_R1_Guideline.pdf
- [55] ICH Expert Working Group. (2004, Nov) Comparability of Biotechnological/Biological Products - ICH. [Online].
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf
- [56] ICH Expert Working Group. (2000, Jul) Choice of Control Group and Related Issues in Clinical Trials - ICH. [Online].
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E10

[/Step4/E10_Guideline.pdf](#)

- [57] ICH Expert Working Group. (1998, Feb) Statistical Principles for Clinical Trials - ICH. [Online].
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf
- [58] Generics and Biosimilars Initiative (GaBi). (2014, Sept) Concerns from EU and US over Colombian biologicals guidelines. [Online].
<http://www.gabionline.net/Guidelines/Concerns-from-EU-and-US-over-Colombian-biologicals-guidelines>
- [59] Wadhwa M. Thorpe R., "Terminology for biosimilars - a confusing minefield," *Generics and Biosimilars Initiative Journal (GaBI Journal)*, vol. 1, no. 3-4, pp. 132-4, Jul 2012.
- [60] Generics and Biosimilars Initiative (GaBI). (2014, Aug) The future of biosimilar use and regulation in Latin America. [Online].
<http://www.gabionline.net/Biosimilars/Research/The-future-of-biosimilar-use-and-regulation-in-Latin-America>

7 Eidesstattliche Versicherung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Unterschrift: