International Cooperation on Harmonisation of Technical Requirements
for Registration of Veterinary Medicinal Products

VICH/17060
May 1, 2018
Final

Internal Guidance Document

Definition of "Biologics"

1. Background

In the "VICH Priorities 2016-2020", it is stated that "Analyse the need for developing guidance on registration requirements for veterinary novel therapy products and initiate the development, or adaptation, of guidance for those types of products considered of greatest strategic importance to VICH". In this context, inclusion of a Biotechnological/Biological products guideline (Bio-products GL) should be one of the major points of considerations.

At the 31st SC meeting in Washington DC, 2015, the SC reviewed the report on the survey and needs assessment for the GLs for veterinary Bio-products prepared by JMAFF and noted that most of the SC members supported possible conversions of corresponding ICH GLs to VICH GLs, under the condition that an appropriate Concept Paper will be proposed and supported by the SC.

Through the survey, the SC also recognized that different terminology is used in different regions, sometimes to mean essentially the same thing. JMAFF then agreed to develop a discussion document on the definition of "biologics" generally being used by the regulatory authorities, industries and academia", so that the members are able to share a single reference point when considering the scope for such GL.

The objective of this internal document is therefore to clarify the meaning of relevant terms in order to avoid confusion when developing a VICH Bio-products GLs.

2. Definition and Taxonomy of "Biologics".

As shown in the list of definitions compiled in the Appendix, it was found that the wording "biologics", "biological products", "biopharmaceuticals", biological drug", etc. are used as a synonym. Although no de facto standard of the wording was found, "Biologics" seemed to be a representative of all for the time being.

This word actually is used also to represent classical immunological products e.g.,

vaccine and serum, as these had been dominating the products of biological origin for a long time. However, nowadays the list of product line categorized in Biologics is extended year by year along with the expansion of modern science such as molecular biology and cell based medicine.

It was pointed out that these definitions would not be legally binding, but this could be overcome by adding some explanatory remarks such as that these are independent of any regulatory framework of the authority.

Although there is a general understanding that “biologics” covers any medicinal products manufactured in or extracted from biological sources, understanding in corresponding products differs depending on the organization and/or the country, which leads to various overviews for such products.

As a springboard for the future discussions by the SC in defining “biologics”, at the 32nd SC meeting in Oct 2015, Tokyo, JMAFF proposed an example of “taxonomy of biologics” classifying numerous kind of products appeared in the Appendix, based on a function and/or physical property. At the following SC meetings, several supportive and constructive comments were provided from the members to the taxonomy proposed.

At the 34th SC meeting in Feb 2017, Buenos Aires, the SC reviewed and adopted the updated taxonomy table per the comments received as shown in Table 1 (Version 2).

The SC reconfirmed that this document, including the Taxonomy table, is informal and internal, not relating to any regulatory framework of any region” and that it will remain an internal VICH document that can evolve over time.

Table 1, Taxonomy of biologics (Version 3.0)*

Class	Subclass	Product type		Example	Mode of action
Biologics *(=Biologicals,Biopharma-ceuticals, Biological drugs)*	Cell/Tissue Products	Blood Products		Erythrocytes T-Cells, Monocytes, Platelets, Plasma	-Supply blood components -Replace/complement existing /lost tissue/cells -Deliver cytomodulators to heal tissues, calm inflammation -Strengthen immunological activity
		Somatic cells		Myocytes, Fibroblasts, Dendritic cells	
		Stem cells		iPS Cells, MSCs	
		Tissues		Cartilages, Bones, Skins, Blood vessels, Tendons, Ligaments	
		Genetically engineered (GE) animals		GE Atlantic salmon, goats, and chicken	
	Nucleotide Products	Gene therapeutics		Virus /Plasmid vector, DNA Vaccine	-Deliver new gene -Interfere with gene expression
		Oligonucleotide therapeutics		SiRNA , CpG oligo, Decoy, Aptamer	
	Immunologicals	Anti-bodies	Antisera	Anti-tetanus serum	-Replace stimulation of humoral immunity, immune component
			Immuno-globulins	Antivirus MAb	
		Immunogens	Vaccines	Organisms (Live, attenuated, inactivated, vector), Toxoid Subunit/component, Peptide, DNA	-Act through direct stimulation of immunity
			Allergenics		
		Immunomodulators		Interferons, Interleukins, CpG oligo	-Modulate immune response
	Cytomodulators	Hematopoietic factors		Erythropoietin, G-CSF	-Act through/on endocrine or paracrine system for growth promotion, cell recruitment, change in biological state
		Growth factors		FGF, HGF, VEGF, NGF	
		Hormones		Insulin, PMSG, CG, Oxytocin, Angiotensin	
	Catalyzers	Enzymes		TPA, lysozyme, Protease	-Act in cell metabolism
		Ribozymes			
	Others	Bacteriophage, probiotics, colostrum, squalene, saponin			

* These classification in this table is independent of any regulatory framework of any regulatory authority.

Appendix: Definition of “Biologics” generally being used by the regulatory authorities, etc...

1. Regulatory authorities

(1) US-FDA

The U.S. regulation of animal biologics differs from the regulation of human biologics. Animal biologics in the U.S. are regulated by the USDA, APHIS, Center for Biologics (CVB) while human biologics fall under the regulatory oversight of FDA’s Center for Biologics Evaluation and Research (CBER). Certain classes of products in the U.S., for example blood products and stem cells, when intended for use in humans, are regulated as biologics while such articles are regulated as drugs for use in animals. Because the Food Drug and Cosmetic Act does not have a statutory definition of “biologic new animal drugs” when intended for use in animals, these types of products are considered to be new animal drugs. The only codified definition for veterinary biologics is for CVB in the Virus -Serum-Toxin Act (VSTA) and 9 CFR Part 101.

(2) USDA

Veterinary Biologics

(http://www.aphis.usda.gov/wps/portal/aphis/ourfocus/animalhealth/sa_vet_biologics/)

APHIS regulates veterinary **biologics** (vaccines, bacterins, antisera, diagnostic kits, and other products of biological origin) to ensure that the veterinary biologics available for the diagnosis, prevention, and treatment of animal diseases are pure, safe, potent, and effective. This work is done by APHIS' Center for Veterinary Biologics (CVB) and is centered around enforcement of the Virus Serum Toxin Act.

(3) EMA

The terms “biological medicinal product” and “biological substance” are defined in European legislation relating to human medicines (Annex I of the Directive 2001/83/EC) as follows:

- A biological medicinal product is a product, the active substance of which is a biological substance
- A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control.

(4) Japan

Regulatory Rules for Veterinary Medicinal Products

(Dec. 24, 2004, Ministry of Agriculture, Forestry and Fisheries Ministerial Ordinance No. 107)

> "Biological products" in this Ministerial Ordinance refer to serums, vaccines and diagnostic reagents (including dried ones) and medical products similar to these which are intended to be used exclusively on animals, and that are to be used for diagnosing, preventing and/or treating diseases.

National Veterinary Assay Laboratory, Guidance for applicants Q&A

(http://www.maff.go.jp/nval/goiken/syonin_sodan/mokuji/QA_3_1.html)

What is Biotechnological Veterinary Medicinal Products (Bio-products), and what kind of technical dossier is required to apply the type of products?

Bio-products are the ones which contain well-characterized proteins and polypeptides, and their derivatives which are isolated from tissues, body fluids, cell cultures, or produced using recombinant deoxyribonucleic acid (r-DNA) technology, as their active ingredients.

This category thus covers cytokines, growth hormones, growth factors, insulins, and monoclonal antibodies. This category does not cover antibiotics, heparins, vitamins, cell metabolites, DNA products, DNA vaccine, allergenic extracts, classical vaccines, cell-based products, whole blood, and cellular blood components.

Bio-products are further classified into biological products or general medicine (excluding antibiotics). A technical dossier is basically the same to the ones for these products classes. However, if the product is classified as general medicine, as the products have characteristics that differs from chemical ingredients, notions below may also be considered;

1) Physical, chemical and biological properties are described more precisely than usual chemical products,
2) Toxicological and/or adsorption testing data are less required than usual chemical products provided it is scientifically justified, and
3) Testing data on the generation of anti-drug antibody (ADA) is required if the product is administered to the animals for a long period of time, to deny the inhibitory effect by the ADA.

(5) Health Canada

What is a veterinary biologic?

Veterinary biologics are animal health products such as vaccines, antibody products, and in vitro diagnostic test kits that are used for the prevention, treatment, or diagnosis of infectious diseases in animals, including domestic livestock, poultry, pets, wildlife, and fish.

The Health of Animals Act defines a veterinary biologic as follows:

veterinary biologic means a thing that is manufactured, sold or represented for use in restoring, correcting or modifying organic functions in animals or for use in the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state – or its symptoms – in animals and that is:

(a) a helminth, protozoa or micro-organism,

(b) a substance or mixture of substances derived from animals, helminths, protozoa, micro-organisms or plants, or

(c) a substance of synthetic origin

What is the difference between veterinary biologics and veterinary drugs?

Veterinary biologics include veterinary vaccines and antibody products used to treat or prevent infectious diseases in animals, as well as diagnostic test kits for the diagnosis of infectious diseases in animals. Veterinary biologics are regulated by CFIA-CCVB under the authority of the Health of Animals Act and Regulations.

The mode of action of a veterinary biologic involves an immunologic response to a particular infectious disease agent. If manufactured in Canada, the label of a veterinary biologic bears the Canadian Veterinary Biologics Establishment Licence number. If manufactured in the United States of America, the label bears the United States Veterinary Biologics Establishment License number.

Veterinary drugs include substances, or mixtures of substances, manufactured, sold or represented for use in the diagnosis, treatment, mitigation, or prevention of disease, disorder or abnormal physical state, or its symptoms in animals. Veterinary drugs may also be used for restoring, correcting or modifying organic function in animals. Veterinary drugs include antibiotics, antiparasitics, sedative and anaesthetic agents, antipyretics, etc. Veterinary drugs are regulated by the Veterinary Drugs Directorate of Health Canada under the authority of the Food and Drugs Act and Regulations. If licensed in Canada, a veterinary drug label bears a

drug identification number (DIN).

The complete FAQ is referenced at the following site:
http://www.inspection.gc.ca/animals/veterinary-biologics/licensed-products/questions-and-answers/eng/1318483540758/1320705655744

2. Industries

(1) AHI

Animal Health Terms
(http://www.ahi.org/about-animal-medicines/animal-health-terms/#B)

Biologicals
Products that detect, stimulate or enhance an animal's immunity to infection, and that are generally derived from living organisms.

(2) EFPIA(European Federation of pharmaceutical industries and associations)

Glossary(http://www.efpia.eu/library/glossary)

Biologic
Biologics include a wide range of medicinal products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins created by biological processes (as distinguished from chemistry).

(3) EBE(European biopharmaceutical enterprises)

Pharmaceutical Biotechnology (http://www.ebe-biopharma.eu/about-biopharma/pharmaceutical-biotechnology)

Biopharmaceuticals are large biological molecules such as proteins that are developed to address targets that cannot easily be addressed by small molecules. Due to their larger size, and corresponding difficulty with surviving the stomach, colon and liver, biopharmaceuticals are typically injected.

3. Academia

(1) Nature biotechnology

26, 743 - 751 (2008)

Ronald A Rader
doi:10.1038/nbt0708-743

(Re) defining biopharmaceutical
Box 3. Regulatory definitions of **biopharmaceuticals**
(http://www.nature.com/nbt/journal/v26/n7/box/nbt0708-743_BX3.html)

Most regulatory agencies, including the FDA, subscribe to the broad biotechnology view (see main text), whereas the European Union has largely adopted the new biotechnology view. However, the FDA and regulators in many other countries have no useful definition of 'biopharmaceutical' or related terms. The official FDA definition of 'biological products' or 'biologics' can be summarized as "any virus, therapeutic serum, toxin, antitoxin or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man". Similarly, the lengthy, official definition (codified in 21 CFR 600.3) vaguely defines biologics on the basis of analogies (that is, products similar to viruses, serums, toxins and antitoxins, as defined in 1902 when the US Virus-Toxin Law initiating the regulation of biologics manufacture was enacted). This definition avoids terms and concepts in use for generations (e.g., proteins, antibodies, genes, microbes, cells, viruses and DNA/RNA). In practice, biologics includes "a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues and recombinant therapeutic proteins". Most biopharmaceuticals (using the broad and new biotechnology paradigms) are classed and regulated by FDA as biologics. However, due to their similarity to products historically regulated as drugs, some simpler biopharmaceuticals are regulated as drugs, mostly recombinant hormones, for example, insulin and human growth hormone, and a few products are regulated as medical devices, with different laws and regulations applying to each class. Because of its specific link to regulation by FDA and complex definition, 'biologics' is best used only in its regulatory context.

European Union regulations define 'biological medicinal products' as "a protein or nucleic acid–based pharmaceutical substance used for therapeutic or *in vivo* diagnostic purposes, which is produced by means other than direct extraction from a native (nonengineered) biological source". This corresponds to the new biotechnology view (that is, by elimination, it is largely restricted to recombinant and mAb products). The terms 'biotechnology medicines' and 'biological medicinal products' are used to broadly refer to all biopharmaceuticals (by the broad biotechnology view). Although these terms are commonly used, European Union use is generally restricted to biological medicinal products (genetically engineered and mAb-based products). As with 'biologics,' these terms are best used only in their specific regulatory context.

(2) ISPE (International Society for Pharmaceutical Engineering)

- Glossary of Pharmaceutical and Biotechnology Terminology
(http://www.ispe.org/glossary?term=Biologic)

Biologic

Any therapeutic serum, toxin, anti-toxin, or analogous microbial product applicable to the prevention, treatment, or cure of diseases or injuries.

Publication Source: ISPE Good Practice Guide: Sampling for Pharmaceutical Water, Pharmaceutical Steam, and Process Gases. First Edition (In Preparation - 08/09/2015) Publication Date: 2015 (Planned)

Biologic

A therapeutic agent derived from living organisms.

Biological Product

Any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of diseases or injury.

Biological Product

(42 U.S.C. 262(a)) A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

Biological Drugs

Biological drugs (or biologics) such as insulin, penicillin, blood and blood products, vaccines, derivatives of natural substances, and extracts of living cells are grown or cultured in separate batches. Just as with beer or wine, the quality can vary considerably by batch depending on small differences in inputs. Thus, in addition to obtaining marketing approval, a biologics manufacturer previously also had to have its production methods and facilities FDA licensed. Moreover, every batch of biologics had to be FDA tested. Recent advances in biotechnology, however, have diminished the variation and made production more like that of nonbiological (or chemically synthesized) drugs. In 1995, the FDA announced simplified rules on “well-characterized” biologics, dropping manufacturing-facility licensing and batch certification in such cases. Today many biologics are treated in the same fashion as nonbiological drugs. The FDA’s rules on biologics were codified in the 1997 Modernization Act.

Publication Source: Committees on Human Research

4. Others

(1) Wiki Pedia

Biopharmaceutical (Redirected from Biologic medical product)
(http://en.wikipedia.org/wiki/Biologic_medical_product)

A **biopharmaceutical**, also known as a **biologic medical product** or more simply as a **biologic** or **biological**, is any medicinal product manufactured in or extracted from biological sources. Biopharmaceuticals are distinct from chemically synthesized pharmaceutical products. Examples of biopharmaceuticals include vaccines, blood or blood components, allergenics, somatic cells, gene therapies, tissues, recombinant therapeutic protein and living cells.

Terminology surrounding biopharmaceuticals varies between groups and entities, with different terms referring to different subsets of therapeutics within the general biopharmaceutical category. Some major regulatory agencies use the terms *biological medicinal products* or *therapeutic biological product* to specifically refer to engineered macromolecular products like protein-based and nucleic-acid-based drugs, distinguishing them from products like blood, blood components or vaccines, which are usually directly extracted from a biological source.

Biologics can be composed of sugars, proteins or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources — human, animal or microorganism — and may be produced by biotechnology methods and other technologies. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available.

In some jurisdictions, biologics are regulated via different pathways than other small molecule drugs and medical devices.[1]