ice PHARMA

The Bile Acids Expert

PRODUCTS OF BIOLOGICAL ORIGIN, PHARMACOPOEIAS AND ASPECTS OF VIRAL SAFETY

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Today's Topics

1 Definition of «Products of Biological Origin» and it's application

2 ICE Case 1: as bile acid derivatives manufacturer under 1069/2009 EU Law

3 European Pharmacopoeia requirements for biological products

3.1 5.2.8 Minimising the risk of transmitting TSE via medicinal products (87/2011:50208)
3.2 5.1.7 Viral safety EP monograph – the approach for viral clearance study on the API manufacturing process

4 ICE Case 2: Thyroid case
FDA Position about desiccated thyroid product used before as compounding and now considered as biological product

1. DEFINITION OF «PRODUCTS OF BIOLOGICAL ORIGIN »

- A biological is something deriving from a living system such micro-organisms, plants,animals and human

- A chemical entity showing pharmacological activity is tipically obtained through chemical synthesis, which means that it is made by reaction through specific chemical ingredients in a defined process

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.

2. ICE Case 1: as bile acid derivatives

manufacturer under 1069/2009 EU Law

- ICE S.p.A. is the main manufacturer of APIs coming from bile derivatives, extracted from bovine bile or alternative source.
- Bile acids - despite their origin - are not classified as biological substance, because they do not satisfy the requirements reported in **Part I of Annex I of Directive 2001/83/EC (as amended by Directive 2003/63/EC).** In fact, they are considered of as products of animal origin.
- The products of animal origin are under **1069/2009 EU regulation** laying down health rules referring to animal by-products and derived products not intended for human consumption and repealing Regulation (EC) No 1774/2002 (Animal by-products Regulation).

ANNEX

Annex I to Directive 2001/83/EC is replaced by the following:

'ANNEX I

ANALYTICAL, PHARMACOTOXICOLOGICAL AND CLINICAL STANDARDS AND PROTOCOLS IN RESPECT OF THE TESTING OF MEDICINAL PRODUCTS

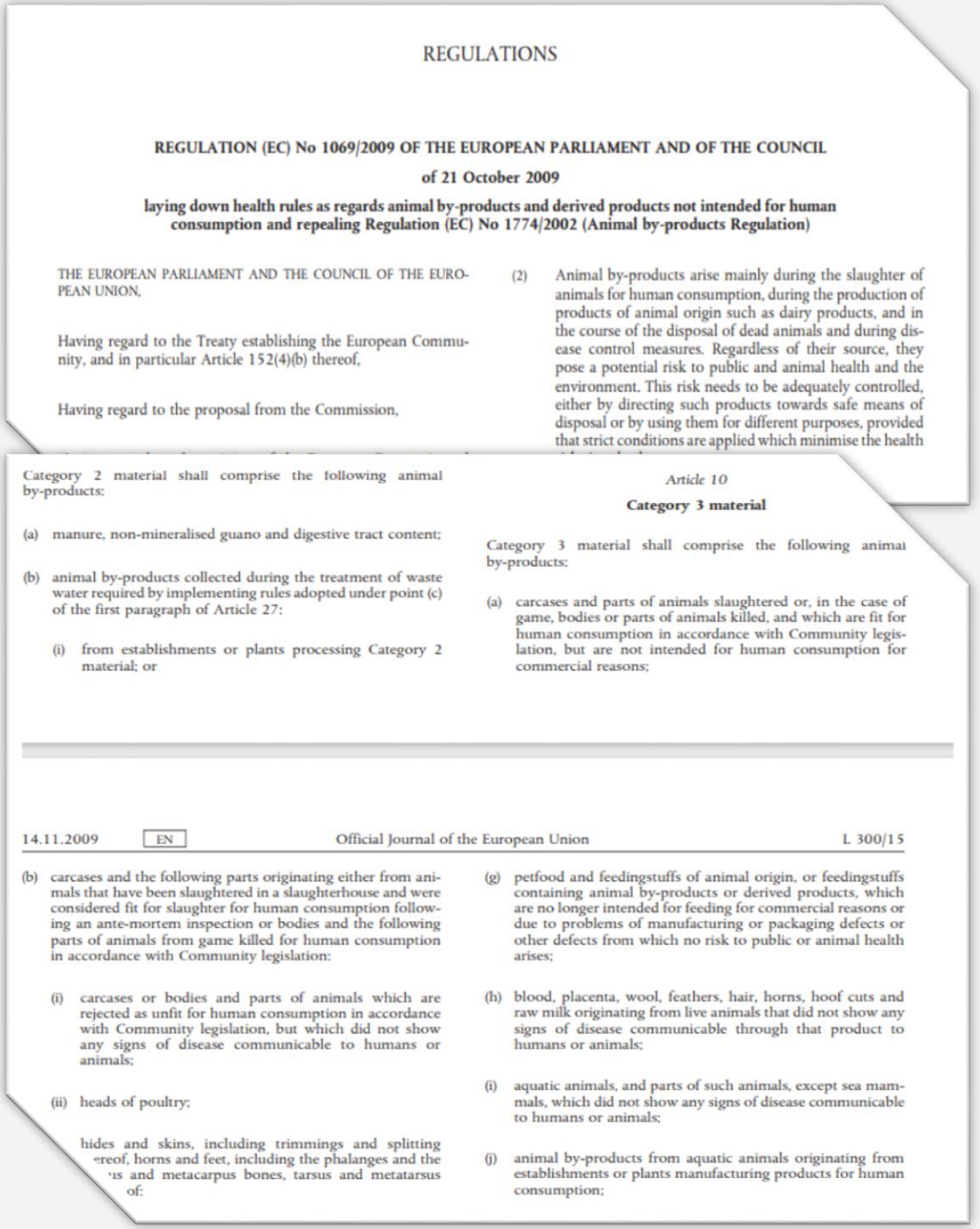
TABLE OF CONTENTS

2. ICE Case 1: as bile acid derivatives

manufacturer under 1069/2009 EU Law

The bile acids derivatives are considered *Category 3* of the above-mentioned regulation which must meet the following requirements:

- The company must have a registration or recognition number.
- The company must be registered into the TRACES (system that is a European Commission's online platform for sanitary and phytosanitary certification required for the importation of animals, animal products, food and feed of non-animal origin and plants into the European Union, and the intra-EU trade and EU exports of animals and certain animal products).
- The company is under Local Sanitary Authority Surveillance (specially the warehouse where the coming material is stored).



REGULATIONS

REGULATION (EC) No 1069/2009 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 21 October 2009

laying down health rules as regards animal by-products and derived products not intended for human consumption and repealing Regulation (EC) No 1774/2002 (Animal by-products Regulation)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 152(4)(b) thereof,

Having regard to the proposal from the Commission,

(2) Animal by-products arise mainly during the slaughter of animals for human consumption, during the production of products of animal origin such as dairy products, and in the course of the disposal of dead animals and during disease control measures. Regardless of their source, they pose a potential risk to public and animal health and the environment. This risk needs to be adequately controlled, either by directing such products towards safe means of disposal or by using them for different purposes, provided that strict conditions are applied which minimise the health

Category 2 material shall comprise the following animal by-products:

(a) manure, non-mineralised guano and digestive tract content;

(b) animal by-products collected during the treatment of waste water required by implementing rules adopted under point (c) of the first paragraph of Article 27:

(i) from establishments or plants processing Category 2 material; or

Article 10

Category 3 material

Category 3 material shall comprise the following animal by-products:

(a) carcases and parts of animals slaughtered or, in the case of game, bodies or parts of animals killed, and which are fit for human consumption in accordance with Community legislation, but are not intended for human consumption for commercial reasons;

14.11.2009 EN Official Journal of the European Union L 300/15

(b) carcases and the following parts originating either from animals that have been slaughtered in a slaughterhouse and were considered fit for slaughter for human consumption following an ante-mortem inspection or bodies and the following parts of animals from game killed for human consumption in accordance with Community legislation:

(i) carcases or bodies and parts of animals which are rejected as unfit for human consumption in accordance with Community legislation, but which did not show any signs of disease communicable to humans or animals;

(ii) heads of poultry;

hides and skins, including trimmings and splitting ereof, horns and feet, including the phalanges and the is and metacarpus bones, tarsus and metatarsus of:

(g) petfood and feedingstuffs of animal origin, or feedingstuffs containing animal by-products or derived products, which are no longer intended for feeding for commercial reasons or due to problems of manufacturing or packaging defects or other defects from which no risk to public or animal health arises;

(h) blood, placenta, wool, feathers, hair, horns, hoof cuts and raw milk originating from live animals that did not show any signs of disease communicable through that product to humans or animals;

(i) aquatic animals, and parts of such animals, except sea mammals, which did not show any signs of disease communicable to humans or animals;

(j) animal by-products from aquatic animals originating from establishments or plants manufacturing products for human consumption;

3. European Pharmacopoeia requirements for biological products

Biological product and product coming from animal must comply with the following European Pharmacopoeia requirements:

- Note for Guidance on «Minimising the Risk of Transmitting Animal Spongiform Encephalophathy (TSE) Agents via Human and Veterinary Medicinal Products (Ph.Eur. Monograph 5.2.8)
- EP monograph 5.1.7 Viral safety

3.1 European Pharmacopoeia requirements for biological products

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

Transmissible Spongiform Encephalopaties (TSEs) are chronic degenerative diseases due to the accumulation of an abnormal isoform of a protein (known as PrP or prion) and this non conventional viral agents (very resistent to heat and denaturation) is consideraed responsible for transmitting TSE disease.

TSE diseases in animals include but not limited to:

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

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

3.1 European Pharmacopoeia requirements for biological products

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

The note for guidance on TSE is published by the European Commission and include the 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 Directives require that applicants for Marketing Authorization must demonstrate to be in compliance with the latest version of the note for guidance. This is a continuing obligation after the Marketing Authorisation has been granted.

3.1 European Pharmacopoeia requirements for biological products

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

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

3.1 European Pharmacopoeia requirements for biological products

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

Minimising the risks TSE transmission is based on three complementary parameters:

- *the source of animals and their geographical origin:*

  shall be derived from animals fit for human consumption following ante- and postmortem inspection in accordance with EU conditions, (materials derived from live animals, which should be found healthy after clinical examination).

  The World Organisation for Animal Health (OIE) lays down the criteria for the assessment of the status of countries in the chapter of the International Animal Health Code on bovine spongiform encephalopathy. Countries or regions are classified as negligible BSE risk; controlled BSE risk; undetermined BSE risk.

- *the nature of the animal material used in manufacture and any procedures in place to avoid cross-contamination with higher risk material*:

  Category IB: Lower-infectivity tissues: peripheral tissues that have tested positive for infectivity and/or PrPTSE in at least one form of TSE.

- *production process(es) including the quality assurance system in place to ensure products consistency and traceability*

3.2 European Pharmacopoeia requirements for biological products

5.1.7 Viral safety EP monograph – the approach for viral clearance study on the API manufacturing process

Pharmaceutical products from animal origin (i.e. cholanic acid from animal bile) can be a vehicle of infectant agents (pathogens) with a consequent risk for human safety.

Regulatory Authorities have issued specific guidelines to control cross contamination from pathogens, especially viruses (Ref. ICH Q5A (R1)).

Viral safety has to be evaluated through a multiple approach:

- Prevention: to consider raw materials safe at source
- Analysis: to test levels of viral contamination
- Clearance evidence: to evaluate the ability of the manufacturing process to remove viruses (viral clearance study)

3.2 European Pharmacopoeia requirements for biological products

5.1.7 Viral safety EP monograph – the approach for viral clearance study on the API manufacturing process

Viral Clearance Study (EMEA- CPMP guidance CPMP/BWP/268/95) the main phases are:

1. Viral risk evaluation;
2. Choice of virus model;
3. Manufacturing process evaluation and selection of inactivation steps to be validated;
4. Scaling down of manufacturing steps;
5. Validation design (at CRO);
6. Result evaluation;
7. Risk assessment on viral safety of the product .

3.2 European Pharmacopoeia requirements for biological products

5.1.7 Viral safety EP monograph – the approach for viral clearance study on the API manufacturing process

2. Choice of virus model

- Virus models have to be similar to the ones which can potentially contaminate the product
- They must be totally rapresentive of the chemical-physical characteristics of viruses (enveloped, non-enveloped, DNA, RNA)
- It can be influenced by the availability of the models at CRO (GLP Contract research Organization)

3. Process evaluation and inactivation step selection

Two «orthogonal» inactivation step have to be selected, i.e. acid/basis treatment, heat treatment, chromatography, filtration, solvent use, on the basis of the virus resistance.

3.2 European Pharmacopoeia requirements for biological products

5.1.7 Viral safety EP monograph – the approach for viral clearance study on the API manufacturing process

4. **Manufacturing Process Scaling Down** (up to 6 weeks of work)

It must be:

- representative of the manufacturing process;
- actable at CRO;
- a worst-case scenario of the manufacturing process (i.e. whether if not closely actable at CRO).

5. **Validation Design at CRO**(up to 8 weeks of work)

The viral clearance study is performed on the SDP (scale down process) by spiking an amount of the virus model before the step that has to be validated. At different times, withdrawals of the spiked product are performed to detect the viral infectivity reduction.

3.2 European Pharmacopoeia requirements for biological products

5.1.7 Viral safety EP monograph – the approach for viral clearance study on the API manufacturing process

6. Result Evaluation

The Reduction Factor (LRV) is calculated by titration on the contaminated product .

The LRV value is defined as per the following formula:

$$LRV = \text{Log}\ [(V1xT1)/(V2xT2)]$$

Where:
V1= initial amount of the product
T1= virus title before the inactivating step
V2= final amount of the product
T2= final title after inactivating step

*The manufacturing process is effective in inactivating/removing viruses when **Log > 4** for each step.*

3.2 European Pharmacopoeia requirements for biological products

5.1.7 Viral safety EP monograph – the approach for viral clearance study on the API manufacturing process

7. Product Risk Assesment

It must be considered that a single step with a very high reduction factor is generally safer than a series of steps that have a high total reduction factor; however, an overall viral reduction is functional to the final risk assessment on the product.

When useful to evaluate more strictly the safety of the product, qPCR analysis can be performed to finally confirm viral removal

4. ICE Case 2: Thyroid case

FDA Position about desiccated thyroid product used before as compounding and now considered as biological product

- FDA has declared desiccated thyroid extract (DTE) to be a biologic drug and therefore ineligible for compounding. DTE is sold in the United States as Armour Thyroid, NP Thyroid, Nature-Throid, and Natural Thyroid, among other names. Thyroid USP is the source of levothyroxine and liothyronine in these products and in compounded preparations.
- On September 16th, 2022 a letter to National Association of Boards of Pharmacy (NABP) CEO Al Carter, FDA states that DTE products “can put patients at harm” and that “therapies containing DTE are biological products subject to licensure under Section 351(i) of the PHS Act.” The letter encourages NABP to share the letter with its members, the state boards of pharmacy, which Carter did in a memo to boards of pharmacy on September 22.

4. ICE Case 2: Thyroid case

FDA Position about desiccated thyroid product used before as compounding and now considered as biological product

U.S. FOOD & DRUG ADMINISTRATION

September 16, 2022

Lemrey "Al" Carter, MS, PharmD, RPh
Executive Director/Secretary
National Association of Boards of Pharmacy
1600 Feehanville Dr
Mount Prospect, IL 60056
acarter@NABP.pharmacy

Dear Dr. Carter:

The purpose of this letter is to bring to the attention of the National Association of Boards of Pharmacy (NABP) that the Food and Drug Administration (FDA) is aware of desiccated thyroid extract (DTE) that appears to have been prepared by state-licensed pharmacies being offered to patients. These products can put patients at harm. We encourage you to share this information with your members.

There are two types of thyroid replacement therapies: (1) synthetic therapies containing only levothyroxine or liothyronine; and (2) therapies made from DTE, which is produced from dried ground animal thyroid glands. DTE is sold in the United States as Armour Thyroid, NP Thyroid, Nature-Throid, and Natural Thyroid, among other names.

While synthetic thyroid replacement therapies containing only levothyroxine or liothyronine are drugs subject to approval under the Federal Food, Drug, and Cosmetic Act (FD&C Act), therapies containing DTE are biological products subject to licensure under section 351 of the Public Health Service Act (PHS Act).

DTE products meet the definition of a "biological product" under section 351(i) of the PHS Act (21 U.S.C. § 262(i)). Under that definition, a "biological product" is "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, *protein, or analogous product*, . . . applicable to the prevention, treatment, or cure of a disease or condition in human beings." 21 U.S.C. § 262(i)(1) (emphasis added). FDA's regulations define the term "protein" in the statutory definition of "biological product" to mean "any alpha amino acid polymer with a specific, defined sequence that is *greater* than 40 amino acids in size" (see 21 CFR 600.3(h)(6); see also 85 FR 10057). DTE meets the definition of a biological product because it is a "protein" or "analogous" to a protein. DTE is derived from animal thyroid glands (usually porcine, meaning from a pig) and necessarily contains thyroglobulin, an alpha amino acid polymer with a specific defined sequence, consisting of 2,770 amino acids.

U.S. Food and Drug Administration
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U.S. FOOD & DRUG ADMINISTRATION

Section 351(a)(1) of the PHS Act prohibits the introduction into interstate commerce of any biological product unless "a biologics license . . . is in effect for the biological product." Biological products subject to licensure under section 351 of the PHS Act are not eligible for the exemptions for compounded drug products under sections 503A and 503B of the FD&C Act.

FDA has not approved any biologics license applications (BLAs) for DTE products. Some biological products, including thyroglobulin products, had historically been approved under section 505 of the FD&C Act (21 U.S.C. § 355). However, the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) required that as of March 23, 2020, all sponsors seeking approval of a biological product that previously could have been submitted under section 505 of the FD&C Act (21 U.S.C. § 355) must submit a BLA under section 351 of the PHS Act (42 U.S.C. § 262).

In addition, unlicensed DTE products have not been reviewed by the FDA to ensure safety, purity, and potency, and therefore may present issues with respect to quality and dosing, among other things. For example, tablets made from the same batches may not always have the same hormone levels. Inconsistent dosage can have serious consequences for patients; too much medication can cause bad side effects, and too little can be ineffective. As a reminder, FDA does not interact with the vast majority of licensed pharmacists and licensed physicians who compound drug products, because these compounders are not licensed by FDA and generally do not register their facilities with FDA. Therefore, FDA is often not aware of potential problems with their compounded drug products or compounding practices unless it receives a complaint. Recently, FDA has received complaints related to the safety, purity, and potency of unlicensed DTE products that appear to have been prepared by state-licensed pharmacies.

We advise that you encourage state boards of pharmacy to submit to FDA any concerns or questions involving the preparation of biological products, including DTE, outside the scope of an approved BLA. States that wish to provide this information to FDA should submit the information by email to the following mailbox: compounding@fda.hhs.gov.

We are also sending this letter to the Federation of State Medical Boards to facilitate communication among associations with shared goals regarding these matters.

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Thank you for your attention!

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