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## Biological substances: traceability and safety

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## Biological substances: traceability and safety

- What does it mean “biological”?
- How do Drugs and Biologics differ?
- What can considered biological active ingredients?
- Why are we speaking of traceability and safety?
- Are there special GMP requirements?
- Are there special regulatory requirements for biological substances?

## What does it mean “biological”?

- ✓ A biological is something deriving from a living system such micro-organisms, plants, animals and human
- ✓ A chemical entity showing pharmacological activity is typically obtained through chemical synthesis, which means that it is made by reaction through specific chemical ingredients in a defined process
- ✓ For biologics the product is related to the process and it is necessary ensuring that the manufacturing process remains substantially the same over time
- ✓ A chemical process can be changed extensively, but the final result is a product that can be demonstrated to be the same as before the manufacturing change
- ✓ A change in the process of biological products can affecting the nature of the product and its activity, safety and efficacy

- ✓ Chemical entities have a well-defined chemical structure and they can be analyzed to determine its purity and the related impurities
- ✓ It is difficult and sometimes impossible to characterize a complex biologic by testing methods analyzed in a lab by routine and some components of the biologic substance may be unknown
- ✓ **But** certain substances, in spite of their biological origin can be well-characterized and they can be considered as non complex active substances

## What do European Authorities consider as “biological”?

We can refer to CMDh (Co-ordination Group for Mutual Recognition and Decentralised Procedures-human) Questions & Answers on Biologicals (Doc. Ref.: CMDh/269/2012, Rev0, October 2012) giving the definition of a biological medicinal product.

“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, such as micro-organisms, organs and tissues of either plant or animal origin, cells or fluids (including blood or plasma) of human or animal origin, and biotechnological cell constructs (cell substrates, whether they are recombinant or not, including primary cells) and for which a combination of physico-chemical-biological testing is required and the production process and its control is needed for its characterisation and the determination of its quality”

## How is such definition applied?

- ✓ Biological medicinal drug products are recombinants proteins, monoclonal antibodies, blood products, immunological medicinal products such as sera and vaccines, allergens and advanced technology products as gene and cell therapy products.
- ✓ Other products meeting the criteria of the biological origin and complexity can be considered as biological.

CMDh provided an “Overview of biological active substances of non recombinant origin” (June 2007)

- ✓ Human chorionic gonadotropin, glycoprotein, extract from human urine
- ✓ Streptokinase, FSH extract from Streptococcus cultures
- ✓ Aprotinin, polypeptide from bovine lung
- ✓ Protamine, polypeptide from sperma/testes of fish species
- ✓ Heparins, glycosaminoglycans from pig intestinal mucosa
- ✓ Pancreatin, amylase, protease and lipase prepared from mammalian pancreas
- ✓ Insuline, from bovine or porcine pancreas
- ✓ Lysatum bacterial mixtum
- ✓ Calf blood low molecular weight portion

## What does FDA consider as biologics?

“Biological products include a wide range of products as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues and recombinant therapeutic proteins. 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, microorganism- and may be produced by biotechnology methods and other cutting-edge 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 contrast to most drugs that are chemically synthesized and their structure is known, most biologics are complex mixture that are not easily identified or characterized....”



## Learn more....

- ✓ Antibiotics are not defined as biological medicinal products, however where biological stages of manufacture occur, reference to guidance to biological active substance manufacture can be done;
- ✓ Regional Authorities can consider as biological active ingredients that are not complex products (well-characterized), because originated by extraction from a natural source and purified or obtained by semi-synthesis starting from substances extracted from a natural source;
- ✓ The FDA considers (1) cells; (2) plants, plant parts, macroscopic fungi, or algae; or (3) animal tissues, organs, or body fluid from which the drug substance is derived to be starting material for a drug substance derived from a biological source. The term *drug substance derived from a biological source* includes drug substances that are the chemical obtained directly from the biological source and semisynthetic drug substances that are produced by modification of a chemical (i.e., intermediate) obtained from the biological source.

## Q11 Development and Manufacture of Drug Substances

### 2. Selection of Starting Materials for Semi-synthetic Drug Substances

#### (5.1.2)


“For purposes of this guidance, a semi-synthetic drug substance is one in which the structural constituents have been introduced by a combination of chemical synthesis and elements of biological origin (e.g., obtained from fermentation or by extraction from botanical material). In some cases, it might be appropriate for the applicant to describe the manufacturing process starting from the source material (microorganism or botanical material). However, if it can be demonstrated that one of the isolated intermediates in the synthetic process complies with the principles outlined above for the selection of starting materials for synthetic drug substances, that isolated intermediate can be proposed as the starting material. The applicant should specifically evaluate whether it is possible to analytically characterize the proposed starting material, including its impurity profile, and whether the fermentation or botanical material and extraction process have an impact on the impurity profile of the drug substance. Risks from microbial and other contamination should also be addressed.”

## Q11 Development and Manufacture of Drug Substance

### 3. Selection of Source and Starting Materials for

#### Biotechnological/Biological Drug Substances (5.1.3)

Cell banks are the starting point for manufacture of biotechnological drug substances and some biological drug substances. In some regions, these are referred to as source materials - in others, starting materials. Guidance is contained in the ICH guidances, Q5A Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin (ICH Q5A), Q5B Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products (ICH Q5B), and Q5D Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products (ICH Q5D).



Eudralex  
The Rules Governing Medicinal Products in the European Union  
Volume 4  
EU guidelines for Good Manufacturing Practice for Medicinal Products for  
Human and Veterinary Use

Annex 2  
**Manufacture of Biological Substances and  
Medicinal Products for Human Use**

Published on June 2012  
Coming into operation: 31 January 2013

## Are there special GMP requirements?

- ✓ Annex 2, part A contains supplementary guidance on the manufacture of biological active substances and medicinal products, from control over seed lots and cell banks through to finishing activities and testing;
- ✓ Annex 2, part B contains further guidance on selected types of biological material source requirements.

This Annex has to be read as supplement of both Part I and II of EU GMP guide.

**Table 1. Illustrative guide to manufacturing activities within the scope of Annex 2.**

Type and source of material	Example product	Application of this guide to manufacturing steps shown in grey			
1. Animal or plant sources: non-transgenic	Heparins, insulin, enzymes, proteins, allergen extract, ATMPs immunosera,	Collection of plant, organ, tissue or fluid <sup>9</sup>	Cutting, mixing, and / or initial processing	Isolation and purification	Formulation, filling
2. Virus or bacteria / fermentation / cell culture	Viral or bacterial vaccines; enzymes, proteins	Establishment & maintenance of MCB <sup>10</sup> , WCB, MVS, WVS	Cell culture and/or fermentation	Inactivation when applicable, isolation and purification	Formulation, filling
3. Biotechnology - fermentation/ cell culture	Recombinant products, MAb, allergens, vaccines Gene Therapy (viral and non-viral vectors, plasmids)	Establishment & maintenance of MCB and WCB, MSL, WSL	Cell culture and / or fermentation	Isolation, purification, modification	Formulation, filling
4. Animal sources: transgenic	Recombinant proteins, ATMPs	Master and working transgenic bank	Collection, cutting, mixing, and / or initial processing	Isolation, purification and modification	Formulation, filling
5. Plant sources: transgenic	Recombinant proteins, vaccines, allergen	Master and working transgenic bank	Growing, harvesting <sup>11</sup>	Initial extraction, isolation, purification, modification	Formulation, filling
6. Human sources	Urine derived enzymes, hormones	Collection of fluid <sup>12</sup>	Mixing, and/or initial processing	Isolation and purification	Formulation, filling
7. Human and / or animal sources	Gene therapy: genetically modified cells	Donation, procurement and testing of starting tissue / cells <sup>14</sup>	Manufacture vector <sup>13</sup> and cell purification and processing,	Ex-vivo genetic modification of cells, Establish MCB, WCB or cell stock	Formulation, filling
	Somatic cell therapy	Donation, procurement and testing of starting tissue / cells <sup>14</sup>	Establish MCB, WCB or cell stock	Cell isolation, culture purification, combination with non-cellular components	Formulation, combination, fill
	Tissue engineered products	Donation, procurement and testing of starting tissue / cells <sup>14</sup>	Initial processing, isolation and purification, establish MCB, WCB, primary cell stock	Cell isolation, culture, purification, combination with non-cellular components	formulation, combination, fill

Increasing GMP requirements

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## Learn more....

- ✓ The table is in line with the corresponding table in Part II of Eudralex, Vo.4, increasing the level of application of GMP from early to later steps in the manufacture;
- ✓ The inclusion of same early steps within the scope of Annex 2 does not imply that those steps will be routinely subject to inspection by Authorities;
- ✓ For tissue and cells used for industrially manufactured products is applicable the Directive 2004/23/EC (setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells and Commission Directive 2006/17/EC implementing Directive 2004/23/EC.


- ✓ For blood or blood components used as starting materials for advanced therapy medicinal products (ATMPs), Directive 2002/98/EC setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components provides requirements for the selection of donors and the collection and testing of these materials;
- ✓ The manufacture and control of genetically modified organisms needs to comply with local and national requirements: appropriate Biological Safety Level should be guaranteed without any conflicts with GMP requirements.



- ✓ Traceability is needed due to the complexity as well as the way the biological active substances are produced;
- ✓ The supply chain traceability and clear roles of participants in the supply chain are required due to the origin of material: QRM principles need to be applied;
- ✓ Differences in sources may result in small differences between molecules of the same active substance in case of complex molecules, which may have an impact on the safety profile of the medicine;
- ✓ Biological medicines are also more likely to be recognised by the body's immune system as 'foreign' and therefore to trigger immune reactions against them.


- ✓ Biological sources require the application of suitable methods of production
- ✓ Biological active substances and medicinal products can be defined largely by reference to their methods of production
- ✓ Methods employed in the manufacture are a critical factor in shaping the appropriate quality control.

(Annex 2)



The manufacture of biological substances involving biological processes and materials may display variability, so the application of QRM principles are particularly important in order to develop a control strategy across all stages of manufacture and to minimise the variability reducing the risk of contamination and cross-contamination:

- ✓ Microbiological contamination
- ✓ Viral contamination



Attention should be pay in GMP application in specific fields:

- ✓ Design of equipment, facilities, utilities
- ✓ Design of processes
- ✓ Training of operators
- ✓ Biological sources

## Premises and equipment

- ✓ The degree of environmental control of particulate and microbial contamination of the production premises should be adapted to the active substance, intermediate or finished product and the production step bearing in mind the potential level of contamination of starting materials and the risks to the product;
- ✓ Manufacturing and storage facilities, processes and environmental classification should be designed **to prevent** the extraneous contamination of products: prevention is more appropriate than detection and removal;
- ✓ Dedicated production areas should be used for the handling of live cells capable of persistence in the manufacturing environment; dedicated facilities should be used in the manufacture of pathogenic organisms.

✓ Manufacture in multi-purpose facility may be acceptable depending on the product types involved and in the presence of a sound and effective control strategy to prevent cross-contamination:

- ☐ Knowledge of the characteristics of cells or organisms or other biological material including any adventitious agents;
- ☐ Use of engineering measures (such as closed systems);
- ☐ Control measures to remove biological contamination before the subsequent manufacturing steps (HVAC);
- ☐ Products, equipment, ancillary equipment (e.g. for calibration and validation) and disposable items are only moved within and removed from such areas in a manner that prevents contamination of other areas, other products and different product stages.

Measures and procedures necessary for containment (i.e. for environment and operator safety) should not conflict with those for product quality

- ✓ **Human tissues or cells** such as certain ATMPs must comply with the requirements of Directive 2004/23/EC, Commission Directive 2006/17/EC and Directive 2006/86/EC implementing Directive 2004/23/EC concerning traceability requirements, notification of serious adverse reactions and certain technical requirements for coding, processing, preservation, storage and distribution of human tissues and cells

**Animals** species are used in the manufacture of biological medicinal products. Two broad types of sources can be identified:

- ✓ Live groups, herds, flocks: for example polio vaccine (monkeys), immunosera, allergens (cats) transgenic products (goats, cattle);
- ✓ Animal tissues and cells derived post-mortem and from establishments such as abattoirs (sources for enzymes, anticoagulants and hormones (sheep and pigs))

Animal derived products must comply with the latest version of the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy (TSE) Agents via Human and Veterinary Medicinal Products and cEP monograph 5.2.8 Minimising the risk of transmitting TSE via medicinal products and 5.1.7 Viral safety



- ✓ In addition to compliance with TSE regulations, risks of contamination due to other adventitious agents typical of source that are of concern (zoonotic diseases, diseases of source animals) should be assessed in order to prevent contamination and decisions documented;
- ✓ Particular care should be taken to prevent and monitor infections in the source/donor animals. Measures should include the sourcing, facilities, husbandry, biosecurity procedures, testing regimen. This is of special relevance to specified pathogens free animals where Ph.Eur. Monograph requirements must be met.

- ✓ For products manufactured from transgenic animals, traceability should be maintained in the creation of such animals from the source animals.

## Traceability and documentation

- ✓ Starting and raw materials may need additional documentation on the source, origin, distribution chain, method of manufacture and controls applied to assure an appropriate level of control including their microbiological quality;
- ✓ Traceability records must be retained for an appropriate period of time (i.e 30 years after the expiry date of the medicinal product in case of material originated from human materials).

## Starting and raw materials

- ✓ The source, origin and suitability of biological starting and raw materials (e.g. feeder cells, reagents, culture media, buffers, serum, enzymes) should be clearly defined;
- ✓ Where the necessary tests takes a long time, it is allowed to process starting materials before the results of the tests are available and the risk of using a potentially failed material and its potential impact on other batches should be assessed applying a risk evaluation;
- ✓ The risk of contamination of starting and raw materials during their passage along the supply chain must be assessed, with particular emphasis on TSE;
- ✓ Microbiological contamination should be considered in the control strategy: controls are required for assessing the quality of starting and raw materials and this is of particular importance for products where a final sterilization is not possible and the ability of the process to remove microbial by-products is limited.

## Seed lot and cell bank system

In order to prevent the unwanted drift of properties which might ensue from repeated subcultures or multiple generations, the production of biological substance and medicinal products obtained by microbial culture, cell culture or propagation in embryos and animals should be based on a system of master and working virus seed lots and/or cell banks.

Seed lots and cell banks have to be stored and used in a way as to minimize the risks of contamination or alteration.

Part B of Annex 2 is a specific guidance on selected product types:

- B1. Animal sourced products
- B2. Allergens products
- B3. Animal immunosera products
- B4. Vaccines
- B5. Recombinant products
- B6. Monoclonal antibody products
- B7. transgenic animal products
- B8. Transgenic plants products
- B9. Gene therapy products
- B10. Somatic and xenogeneic cell therapy products and tissue engineered products

### 5.2.8 Minimising the risk of transmitting TSE via medicinal products (87/2011:50208)

Transmissible Spongiform Encephalopathies (TSEs) are chronic degenerative diseases due to the accumulation of an abnormal protein (known as PrP or prion) and this non conventional viral agent (very resistant to heat and denaturation) is considered responsible for transmitting TSE disease.

TSE in animals include:

- bovine spongiform encephalopathy (BSE) in cattle
- scrapie in goats and sheep

TSE may affect also humans in different forms, the most important is the Creutzfeldt-Jakob Disease



The note for guidance on TSE is published by the European Commission, following:

- Annex I, Part I, module 3, section 3.2: Content: basic principles and requirements, point (9) of Directive 2001/83/EC (medicinal products for human use)
- Annex I, Title I, part 2, section C, Production and control of starting material of Directive 2001/82/EC /medicinal products for veterinary use)

These directive require that applicants for marketing authorization must demonstrate to be in compliance with the latest version of the note for guidance.



The note and the EP monograph is applicable:

- ✓ to materials derived from “TSE relevant animal species”, used in the preparation of:
  - active substances
  - excipients and adjuvants
  - raw materials and starting materials and reagents used in the production (e.g. bovine serum, albumin, enzymes, culture media including those used to prepare working cell banks or new master cell banks for medicinal products submitted as new marketing authorization)
- ✓ To seed lots , cell banks for vaccine antigenes, for bio-technology-derived medicinal products and routine fermentation production

Minimising the risks of transmission TSE is based upon three complementary parameters:

- ✓ the source of animals and their geographical origin
- ✓ the nature of the animal material used in manufacture and any procedures in place to avoid cross-contamination with higher risk material
- ✓ production process(es) including the quality assurance system in place to ensure products consistency and traceability

### 5.1.7 Viral safety (01/2008:50107)

- ✓ This monograph is applicable to medicinal products manufactured starting from materials of human or animal origin.

Complementary measures can be applied:


- Selection of source materials and testing for viral contamination
  - Testing the capacity of the production process to remove and/or inactivate viruses
  - Testing for viral contamination at appropriate stages of production
- ✓ Detailed recommendations, including validation studies, are provided by the Note for Guidance on virus validation study: the design, contribution and interpretation of studies validating the inactivation and removal of viruses ( CPMP/BWP/268/95)
  - ✓ Risk assessment

## Biological active substances: compliance according to the Italian law No. 17 issued on February 19, 2014, that modifies the Decree No.219/2006 implementing Directive 2011/62/UE

According to the implementation guide of Decree No.17:

“A biological substance is a substance produced by or extracted from a biological source (including those of vegetable origin) and which requires for its characterization and for determining of its quality a combination of physico-chemical-biological testing, together with the process production and its control. All other substances as well as any other materials used for manufacturing or extracting and active substance, but from which the active substance is not directly derived, such as reagents, culture media, fetal calf serum, the additives, and buffers involved in chromatography, etc., are known as ancillary materials (raw materials). Also those substances obtained through cell culture techniques and techniques of biotechnology are biological (Annex 1, Section 3.2.1 of D.Lvo. 219/2006)”

(Questions&Answers, Question 1, Nota esplicativa all'applicazione del Decreto No.17/2014)



With coming in force of Decree No. 17/2014 active substances are covered by registration, but biological active substances are still subjected to the procedure in force until March 2014 that means any biological API manufacturers must have authorization for manufacturing and importing.

## Starting from February 2011 EDQM excludes biological active substance from CEP procedure

EDQM does not accept new CEP applications for biological active substance (those listed in the Overview of Biological Active Substances of non-recombinant origin, July 2007). In fact, in light of the discussions held at the European level concerning the classification of biological products, the EDQM has decided to exclude from the scope of the procedure those products that have been classified, by the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMD(h)), as "other biological substances". The reasoning behind this decision is as follows: the characterization and determination of biological substances require not only a combination of physico-chemical and biological testing, but also extensive knowledge of the production process and its control.

The EU “Guideline On Active Substance Master File Procedure ([CHMP/QWP/227/02](#)) specifies that the ASMF concept is not applicable to biological active substances. The MAH/applicant of a biological medicinal product could not comply with the requirement to “take responsibility for the medicinal product” without having full and transparent access to these quality-related data. The use of an ASMF would prevent such access, and for this reason it is not allowed for biological active substances.

THANK YOU