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TSE Risk for Medicinal Products Marketed in Europe

Strasbourg Conference Outlines Status and Limitations of the System
March 1, 2001 is Certification Deadline!

by James C. Lyda, PDA Europe

Note: On January 11, 2001 a capacity crowd attended a conference in Strasbourg, France entitled, "Certification for TSE Risk Products." The event was organized on short notice by the European Directorate for the Quality of Medicines (EDQM), publisher of the European Pharmacopoeia (Pharm. Eur.), at the request of the EMEA (The European Agency for the Evaluation of Medicinal Products) and the national drug regulatory authorities in Europe. The purpose of the conference was to discuss the status of the European certification system for drug products from animal origin, issues surrounding the implementation of the program and related topics.

The following report is based on notes taken during the conference. While every attempt has been made to maintain accuracy, readers should rely on the official transcript, to be published by EDQM, as the definitive report on the conference. Additional information may be obtained from the EDQM Web site at www.pheur.org and EMEA's new Web site at www.emea.eu.int. For specific information regarding the certification procedure, contact EDQM at certification@pheur.org. For information regarding the European Federation of Pharmaceutical Industries and Associations' (EFPIA) TSE survey, visit www.efpia.org. Thanks are in order to Brian Matthews, Alcon Laboratories, London, for technical assistance.

Copies of the EDQM conference materials are available from PDA pending the issuance of the final conference proceedings. (See "Technical and Regulatory Resources Available," referenced in the Table of Contents elsewhere in this Newsletter, for a list of available documents.) In addition, copies of PDA technical information on cleaning and cleaning validation, discussed later in this article, are also available from PDA. (Refer again to the "Technical and Regulatory Resources Available" section of this Newsletter.)

Below is a summary of the Strasbourg Conference highlights, arranged by major topic.

I. Legal aspects and guidance development

M. Robert, DG III, *European Commission, Brussels*
Dr. John Purves, *EMEA, London*
Prof. D. H. Calam, *European Pharmacopoeia, Strasbourg*
Dr. W. F. van der Giesen, *Medicines Evaluation Board, Netherlands*

Industry requirements on Transmissible Spongiform Encephalopathy (TSE) for pharma products started with European Commission Decision 97/534/EC, July 1997. This decision was hence recognized to be too strict and would have adversely affected the majority of the medicinal products sold in Europe. The original decision was subsequently repealed and replaced by Commission Decision 2000/418/EC, June 2000, which specifically excludes cosmetics, medicinal products and medical devices.

Medicinal products came under specific coverage with EC Directive 1999/82/EEC September 1999, and EC Directive 1999/104/EEC, December 1999, covering requirements for human use and veterinary use products, respectively. The effect was to modify directive 75/311/EEC by adding paragraph C.a. which requires that "the applicant must demonstrate that the medicinal product is manufactured in accordance with the Note for Guidance (NfG) on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products." In addition, the directives require that all

Members States (1) assure that marketing applications received after July 1, 2000 comply with the directive, and (2) all existing marketing authorizations for medicinal products comply with the directive by March 1, 2001.

Manufacturers may choose to use the EDQM certification procedure. If successful, it would be treated as a Type I variation. This is the preferred method, as it lessens the review time. As an alternative, manufacturers can submit separate scientific data, in which case it would be treated as a Type II variation. A number of Type II variations have been submitted and industry participants offered a number of explanations for these results (see questions and comments below). For products under the centralized procedure, the first variations were received by the EMEA in late 2000 and a large number have been received in November and December.

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The following products for human use are currently exempt from the TSE procedures: milk and milk products derived only from milk; and derivatives of wool and hair (lanolin, wool fat, etc.) providing they are taken from live animals. (There is a concern about cross-contamination from dead animal sources.)

In June 1999, The European Pharmacopoeia proposed a new general monograph and general chapter 5.2.8 on TSE risks and expanded the scope of the existing certification scheme which had been implemented in 1994 for regular compendial certifications. In January 2000, the general monograph and general chapter became effective. Chapter 5.2.8 reproduces verbatim the CPMP Note for Guidance on minimizing TSE risk. Under existing treaty, the European Pharmacopoeia and the new monographs and chapters apply to all 27 member countries of the convention, not just the 15 Member States of the European Union (EU).

The implementation of the TSE directive not only places tremendous burden on the pharmaceutical and supplier industry, but places a similar burden on the national authorities of each Member State of the EU. For example, by March 1, 2001, the Medicines Evaluation Board (MEB) of the Netherlands will have to apply the terms of the directive to 10,000 nationally authorized products registered by 350 different companies, or Market Application Holders (MAH). To do this, each MAH will have to check the origin of all of their starting materials and provide proof of compliance with the new TSE requirements by either the EDQM certificate or submission of detailed information to the MEB as a Type II variation. The MEB currently has received about 50 such variations.

The regulatory problem is that there is no approval system for 'starting materials' in the EU (only for 'finished products'). Therefore, for each medicinal product, the MAH has to provide proof of compliance with the TSE requirements. This could result in multiple repetitions of providing authorities with the same information. The EU Commission agreed in March 2000 that multiple submissions of the same information should be avoided where possible and the use of EDQM TSE certificates should be encouraged.

To comply with the directive, the MEB of the Netherlands issued a letter to all MAHs in May 2000 requesting that all medicinal products be listed as follows: (1) products with starting materials with TSE risk and for which EDQM certificates are available; (2) products with starting materials with TSE risk for which a certificate is not available; and (3) products with no starting materials with TSE risk (as defined in section 2 of the NfG). Each MAH was asked to submit the listing by December 1, 2000, along with a signed declaration that all registered products were included in the lists. The MEB is archiving all of the certifications in their database of registered products. In addition, all assessment reports by MEB on TSE will be made available to the other EU Member States electronically, in English, via Eudratrack mail box. Similar actions are being conducted in the other EU member states.

II. Scientific issues and implementation of the directives

Prof. J.H. Trouvin, *Biotechnology Working Party (BWP), EMEA, London*
Prof. P.P. Pastoret, *Immunology Working Party (IWP - Veterinary), EMEA, London*
Dr. A. Artige, *EDQM, Strasbourg*
Dr. C. Pouget, *EDQM, Strasbourg*
Dr. Harold Tietz, *Lilly (Deutschland), representing EFPIA*
Dr. Sol Ruiz, *Agencia Espanola del Medicamento, Madrid*

The TSE directive provides the pharmaceutical manufacturer some guidance in how to approach the TSE risk assessment of materials used in production. The safest choice is to choose non-ruminant animal source materials, or avoid animal materials altogether. Where this is not possible there are several parameters which the manufacturer can use:

A. Geographical origin—by category, based on Scientific Steering Committee (SSC) criteria.

1. Source country with no-BSE/TSE cases—e.g Argentina;
2. Countries with no case reports, for which there is a higher possibility—e.g. Finland, Sweden, USA, Canada;
3. Countries with average to high cases—e.g. most other countries in Europe; and
4. Countries with high frequency of cases—e.g. UK and Portugal.

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B. Age of animal—Younger animals are encouraged for use whenever possible.

C. Animal parts used—four categories based on WHO.

1. High risk—e.g. brain;
2. Medium risk—e.g. spleen, proximal ileum;
3. Low risk; and
4. Not detectable—e.g. milk products from milk only.

D. Manufacturing process—The choice and design of the manufacturing process can have a bearing on the TSE risk. This may particularly be valuable to avoid cross-contamination and to possibly reduce or eliminate the TSE agent. The impact of the manufacturing process is difficult to determine as the TSE agent can't be readily destroyed and there is incomplete evidence that it can be reliably removed. Process validation studies are required only if the manufacturer claims the process removes or inactivates the TSE agent.

It is the responsibility of the pharmaceutical manufacturer to select adequate measures. There appears to be a consensus that the careful selection of the source of animal and animal products, particularly by geographic basis, is the most reliable method to assure TSE suitability. It is important to have a system for the traceability of the animal source materials used in manufacturing and it is the responsibility of the drug manufacturer to audit the supplier.

There are currently two classification systems for countries with BSE cases: The Scientific Steering Committee (SSC) of the EU Commission, which may be found at http://europa.eu.int/comm/food/fs/sc/ssc/outcome_en.html and the Office of International des Epizooties (OIE), France, which can be found at www.oie.int/eng/info/en_esb.htm.

EFPIA has conducted a survey of its members on experiences with TSE certification. The results will be posted on the EFPIA home page (www.efpia.org). Industry concerns on TSE risk procedures include:

1. Most producers of products requiring certification are not normally regulated and are not used to preparing the type of information needed in a dossier;
2. Will pending certs be available form EDQM by March 1?;
3. The certification procedure will be undermined if EMEA asks for additional TSE safety information for centralized products, not fully accepting the EDQM certs;
4. The EMEA and some of the national authorities have slightly different tables to be completed by the MAH; and
5. A retrospective certification may not be possible—i.e. a finished product, now in stock, which was made from uncertifiable material.

- **Veterinary Issues**

The CVMP note for guidance on veterinary products differs slightly from the CPMP counterpart, the main reason being the absence of species barrier (i.e. sheep have been shown to contract BSE) and the fact that many animal drugs are administered via the parenteral route. Therefore the risk may be greatest when bovine or ovine materials are used in products intended for either ovine or bovine animals. In the CVMP guidance there is no exemption for milk and milk products, but wool and hair are excluded.

Veterinary vaccines are a large part of the veterinary medicinal products (estimated at 25%) and the status of old master seeds need to be addressed. The CVMP will be issuing a position paper very soon which addresses the issue of master seed materials used in production of vaccines.

The development of rapid immunological detection tests for use in the field is an important area of development. Current tests are from: Prionics (Western blotting), Enfer (Elisa) and Biorad (Elisa). The Biorad test shows a detection sensitivity significantly higher than the other tests. Using such tests a Swiss survey demonstrates that pre-clinical cases of BSE can be detected. A French survey of 15,000 animals showed detection in 2.1 of 1000 animals tested. While these tests are very useful for detecting TSE in animal tissues, they cannot be interpreted as certification that the animal is not contaminated. Similarly, there is no data or suggestion that they would be of use for raw material testing in the pharma manufacturing environment.

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- **Implementation of the EDQM certification system**

Originally applicable only to organic and inorganic active substances, excipients and certain fermentation products, the EDQM certification system was set up in 1994 to facilitate and simplify information exchange on the quality of substances which need to comply with the European Pharmacopoeia. In 1999, the certification procedure was broadened to cover TSE suitability. Less than 20 certificates were granted in 1994. In 2000 the total will be almost 140, of which almost 40 relate to TSE.

Certificates are currently required for the materials used in the medicine, not for the finished medicinal product (though there reportedly has been some discussion of this). Under the procedure, suppliers of any product (raw material, ingredient, etc.) with TSE risk and used in the production or preparation of medicinal products, can apply for a certificate concerning evaluation of the risk under new general monograph (1483) 'Products with risk of transmission of

agents of animal spongiform encephalopathies' and the associated general chapter 5.2.8. The certificate can then be used by manufacturers of medicinal products in the marketing authorizations for demonstration of compliance with the EU Directives.

TSE certificates are initiated by the submission of a dossier or file to EDQM which includes the information in the note for guidance on minimizing TSE risk. EDQM has four months to designate two rapporteurs for the review of the file, and one month to implement the review outcome (total of five months maximum to process the request). If additional information is requested, there is an additional three months for review once it is received. Manufacturers can apply for a combined certificate covering both TSE evaluation and chemical/microbiology purity.

"Process validation studies are required only if the manufacturer claims the process removes or inactivates the TSE agent."

Information in the dossier is divided in to five areas:

1. General information;
2. Origin of raw material and type of tissue used;
3. Manufacturing process;
4. Traceability; and
5. Auditing system.

Certificates are granted for five years and specify the country of origin of the source material, the nature of animal tissues used in manufacture, and when appropriate, the manufacturing process applied.

As of January 5, 2001, EDQM has approved 37 certificates in the following categories:

1. 22 gelatins;
2. 14 for FBS; and
3. 1 aprotinin.

More than 120 dossiers are under evaluation, 20 have been returned as out of scope (e.g. milk derivatives, poultry, etc.). Dossiers can be submitted in English or French. The cost is EUR 3000 for TSE, EUR 5000 for combined chemical and TSE.

III. Gelatin, Tallow, Serum and other media

Dr. M. Ruffing, *BfArM, Germany*

Dr. Alexandrine Maes, *Scientific Institute of Public Health, Belgium*

Gelatin for pharmaceutical use is mainly produced by acid or alkali treatment of bovine hides or bones. It is used in the manufacturing of capsules, microencapsulation and tableting, or chemically modified as a blood plasma substitute. Appropriate selection of the source animals is crucial to the safety of the gelatin. Skulls and spinal cords must be removed from processing. Gelatin made from bovine hides from any country is considered safe, providing cross-contamination from infectious material is avoided.

The validation of the alkaline manufacturing process has shown higher potential to inactivate TSE agents than acid treatment and is currently preferred. Gelatin manufacturers should implement Hazard Analysis and Critical Control Point Procedures (HACCP) to ensure quality.

Tallow is generally used as a starting material for production of derivatives, e.g. magnesium stearate, glycerol and polysorbate. For TSE purposes, all of the same precautions prevail, e.g. sourcing of materials, use of animal parts, etc. Commission Decision 92/562/EC lists the critical parameters that have to be monitored during different rendering processes for the production of tallow. It is generally accepted that tallow derivatives are unlikely to be infectious provided that tallow is produced according to a system which complies with this decision and processes as mentioned in 5.2.8 of the Pharmacopoeia.

Bovine serum is used during production of medicines such as vaccines, monoclonal antibodies and recombinant proteins. It can be sourced from the foetal, calf or adult animal. In general, animals from countries with a high incidence of BSE should not be used for sourcing of the raw materials. For serum, the method of slaughter is the critical point. Other media components such as blood derivatives, peptones and brain extract are mainly used during production of biological/biotechnological medicinal products. The risk assessment for certification is based on the same parameters as for serum and the safety is best assured by controlling the animal source.

In general, adequate cleaning of manufacturing equipment, including removal of protein residues, should be helpful in the reduction of any TSE materials and in avoiding cross contamination of co-processed materials.

IV. Comments from Conference Participants:

- **On Medical Devices**: Many health care product manufactures make products classed as both drugs and medical devices. Many of these incorporate the same materials and are the subject of the pharmaceutical directives (e.g. heparin, gelatin, tallow, etc.) The European Commission is reportedly working on a separate, mandatory guidance for medical devices which does not seem to recognize the EDQM certification system. Rather, the guidance will require the use of 'notified bodies' and other approaches more characteristic of medical devices and the ISO 9000 approach (which will cover one product at a time). There has been poor transparency on this guidance with very little public input. If published as drafted (and this reportedly is very close to happening) it will be a tremendous burden on many companies. There should be one way to handle the TSE risk process for a manufacturer of health care products, be they classed as drug or device.

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• **On Proportional Risk**: While the pharmaceutical industry is being required to commit tremendous resources to eliminating almost any conceivable risk of TSE contamination, what is being done about the food industry? Most of the gelatin produced worldwide ends up in food products with no certification. For example, less than 1% of the world gelatin production is used in pharmaceuticals. There needs to be a measure of proportionality in the response to this problem. (Note: a round of applause followed this comment.)

• **On why there are fewer certificates than the EMEA or the national authorities would prefer**: While the TSE rules apply to the MAH, it is the supplier of the starting material who must take the lead in preparing a dossier and securing EDQM approval. Many of these products, e.g. wool fat, have minimal economic value to the producers. Also, producers do not have the expertise to prepare an acceptable dossier. Finally, there are sometimes trade secret issues which companies refuse to divulge. For these reasons many suppliers simply do not want to deal with the certification system. As a result, the number of certification applications hoped for will simply not materialize.

• **On technical information for cleaning validation**: It has been stressed that suppliers of TSE risk materials must perform adequate cleaning to prevent cross-contamination of materials. However, the only industry-wide guidance on cleaning relating to the pharmaceutical industry are the Technical Reports issued by PDA. The starting material manufacturers and suppliers who need this information most may not be aware of the PDA publications [Ref: PDA Technical Report No. 29, *Points to Consider in Cleaning Validation*, 1998, and *Cleaning and Cleaning Validation: A Biotechnology Perspective* (PDA 2), 1996. Both available from PDA, see page 40.]

• **On revoked or rejected certifications**: When an EDQM Certificate is revoked or refused on scientific grounds, this information needs to be shared in a public fashion so other users of the material will be made aware of the TSE risk.

V. Questions from Conference Participants:

Q. Some materials can be from animal origin or from synthetic process. How much information must a manufacturer provide to prove that such a material is of non-animal origin?

A. A clear statement to that effect will normally be adequate.

Q. How far back in the production system for a TSE risk material must a pharmaceutical manufacturer conduct traceability and supplier audit?

A. There can be no single answer and it will depend on the material and it's source. In general, it is the responsibility of the user to do whatever they believe is appropriate to reduce the TSE risk to acceptable levels.

"There should be one way to handle the TSE risk process for a manufacturer of health care products, be they classed as drug or device."

Q. In coming months and years, inspectors from all the national authorities will be dealing with the TSE control steps taken by manufacturers. The directives are very fluid and generally give manufacturers much latitude in how to handle this problem. Has any thought been given to the guidance which should be given to Inspectorates and how they should audit a company's performance?

A. For both Type I variation (EDQM certification) and Type II (data in the dossier) the inspector should only review conformance with the approved dossier submission. They should not do more.

Q. On March 1 what is the status of 'pending' certifications which have been supplied to EDQM but which are not yet approved?

A. Small delays (a few days or weeks) will not be a problem. It should be remembered that there is a common interest by all parties (regulators, drug producers, and the material suppliers) to get the problem under control and to assure the public confidence in the medicines supply.

Q. If a country's BSE status changes from BSE-free to BSE cases, how will that impact any certificate already issued?

A. If certifications are shown to no longer be reliable they can be revoked.

Q. Are clinical trial materials subject to the TSE directives?

A. Probably yes.

Q. Should a medicines manufacturer audit a supplier who holds a TSE certificate?

A. Periodic audits are a normal aspect of GMP. ■