



CERTIFICATION FOR TSE RISK PRODUCTS
International Workshop
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PROCEEDINGS

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SESSION I: LEGAL AND SCIENTIFIC BACKGROUND

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**LEGAL BACKGROUND PRESENTED BY THE EUROPEAN
COMMISSION**

Dr M. Robert, DG Enterprise Pharmaceutical and cosmetic unit, Brussels, B

The European Commission did not wait for the BSE (bovine spongiform encephalopathies) crisis of 1996 to take account of the possibility of transmitting spongiform encephalopathies to human beings, as well as animals, through medicinal products containing substances of animal origin. This has been a matter of concern for the European Commission for a long time and, of course, still continues to be the case. Indeed, as early as 1991, the CPMP (Committee for Proprietary Medicinal Products) elaborated a guideline addressed to manufacturers to minimize TSE (transmissible spongiform encephalopathies) transmission via starting materials used for the preparation of medicines.

1. In 1997, following (i) the occurrence of new developments strongly suggesting that BSE could likely be transmitted to human beings through consumption of beef and beef products, as well as (ii) to respond to strong criticism emanating from the European Parliament which considered that appropriate means to stop the spread of the BSE epidemic had not being adopted at Community level, the Commission decided to take further steps in this area. Thus, a much more stringent approach was taken by adopting Commission Decision 97/534/EC of 30 July 1997, the purpose of which was to ban a wide range of products, for any use, containing listed “specified risk materials” (SRMs) of bovine origin, the ban being effective after a short transition period of six months only.

With such a wide scope, it became rapidly obvious that such a general ban was almost impossible to implement in practice, particularly in the case of medicinal products. Indeed, the wording of the said Decision was such that a retroactive application of it was compulsory and, as a result, around 80% of medicinal products available in the shelves of every part of the European Community should have been withdrawn from the market place as of 1st January 1998. Given the absence, in the Decision, of specific provisions dealing with essential medicinal products for the treatment of patients and to avoid any chaos that would have been triggered by a sudden shortage of these products, stakeholders proposed a much more realistic and pragmatic approach to the problem.

That is why the date for the coming into force of the Commission Decision of July 1997 was postponed several times. The Decision was finally repealed last June and replaced by a new Commission Decision, 2000/418/EC of 30 June 2000, which is mainly focussed on foodstuffs since, inter alia, it explicitly excludes medicinal products from its scope.

2. As regards the exclusions, it was then proposed to adopt a specific (or vertical) legislation adapted to particular products which incorporate ingredients of ruminant (including bovine) origin such as, medicinal products, cosmetics (Commission Directive 98/16/CE of 5 March 1998 amending Annex II to Council Directive 76/768/EEC of 27 July 1976, as amended) and medical devices.

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Since its inception, Community legislation specifically devoted to medicinal products for human use, and to veterinary medicinal products, has laid down a detailed set of requirements aiming to control the risk of transmission of infectious agents. Therefore in the case of non-conventional infectious (or transmissible) agents, specific measures concerning spongiform encephalopathies of animal origin only had to be strengthened, thanks to the following legal instruments.

The Annex to Council Directive 75/318/EEC on technical requirements for the granting of a marketing authorization of a medicinal product for human use was amended accordingly by Commission Directive 1999/82/EC. The latter states that CPMP/BWP/1230/98, rev.1 Note for Guidance (NFG) “on minimizing the risk of transmitting animal spongiform encephalopathy agents via medicinal products” and its subsequent technical updates is mandatory and gives a timeframe for its application to new products and existing products.

Given the technical complexity of the matter and also the rapidly evolving knowledge concerning technical requirements in this area, it was considered more appropriate and practical to impose a NFG which can be easily and frequently adapted rather than a more rigid legal procedure.

By contrast to other existing Community legislation on TSEs based on the ban of listed SRMs, Community pharmaceutical legislation relies on a totally different philosophy. Instead, the TSE risk assessment relies on a multifactorial analysis, namely, (i) the geographical or country of origin of ruminant animals, (ii) the type of tissues involved in terms of infectivity, as well as the age of the animals in question, and finally, (iii) the physico-chemical process used for the manufacturing of ingredients of animal source entering into the composition of pharmaceuticals.

As a result of this legislation, all new medicinal products to be placed on the market as of 1st July 2000 have to comply with the requirements of the aforementioned NFG. In the case of old products (which were granted a marketing authorization before 1st July 2000), marketing authorization holders must demonstrate, before 1st March 2001, that they comply with the NFG requirements.

The same reasoning is applicable to veterinary medicinal products, which fall under a parallel Community legislation. In that case, the deadline for compliance of old veterinary products is 1st June 2001. To streamline the assessment of marketing authorization dossiers, a NFG common to both types of medicinal products is being finalized.

3. In order to be granted a marketing authorization, each individual medicinal product is subject to an assessment carried out on the basis of three criteria, namely, quality, safety and efficacy.

According to Community legislation, the demonstration of compliance with TSE requirements deals with the quality aspects of the dossier, and more precisely, with the control of all starting materials which are part of the medicinal product in question.

This is particularly true of (i) the ingredients of the “excipient” which are often of animal origin, as well as (ii) the “source material” in the case of biological (including biotechnological) medicinal products because they generally use media containing fluids of animal origin or cells (cell lines) and tissues of animal origin. In terms of TSE risk, the emphasis is placed on these particular elements.

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4. It is of course important to see, in practice, how to bring the demonstration of compliance with the two Commission TSE Directives, inasmuch as new provisions introduced in this domain have been differently interpreted by interested parties like competent authorities in the Member States, Industry associations, applicants and/or marketing authorization holders.

The situation is quite clear as to new products (as yet unauthorized) which must follow requirements of the TSE legislation that is, to submit a dossier containing appropriate documentation.

The situation appears, however, more complex with medicinal products already on the market, to the extent that their holders must formally give the proof that their products fit with the TSE requirements. As a result, it is incumbent on competent authorities, both at Community level and at national level, to verify that this is the case.

For marketing authorizations falling under the scope of the two Variations Regulations (541/95 and 542/95), the application for demonstrating compliance with TSE Directive would have, in normal circumstances, to be handled as a Type II Variation. For marketing authorizations not falling under the scope of the two Variations Regulations, Member States are free to follow appropriate national procedures.

Owing to the enormous amount of concerned authorized products currently on the market place, one can easily imagine the gigantic task, both for rapporteurs in charge of the medicinal product assessment and for competent authorities, entailed by this verification. That is why, it was proposed to alleviate this burden, by means of the delivery of a “Certificate of suitability to the European Pharmacopoeia TSE monograph” for starting materials. In cases where certificates of suitability can be provided, a Type I Variation procedure needs to be followed (in fact, according to a revision of the Notice to Applicants to take account of TSE Directives, practical arrangements can be made whereby the notification of the certificate can suffice).

This particular aspect of the practical implementation of TSE Directives will be abundantly detailed in the course of this workshop. The “TSE certificate procedure” through the European Pharmacopoeia, albeit not compulsory, is highly recommended for products, whether they are, or not, covered by Variations Regulations 541/95 and 542/95. For products, which warrant a national marketing authorization (without mutual recognition), it is even possible to set up a horizontal procedure affecting several marketing authorizations to streamline and alleviate the burden of multiple assessments.

**MEASURES TAKEN BY THE EUROPEAN PHARMACOPOEIA
COMMISSION**

Prof. D. H. Calam

(European Pharmacopoeia Commission)

Until 1995 there were no specifications in monographs of the European Pharmacopoeia with respect to BSE. During 1995, some statements about animals were introduced on a case by case basis as monographs were prepared or revised. However this approach was seen to be inadequate because of problems of identifying all products concerned and of assessing the processes used. The European Pharmacopoeia Commission therefore set up a Working Party to consider how the necessary requirements for products derived from warm-blooded animals could be brought into monographs in the Pharmacopoeia. The Working Party acted in collaboration with the EMEA and the European Commission and was concerned with mainly viral but also other types of contamination. The following year, guidelines specifically related to BSE were produced by WHO. A CPMP Note for Guidance based on the WHO document was developed and made available in 1998 for the benefit of those seeking or already holding marketing authorisation for their products. This was a statement of scientific principles and formally was not binding but any deviation from its recommendations would have had to be thoroughly justified. Meanwhile, the Working Party initiated an inventory of types of possible contamination with the aim of also identifying decontamination methods, and a listing of monographs for which a general text would be applicable. A draft general monograph was prepared in November 1997 but a decision on it was deferred until the CPMP and European Commission had completed their work on the Guideline and Directives respectively.

When it became aware of the impending EC Directives for human and veterinary medicines amending the parent pharmaceutical Directives, the European Pharmacopoeia Commission in 1999 finalised the new general monograph 'Products with risk of transmitting agents of animal spongiform encephalopathies' which gives mandatory force to the CPMP Note for Guidance as a general chapter 5.2.8. This monograph was adopted in June 1999 and came into effect on 1st January 2000 as a mandatory requirement in the 27 signatory countries of the European Pharmacopoeia Convention. It thus has wider application than only within the 15 countries of the European Community. The date of implementation was the same as that for Member States to comply with Directive 1999/82/EC for human medicinal products.

The monograph defines:

- products at risk as 'those derived from tissues or secretions of animals susceptible to transmissible spongiform encephalopathies other than by experimental challenge.'

and

- the scope of application of the monograph to 'all substances or preparations obtained from such animals and to all substances or preparations where products obtained from such animals are

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included as active substances or excipients or have been used during production, for example as raw or source materials, starting materials or reagents.'

The monograph contains a Production section that requires compliance with the general chapter 5.2.8 'Minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products' which reproduces the CPMP Note for Guidance.

The effect of implementation of the general monograph and general chapter is that compliance with the Note for Guidance is binding on all substances at risk whether or not an individual monograph is included in the Pharmacopoeia.

The existing Production statements in monographs for animal-derived products were replaced by a reference to the new general monograph.

It was recognised that when the general monograph came into effect, considerable advantages would be gained by extending the scope of the scheme for Certification of Suitability since this would allow a single centralised assessment by experts drawn from regulatory authorities of the risk associated with a given substance from an individual manufacturer. Therefore at the same Session of the European Pharmacopoeia Commission, the scheme for Certification of Suitability was amended with effect from the same date of 1st January 2000 to cover all products subject to the requirements of the new general monograph.

The two amending Directives, 1999/82/EC for human medicines and 1999/104/EC for veterinary medicines, came into effect in September and December 1999 respectively. They require demonstration by stated dates of minimised risk for all substances derived from animals involved in the manufacture of or incorporated into medicinal products. The dates for new applications were set as 1st July and 1st October 2000 respectively and for existing authorised products by 1st March and 1st June 2001. These very tight deadlines posed enormous problems for regulatory authorities and for companies for obtaining, submitting and assessing the necessary information. The availability of the scheme for Certification of Suitability was seen as the most effective way of reducing the work and harmonising the assessments involved.

The first submissions for certification were received early in 2000 and the numbers increased rapidly through the year. At the same time the number of assessors has also increased. The availability of the general monograph allowed this route of approval to be activated very rapidly.

Following the revision of the CPMP Note for Guidance effective from 31st October 2000, to address issues relating to milk and milk-derived products and products derived from wool and hair, the European Pharmacopoeia Commission in November 2000 revised the general chapter 5.2.8 to reflect the changes and this revision is effective from 1st January 2001.

The speed with which the decisions and actions have been carried out, necessary to put in place the legal and administrative systems to implement the Directives, would not have been possible without close co-operation between the European Pharmacopoeia Commission and Secretariat and the EMEA and European Commission. The delegations of the European Pharmacopoeia Commission have taken the necessary decisions swiftly but with due deliberation. National regulatory authorities have nominated the assessors with appropriate expertise to allow the

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Certification process for animal-derived products to proceed smoothly as the applications have been received.

The European Pharmacopoeia Commission will continue to examine the requirements in monographs for animal-derived products with a view to introducing or modifying statements about other potential types of contamination.

MEASURES TAKEN AT NATIONAL LEVEL

Dr W.F. Van der Giesen (Medicines Evaluation Board, NL)

It is a real pleasure for me to explain to you what we have done to be able to cope with the new TSE requirements for medicinal products in The Netherlands. In good liaison with the other Member States of the EU we have developed some procedural and administrative rules which are supported by the European Commission and which are also applied by most of the other EU Member States.

The TSE amendment to the Annex to Directive 75/318/EEC states that all authorised medicinal have to comply with the new requirements by the first of March 2001.

That means that the competent authorities in the EU Member States are obliged to check whether the marketing authorisation holders have fulfilled their duties for all their medicinal products before the first of March of 2001. This is not a simple task for the authorities because of the number of products: in The Netherlands for instance we have about 10.000 authorised medicinal products and the number of registration holders we are dealing with is about 450. It is in fact an enormous task.

It also is an enormous task for the marketing authorisation holders. They have to check the origin of all their starting materials used as active substance, excipient, or as reagent during manufacture of their medicinal products. There are sometimes surprises that a substance originates from animals. So it is really needed to check the origin of all the starting materials and to contact all your suppliers of starting materials to get the information needed. If a starting material is of ruminant origin then it is needed to collect further relevant information about the animals used, geographic origin, tissue(s) used, manufacturing process. Thereafter it has to be checked whether the starting material complies with the new TSE requirements and at the end of the day the marketing authorisation holders have to submit the proof of compliance with the new TSE requirements to the competent authorities either by submission of a Ph. Eur. TSE certificate, or by submission of detailed information regarding origin and production of the starting material.

However, we have a kind of a regulatory problem since there is no approval system for starting materials as such in the EU, there is only an approval system for finished products.

So, for each individual medicinal product the marketing authorisation holder has to provide proof of compliance with the TSE requirements. However, a certain starting material (take as an example Mg-stearate) may be an excipient present in several medicinal products of the same manufacturer. The consequence of this would be a multiple repetition of providing the authorities with the same information. It is a bad situation for both industry and authorities.

Attention for this problem was drawn in the Pharmaceutical Committee. After a fruitful discussion in the committee the European Commission made a statement that multiple submission of the same information should be avoided where practically possible (so, no need to send multiple copies of TSE certificates) and further it was reaffirmed that the usage of Ph.Eur.

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TSE certificates would simplify life for both industry and authorities. So, the Commission statement included that use of the TSE certificates should be encouraged.

Further details about the administrative rules should be developed within the Notice to Applicants Group and the Mutual Recognition Facilitation Group (MRFG).

In May 2000 an agreement was reached in the MRFG about the rules to be applied which were also endorsed by the European Commission and which were put on the Internet site of the Commission.

At the same time the Medicines Evaluation Board in The Netherlands sent a letter with these rules to the marketing authorisation holders (MAHs). In this letter MAHs are requested to make three listings of their medicinal products.

The first list:

Medicinal products for which starting materials are used as defined in section 2 of the 'Note for guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy via Medicinal Products` and for which Ph.Eur. TSE certificates are available.

Materials used as defined in section 2 of the Note for guidance means: materials of ruminant origin which are used as active substance, excipient, or as reagents during manufacture and which come into contact with (intermediates of) the medicinal products. This is especially important for biotech products.

The second list is the following:

Medicinal products for which starting materials are used as defined in section 2 of the 'Note for guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy via Medicinal Products` and for one or more of these materials no Ph.Eur. TSE certificate is available, but that scientific data demonstrating compliance with the new TSE requirements have been/will be submitted prior to 1 December 2000.

For the products mentioned on list II we know that an assessment of information to support compliance with the new TSE requirements is needed.

The third list is the following:

Medicinal products for which no starting materials are used as defined in section 2 of the 'Note for guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy via Medicinal Products`.

Each of the lists has a part A and B. Part A for authorised products and part B for products for which the MAA is still pending.

Templates for the listings can be downloaded from the MEB Internet site (www.cbg-meb.nl). If a TSE certificate is available then only one copy of that certificate has to be annexed to the list.

The MA holders are requested to submit the listings prior to the first of December 2000 together with a declaration that: a.o. each pharmaceutical product which is registered in his name on the first of July 2000 and each product for which a marketing authorisation application has been

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submitted in his name prior to the first of July 2000 is included in one of the above mentioned listings. This declaration has to be signed on behalf of the MA holder!

The date of the first of December is chosen because this gives the authorities the possibility to assess the information and to take corrective measures if needed.

The listings, together with copies of the TSE certificates, are in fact annexes to the declaration.

The matter was of course also discussed in the MRFG. The Reference Member States (RMSs) have to play an important role. The following agreement was reached:

Products mentioned on list I: No formal Type I variation procedure is needed; the RMS will check the information provided by the MAH and will notify the receipt of the certificates to the Concerned Member States (CMSs).

Products mentioned on list II: Assessment of the information by the RMS is needed through a Type II variation procedure.

Products mentioned on list III: No specific dossier and assessment is required.

It was also decided by the MRFG that: Each month the RMSs would inform the MRFG about the progress made in checking the compliance with the new TSE requirements for products for which they are responsible.

It is not the intention of the MEB to open the dossiers of all our 10.000 authorised medicinal products. The TSE declarations and annexes are archived per MAH. Scientific proof of compliance via a Type II variation procedure is archived in the dossier of the relevant medicinal product. In the MEB electronic database it will be included how and when proof of TSE compliance was completed for each medicinal product.

When no usage is made of the Ph.Eur. TSE certification we as registration authorities have to assess the scientific information ourselves. In the MRFG an agreement was reached that, also for starting materials used in nationally authorised products, assessment reports on TSE information would be made available as much as possible to the other Member States via a Eudranet facility. This is another measure to avoid duplication of work.

In conclusion:

Fulfilling the new TSE requirements from the amended Annex to Directive 75/318/EEG is a huge task for both industry and competent authorities. The rules outlined above avoid duplication of work and simplify the administrative burden where possible.

RISK EVALUATION FOR MEDICINES FOR HUMAN USE

Dr. J. H. Trouvin (BWP, EMEA)

I would like to present to you the BSE risk evaluation for medicinal products for human use by presenting the guideline which has been developed by the Biotechnology Working Party (BWP) and which is also kept under maintenance by the Biotech Working Party.

To remind you that the story started at the end of the 80's when the epizootic situation became evident in the United Kingdom. The very first question was: is the disease transmissible to humans, essentially via the food chain? Clearly, at that time, we had a very long experience with scrapie, which is a spongiform encephalopathy in sheep, and apparently there was no reason to fear any transmission. However, for the experts, it was necessary to take into account that the biological properties of the BSE agent were different to those of scrapie and for that, the experts considered it would be prudent to pose the hypothesis of a possible risk of transmission of the BSE agent to human, despite the existence of a species barrier. Therefore, we had to put some safety measures in place to minimise the risk of transmission and in particular, via medicinal products.

As you know, there have been some national measures which have been taken at the end of the 80's but very rapidly, emerged the notion that a European approach was needed so as to find a common set of evaluation criteria. Clearly in 1990, the EU Member States had different approaches regarding this risk. Therefore, the development of a European guideline was necessary to identify the risk factors, and to propose safety measures. The first version of the guideline was issued in 1991. A very important revision took place in 1997 and then a further revision in 1999, for the implementation of the certification procedure. The very last update took place in December 2000, essentially to clarify some points on the risk factors (e.g. cross contamination), and to deal with some specific products and particularly gelatin, tallow derivatives and milk.

Lets go in some details of the guideline. First, the title: "*Minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products*". The products concerned are explicit in the title, i.e. the medicinal products. Clearly, this means, as explained in the scope, that not only the active substances are covered, but also the excipients and the raw and source materials and reagents, which are used in the production of the medicinal products.

In the guideline, besides general recommendations, you have essentially three criteria, which have to be taken into account in the risk assessment.

First, the general recommendations insist on the use of animal-derived materials. I would like to highlight these general recommendations:

Where manufacturers have a choice, the use of non-ruminant material is preferred

The preferred option should be to avoid the use of material derived from animals known to be susceptible to TSE.

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The pharmaceutical manufacturers and producers are responsible for the selection and justification of the use of the materials.

Clearly, it is the scientific responsibility of the pharmaceutical industry to develop medicinal products that fulfil these recommendations.

Lets go now to the three parameters which have been presented and detailed in the guideline: firstly, the geographical origin. As you know, there is currently no valid test, which could be used on a routine basis to test all bovines entering the abattoirs and from which is collected some bovine material. As there is no test at the moment, the most important criteria is the selection of source material. In the guideline, the geographical criterion is well explained. Obviously, the most satisfactory source is from countries that have no reported cases of BSE. To use this criterion, we now have the country classification proposed by the scientific steering committee, the so-called Geographical BSE Risk (GBR), as well as the OIE criteria.

The second parameter to be considered in the risk assessment, deals with the part of animal to be used, i.e. the tissue or body fluid that is used as starting material to prepare these bovine-derived materials. In the guideline, the WHO classification is proposed to help to estimate the initial infectivity (if any) of the concerned tissue. It is noteworthy that this classification is based on scrapie data, which could be considered, for the bovine tissues, the worst case scenario because, as you know, it is well acknowledged that in the bovine species, the BSE agent seems to be essentially concentrated in the central nervous system, whereas in the scrapie model, the distribution is wider, including peripheral tissues.

With the tissue criterion, one should also mention the age of animals. Indeed, as you know, there is no clinical TSE sign in young animals. In the BSE model, the age, for clinical symptoms is ca. 5 years, whereas infectivity is detectable in the central nervous system after 12 months of age. As such, collecting tissues from young animals should be recommended. However, we also know that for some products this is not possible. This point (age of animals) is a good example that, all criteria are not inclusive but that each criterion should be considered as complimentary to each other.

Also, in the "tissue criterion", an important point to be considered (and this has been well developed in the 1997 revision), is the risk of cross-contamination. This is to say that, even if you are considering a tissue, which is in class IV (e.g. muscle meat), and for which there is no detectable infectivity, there is still a risk of cross-contamination during slaughtering and collection of the tissue of interest. For this reason, you have to consider, in the risk assessment, the risk of cross-contamination, which is largely depending upon the quality of slaughtering and collection conditions. These should be part of the audit of the suppliers of the tissues or fluids.

The third criterion to be taken into consideration, is the manufacturing process. Again, the guideline acknowledges that this is the proper control of the sourcing which is the most important criterion. This is because it is well known that the TSE agent is very resistant to any inactivation or elimination process. Therefore, for most of the bovine-derived material there is no possibility to put in the production process an inactivation step. Sometimes, where it is possible a step, capable of inactivating or eliminating the TSE agent can be envisaged. In this respect, there are

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some processes, which are applicable, for example for the tallow derivatives or gelatin. We also have some validation studies, which are currently available, and in particular for gelatine, for which we can also prove that the manufacturing process can participate in the reduction of the infectivity in the final product, if present in the starting material.

In the guideline, some specific products are addressed. Dr John Purves has illustrated the case of milk and milk derivatives, or derivatives of wool and hair of ruminants. These products (milk, gelatin, tallow) have been considered in the guideline, because clearly they are products for which general consideration can be made in a guideline, whereas for all the other products it would be very difficult to have specific consideration product by product. This is essentially the three criteria, which should be considered.

Finally, in the guideline, further considerations, which have been introduced in the guideline in 1997, have to be mentioned. In particular, I would like to insist on the question of traceability and quality assurance system to be put in place at each stage of the chain, from collection up to supply of the desired product. When you consider that, the safety of all these bovine-derived material, is essentially depending on the quality of the sourcing, it is clear that the only way you can insure the real geographical origin, is through the traceability system. This is why, in the last version of the guideline, we have insisted on the traceability system. In this context, the guideline insists on the responsibility of the producers and in particular, that the producers or manufacturers should audit the suppliers of materials, in relation with the traceability system.

The last recommendation is that the manufacturers are responsible for the selection and the justification of adequate measures.

In conclusion, we know that the TSE agents is a public health issue and very likely in the near future we will have to deal with many other questions not only in connection to BSE but also with scrapie. We have to set up and maintain safety measures to minimise the risk of transmission via medicinal products. For the assessment of the risk, it is very important again to stress that this is a multi parametric approach which has to be used and for which we have not got a magic recipe to say if a product is safe or not. We have to consider all the criteria, summarised above. No single criterion will establish the safety of a product and particularly, if we only rely on the geographical source, I am not sure whether the geographical origin should be the golden standard, even if the tissue comes from a category I or II country. The guideline should be, and is, a scientific living document. This document should be used as a scientific tool to help the manufacturers and the evaluators in the assessment of the risk and to identify the proper safety measures to be put into place. Obviously, as it is a scientific document it needs to be updated according to the scientific developments.

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TSE RISK ASSESSMENT FOR VETERINARY MEDICINAL PRODUCTS

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I – Abstract

The CVMP Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Veterinary Medicinal Products differed slightly from its CPMP counterpart; the main reason being the absence of a species barrier in the former case and the fact that veterinary medicinal products are often applied directly via the parenteral route. Therefore the risk may be greatest when bovine or ovine materials are used in products intended for either sheep or cattle. Fortunately these discrepancies have now been resolved and, as a consequence, a common Note for Guidance is now available.

As veterinary vaccines comprise a large part of the market for veterinary medicinal products, it would be undesirable to lose old master seeds due to the TSE certification procedure, particularly in view of the long history of safe use of many veterinary products. Therefore a Position Paper has been produced by the CVMP on assessment of the risk of transmission of animal spongiform encephalopathy agents by master seed materials used in the production of veterinary vaccines. The state of the art in using rapid immunological tests for the detection of TSEs in raw materials is also discussed.

II – Introduction

The former CVMP (Committee for Veterinary Medicinal Products) “Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Veterinary Medicinal Products” differed slightly from its human CPMP (Committee for Proprietary Medicinal Products) counterpart. The rationale for these discrepancies are described below. The existence of two, different Notes for Guidance had the potential to be confusing for companies producing veterinary medicinal products when they want to follow the TSE certification procedure for starting materials put in place by the European Directorate for the Quality of Medicine (EDQM). The main differences were twofold. First, although the scope of the CPMP Note for Guidance was altered to exclude milk and milk derivatives, these materials remained within the scope of the CVMP guidance. The CVMP wished to retain milk as a category IV material. In contrast, the exemption introduced into the CPMP guidance for hair and wool was carried over by the CVMP. The major reason given for retaining milk within the scope of the CVMP Note for Guidance is that whilst the risk for humans of this exemption may be considered negligible as they would consume, in any case, milk from such animals, the risk for cattle may be greater since milk carrying the infectious agent could be used as a source material for veterinary medicines applied directly via the parenteral route to the very same species, i.e. in situations where no species barrier prevails. Secondly, the CVMP wished under section 3 to include the following statement : “Available epidemiological and laboratory data on

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natural spongiform encephalopathies and the absence of species barriers indicate that in the case of veterinary medicinal products, the risk may be greatest when bovine or ovine materials are used in products intended for either ovine or bovine animals”. The rationale for the discrepancies was mainly due to the fact that ruminant species are not “dead end” species and may increase the pool of transmissible agents which can afterwards enter the food chain and infect man. It must also be remembered that, for veterinary medicinal products, scrapie represents a risk in terms of transmission to small ruminants but not to man.

There are therefore major concerns for both public and animal health.

It was later on nevertheless decided both by the CVMP and later on by the CPMP that common Note for Guidance should be proposed to the European Commission. The CVMP agreed that the CPMP Note for Guidance should also apply for the certification of starting materials for veterinary products provided that a new sentence would be added : “When assessing, and minimising, the risks associated with veterinary medicinal products intended for use in ruminant species, additional factors of specific relevance only to these species must be considered by the Applicant and relevant Competent Authorities. These factors are detailed in related Position Paper (EMEA/CVMP/121/01)”.

This was also agreed by the CPMP. As a consequence, when a registration dossier is submitted by an Applicant to the relevant Competent Authority, products intended for use in animal species such as the horse, dog, chicken, fish, pig and even the cat undergo the same TSE risk assessment procedure as those intended for human use, whereas products intended for use in ruminant species (cattle, sheep, goat, cervidae) require a further risk assessment to take into account factors specific for ruminants. The introduction of a new sentence in the common CVMP/CPMP Note for Guidance has no impact at all on the certification of starting materials used for the production of medicinal products intended for human use.

In order to facilitate the risk assessment of products intended for use in ruminant species by the Applicant, and its evaluation by the relevant competent authorities, the CVMP asked the Immunologicals Working Party (IWP) to prepare the Position Paper detailed below.

As noted in the Position Paper, special care should nevertheless be taken when assessing the risk of products intended for use in cats and other felidae since these species have been shown to be particularly susceptible to infection by the agent responsible for Bovine Spongiform Encephalopathy (BSE), developing a similar disease termed Feline Spongiform Encephalopathy (FSE).

The common CVMP/CPMP The CVMP Note for Guidance for Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products is given in Annex I. This Note for Guidance will undoubtedly still evolve as new scientific data become available.

Manufacturers of veterinary vaccines had been concerned for some time how they might demonstrate compliance of master seed material laid down at a time when the BSE risk either did not exist or was not fully appreciated. In these circumstances, records may no longer exist to

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document exactly how the seed was laid down and what materials were used during the production process of the master seed. Although several different regulatory authorities have considered this issues and decided that the risk posed by master seed material is likely to be extremely remote in most cases, it was necessary to lay down a framework which could be used by both applicants and Competent Authorities to formalise the process of risk assessment for these materials. This was carried out by the Immunologicals Working Party of the CVMP in the form of a Position Paper entitled ‘CVMP Position Paper On The Assessment Of The Risk Of Transmission Of Animal Spongiform Encephalopathy Agents By Master Seed Materials Used In The Production Of Veterinary Vaccines (EMEA/CVMP/019/01)’ which is included under Section IV.

III - CVMP position paper on risk assessment of the use of starting materials of ruminant origin in veterinary medicinal products intended for use in ruminant species (EMEA/CVMP/121/01)

Introduction

When assessing the risk of the use of veterinary medicinal products intended for use in ruminant species, a number of factors need to be taken into account which are additional to those detailed in the Note for Guidance For Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Medicinal products (the Joint CPMP/CVMP Note for Guidance). Ruminants are susceptible to BSE by the oral route and the risk of transmission is greatest when animals are exposed to infectious material derived from the same species. Transmission of infectivity to food producing species represents a risk of amplifying TSE infectivity in a form that is readily transmissible to man. It therefore follows that manufacturers should demonstrate that they have addressed the additional considerations that relate to ruminant species when analysing, and minimising, the risk of transmission of TSEs by veterinary medicinal products intended for use in ruminants.

Although particular attention is paid in this Position Paper to milk and milk products due to their exclusion from the Note for Guidance, it is important to note that the scope of this Position Paper extends beyond milk to cover all substances of ruminant origin when used in products intended for ruminants.

Manufacturers of products intended for use in non-ruminant species, whether food producing or not, i.e. pigs, poultry, horses, dogs, fish, rabbits and cats, need only address the factors detailed in the Joint CPMP/CVMP Note for Guidance¹.

This Position Paper details under what circumstances an additional risk assessment should be carried out, and the factors that should be taken into account, when minimising the risks of

¹ Cats and other felidae have also been shown to be susceptible to TSEs when exposed to infectivity by the oral route. Although there are no additional requirements for products intended for use in these species, manufacturers should address, where relevant, any particular issues related to the TSE risk for felidae.

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transmission of TSEs to ruminant species Manufacturers have the option of obtaining a Certificate of Compliance from the EDQM to demonstrate compliance of starting materials of animal origin that fall within the scope of the Joint CPMP/CVMP Note for Guidance. The risk assessment referred to in this document is a separate requirement from the certification procedure. The additional risk assessment is required for all products intended for ruminant species, irrespective of whether or not a certificate is available for one or more starting materials used in their production and should be carried out by the Marketing Authorisation Holder or Applicant.

As indicated in the Joint CPMP/CVMP Note for Guidance applicants for marketing authorisations should take account of the latest available scientific information when preparing a risk assessment. In the event of a change in the state of knowledge or the disease situation, the risk posed should be re-assessed. Likewise, this Position Paper will be updated in line with future changes to the Joint CPMP/CVMP Note for Guidance.

Scope

This document relates to the use of:

- (i) substances of animal origin that fall within the scope (Section 2) of the Joint CPMP/CVMP Note for Guidance when used in the manufacture of veterinary medicinal products intended for administration to ruminant species i.e. cattle, sheep, goats and deer.
- (ii) Milk and milk derivatives under the following defined circumstances;

Whereas milk and milk derivatives are specifically excluded from the Joint CPMP/CVMP Note for Guidance provided the milk is obtained from healthy cows and is fit for human consumption, these materials fall within the scope of this Position Paper when used under the following conditions, both of which must apply;

the veterinary medicinal product is intended for parenteral administration to a ruminant

AND

the milk or milk derivative is used as a source of the active substance, as an excipient, stabiliser or component of the final formulation (i.e. not when used as a component of a medium or solution used during the production of one of the final ingredients).

Risk assessment

Manufacturers should perform a risk assessment and justification for use of substances falling within the scope of this document taking into account the following factors;

Where possible, manufacturers should use substances of non-ruminant origin for products intended for ruminant species. Where this is not possible, a justification should be provided for the use of ruminant-derived material.

When milk and milk derivatives fall within the scope of this document (see section 'Scope', above), full compliance with Joint CPMP/CVMP Note for Guidance should be demonstrated in terms of the origin of the milk and, where relevant, the treatment applied (such as removal of cells).

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Use of specified risk materials (SRMs) as a starting material at any stage of the production process will be unacceptable to Competent Authorities in all but the most exceptional cases. Only where a risk-benefit analysis clearly shows that it is in the interests of public and animal health for a particular veterinary medicinal product to be made available would use of SRMs be permitted. In these circumstances, manufacturers shall demonstrate that the use of all other possible sources of starting materials has been explored and eliminated and that every possible measure to minimise risk has been taken. Such measures would include sourcing starting materials from a country officially classified as being free from animal TSEs, use of animals less than 1 year of age, pre-mortem inspection and, where relevant, testing for the presence of infectivity.

The presence of SRMs as contaminants of other starting materials of animal origin is of particular concern in products intended for ruminants. Particular attention should be given to ensuring, and describing, that measures and quality systems are in place to ensure that contamination with SRMs does not occur.

The risk of transmission will be related both to the route of administration and the quantity of risk material that might be present in the final product.

Attention must be paid to minimising the potential risk of transmission of scrapie by sourcing materials of small ruminant origin that fall within the scope of this Position Paper from a country free from scrapie or by taking other measures to ensure that the herds of origin from which the source animals are derived are adequately monitored and controlled for freedom from TSEs. These requirements do not therefore apply to substances such as lanolin that fall outside the scope of the Joint CPMP/CVMP Note for Guidance and this Position Paper.

All of the factors listed above should be specifically addressed when carrying out a risk assessment of seed materials for use in a vaccine intended for ruminants, as described in the CVMP Position Paper EMEA/CVMP/019/01.

Practical outcomes

The basis of demonstrating compliance of starting materials used in the production of veterinary medicines should rely, where possible, on the issue of a certificate of compliance by the European Department for the Quality of Medicines, following assessment of a data package submitted by the manufacturer of the raw material to demonstrate that the requirements of the Joint CPMP/CVMP Note for Guidance have been met.

When a marketing authorisation holder is seeking to demonstrate compliance of a veterinary medicinal product intended for ruminant species for which EDQM certificates are available for all relevant raw materials, the certificates should be presented together with a risk assessment that addresses the additional risk factors listed in this Position Paper.

When a marketing authorisation holder is seeking to demonstrate compliance of a veterinary medicinal product intended for ruminant species for which EDQM certificates are not available for all relevant substances, certificates could be presented for those substances for which they are available. For those raw materials (including milk derivatives, where relevant) for which

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certificates are not available the applicant should submit the data necessary to demonstrate compliance of the raw materials with the Joint CPMP/CVMP Note for Guidance together with a risk assessment that addresses the additional risk factors listed in this Position Paper for the veterinary medicinal product as a whole.

IV - CVMP position paper on the assessment of the risk of transmission of animal spongiform encephalopathy agents by master seed materials used in the production of veterinary vaccines (EMEA/CVMP/019/01)

Background

Since 1993, manufacturers of immunological veterinary medicinal products (IVMPs) have been required to comply with the 'Note for Guidance For Minimising the Risk of transmitting Animal Spongiform Encephalopathy Agents Via Veterinary Medicinal Products', as adopted and periodically updated by the Committee for Veterinary Medicinal Products (CVMP). Commission Directive 1999/104/EC gave this Note for Guidance the force of Community law. To ensure consistency in terms of the requirements imposed on manufacturers, Member States need to have a harmonised position on TSE risk assessment for starting materials used in the manufacture of IVMPs.

In January 2001, the CPMP and CVMP agreed to harmonise the separate Notes for Guidance into one Note for Guidance for medicinal products for human and veterinary use. The CVMP, having considered that the exclusion of milk and milk derivatives would be inappropriate for veterinary medicinal products administered to ruminants, have added the proviso that, when assessing and minimising the risks associated with veterinary medicinal products intended for use in ruminant species, additional factors of specific relevance only to these species must be considered by the Applicant and relevant Competent Authorities.

This Position Paper therefore makes reference to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and Veterinary Medicinal Products ("the Joint CPMP/CVMP Note for Guidance").

Seed materials used to produce vaccines lodged for registration after the 1st of October 2000 should fully comply with the requirements of the Joint CPMP/CVMP Note for Guidance, in accordance with Directive 1999/104/EC (new seeds). This Position Paper is therefore restricted to consideration of seed materials used to produce vaccines with marketing authorisations lodged before this date (established seeds).

This paper assumes that compliance with the Joint CPMP/CVMP Note for Guidance eliminates, as far as possible, the risk of introducing TSE infectivity into an IVMP during the process of manufacture through the use of materials of biological origin which are used in routine production (e.g. serum and blood products, tissue or tissue extracts). If this assumption is correct, then the only risk that remains to be addressed is that posed by the seed materials i.e. master and working seeds.

Scope of the document

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This paper considers the factors that should be addressed when assessing the risk posed by established seed materials so that a systematic and consistent risk assessment can be made. Seed materials (SM) are defined as Master Seeds and Working Seeds for viruses, micro-organisms, parasites and cells. The individual risk factors are identified and the likelihood of their occurrence is discussed in relation to different types of vaccines. Where relevant, the potential consequences of the risk are assessed.

1 - Risk that seed materials are contaminated with TSE infectivity

Likelihood of occurrence

Contamination of seed material could arise from either the original source of the agent/cell line or from materials used in the production and/or storage of the seed.

The risk of contamination either at source or during production of a seed with TSE infectivity can be assessed by reference to the Joint CPMP/CVMP Note for Guidance in relation to the source of the animal of origin, the nature of the material and the process used to derive or treat the seed or any material used in its production. Particular attention should be paid to the species of origin in relation to both TSE risk at source and in relation to the intended species of use. As much information as possible should be gathered about the nature and source of substances of animal origin used in the isolation, passage and storage of the seed material.

In relation to seed materials, the following factors should be considered in particular:

The time that the seed was isolated/laid down in relation to the history of BSE in the country of origin of the material concerned. This is particularly relevant for seed materials laid down before the emergence of BSE. The FDA considers 1980 to be the cut-off date after which a risk assessment should be carried out on materials of animal origin sourced from European countries.

In the case of other TSE's, such as scrapie, the history of the material should be reviewed in relation to the history of the TSE concerned, the origin of the material and the susceptibility of the target species.

The passage history of the material and whether or not infectivity could have been introduced subsequent to the original isolation/laying down of the seed. This is particularly relevant to Working Seeds which may have been laid down later than Master Seeds at a time when the risk of infectivity in the starting materials used in media production etc. was higher.

Cell cultures may be used either as the substrate for Master or Working Seed Viruses or as Master or Working Cell Seeds themselves. In either case the risk of contamination will usually be increased if primary cell cultures are used and reference should be made to the Joint CPMP/CVMP Note for Guidance in relation to the source of origin of the cell culture.

It is likely that for old master seed material some of the required information will not be available either because it was never recorded or because it has been lost. In such cases an assessment shall be made of the potential significance of this missing data in terms of overall risk of TSE infectivity. Factors such as the country in which the material was handled at the time and the

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actual or likely sources of any substances of animal origin used should be taken into account, together with any relevant history of TSEs in the countries or species concerned.

Consequences

In many cases, the risk of contamination will be judged to be low or extremely low, due to either the time that the seed materials were laid down or due to the species of origin of the materials used to produce them. However, unless full compliance with the Joint CPMP/CVMP Note for Guidance can be certified and justified, then the overall risk of transmission that the seed represents should be assessed taking into account the following factors.

2- Risk that TSE infectivity could be propagated during the manufacturing process

Scientific evidence to date indicates that it is difficult to establish, and to maintain, TSE infectivity *in vitro*. In general, high titres of infectious material have been required to initiate the *in-vitro* changes that are correlated with infectivity and specialised cell lines and *in vitro* conditions are required to maintain these presumed correlates of infectivity. There are currently no published reports which demonstrate transmission of disease through the use of “infectious” material generated *in vitro*.

Taking into account the above factors, the risk of *in vitro* propagation of TSE infectivity during vaccine manufacture is likely to be low in the majority of cases. However, TSE infectivity can be passaged by experimental inoculation between species, whether or not the recipient species is susceptible to the particular TSE concerned. A risk assessment taking into account this uncertainty shall therefore be carried out where the production process itself involves inoculation of animals and harvest of material from those animals. In addition, an assessment of risk shall be carried out in those exceptional cases where a particular cell type capable of *in vitro* propagation of TSE infectivity (e.g. a neuronal cell line) is used either as a seed material or to propagate other seed materials. In these cases reference should be made to the Joint CPMP/CVMP Note for Guidance and, in very exceptional cases, it may be necessary to require additional data to assess directly whether or not there is a risk of propagation of TSE infectivity.

3- Risk that infectivity present in the master seed material could still be present in the final product and transmit infection

This risk is relatively straightforward to estimate and will vary according to the method of manufacture. For bacterial vaccines, a dilution estimate can usually be made of how much seed material might be present in the final harvest. For viral vaccines, the amount of original material remaining will depend on the method used for passage (e.g. dilution vs. adsorption followed by washing off of the original material). It should be possible to estimate approximately how much of the original volume of inoculum could remain in the final harvest. This estimation should take into account the effect that any subsequent purification steps might have on the amount of infectivity remaining e.g. washing of bacterial harvests, centrifugation, purification, concentration steps, and dilution of the antigen concentrate for final formulation. For vaccines blended from different bulks, the amount of potential residual infectivity could vary on a batch-by-batch basis.

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For the majority of vaccines the dilution factors are likely to be high and the amount of possible infectivity present in the seed material low. This will often result in incalculably small amounts of possible infectivity potentially remaining in the final product. However, until such time as the infectious doses for the various TSEs are established, the risk posed by residual infectivity cannot be completely overlooked. In addition, for vaccines, there is at least a theoretical risk of accumulated infectivity as they are often administered on more than one occasion to the same animal.

The risk of transmission of a TSE due to any residual, contaminated seed material present in the final vaccine will depend principally on the species to which the product is administered and the route of administration. The species of origin of any potential infectivity should be assessed in relation to the recipient species of the vaccine and the consequent presence or absence of 'species barriers' to infectivity. Susceptibility to experimental TSEs varies according to the route of administration of the infectious material. The relative efficiencies of transmission, ranked in decreasing order are; intra-cerebral, intra-venous, intra-peritoneal, subcutaneous/intra-dermal and oral/intragastric. Efficiency by the intramuscular route is thought to be similar to that of the intra-peritoneal route. The risk of transmission is also related to the dose administered but, relative to the other factors involved, this is unlikely to be a major factor in the overall risk assessment.

Overall risk assessment

By combining the assessments of the individual factors it should be possible to arrive at an overall risk assessment for the seed materials contained in a vaccine.

Practical outcomes

This Position Paper does not address the requirements for seed materials used for the production of vaccines for which authorisations are lodged after 1st October 2000. All materials used in the storage and passage of such seed materials shall fully comply with the requirements of the Joint CPMP/CVMP Note for Guidance. In the case of establishing a new master seed, the Joint CPMP/CVMP Note for Guidance should be followed to minimise the risk of contamination at source. Full attention should be given to factors such as the TSE history of the animal, herd and country of origin, the type of material from which the strain is isolated and any possible measures that can be taken to minimise the risk following subsequent processing.

For established master seed materials, Marketing Authorisation Holders (MAHs) should demonstrate that they have assessed the risk posed by these materials by reference to this Position Paper. Conversely, Competent Authorities should refer to this Position Paper in their assessment as to whether or not these risks are considered acceptable in the overall risk/benefit analysis of the product.

In view of (i) the factors described in this Position Paper, (ii) the control measures indicated below that can be put in place to minimise the risks associated with working seeds and (iii) the likely history of the safe use of the product over several years, it is likely that only in exceptional circumstances might the Competent Authority consider the risk represented by the use of a

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master seed material to be unacceptable. In these exceptional cases, the MAH should discuss with the Competent Authority how this risk might be reduced to an acceptable level, possibly through a combination of manipulation through replacement by an equivalent but compliant master seed or, if no other alternative ultimately exists, by removal of the product from the market.

Use of working seeds should only be accepted by Competent Authorities if full compliance with the Joint CPMP/CVMP Note for Guidance can be certified and justified. In situations where full compliance of working seeds cannot be certified, a commitment should be received from the MAH that they will submit a variation to their authorisation to replace such materials with working seeds produced using starting materials fully compliant with the Joint CPMP/CVMP Note for Guidance as soon as possible and within a specific timescale agreed with the Competent Authority. Unless new information or events result in a substantially revised risk assessment for the established working seeds, Competent Authorities should generally allow sale of vaccines produced using these seeds up to the end of their shelf life.

V – New rapid diagnostic tests for the detection of abnormal prion protein

Several rapid immunological diagnostic tests have been proposed for the detection of abnormal prion proteins in the central nervous system of cattle for the diagnosis of bovine spongiform encephalopathy after slaughter.

At the present time (February 2001), three of these diagnostic tests have been validated by the European Commission; namely Prionics (Western blotting), Enfer (ELISA using a polyclonal serum and a monoclonal antibody) Biorad (former CEA, using 2 monoclonal antibodies). Of these, the last is currently considered to be the most sensitive. These tests are able to detect abnormal prion proteins as a marker of infection in animals slaughtered at the preclinical stage (e.g. 3-6 months before the onset of clinical signs for the Biorad test). A positive result is considered as clear evidence that an animal was infected with BSE. However a negative result could mean either that an animal was not infected or that it was sampled before infectivity reached a level detectable by the test concerned. Therefore the tests cannot yet be used definitively to certify freedom from infection with BSE. It follows therefore that these tests also cannot yet be used to detect TSE contamination of raw materials, especially when taking into account that they are not validated for this purpose. Until such time as reliable *in-vitro* diagnostic tests for TSE agents in raw materials are developed, minimising the risk of transmission via veterinary medicine will continue to rely on the three 'pillars' of TSE control, namely control of the source of the animal, the nature of the tissue used and the treatment applied.

DISCUSSION SESSION I

Prof. Pastoret: Prof Trouvin told us that WHO's four categories were based on scrapie in sheep and I would like to add there are experiments going on now in the United Kingdom in order to have the same kind of results as far as BSE is concerned in cattle. Hopefully, we shall have data on the level of infectivity of different organs in the relevant model, that is, BSE infection in cattle.

Dr S. Zänker: I have a lot of interest concerning the outcome of the CVMP discussions of yesterday, because the animal health industry has deadlines pending and the discussions dealing with the master seeds and vaccines have been pending for the last two years. Prof. Pastoret said that a position paper has been submitted and approved yesterday by the CVMP for the master seeds - could you let me have the timing when this paper will be implemented? For the vaccines for which no certificate has been granted can these remain on the market? In principle, the CVMP suggested that the CPMP guideline should be adopted with a specific sentence on risk assessment of ruminant products to be included. I am not sure that the CPMP will be able to discuss this in January? If this is accepted, what are the responsibilities on off label use? For example, a veterinarian will use a product, which has an MRL, and which is initially intended for horses only since no other product is available for ruminants. He therefore uses the horse product for which in fact, the risk assessment has not been done because it is only intended for horses. Has this been discussed?

Prof. D. H. Calam: To set your mind at rest concerning the CPMP, Dr Trouvin is going to a meeting this afternoon where this will be discussed.

Prof. P. P. Pastoret: I ought to mention the different deadlines. As far as the sentence which we proposed to add to the CPMP guideline, normally will be discussed during the next CPMP meeting after having been discussed by the Biotech meeting next week. We shall have the answer within two weeks. It was admitted by the CVMP that we should use this sentence in the guideline provided that the CPMP agrees. As far as the position paper concerning master seeds, this has been adopted. Normally and hopefully, this will be on the Internet site of the EMEA within the month. Concerning the risk assessment for ruminants added to the CPMP guidelines, the CVMP has asked the Immunological Working Party to put this on its agenda during its next meeting. We shall follow the same procedure, that is a position paper being discussed at the beginning of February and hopefully being approved during the next CVMP meeting and then to put this as soon as possible on the EMEA's Internet site. Concerning off label use we have not yet discussed this at length. Clearly, however, we have solved part of the problem since if a product is to be used in horses, dogs, cats, poultry and pigs you do not have to have a risk assessment. This is only for products specific to ruminants. Of course, I agree with you that later on we should look at off label use.

Comment from the floor (Baxter): We have many problems with materials and the question is how far should we look back or go back? We got answers from our suppliers that many materials are produced synthetically but after more questions we found out that in the former processes of

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this material a bovine material was used eg chromatography resins which were built up synthetically by a bacterium in a nutrient medium which contains bovine materials. How far should we look back on these processes? Concerning the certificate, if you go through the certification scheme and have been granted a certificate does this mean that the note for guidance is fulfilled for us as a pharmaceutical manufacturer? My concern is relative to inspection in the note for guidance - inspection of the supplier of the starting material. My last question concerns the age of the animals. It is ask to use animals as young as possible but surely it is better to use animals that have been tested for BSE than animals which are too young and therefore the tests show no results as the infectivity is not yet detectable?

Dr J.-H. Trouvin: How far do we have to go with the evaluation of the implication of the bovine derived material in the production - I have no answer. It is clear that the first thing would be if it is a biological derived material then it would be, of course, more important. However, if it is the very, very first step I would not know. Obviously, you have to have exactly the same criteria in the two cases but it is essentially when you know that such a material is used in the very first step of the production, I do not know to what extent we have to be so exhaustive in the review. At the moment I would say that what is most important is for those products which are directly derived from bovine material. In a second step we will be able to see what we can do for other products because we will identify in the future the products which you are mentioning that some part of the resin is bovine derived. When it is not obvious that a bovine derivative is used, we can deal with this at a later stage.

Concerning the certificate and inspection. If you have received a certificate from your provider, this is then the responsibility of the provider to fulfil the requirements of the certificate. If you, in your files have a certificate from a provider, that is enough for your dossier. Regarding the age of animals and the use of testing of these animals I will remind you that in the guideline it is not asked but suggested to use young animals. It says that if you consider the risk you have to consider in the risk analysis the age of the animals. This does not mean that we recommend or even require the use of young animals, as we know that sometimes this is not possible. Regarding the use of a test I am not so sure that at the moment, and in particular following the presentation of Prof. Pastoret, that even a test will provide a guarantee that the animal is safe. Again, this is a multi-parameter approach and if you can use safe animals because sources in the geographical origin plus the age of animals plus other factors etc. maybe the need for the test becomes less important.

Prof. P. P. Pastoret: A comment on the issue of all products has been addressed in our position paper concerning all master seeds and this paper will be submitted to the Biotech working party.

Mr J. Turner: I can accept the excellence of the scientific advice and guidance in the Biological working party's paper but after March 2001 all member states will have inspectors being asked to check whether this guidance was complied with. This guidance however, includes words like 'prudent to do this', 'it is preferred to do that' - therefore it will be difficult for the inspectors and the people who they are inspecting to decide whether they comply or not? Has the BWP any

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intention of giving more specific advice on their best judgement at the time, like the advice given on good manufacturing practice?

Dr J. H. Trouvin: I understand your point. However, I think that the guideline provides scientific recommendations for producers, developers of products and also for assessors. At the end what is important is what is declared in the dossier and what has been evaluated and assessed by the assessors. For a dossier for which a marketing authorisation has been granted or maintained through the certification scheme or through a type II variation, this means that after this, no further evaluation is to be made. The inspectors' role is only to check that what is claimed in the dossier is in fact applied on a routine basis and under field conditions. You do not need to interpret the guidelines for the inspectors - this is only for the developers and evaluators. Clearly the inspectors have to check what is in the dossier and whether the declarations are true.

Mr G. Blocks: Prof. Pastoret, you started the last part of your talk raising the question as to the feasibility of raw materials testing with these immunological tests for prion infectivity and then you described the performance of these tests under field testing conditions. However, field-testing and raw materials testing is hugely different. Raw materials testing has constraints with huge volumes, distribution of the infectivity within these volumes etc., but you did not come back to the question which you raised at the beginning as to the feasibility of raw materials testing - do you have a position on this and criteria for feasibility, for a given test, criteria for given conditions.

Prof. P. P. Pastoret: No - I think that what would be required is that it is validated for raw material. I agree that this is a completely different situation though I know that some manufacturers were willing to use it for testing the raw material. I would like to mention that it is not validated for the certification of the absence of contamination even when you take a sample from the most infected part of the animal. I would be really cautious about the use of these tests presently for raw materials even if it would be, of course, the easiest situation, maybe the best one. I was surprised about traceability - if we look at the recent events what is traceability? If a country does not declare any cases of BSE is this because there are no cases or because they do not what to declare their data. I think that it would be better to have a good test which is able to distinguish between contaminated material or not, rather than a vague notion of a country of origin or the declaration of cases.

Dr J. H. Trouvin: A test would be the best solution. At the moment, however, as we have no test, the best solution is the control of the geographical origin and traceability is part of this control. This is a complementary measure.

ROUND TABLE DISCUSSION FIRST PART

Dr B. Matthews: My question concerns veterinary products. My understanding is that milk derived products such as lactose may present an issue for veterinary medicines. How many veterinary medicines tablets contain lactose and what will be done about this? Secondly, a lot of human medicines are used off license in veterinary medicines and what will happen concerning the lactose-containing tablets there?

Prof. P. P. Pastoret: What I have tried to explain is that, at least for veterinary products for EU in species like dogs, cats, horses, pigs and poultry the CPMP guideline will be used for the certification procedure. As far as products for use in ruminants are concerned, and as always mentioned for the certification procedure, the CPMP guideline will be used though, the applicant shall also be asked to make a risk assessment concerning the use of products intended for ruminants. We shall try to write an opinion paper next month within the immunological working party and of course, some people are still insisting to include milk and milk derivatives within the risk assessment. Most probably the opinion on risk assessment for ruminant species will include milk and milk derivatives. This will be a risk assessment and you have to take care of other parameters such as the route of administration. In the risk assessment you see that you lower the level of the risk if you use it by the oral route rather than the parenteral route or, if you only have a small amount of the product rather than large amounts. We shall define all the parameters to be included.

Question from the floor: Question to Dr J. Purves: Concerning the classification of the countries in the CPMP note for guidance. This classification is based upon OIE information and agricultural safety measures in the various countries. The scientific steering committee has come out with an opinion where it has classified countries - based on risk. Is the CPMP guideline going to be updated with the new scientific steering committee classification? The reason for this question is that we have had the experience that the EDQM, in its evaluation of an application, actually asked a company to justify their country source based upon the steering committee classification and not on the monograph classification.

Dr J. Purves: the BWP will be addressing this issue. In actual fact, there was some preliminary discussion about this in December during the BWP meeting. Dr Trouvin made a comment that the guideline is a living guideline and since 1997 we have been keeping in close communication with our colleagues in the various DG's within Brussels and the identification of the differences in geographic definition has been mentioned at BWP. We also have other aspects, which we will be looking at during the next meeting. Obviously, our interest there is to be in line with our colleagues from DG Sanco and their scientific committees so that there is a clear European position. Back in 1997, we put a general statement at the very beginning of the guideline saying that the document would be taking into account positions made elsewhere within the Commission.

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Comment from the floor: If a certificate, one which has already been issued, states a country of origin which is claimed to be BSE free, but has now indicated that it has got infection, what is the status of the certificate? Is this certificate still valid?

Dr J. Purves: If we have a change in the situation, a change in the status of the country, we have new information and on the basis of new information any evaluation procedure needs to take that into account. I think that we would have to look at the validity of that certificate again.

Dr A. Artiges: I agree and this is said in the procedure that any change in the classification has to be taken into account. This means that we will ask the company either to update its dossier or change its source or we will suspend or withdraw the certificate. We already have an example of that.

Dr M. S. Ruiz: A comment to Dr Tietz: maybe I have misunderstood the content of one of your slides but, we have been asked many times *if master cell banks are a subject for certificates* - and I would like to clarify that they are not. It would be the specific component of bovine origin, which would be the subject of a certificate but not the master cell bank or a virus seed bank per se. These are associated with a specific medicinal product and the evaluation is always done in connection with the product. It would only be the foetal calf serum or whatever protein from the ruminant in the composition of the master cell bank but the master cell bank is not an entity subject to certification.

Comment from floor: Yes, that is clear but I think that the question was really *concerning the new master cell banks* when you know about today's requirements you can go to the supplier and ask them for a certificate or for the appropriate documentation. However, for an established master cell bank, which was used twenty years ago and therefore preceding the existence of BSE and because these suppliers are not in a GMP regulated industry, you do not have the possibility of obtaining a certificate for the components that were used to established the master cell bank.

Dr J. Purves: The intent is not to get information on the master cell bank and we can obviously get clarification on to the Internet site following a discussion at the January meeting of BWP. Again, we had some discussions at the end of last year concerning this issue, but to reflect a little bit on why that information has been sought, if we look historically at situations and consider what has happened in the UK in the latter part of the 80's, when one gets the opportunity of asking the industry to provide information on certain aspects, it is probably better if we make that as comprehensive as possible when we go out on one occasion rather than having to go out to the industry on several occasions to get information on different stages of the manufacturing procedure or getting information on different periods of time. It would be nice if we could create a database of information on biological materials used in the manufacture of the product. If in five years time, suddenly questions are asked about the master cell banks what do we do? Do we put our finger up and say that we did not think of asking that question or, do we say that we have asked that question and this is the information which we received, so that we have a very transparent amount of information on the master cell banks. I think that it has been helpful to have your presentation this morning Dr Tietz because there are a number of points in it that I think would be useful to discuss at the BWP meeting next week. If I put my EMEA cap, we as an

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agency are there to co-ordinate and manage the centralised procedure. We do not have any responsibility for mutual recognition applications or national applications, we would be going beyond our remit. But staying on this point, you did make a comment concerning the differences in tables used in the various member states - which needs to be discussed. We also need to make sure that, in discussing it at the BWP, we do it under a remit that is acceptable to the Commission and the member states. If we have a discussion at the BWP then that could be taken on to mutual recognition and CPMP and when the opportunity is there, we could find a topic that everybody will agree is of community interest and can be discussed in the appropriate forum so that we have a more consistent table asking for information of this nature.

Mrs M. Dow: my question concerns established master cell banks and the number of times that this subject has come up this morning it shows that there is concern amongst the industry. The CVMP member mentioned that a position paper is being prepared regarding the risk assessment requirements for established master cell banks and that the contents of this paper will be passed on to the CPMP, presumably for endorsement or acceptance. The TSE guidelines at present exclude existing master cell banks and I think my first question has been answered, which was: is this necessarily going to continue to be the case? My second question is when preparing a risk assessment for established master cell banks, will the application of a dilution factor be accepted?

Dr J. Purves: Will the position regarding master cell bank's be maintained? There was discussion on the position paper for master cell banks at the CVMP yesterday. I think that that paper will be taken to the BWP next week and CPMP the following week so that we can review what was said there. I think that we will only know once we have had the discussion, whether or not the situation is going to be maintained that master cell banks are excluded. I would anticipate that would be the case - we will have to await the debate next week. I think that you can see from the work done at CVMP and CPMP that there is very good communication between the committees. Your second point concerns a dilution factor, which is a very open question. I would say that it depends on a case by case basis. Any evaluation procedure is multi-factorial as Dr Trouvin said earlier. The dilution factor is one of the parameters that would be taken into consideration. In any risk assessment, we need to identify all of the elements which need to be evaluated and once all those elements have been identified, we then need to look at them together because they relate one to the other. The conclusion that would be reached would take into account the consequences of the total evaluation, rather than the evaluation of the individual elements in isolation.

Dr C. Berger: I was told that there was the possibility of excluding tallow derivatives as fatty acids from the scope of the TSE guideline. Is this true?

Dr J. Purves: I think that this is a topic which was mentioned briefly when we discussed the updating of the TSE guideline between September and December and it was discussed following the discussion that we had on milk and milk derivatives. When we initially considered the certification procedure, we thought that it was a very efficient procedure for arranging one assessment within the European Union for all of the materials of biological origin used in the manufacture of pharmaceuticals. In July 1999, we had a meeting with a number of associations to try to identify at that time, each of the different types of biological material that may be used in

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the manufacture of medicinal products. Unfortunately, we did not get the list of the products that were concerned. The milk derivatives were felt to be safe and should be excluded, that was the view shared by the industry. It was then discussed at the BWP in September and, after long discussions, we came to the conclusion that I presented earlier on this morning. For tallow derivatives this will have to be taken back to the Biotech working party to be discussed as well. This raises a point in relation to communications. We tried to stimulate this debate in June 1999 and now at the 11th hour we are getting requests for easement of the system. With regards to the certification procedure from our initial discussions it was felt that there was scope within the certification procedure to have a system set up whereby, for products such as milk derivatives and tallow derivatives, we need to consider how much information is really needed for these products and how much information needs to be supplied for certification. If one looks at milk products, tallow derivatives and work along the spectrum of products to perhaps active ingredients, one could envisage a different level of information being provided to satisfy the certification procedure.

Dr H. Tietz: What *about wool derivatives* because some companies indicated that the decision which was taken last year may still be a problem as far as it concerns sourcing from living animals.

Dr J. Purves: Again, I thought that from the discussion that we had at BWP a fairly pragmatic decision had been made, saying that provided that the material was obtained from living animals, there was no need for certification. The reasoning behind that was that, if you obtain the material from living animals, you do not have the risk of cross-contamination in an abattoir.

Comment from the floor: We use bovine meat, New Zealand origin, as a starting material for a fermentation medium. The supplier of the meat applied for a certificate but the application dossier was returned by the EDQM on the grounds that it is only possible to apply for a certificate for substances derived from ruminant tissues - why?

Dr C. Pouget: The only example which I know of refusing an application was because the application was for the tissue itself and not on the product. The board decided that it was not acceptable. We will surely accept the application if it is for the substance itself but not part of the animal itself.

Comment from the floor: Yes, it was mentioned that only tissue-derived material can be certified by the EDQM, but in the CPMP guideline it was mentioned that raw materials from ruminants have to be certified.

Dr C. Pouget: We will discuss this with our board again, but the view of the board was that the organs themselves could not be certified as such as the "third pillars" of the CPMP guideline cover "the manufacturing process" including inactivation of the product.

Comment from the floor: Is it possible to apply for *a certificate for working cell banks* as active ingredients or vaccines?

Dr J. Purves: This is another topic, which we will have on the agenda next week! There are a number of very interesting points that Dr Tietz has raised which have not been discussed amongst

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the TSE experts in London. I have seen some of those questions this morning, and whilst I may have an opinion, because of the limited remit of the EMEA I think that it would be wrong of me to make a statement. The EMEA is responsible for the centrally authorised products but not responsible for mutual recognition products, not responsible for national products and on that basis, we really do need to have a discussion amongst the experts of the member states.

Dr H. Tietz: (Comment as a colleague, not speaker) If you establish a new working cell banks, I would assume that if you have a ruminant derived material used to establish this new working cell bank, you would seek a certificate for this particular component. Not for the working cell bank itself, but for this particular component.

Dr B. Matthews: *Changes to the status of a certificate:* Dr Artiges mentioned that certificates could be withdrawn or suspended. How is that information put into the public domain and how quickly? Because, for example, we may be developing a product using a particular source we can go to the European Pharmacopoeia Internet site and find that it is a certificated source. This does not mean that we are buying it directly from the suppliers so they may not know that we are using it. There needs to be a mechanism for the industry to be aware, in particular when a certificate has been revoked or suspended and this information needs to be available extremely quickly, and in a user friendly way because it is not always easy to find out when things have changed in the EDQM. For example, when the monographs taking into account when the TSE issues were published, they were adopted at the end of November, came into effect January 1 and were not published on the EDQM's Internet site until after the date when they came into effect - this makes it very difficult to comply.

Dr A. Artiges: When changing a category of country I said that this is written on the certificate. There is a template for a certificate in an annex of the procedure. You can see from this template that this certificate is valid as long as all the information which was supplied in the application is correct and as long as there is no significant change in the information or in the categorisation. This is to make it clear and transparent for the users and the holders of the certificate. And we have the example recently on gelatin prepared by the acid method; we have one or two examples where animals came from category III countries, and we contacted the company to find out where they stood. If they want to keep the certificate they will have to change a part of the dossier, in this case the part about the source of the product, and if not then we will withdraw the certificate. We publish on our Internet site the list of withdrawals of certificates as well as the list of certificates granted. In the list of the certificates published, we add revisions. If there is a revision you need to refer to the last valid version of the certificate. This is on our Internet site, which is updated every month. It is also published in Pharmeuropa and we also inform all the licensing authorities. It is also the duty of the holder of the certificate to take appropriate action to inform its users. We have the mechanism in place and it works well. As regards the very scientific case of the general monograph on products with TSE risk last year, it was on the Internet site on January 1. This monograph, as you know, was referring to the CPMP guideline already available for many months to industry and implemented by the EU Directive of September 1999. It is difficult to say that the content of this general text was a surprise for industry! In addition, as you

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know, this general monograph was adopted in order to extend the certification procedure to this category of products and facilitate for industry the compliance with EU Directives.

Dr M.S. Ruiz: An additional clarification concerning *cell banks*. In the working cell banks are the cells of bovine origin or are it some other component of the cell bank?

Comment from the floor: To produce these working cell banks we use three or four ruminant components and this is the problem. If I have to apply for a certificate for each ruminant material I have to submit three dossiers and it would be much easier to submit one dossier for one working cell bank.

Dr M. S. Ruiz: In my opinion the only way to give a certificate and to evaluate a working cell bank would be if the cells themselves are of ruminant origin, if not, they are always connected to a product e.g. a vaccine and this should be evaluated with the rest of the information.

Mr H. De Lange: *Question regarding wool fat*. Wool fat is exempted from the TSE regulations provided that it sourced from live animals and it is that very wording, which makes it impossible to meet the conditions. Sheep are kept also for meat and not only for wool. Meat sheep are slaughtered first, and then shaven. The wool from these sheep is combined with the wool from other sources. It is impossible to obtain a certificate that the wool fat is from live sheep. What is happening on the wool fat market is governed by the interest of the wool producers. For them, wool fat is just a cheap, minor side product; therefore, we cannot influence what is being done in the collecting process. Hence, must I conclude that although in theory, wool fat is excluded is it necessary to apply for a TSE certificate for products derived from wool fat?

Dr J. Purves: I mentioned earlier that one of the reasons for us excluding wool fat was that following discussion at a Biotech working party by the TSE experts, they felt that these materials could be excluded provided that they were taken from live animals. Their concern, from a scientific point of view was that, if the material is obtained at the slaughterhouse from killed animals that there is the risk of contamination.

Dr W. van der Giesen: I would like to come back to *the status of certificates and revocation* and revision. I think that it is also the duty of the supplier, the holder of the certificates to inform all the buyers of his product. I can imagine that there is a contract between the supplier and the buyer, that in the case of new information relevant to the certificate, that the buyer is informed immediately. If this is not the case, I am surprised.

Dr H. Tietz: Yes, usually there is such a contract and it contains such an obligation and the reality is different. Sometimes the suppliers do not tell you

Dr W. van der Giesen: I know this situation because this is a problem for certificates in general, not just TSE certificates. But at least there should be a contract between the supplier and the buyer of the product.

Dr H. Tietz: All the requirements and legislation address the marketing authorisation holder but the companies or industries that need to apply for the certificates are the manufacturers of these individual ingredients and we have little means to persuade them, force them, and go out and submit that information. Some of the suppliers say that it is a little by-product, it is not profitable

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for us and instead of doing this we prefer to give up making it. If there is only one manufacturer making it then there is little that we can do. It is low priority and time consuming for them to assemble the dossiers, make the submissions etc.

Comment from the floor: Is the TSE regulation for active pharmaceutical ingredients also applicable to those exclusively *used in topical products* and if so, why? Is the same level of documentation required as for oral active ingredients?

Dr W. van der Giesen: It would not be good to exclude products for topical use. This is because, topical can also mean application on a wound or damaged skin etc., I do not see any reason to exclude products for topical use.

Comment from the floor: How *about cosmetic* use? Is the TSE regulation applicable?

Dr M. Robert: Yes of course since 1997 there is a regulation specifically devoted to cosmetic products and they adopted a different approach which is a list of specified risk materials to be excluded, namely, the brain, the eyes, tonsils, the spinal cord and there is a derogation for tallow derivatives provided they are manufactured according to a specific physical chemical procedure, temperature and pressure.

Comment from the floor: These are the only cases, which are covered? A little less extensive than the APIs.

Dr M. Robert: This is exclusion because the system is described in the directive for cosmetics but is different as there is annex II banning certain products or substances. The parts of the animal, as mentioned above, are on this list and therefore you cannot use them except for tallow derivatives if there are produced according to specific chemical physical requirements for the manufacturing.

Dr R. Winsnes: In the mutual recognition procedure, how do the national authorities treat it if, for instance, gelatine is produced by the acidic procedure and not the alkaline one at pH 13, would the different MRP states, or central procedure says, that a certificate used for gelatin made by the acidic hydrolytic procedure, is alright for an injectable or will it only be acceptable for topical application?

Dr W. van der Giesen: I cannot give you a straightforward answer, but it has to be decided especially when used for parenteral purposes, on a case by case basis. We will, however, certainly take this into account.

Dr J. Purves: I would agree. We need to look at the whole issue of TSE risk assessment. As Prof. J.H. Trouvin mentioned earlier, it is multifactorial and we need to look at the products and all the parameters that may imply a risk.

Dr R. Winsnes: Could it be evaluated differently by different countries and different assessors?

Dr W. van der Giesen: I cannot exclude this because there was an agreement in the Mutual Recognition Facilitating Group (MRFG) that the work has to be done by the reference member states and since there are different reference member states there could be differences in assessments. I can imagine that most, if not all the member states, will feel a need to liaise with the other member states, so that they can take a position on this.

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Dr J. Purves: If there is concern about the way that member states are going to be dealing with this issue and if that question is coming from a member state, then that member state has the opportunity of taking it to one of the committees, CPMP, BWP and having discussion to resolve the situation. If Dr Winsnes, you are thinking of a particular issue in relationship to a particular product where you feel that there may be differences in the approach to assessment, for that product amongst the member states, then it would be beneficial if that were taken formally to the Biotech Working Party so that there could be some discussion there so that the experts from the member states can come to agreement and conclude if there is a need for looking at this issue in a different way.

Comment from the floor: Is it allowable that certain countries require additional confidential scientific information beside the certificate?

Dr W. van der Giesen: Our position is that we will not ask for additional information. I think that the information on the certificate is sufficient for us. For example, for gelatine, there is an indication of the process used for manufacturing and purification - that is sufficient.

Dr H. Tietz: However, Belgium asks for information on all animal derived material, not only ruminant derived material. It is difficult then for a country to go through the lists again, write to all the suppliers for materials that are not covered even by the TSE legislation.

Dr W. van der Giesen: That is up to Belgium! All members have the right to ask for additional information - that can be quite difficult for industry but if a member state feels that there is a need to ask for more information they are allowed to do it.

Comment from floor: Directive 199/82 addresses medicinal products approved and new. What *about materials for clinical trials*? Are these also covered?

Dr W. van der Giesen: Yes, I think that materials used in clinical trials have to comply with these requirements. Normally, the case is that the product tested in clinical trials is the same as later on when the application for marketing authorisation will be made. For new applications they have to comply with the new requirements. The same for materials used for clinical trials.

Comment from floor: I mentioned that Spain will probably ask for additional information and this is officialised in a circular. It could be that the information they request is of confidential nature, so as an API manufacturer we are supposed to inform the applicants, for example, about in which stage the animal derived product would enter into our API process. This is confidential information, or could be, depending on the extent of details.

Ms K.L Plough Larsen: I would like to clarify that for us we might ask for additional information when looking at the dossier presented together with the pharmaceutical. We might ask if it is for injection because when a certificate is granted we do not know what the material is used for.

Dr W. van der Giesen: It is true and of course it is not known when the certificate is issued how the raw material will be used - in what kind of pharmaceutical product. There may be cases where you feel that there is a need for further information before you can accept that specific raw material - I agree with you.

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Mr A. Tomczak: I work at Sigma-Aldrich, which supplies about one hundred thousand different compounds to about 70% of the scientific community. I saw that on the list of the participants here that these are few suppliers of raw materials and are mainly manufacturers of medicines. Is it intended to have such a conference or workshop especially for the manufacturers of the raw materials?

Dr A. Artiges: We make advertisements for our conferences and everyone is invited to participate. We are preparing another conference on the certification procedure in general at the end of the year. Perhaps pharmaceutical companies can make sure that their suppliers will attend.

Mr A. Tomczak: We have many, many different compounds as laboratory chemicals for use in research and development, analysis etc, but the German Arzneimittelgesetz refers to the European Pharmacopoeia which then requires GMP manufactured raw materials. I get dozens of enquiries for TSE certificates for such products as phenyl mercury acetate, sodium thiosulphate, copper sulphate and propanol etc., how would you recommend to answer this kind of request?

Dr A. Artiges: Part of the quality is GMP, the batch to batch consistency and the traceability of components. We have included in the procedure, years ago, the need for the manufacturer of starting materials to have a quality assurance system in place. As regards some TSE products, the GMP does not exist, this kind of manufacturer would not be accustomed to this concept, so we ask for reference to other quality assurance systems and they have to specify to which system they are referring. We ask them to certify that there is a system in place and sooner or later, an inspector will check this.

Dr H. Tietz: I would like to follow up a comment made concerning the clinical trial materials. Dr van der Giesen said that he would assume that the material used in clinical trials is the same that is eventually applied for marketing authorisation. In early trials phase I or II you just want to get some early data. Secondly, it is national legislation that applies for any documentation to be available for clinical trial material. It may be an important clarification that national authorities may ask for some sort of confirmation that the CPMP guidelines are followed, however, there is no European requirement regarding clinical trial material.

SESSION II: CONTENT OF THE DOSSIER AND SPECIFIC CASES

The European Pharmacopoeia Certification Procedure: legal and organisation aspects, links with the inspection, the licensing and the Pharmacopoeia

Dr. A. Artiges (EDQM, Strasbourg, F)

How it works:

Dr. C. Pouget (EDQM, Strasbourg, F)

Constitution of the Dossier: general presentation

Dr. M. S. Ruiz (Agencia Espanola del Medicamento, Madrid, E)

Gelatin

Dr. M. Ruffing (BfArM, Bonn, D)

Tallow Derivatives

Mrs A. Maes (Institut Scientifique de Santé Publique Louis Pasteur, Brussels, B)

Fœtal Serum and Media Components

Mrs A. Maes (Institut Scientifique de Santé Publique Louis Pasteur, Brussels, B)

Round table Discussion Part II

**THE EUROPEAN PHARMACOPOEIA CERTIFICATION PROCEDURE:
LEGAL AND ORGANISATION ASPECTS, LINKS WITH THE
INSPECTION, THE LICENSING AND THE PHARMACOPOEIA**

Dr. A. Artiges (EDQM)

The certification procedure was set up in 1994 and it is a particularly dynamic procedure. It is based on practical needs, mutual assistance between member states and consensus among the various partners.

The certification procedure is a complement and a bridge between the public standards described in the European Pharmacopoeia and the need to prepare a file for licensing. This procedure is the result of much discussion and agreement. It was in fact made to measure, in collaboration not only with the European licensing authorities so that they could totally rely on it and unreservedly recognise its validity but also with the industries so that they could be absolutely sure of the protection of industrial property. It should be noted that this procedure is based on a voluntary action by a company; there are different ways to provide the appropriate information in the licensing file, nevertheless, for pharmaceutical substances that have a monograph in the European Pharmacopoeia it is the most appropriate procedure.

The certification procedure can be summarised in three words: Consultation, Co-ordination and Collaboration

Consultation. This is to define the needs of the health (licensing and pharmacopoeia) authorities on the one hand and the needs of the industries involved in the production of all kinds of raw materials for pharmaceutical use and in the manufacture of medicines on the other hand.

Co-ordination. The procedure is where the needs of the national and European licensing authorities converge with those of the pharmacopoeia authorities. For examples, following suggestions by the Biotech working party of the CPMP (EMEA) to the Pharmaceutical Committee of the Commission of the European Communities, the EDQM studied the means and conditions for adapting the procedure to products with TSE risk.

Collaboration. Certification is the meeting point for national assessors, who work together to harmonise evaluation methods.

The certification procedure is also a bridge between industries and health authorities with the goal of protecting the health of consumers by ensuring that specifications are appropriate.

The procedure for certification of suitability of the European Pharmacopoeia is at the junction of:

public standards imposed by the general specifications of monographs that often cover several manufacturing methods and products with various sources, all of which should have a quality deemed to be optimal and harmonised.

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Information needed by the licensing authorities, which must make sure that the manufacturer of a specific substance has demonstrated that it really complies with the specifications prescribed by both the general monographs and the specific monographs of the European Pharmacopoeia. Indeed, to cover the various possible ways of manufacturing a substance, a number of tests for impurities are described together in general monographs of the Pharmacopoeia (eg, residual solvents, products with TSE risk). On this basis the certification procedure provides a framework within which the manufacturer can submit the appropriate required information on their production methods and the origin of the raw materials for assessment under conditions that ensure that this information remains confidential. Application dossiers for certification are evaluated, as described in procedure AP/CSP/99 (4), by assessors who have been appointed by the national licensing authorities and who have submitted a declaration of non-interest.

Inspection, which visits production sites to make sure that manufacturing takes place under the conditions described in the dossiers and that the quality assurance systems or GMP that are required for certification are implemented properly.

The three “C” characteristics contribute to a fourth characteristic of the procedure: its dynamism.

This recently set up procedure is close to its users, who are regularly involved in elaborating its structure and adapting its functioning. Hence the EDQM regularly organises scientific conferences, like today’s conference, with the support of the sponsors of the procedure, the chair of the European Pharmacopoeia Commission and the chairs of the EMEA working parties: the QWP, the Biotech WP and more recently the IWP. These conferences are intended not only to inform and explain but also to identify possible needs for adaptation and improvement.

The industry has confirmed its support of the procedure since, in 5 years, the number of applications for certification has increased ten-fold in the general area of physical-chemical quality control.

As regards the extension of the procedure to products with TSE risk, more than 245 dossiers have been submitted over the past few months. Unfortunately, and Ms Pouget will discuss this later in more detail, it took quite a while for the first dossiers to arrive, even though the Health and Pharmacopoeia authorities had advised the industry to prepare their dossiers quickly.

As shown in the figure, the number of certificates granted has increased exactly at the same rate as the number of applications, which suggests that we have been able to adapt our working methods to keep pace with growing needs. The relatively small number of TSE certificates reflects the small number of applications received initially.

On the basis of the data collected during the elaboration of the monograph and the specific data provided by a specific manufacturer on a specific substance, it certifies that both types of data make it possible to conclude that the quality of the substance corresponds to the quality defined in the European Pharmacopoeia monograph.

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The procedure is regularly adapted as regards its scope or the content of the dossiers in response to new needs of the various partners (health authorities and industries). For example, previously the procedure was applicable only to organic and inorganic active substances and excipients and certain fermentation products, but in view of the recent amendment to EU Directives 75/318/EEC and 83/852 EEC for human and veterinary medicines it has been found opportune to extend the scope to enable certification of all relevant products from the point of view of reduction of TSE risk. A general monograph (1483) “Products with risk of transmission of agents of animal spongiform encephalopathies” and its associated general chapter (5.2.8) based verbatim on the EMEA CPMP/CVMP Guidelines having been enforced in the European Pharmacopoeia.

The certification procedure functions under the responsibility of a Steering Committee which has defined and adopted its terms of reference. The Steering Committee consists of the following:

The Chair of the CPMP / CVMP Quality Working Party (QWP);

The Chair of the CPMP Biotech Working Party;

The Chair of the CVMP Veterinary Immunology Working Party (where relevant);

A representative of licensing authorities from countries that are members of the European Pharmacopoeia Commission, but not members of the EU/EEA and which are sending assessors for the Certification Procedure;

The Chair of the European Pharmacopoeia Commission;

The Chairs of the Technical Advisory Boards (TAB);

A representative of the European Commission (Brussels) (from the Pharmaceutical Unit);

A representative of the EMEA;

The Director of the European Directorate for the Quality of Medicines.

The Steering committee is in charge of:

Monitoring the procedure;

Giving appropriate advice on all regulatory or administrative problems associated with the application of the procedure;

Ensuring that the needs of the licensing authorities, the European Pharmacopoeia Commission and the applicants are satisfied; making proposals for adaptation or updating of current regulations, guidelines, monographs or chapters as necessary;

Appointing assessors proposed by the relevant authorities;

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Informing the European Pharmacopoeia Commission and the CPMP/CVMP and their relevant WP of any relevant issue.

To harmonise the assessment of dossiers, the Steering Committee has also created two technical advisory boards TAB: one for chemical products and the other for products with TSE risk. The primary task for the relevant TAB is to assist the assessors and the Certification Secretariat in case of doubt or disagreement.

The extension of the procedure to products with TSE risk was incorporated into resolution AP/CSP (99) 4 and implemented on 1 January 2000. The content of the dossier for such products is described in annex II and templates for certificates are provided to cover any product whose origin or production method involves a risk.

For products bearing a risk of transmitting animal spongiform encephalopathy agents, and for which a specific monograph exists in the European Pharmacopoeia, the applicant may apply for a certificate concerning the general monograph Products with risk of transmitting agents of animal spongiform encephalopathies as well as for the specific monograph, or may wish only to apply for a certificate concerning the general monograph.

For products for which a certificate has already been granted with respect to a specific monograph and which have a risk of TSE, an additional TSE certificate must be obtained by the holder or the initial certificate will be rendered void.

A very close co-operation between licensing, pharmacopoeia authorities, inspection and industries has been developed for a special survey of this procedure in order to fulfil the requirements and the short deadline of the revised Directives 75/318/EEC and 83/852/EEC.

The procedure makes it possible to avoid duplication of work not only by manufacturers of raw materials and manufacturers of medicines (finished products) when they prepare licensing dossiers but also by the national and European licensing authorities when they assess these dossiers.

Differences among the various licensing authorities in approach and in the assessment of compliance with European Pharmacopoeia monographs and chapters are also avoided, and more transparent communications are facilitated.

Under the revised certification procedure, suppliers of any product (raw material, ingredient, etc.) with TSE risk used in the production or preparation of medicinal products can apply for a certificate concerning the evaluation of the reduction of TSE risk according to the new general monograph. This certificate can be used by manufacturers of medicinal products in their marketing authorisations for demonstration of compliance with the amended EU Directive (type 1 variation).

HOW IT WORKS

Dr. C. Pouget (EDQM)

A manufacturer requesting a certificate of suitability has to submit in duplicate a dossier, preferably in English or French (please note that submitting a dossier in French may delay its evaluation because of the limited availability of French speaking assessors in our international panel of assessors. The dossier contains all the information required for the purpose of the procedure ie to demonstrate that the substance obtained as described in the dossier meets the criteria of the general monograph of the Ph Eur "Products with risk of transmitting agents of animal spongiform encephalopathies" and its general chapter (5.2.8). The documentation to be provided is described in appendix II of Resolution AP CSP (99) 4 and corresponds to the requirements of this general chapter, which is similar to the CPMP guideline, as already mentioned this morning. A fee of 3000 Euro is to be paid and the manufacturer has also to include a declaration that the manufacture of the substance is performed according to a suitable Quality Assurance System, such as HACCP or ISO 9000 standards (specifying which one(s) is/are applied) and that he is willing to be inspected, if so required by a relevant competent authority. This latter requirement is also applicable for cases where the holder of the certificate will not be the manufacturer itself. For cases, where the intended holder of the certificate will not be the manufacturer itself, a letter is required, signed by both parties indicating that the manufacturer agrees not to be the holder and that it commits itself to provide all the necessary information, particularly in case of changes, to the authorised representative. These declarations are included in an administrative form, which is to be duly filled in.

The substances for which a Certificate of Suitability can be applied for are those defined in the general chapter 5.2.8 ie, any material of ruminant origin, whatever they are:

- active substances,
- excipients,
- raw or source materials and reagents used in production.

It is recommended to apply for a TSE CEP for individual materials concerned. Applying for a common intermediate reagent or raw material would avoid requests for individual CEPs for all the "final" substances obtained using this material, provided that no other materials of ruminant origin are entering into the process. Furthermore that would facilitate the procedure and the submission of the information in due time if the producer of the material concerned applies for a CEP rather than the manufacturers of the resulting substances.

A manufacturer can apply for a combined CEP i.e. a CEP covering both the evaluation of the TSE risk and of the chemical and microbiological purity, only when a specific European monograph exists for the substance; this is the case for gelatin, oleic acid, aprotinin. In such cases a complete dossier containing all the information (as described in annex 1 of the procedure) should also be submitted on the manufacture, the quality control, the potential impurities of the substance and their control demonstrating that the quality of the substance is suitably controlled

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by the corresponding specific monograph and additional tests when necessary. Fees are 5000 Euro.

A delay in the evaluation of the chemical part (for instance because of request for additional information) will not block the granting of the CEP for the TSE aspect: a TSE CEP will be granted and then revised as soon as the chemical part is approved. Each time a chemical CEP application seems to be concerned by the TSE issue (eg fermentation products), the applicant is asked to confirm the absence of use of any TSE risk material in the manufacture of its substance, or to submit a TSE dossier. The chemical CEP will not be issued as long as the TSE compliance is not demonstrated and approved by the assessors.

On receipt of the dossier, the Secretariat assigns an identification number, which will be amended at each revision of the certificate.

An acknowledgement of receipt is sent within 2 weeks after an administrator of the Certification Unit has verified whether the dossier is:

- acceptable regarding the scope of the procedure,
- and complete.

If necessary, missing information is requested at this stage to allow the applicant to send it before the dossier is assessed (eg applicant may be asked to better define its substance).

The dossier is then stored in a locked room in a specific area with restricted access within the premises of the EDQM. The dossier will not be taken out of this area, even for the assessment.

The dossier will be examined within 4 months on the EDQM premises. For each dossier two assessors are designated by the Secretariat from a list of assessors proposed by National Authorities and approved by the CEP Steering Committee.

This list is periodically published in *Pharmeuropa* (which is the forum of the Ph Eur) and on our Internet site.

The impartiality of the assessors is guaranteed by their status (they are officers from administrations responsible for the evaluation of medicines) and by their signing a confidentiality agreement and a declaration that they have no direct or indirect interests in the dossier/substance.

The team of assessors prepare a confidential report, which is an exhaustive critical review of the data provided, and which will be kept with the dossier. With the prior consent of the applicant it can be made available to any licensing authorities of a State party to the Ph Eur Convention in the context of a marketing application referring to the Certificate.

In their report, assessors may request revision of the monograph or the general chapter/guideline if that appears necessary in view of the information provided in the dossier.

They can also add to their report any useful information for possible inspection or for justifying any request for an inspection. As Dr Artiges has just explained in her presentation, a pilot phase has been ongoing within the Certification Scheme since the end of 1999 and TSE risk products covered by a CEP will be included in the further phase of our programme.

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The team of assessors finally comes to one of the possible conclusions after the evaluation of the dossier:

- the compliance with the criteria of the Ph Eur general monograph is suitably demonstrated and therefore the certificate is granted;
- or, on the contrary, the information submitted is incomplete or unsuitable and does not allow a conclusion. No certificate is granted at this stage and the applicant is requested to supply the missing information, which will be assessed within 3 months of receipt, whenever possible by the same assessors;
- the application is outside the scope of the procedure i.e. for a substance not concerned such as milk derivatives or material not originating from ruminants. Usually that is noted by the Secretariat upon receipt of the application, but in some cases this is not so obvious and such a conclusion can only be taken after detailed examination of the dossier;
- At any time, in case of doubt or disagreement, the assessors can ask for advice or assistance from of a panel of assessors and administrators of the EDQM CEP Unit.

The Secretariat notifies the applicant of the decision within 1 month of the assessment by sending either the certificate granted, or a request for additional information, or a refusal.

In summary, the applicant will be informed of the decisions of an assessment within 5 months of the receipt of the original dossier and within 4 months of receipt of any additional information.

These are maximum deadlines, which are, in the light of our experience, necessary for the running of the procedure and to suitably perform an assessment. We obviously try hard to reduce them as far as possible for TSE CEP considering the deadlines of the EU Directive (and we have done this so far). Please note that, unless these deadlines are not met, we do not give any information on the status of an application and especially not by phone and this is for confidentiality reasons and to save time and resources and concentrate them on processing the applications in time. And I am sure you all understand and accept that position.

This is an example of a template for TSE CEP; you can also find such examples in appendix IX and X of the resolution.

Besides general statements such as reference to legal texts (Directives and monographs), conditions for validity, name and address of the holder, the CEP mentions:

- the name of the substance defined as clearly as possible; to that end, technical characteristics, name of a grade or even internal code number can be added as a subtitle;
- the manufacturing sites involved;
- all the countries from where the animals used are sourced;
- the animal and nature of the tissues used
- when necessary the manufacturing process applied; this is the case for gelatins, tallow derivatives;
- the quality assurance system(s) declared to be applied by the manufacturer;

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- the starting date for the validity of the CEP which will be unchanged during 5 years even when the CEP is revised.

A certificate is granted for a period of 5 years, after which it has to be up-dated by the applicant, with at least a statement that no changes have been made since the original dossier or its last revision. The certificate will then be renewed.

In any case, any change (such as change in the source or supplier, in the purification or inactivation procedure or in process parameters...) must be reported to the EDQM without delay. The information provided will be assessed and the certificate revised if necessary.

Failure to comply with the both cases will render the certificate void.

If the general monograph or its associated chapter or the CPMP guideline is revised or if any decision affecting these texts is taken, the secretariat will check its potential impact on the granted CEP and will take the necessary actions and inform the CEP holders as necessary.

For example that has just happened following the CPMP decision to restrict the pharmaceutical use of acid bone gelatin when originating from animals sourced from category I and II countries. The holders of CEP including sources from level III countries have been immediately informed of the consecutive withdrawal of the current CEP and, when applicable, of the possibility of revising the CEP for covering exclusively accepted sources.

The certification procedure has been extended to TSE on December 1999. Since then 37 TSE certificates have been granted (22 for gelatins, 14 for foetal bovine serum and 1 for aprotinin).

The list of the certificates granted is regularly up-dated and published in Pharmeuropa and our Internet site (up-dated monthly for the moment).

More than 120 dossiers are under evaluation (ie have been examined by assessors at least once), 20 dossiers have been returned since out of the scope: they concerned milk derivatives, poultry materials, ...

More than 245 TSE dossiers have been received so far and this histogram speaks for itself: despite several reminders and warnings to manufacturers via industry associations from ourselves, and authorities, the dossiers were submitted late, very late regarding the deadlines. To face this increase in the number of submissions we have received since the summer, we have, with the co-operation of national authorities, enlarged the panel of assessors, increased the number of evaluation sessions (to at least twice a month) and also enlarged our own staff.

We are doing our utmost to process the dossiers in due time. And this workshop is a good occasion for all parties involved to discuss and try to find solutions.

Here you have a short overview of the distribution of the dossiers received so far for CEP applications. They mainly concern the individual materials concerned (reagents, media, ...) meaning that the advantage of applying the procedure by going back as far as possible to the material directly concerned has been well understood by manufacturers.

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Finally I would suggest that you visit our web-site where you can find, not only the text of the Resolution, the list of CEP granted, the list of our assessors but also any new information, answers to frequently asked questions and last but not least information on the activities of EDQM.

And you can contact us for questions at our e-mail address

CONSTITUTION OF A DOSSIER: GENERAL PRESENTATION

Dr M. S. Ruiz (Agencia Espanola del Medicamento)

The applicability of the Certification scheme for the review of components from bovine origin incorporated into medicinal products was feasible due to two new Resolutions adopted: i) Resolution AP-CSP (99) 5, implementing a new EP monograph *Products with risk of transmitting agents of animal spongiform encephalopathies (1483)* and a new General Chapter 5.2.8. *Minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products*, incorporating the text of the CPMP/BWP/1230/98 Note for Guidance; ii) Resolution AP-CSP (99) 4, including the Content of the Dossier for a Substance for the TSE Risk Assessment under Appendix II.

The information to be incorporated in the dossier has been divided in five general sections:

- 1) *General Information*, including administrative data [name of the specific product, name(s) and address(es) of intended holder, manufacturer(s) and manufacturing site(s)], history of the product, and a declaration regarding the QA system in place and the willingness to be inspected;
- 2) *Origin of Raw Material and Type of Tissue used*, i.e. country(ies) of origin of animals, status of the country(ies) according to the OIE criteria, health status of the animals, type of tissue(s) or organs collected and age of the animals;
- 3) *Manufacturing Process*, including both an outline of the manufacturing process and a detailed description of each step, QC during manufacture and any validation process regarding TSE that might have been performed;
- 4) *Traceability*, i.e. system in place to ensure the traceability both for the raw materials used in the production process and for intermediates and final products;
- 5) *Auditing System*, including SOP and auditing schemes both for the suppliers of the raw materials and for self-auditing. Additionally, the dossier should also include an *Expert Report* consisting of a critical evaluation of the content of the dossier and a discussion on the TSE risk assessment in accordance to the scientific principles established in the a.m. General Chapter 5.2.8.

CERTIFICATION OF GELATIN

Dr. Michael Ruffing

Federal Institute for Drugs and Medical Devices (BfArM), Germany

This presentation will mainly focus on the requirements to be met concerning the sourcing of the raw material and the manufacturing process to control the TSE risk of bovine gelatin.

Gelatin is a mixture of polypeptides obtained by partial hydrolysis of animal collagen. Depending on the raw material and the production process, different types of gelatin with different physicochemical properties can be produced.

In pharmaceuticals, gelatin is used for different purposes, only some of them are mentioned here. It is mostly required for the manufacturing of hard and soft gelatin capsules. Moreover it is used in microencapsulation and tableting, in the production of suppositories and as stabiliser in emulsions. Gelatin may also serve as a blood plasma substitute or an ingredient of haemostatic sponges for the treatment of wounds.

Gelatin for the pharmaceutical purposes is almost exclusively manufactured from bovine bones and hides and/or pig skins. Therefore, Chapter 5.2.8 of the European Pharmacopoeia also applies to gelatin produced from bovine raw materials. It includes specific requirements and recommendations referring to

the origin of the animals used as source of the raw material,

the tissue or organ selected and

the manufacturing process.

The most important parameter contributing to the safety of gelatin is the geographical origin of the source animals.

According to Chapter 5.2.8, raw materials should not be sourced from animals originating from the countries with a high incidence of BSE. The use of animals from the countries with a low number of indigenous cases is acceptable, provided the requirements specified in Chapter 5.2.8 are met e.g. concerning the surveillance and notification system or the implementation of a feed ban of mammalian proteins to ruminants.

The criteria to classify countries were defined first by the World Organisation on Animal Health (OIE). Recently, the Scientific Steering Committee (SSC) of the EU Commission elaborated a scheme on the Geographical BSE Risk (GBR). On the basis of information provided by the respective country the stability of the cattle system and the external challenge by import of infected animals and meat-and-bone-meal from the UK was assessed. So far, 23 countries have been assigned to four categories or levels indicating the probability that one or more cattle infected with BSE are present.

In level I countries such as Argentina, Australia, Chile, Norway, New Zealand and Paraguay, the presence of infected animals is looked upon as highly unlikely.

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BSE cases are unlikely, but not excluded in level II countries including Austria, Finland, Sweden, Canada and USA.

Most countries of Central Europe are classified in level III due to the likely but not confirmed presence or the confirmed presence of some infected animals.

UK and Portugal are grouped as level IV countries due to the presence of infected cattle confirmed at a high level.

The GBR scheme has not been adopted yet as an official categorisation of countries by the EU Commission, but has been already referred to in a recent CPMP explanatory note on acid bone gelatin.

The second parameter to control the TSE risk is the nature of the bovine tissue used as raw material. Since brain and spinal cord represent a particularly high risk, the removal of these tissues has a high priority. To avoid central nervous tissue attached to bones of the skull, the complete skull is removed from the raw material. The association of Gelatin Manufacturers of Europe (GME), which represents the most of the EU's gelatin producers and some manufacturers outside Europe, has confirmed to exclude skull bones since 1997.

In Chapter 5.2.8, it is recommended to remove the vertebrae from the raw material, especially depending on the geographical origin of the source animals. This recommendation has been given because it can not be excluded that the vertebral column is contaminated with spinal cord and infectivity was detected in the dorsal root ganglia, which are located within the structure of the vertebral column.

In addition to the sourcing of the raw materials, the production process is also considered to contribute to the TSE safety of gelatin. So far, only bone gelatine produced either by an alkaline or an acid process has been granted a certificate of suitability. The standard gelatin production process starts with a degreasing step of fine crushed bones in hot water. By this treatment a high percentage of proteins is removed. In the next step the bone chips are demineralised with hydrochloric acid. After washing the material is either subjected to a treatment with lime at pH 12.5 in the alkaline process or by another acid treatment. Following extraction and washing steps, filtration and purification by ion exchange resins is performed. Finally, the gelatin solution is concentrated and sterilised.

In order to get some information about the efficiency of the demineralisation step and the alkaline treatment to inactivate TSE agents, validation studies were performed. The alkaline treatment showed to be more efficient than incubation with hydrochloric acid. Based on these results and the assumption that the second acid step is not more efficient than demineralisation, it is stated in Chapter 5.2.8 that the current preferred manufacturing method for gelatin produced from bovine bones is the alkaline process.

Most of the bovine bone gelatin used in pharmaceuticals is indeed produced by the alkaline treatment, but acid bone gelatin is still needed in some important medicinal products e.g. in special soft gelatin capsules to ensure the bio-availability of liquid ingredients.

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Since the acid production process is considered to be less efficient in inactivating TSE agents, the CPMP recently published an explanatory note (EMEA/CPMP/4306/00/v 0.2) stating that raw material for acid bone gelatin used in pharmaceuticals has to be sourced exclusively from category I or II countries according to the SSC GBR scheme. This statement also affects those EDQM certificates of suitability granted for acid bone gelatin made from source material from category III countries.

As the manufacturing is considered to contribute to the safety of gelatin, the dossier submitted for certification should also contain information about the quality control during manufacturing, especially about in-process controls, action limits and the quality assurance system in place. It should be shown how the traceability of raw materials, intermediate and final products is ensured and how self-audits and audits of the suppliers are performed.

The situation concerning the safety of gelatin produced from bovine hides is less complicated. According to chapter 5.2.8, it is considered as safe no matter where the hides come from if the risk of cross contamination by potentially infectious tissues, e.g. brain, spinal cord or ocular tissues, is minimised.

Finally, it should be mentioned that further validation studies initiated by the GME are ongoing. The results are expected to give additional information about the inactivation and removal capacity of the standard gelatin production processes currently used.

TALLOW DERIVATIVES

Mrs A. Maes (Institut Scientifique de Santé Publique Louis Pasteur)

Tallow is fat obtained from animal material by rendering processes. The main sources of tallow are subcutaneous, abdominal and intermuscular fats, organ fats, offal and bones. Tallow is not used as such in medicinal products but is the starting material used for the production of tallow derivatives. Examples of the latter are magnesium stearate (used as excipients in tablets), glycerol (used as excipients or as a reagent in the manufacturing process of biological/biotechnology/medicinal products) and polysorbate (used as a stabiliser in medicinal products or as a reagent in a viral inactivation step applied to many plasma derived medicinal products).

The risk assessment for the certification of tallow derivatives is based on the parameters mentioned in the General Chapter 5.2.8 of the Eur. Ph. "Minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products»: origin of the raw material, type of tissue and manufacturing process.

In general animals originating from countries with a high BSE incidence should not be used for sourcing of the raw material.

According to the Scientific Steering Committee opinion on the use of vertebral column for the production of tallow and gelatine, it is considered that the additional safety gained from the removal of the vertebral column is limited in countries with a lower BSE risk, but should be considered as sufficiently important to exclude it in higher risk countries.

The production of tallow involves rendering or fat melting. Typically the raw material is minced, heated, mechanically agitated and the moisture evaporated or separated. The lipid fraction is separated from the protein by centrifugation and pressing. Experimental transmission studies performed by Dr. D.M. Taylor demonstrated that tallow produced using the minimal conditions showed no detectable infectivity. The protocol followed was a continuous vacuum processing with high fat content². The production of tallow derivatives involves additional steps, which include the use of high temperatures and/or high alkalinity.

Since the production process is one of the critical steps which contributes to the safety of the product, the manufacturer of the tallow derivatives should control appropriately the manufacturing process according to a suitable quality system. Internal audits and audits at the raw material suppliers should be performed on a regular basis.

Commission Decision 92/562/EC lists the critical parameters that have to be monitored during different rendering processes for the production of tallow. Although no minimal values are stated in the above mentioned decision 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

² Taylor et al., The Veterinary Record, December 9 1995, **137**, 605-610

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decision and that tallow derivatives are manufactured by rigorous processes as mentioned in the General Chapter 5.2.8. of the Ph. Eur.

FCETAL SERUM AND MEDIA COMPONENTS

Mrs A. Maes (Institut Scientifique de Santé Publique Louis Pasteur)

Bovine serum is used during the production of medicinal products such as vaccines, monoclonal antibodies and recombinant proteins. Bovine serum can be sourced from the foetus, calf or adult animal. When it is sourced from the calf a difference can be made between donor calf serum and calf serum, which means respectively that the animal, is alive during collection or slaughtered.

The risk assessment for the certification of serum is based on the parameters mentioned in the General Chapter 5.2.8 of the Eur. Ph. "Minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products»: origin of the raw material, type of tissue and manufacturing process.

In general animals originating from countries with a high BSE incidence should not be used for sourcing of the raw material. Blood from which serum is produced belongs to category IV which means no detectable infectivity³ but according to paragraph 3.2 of the General Chapter 5.2.8. "Parts of animal bodies, body fluids and secretions as starting materials" cross contamination can occur during the collection of the raw material. For calf serum and adult bovine serum this means that the method of slaughtering is a critical point. According to an opinion of the Scientific Steering Committee captive bolt stunning with compressed air or followed by pithing should be avoided. In case of foetal calf serum, the removal of the foetus from the uterus is more critical because of potential cross contamination with maternal tissues including the placenta, amniotic and allantoic fluids.

The processing of FCS includes blood collection, serum preparation and heat treatment at temperatures of 60-70°C. No validation studies are available regarding the inactivation of TSE agents for these steps and it is assumed that this does not contribute to the safety of the product.

Other media components such as blood derivatives, peptones, brain extract are used mainly during the production of biological/biotechnological/medicinal products. The risk assessment for the certification of these components is based on the same parameters as for serum. The safety of these products is mainly assured by the sourcing of the animals and the type of tissues used.

³ Blood from cattle affected with natural BSE have shown no detectable infectivity after bioassay in susceptible mice (MAFF, 1999)

ROUND TABLE DISCUSSION PART II

Comment from the floor: Concerning cleaning procedures, the validations required were, up until now, only looking for proteins, TOC or the hygienic requirements for endotoxins and germ counts but they never asked for virus inactivation and TSE inactivation or detection. This is very critical.

Mrs A. Maes: It is only protein removal, which we are looking for and not inactivation.

Dr R. Hutton: We have hardly spoken on inspection issues apart from saying that to get a certificate you have to state that you are willing to be inspected. Please could you give further information regarding the inspections which have been undertaken so far and the number and extent of the inspections which they foresee will now be undertaken now that we are way out of the pilot phase and give us some information as to the extent of these inspections. How far back, in the process, will these inspections will be undertaken?

Dr A. Artiges: Inspection is a very critical part of the assessment of the quality of the substance. As you know in Europe, and at least at the European Commission level, we are waiting for an EU directive, a draft is on the way and our colleagues from the Commission could comment on this, in addition we know that under the ICH process and topic Q7, the guideline for GMP for active pharmaceutical ingredients has been recently adopted and certainly the European Commission will take action to implement this kind of guideline. It is not therefore, within the remit of the EDQM to set up its own system of inspection, as our basis is co-ordination, collaboration and we do not want to duplicate other activities. Nevertheless, compliance of GMP and inspection are very important and we need this to gain experience in this field. Last year we started a trial phase on a voluntary basis with some national inspectorates, which already have a system in place or which wanted to gain experience and on a voluntary basis with some companies. We intend to develop this trial phase to continue to gain experience. This will however, be one of our major concerns for the future, and a very near future.

Dr H. Tietz: As we have seen from the presentations, the assessment of a dossier at the EDQM takes about five months. As I have already mentioned, industry is quite concerned about the availability of certificates by March 1. Do you see a possibility to speed up this assessment of dossiers at the EDQM and what is the year expectation?

Dr A. Artiges: As a principle, it has been clearly stated for years that the procedure for certification application needs up to five months for the first evaluation. Companies know this very well and companies know that they need to implement this guideline on March 1. It was quite easy then to work out when you need to send your dossier to be ready for that date. We received many dossiers from industry at the beginning of the year, which proves that industry did have enough time to prepare the dossiers, especially since this legislation has been around since 1991 and we all have had time to prepare for the implementation. I wonder why, if you managed to send some dossiers on time, we did not receive more?

Dr H. Tietz: Briefly I would comment that it is the suppliers and manufacturers that need to make these submissions and not the vast majority of people at this workshop. It is very difficult

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to convince some suppliers or even the majority of the suppliers to make these submissions at the end.

Dr C. Pouget: Each partner has responsibilities, for the deadline not being met, and each of the parties should accept its own responsibilities. It is not really fair to say that the last link of the chain is responsible in case of non-respect of the deadline though we have to do our best to meet our deadlines, which were for many of them less than five months. We did our best to meet 'our' deadlines and we even went quicker but I said 'did' because now we are in it and facing a great number of dossiers. You have seen the diagram, we have received 100 dossiers in two months, in November and December. This means that manufacturers were already late in submitting their information, because the deadline in most of the countries for submitting declarations and when necessary a dossier was December 1. I understand, however, that manufacturers have problems in obtaining information but did our utmost and we have been ready since January 2000! We received very few dossiers at that time now there is an enormous increase in the number of dossiers submitted. We have therefore, increased the panel of experts, we have increased our own staff and have doubled the evaluation sessions - I do not see what we can do more?

Each of the parties has, however, their own responsibilities in meeting the deadline - five months is the maximum deadline but it also depends on the quality of the dossier. If the information is not sufficient and additional information has to be requested that will delay the granting of the certificate. We need this time to properly assess the information. It is not just a matter of performing an assessment fast enough for it to be done before the deadline but we need to have a proper assessment and in light of the experience that we have for the chemical part, five months has been proved necessary.

Dr H. Tietz: Could you discuss at the Biotech Working Party a possibility regarding the deadline of March 1 for applications that have been made at the EDQM and have been accepted but unavailability of a certificate is not the matter of concern?

Prof. D.H. Calam: One of the things which people are concerned about is what happens after this meeting. Immediately after the meeting there is a debriefing of all the speakers to consider all the points, which have been raised and to consider what potential actions might be taken.

Dr J. Purves: A remark concerning the comment, which was made by Dr Tietz, *could we take this issue of changing the date back to the Biotech Working Party? The answer to this is no.* The Biotech Working Party is a scientific working party and what you are asking is a change in procedure and if you want a change in procedure, you have to go through other routes to obtain discussion to allow you to take that forward. For procedural matters, these need to be dealt with through the Commission which raises the other point which I have already mentioned, the EMEA is concerned with centralised applications, and not with national applications and not with mutual recognition applications and we have to stay within our remit - it would be wrong to do anything other than that. The points which were raised this morning during Dr Tietz's talk will be considered by the Commission, the scientific aspects that you included in the points that you raised today will be considered in the Biotech Working Party next week, but procedural issues and the changing of the date is outside our remit.

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Dr M. Robert: I am in total agreement with Dr Artiges and Dr Pouget on the implementation of the TSE directive. Given the current crisis situation in German and in France and elsewhere in the *European community*, *I cannot imagine my institution taking the initiative today to postpone the deadline of March 1 for medicinal products for human use, or even for veterinary use which will be on June 1 this year too.*

Dr B. Matthews: There is no guidance in the European Union for clean in-place apart from a PDA document which addresses the issue of clean in-place but this does not address to the issues relating to TSE or viruses. As far as I am aware, nobody has given any thought to how you would demonstrate clean up being effective against TSEs. It would be very difficult to do, and I know that it is a protein, and in theory you can monitor protein removal, but the levels you are talking about would be impossibly small for an analytical procedure to pick up. Is the PDA document the document that these companies should be looking at? A lot of people who need the PDA document do not know that it even exists because they are not in the pharmaceutical industry.

I note that on several occasions, HACCP has turned up on the list of things to consider. In Dr Ruffing's paper, it says that HACCP should be respected. If that means that it should be there, this implies a big challenge for a number of manufacturers. Not everybody will have HACCP or even know what it requires to put it into place. Again, lets me reverse this, as if it is a food industry company, the chances are that they will know at least what this means, even if they do not use it. The pharmaceutical industry however, does not usually use HACCP.

I would like to make a further observation on the comment, which was said on the delays on the part of the pharmaceutical industry. One of the problems has been that, once the legislation was passed, and you always have to wait until you see the final text before you do anything because it has a habit of changing, then you start looking into the implications of it. I am afraid that, in the particular case of TSEs for ingredients for manufacturing processes, it has been very difficult to get any sense out of our suppliers. Usually we have to go back at least twice to get an answer. Not uncommonly the answer changes if you ask the question a third time, because they have been back to their suppliers and surprisingly often, a material of animal origin suddenly comes out of the woodwork. That is the reason why the industry could not give the list of effective materials, when the original enquiry was made. Once we have identified the areas of concern and we pass that message onto our suppliers, then they passed it on to their suppliers and of course there is a delay. I would be most interested to know just how many of the applications that the EDQM have received come from outside the EU? One of my experiences is, and especially for Japanese companies, they do not know that this requirement exists, they have no idea how to approach it and I have a nasty feeling that you will be receiving a bunch of applications from Japanese companies in particular on 28th February.

Mrs A. Maes: *Regarding the cleaning procedures* - this is about removal of the protein and nothing else. You have to show that your cleaning methods can remove proteins or not. I have seen in dossiers that there are tests that can prove or can show that proteins have been removed.

Dr D. Jäkel: I would like to go back to the question raised this morning whether fatty acids might

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not be eliminated or exempted from the programme. I understand from information obtained from industry that after the hydrolysis of the fat, the tallow, and all the fatty acids are normally distilled. This means they have been through the vapour phase and this I have not seen in the presentations. I am interested to know if any information is available on the effect of the vapour phase. If this is so, would it not be feasible to eliminate or exempt fatty acids, which are distilled from the programme, looking at the extremely wide use of the fatty acids and this, would reduce all the workload.

Mr A. Hinze: Yes, fatty acids after they have been split and the temperatures that you saw 200°C minimum at the appropriate pressure for at least 20 minutes, fatty acids are distilled and that is normally a temperature of 220°C or 230°C depending on how fast you want to operate. Some companies may distil fatty acids first before it goes to a splitting facility and some companies do not distil prior to this separation process but certainly do after. Some do both, before and after.

Dr D. Jäkel: I think that not all the proteins will not be able to go through the vapour phase.

Mr A. Hinze: No they will not. In the company we have done some tests on amino acids and what you find is the area of ppbs of individual amino acids - that is all you find.

Dr P. Langlade: My question concerns the timing. According to the European guideline, you have to submit the type I variation by March 1 this year but according to national legislation you have to submit type I variation before. Therefore, when you have products that have already been through a national path, what happens when you have a product that is registered through a MRP, you have to follow which timing - the national, European, RMS timing?

Dr W. van der Giesen: We have the same time limit for all products. All products have to comply by March 1. We all understand after the presentations of today, that there is a difficulty especially with regard to the time of issue of the TSE certificates because the applications were received late. What is important, and I speak for my country, NL, that at least we know what a company has done before the March 1. I have to discuss this in my country with my experts, however, it could be the case that if we know, by March 1 that you have made an application for a certificate, and that you can inform us about the anticipated date of issue of the certificate, that we will in some cases accept this. There is no difference between products approved by the centralised system, MR or nationally.

Dr P. Langlade: In other countries, where you have to submit type I variation before March 1, we do not know when we should submit this variation.

Dr M.S. Ruiz: Speaking from the Spanish Medicines Agency we know what internal resources are available, in order to make the evaluation and I think that it can be a case by case evaluation, but I presume that there are some flexibilities, for all of us. We have to work together and the workload is enormous, both for you and for us.

Dr P. Langlade: For Greece for example, type I variation, when will this be submitted, 20th January?

Dr H. Willkommen: I speak for the Ehrlich Institute. We also think that we have to be flexible and in this case of the evaluation of the procedures. We will accept I think that if we know that

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you get the acknowledgement of receipt so that we know that for specific products a certification is underway and the application is made. It depends on the product, for example if it is a high-risk material etc.

Comment from the floor: Comment to Dr Tietz on a remark. It is easy to see from the data on the number of applications you have received that an enormous task has been put on you in the last year and especially these last months. As a manufacturer and representative of a manufacturer I have to say that we have been out very early to contact our suppliers to tell them what will be required of them and working with them to give them the wording and what this all means. In reality what you see is that they have to prepare what was a small file five years ago and they are not used to this. Also what you see is that they are actually positive to doing it. I understand that we cannot change the procedure but what I also hear is some flexibility and that is all that we are asking for as it is also a big disappointment for the manufacturers that we are not just able to submit an application because we depend on the raw material suppliers delivering to us and they have to understand this new procedure which takes time. Many are now hiring people with the necessary skills to get this working. But it is a huge task.

Dr M. Rack: Dr Ruffing mentioned that there is a TSE inactivation and it differs between alkaline and acidic process. Do you know how many potencies can be decreased or is this a general correlation between the two processes.

Dr M. Ruffing: I talked about the liming step and the hydrochloric acid step. There is a difference of about one log. It also depends on what you use during the alkaline treatment. Using sodium hydroxide instead of lime it will result in a higher inactivation of at least two logs. There are also ongoing studies on sodium hydroxide treatment for the acid process.

Dr M. Rack: Dr Pouget has showed us a slide with the number of granted certificates of gelatins and FBS. I could not find any tallow derivatives, what is the reason for this to be missing because I know there are a lot applications that were done in case of stearic acid, magnesium stearate. I know that the applications were given last summer so a good few months have passed. Are there problems with this - why are they not granted?

Dr C. Pouget: I cannot tell you what the problems are with these dossiers, if there are any problems at all. However, I will repeat that five months are needed for the first evaluation. This means after the first evaluation that we might have asked further questions to the applicants and the answers may be under evaluation again or we are waiting for these or that the certificates are in the pipeline. We did not receive applications for tallow derivatives before this summer and I feel that we are still well within the deadline.

Dr M. S. Ruiz: I would like to add a comment concerning Dr Rack's question on the alkaline and the acid process, for the manufacture of gelatine. We have to make clear that in the current processes in practice for alkaline and the acid treatment the validation studies show that only one or two logs maximum, would be reduced between the two processes. The alkaline process would be the preferred process. This however, represents a very low reduction. If there is a higher infectivity would it still be there. It does not mean that it is completely eliminated. We cannot therefore rely only on the production process and say that alkaline gelatin for example would be

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accepted because there are other considerations. The country of origin for example or the tissues, the exclusion of certain risk materials that will contribute to the safety of the products; so we cannot only rely on the manufacturing process to say that this is more safe than the other. We need both and this is a multifactorial approach.

Dr R. Winsnes: I completely agree. I am not totally familiar with all the experiments which have been performed but it does seem unlikely if you have dispersed this material and then treat it with alkaline that it could be pH 9 in this alkaline process and then it should be two log reduction. We heard that the gelatin manufacturers in Europe have done some experiments with very acidic conditions and hydrolysed and dispersed the material and then they used another with pH 13 and this is completely inactivated. I would suppose that between pH 9 and pH 13, if it is properly dispersed, there must be more than two-log inactivation. Dr Ruffing mentioned a preliminary 6-log reduction - what was the pH of that alkaline process because I understood that the pH could vary from 9 to 12.5 with GMS.

Dr M.S. Ruiz: These are the current procedures in place for industry and these are the results. I know that the gelatin manufacturers association have a list of eleven different processes now in the experimental phase and there will have the results in two years.

Dr M. Ruffing: The information I have concerning the liming step is that the pH is at least 12.5 for at least 22 days. This parameter should also be verified by an in-process control.

Dr B. Matthews: Should the term starting material be extended *to include containers* and things used in their manufacture such as polymers, whatever is used in the conversion process and so forth. Please could you clarify?

Prof. D. H. Calam: According to the European Commission the answer is yes.

Dr B. Matthews: I am glad that you said this as I have never heard it mentioned. It is of some significance because, for example, stearates are quite commonly used in container manufacture and I believe that there is at least one polymer, which in its initial synthesis involves gelatin. My understanding was that starting materials was not intended to cover that sort of component. If that is an interpretation that is being expressed today, the people from industry might have to go away and take a closer look at a wider range of materials.

Dr M. Robert: According to the existing legislation on pharmaceuticals, starting materials includes, active substances, excipients, containers and source materials. Dr Trouvin spoke about this morning and gave certain clues about the approach to be taken concerning a system of purification, resins etc.

Mr J. Lyda: I would like to contribute to the comment that Dr Matthews made on *cleaning validation* and that there is not a lot of data available. I would like to let you know that there is technical reports and a book on cleaning validation for the biotech industry from our Internet site www.pda.org.

Comment from the floor: Are the TSE regulations applicable to *non-ruminant derived APIs*, for example, with the origin from pigs.

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Dr W. van der Giesen: These products are not mentioned in section II of the note of guidance, so therefore these are outside the scope.

Comment from the floor: Are *synthetic peptides* to be regarded as TSE risk products given that the process is an amino acid converted to a derivative and the derivative is converted into peptides and there is a caveat where the amino acids are not of ruminant origin but the information on past suppliers is not available because it goes back too far - what happens in this case?

Dr M. S. Ruiz: I think that we will have the same problem with many other things and I think that it will be a matter of individual evaluation of that particular product. If you have something which is necessary on the market but you have no other sources I suppose that you either take it off or leave it. As long as you have information, and it is always better if it is of biological origin, but if it is impossible then this will have to be individually evaluated.

Comment from the floor: In a case like this assuming that you are dealing with product of ruminant origin, would it be possible to get a certificate that would cover a whole range of synthetic peptides. In other words, could you get a *process specific certificate* rather than a certificate for each individual compound, given that presumably all the source amino acids are going to be same for all the peptides?

Dr A. Artiges: I cannot answer this question by "yes" or "no". The scope of the general monographs addressed "substances or preparations..." and not "process of manufacturing" by we may look for a simplified assessment in case of common methods of manufacture of similar products. What we usually do when we receive such kinds of questions - and we have received a lot of questions during the previous months. If we cannot give an answer straight away, we put this query or question on the agenda for the certification steering committee or the appropriate group of experts for discussion and risk assessment. Every time we have a question for which an answer is not self evident, we will put this on our Internet site as we have started doing with others.

Comment from the floor: Do you think that it is necessary for the pharmaceutical industry to perform audits at their suppliers who have obtained a certificate of suitability?

Dr A. Artiges: It is one of the requirements of the guideline.

Dr W. van der Giesen: It is part of GMP - from time to time you have to do an audit.

Dr H. Tietz: Assume you have used traditional magnesium stearate of bovine origin, and because of the regulation and the time of March 1, you decide to eliminate that and substitute it by magnesium stearate of synthetic origin. You still manufactured tablets with the old magnesium stearate in January or February and come March or April you would like to pack and release them. By the time of the manufacturing operation you have completely complied with the contents of your dossier, but would you agree that in March or April you could still pack and release those tablets?

Dr W. van der Giesen: If the old magnesium stearate does not have a TSE certificate, we would be very reluctant to accept that after March 1 such a batch would be released. The legislation is

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that by March 1 all products have to comply with the new requirements. There is a difference between two possible cases where there is an application for a certificate, which is pending, or the one where there is no certificate at all.

Mrs F. Leonardy: I would like to know if in Prof. Pastoret's *position paper on master seeds* if they will address the problem of the cell lines. We have this issue with bovine vaccines.

Prof. P.P. Pastoret: Yes, it is also addressed.

Mr J. Turner: Because the applicants have been asked in their applications to agree to inspection, do you feel that you need to wait for the directive? How do the inspectors get hold of the dossiers if they are all locked up in the EDQM's offices? Could you comment on the arrangement for paying for the inspections?

Dr C. Pouget: It is mentioned in the resolution, which is a legal text, that the declaration should be made by the manufacturer that they are willing to be inspected and based on that we can perform an inspection. It is on this basis that we carried out our pilot phase last year.

Since the dossiers are confidential, they are kept in our archives. What we did in our first pilot phase and will do it again for the continuation of the pilot phase, is that we sent back the dossier with "copy" stamped on it to the manufacturer and the inspectors reviewed the dossiers on site on the first day of the inspection. The only documentation that the inspectors had in advance was a site master file.

For the time being, during the pilot phase, this was an agreement between authorities, the EDQM and the manufacturers. The fees were shared between the three parties. The national authority, the industry inspectors and EDQM. This were joint inspections with two inspectors, one from the country of the manufacturing site to be inspected and another from another country. This team was joined by a representative of the certification staff to make the link with the dossier and explain how certification works.

Dr M. Robert: The famous directive of the starting materials is a long story! This was initiated more than five years ago and several proposals were made by the Commission services to amend directive 75/319, and apparently there was no consensus between the member states to agree on a final text. The matter was recently discussed before the pharmaceutical committee and a questionnaire has been sent to the member states on different issues. I think there is a consensus on the part dealing with inspections, and this year we will see how to implement this in the framework of the revision of the legislation. So far we do not have a specific legislation on this.

Dr W. van der Giesen: That is draft directive on starting materials and it will contain active substances. The big question is to what extent will excipients be included in the directive? Is it only certain excipients for which a certain risk can be identified? This is still a point of debate and will be on the agenda of the next meeting of the pharmaceutical committee.

Comment from the floor: Speaking from the Swedish authorities concerning these dates because we had set February 1 as the deadline for the certificates and yesterday we took a new decision due to the problems and it is March 1 in Sweden too.

BIOGRAPHICAL NOTES

Dr Agnès Artiges graduated in pharmacy and has a PhD in the same subject, as well as a degree and a PhD in law, the latter from the University of Paris, France. In her postgraduate law degree she specialised in European Institutions.

She was Assistant and Assistant Instructor in the Toxicology Laboratory of the Faculty of Pharmacy of Bordeaux before joining the French Ministry of Health in 1971. During her career with the Ministry, she has held the posts of Head of the French Pharmacopoeia, Head of the Registration Authority for Medicinal Products for Human Use and Head of the Sub-directorate of Scientific and Technical Affairs.

In addition, she was Chairman of the European Pharmacopoeia Commission from November 1989 to November 1992 and a member of the former Quality Working Party of the Committee for Proprietary Medicinal Products (CPMP) of the EC and was Chairman of this Working Party from December 1991 to March 1993.

Dr A. Artiges left the French Ministry of Health in April 1993 to take up the post of Director of the European Directorate for the Quality of Medicines (European Pharmacopoeia and European Network of Official Medicines Control Laboratories/OMCL) - Council of Europe.

Prof D. H. Calam obtained his degrees from Oxford University, UK. After posts with the UK Agricultural and Medical Research Councils, he joined the National Institute for Biological Standards and Control becoming Head of Chemistry and now European Co-ordinator. He is currently Chairman of the European Pharmacopoeia Commission. He is also Chairman of the British Pharmacopoeia Commission.

Mrs Alexandrine Maes, Pharmacist, graduated in 1998 from the University of Ghent in Belgium. Since 1999 Ms. Maes works at the Scientific Institute of Public Health, Brussels, in the Biological Standardisation section as a scientific collaborator where she is responsible for the evaluation of medicinal products regarding the TSE risk.

At the European level, she attends the CPMP Biotechnology Working Party meetings at the EMEA in London and is a member of the TSE certification expert group at the EDQM in Strasbourg.

Dr Corinne Pouget studied Pharmacy at the University of Grenoble, France, where she worked in the Analytical Chemistry and Pharmacognosy Departments for two years after receiving her degree in 1985.

She was in charge of the analytical part of the licensing dossiers in a French pharmaceutical company (Laboratoires Guerbet) for three years. Then, she joined the European Pharmacopoeia in 1991, where she is now Head of the Certification Unit.

Dr John Purves, Qualified as a pharmacist from the University of Heriot-Watt, Edinburgh. Doctor of Philosophy degree in pharmaceutical microbiology, from the University of Strathclyde, Glasgow. From 1972 to 1974, Dr Purves worked in the pharmaceutical industry. Between 1974

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and 1996, he held various posts in the UK Medicines Division and then in the Medicines Control Agency. These posts included inspector of pharmaceutical manufacture, reviewer of dossiers and manager of the Biotechnology and Biological Unit. He was the UK representative at the Biotechnology Working Party and involved in the generation of many guidelines relating to biotechnology and biological products. Dr Purves is currently Head of Sector – Biotechnology at the EMEA

Dr M. P. Robert is French by birth. He received a double training: first of all, he took different degrees in Biology, Biochemistry and Human Biology at the University of Sciences in Lyon (France). After which, he obtained a PhD in 1977. He started his career as a researcher at the French INSERM (Institut National de la Santé et de la Recherche Médicale) specialising in immunological questions in a transplant unit in Lyon. Then he decided to go into policy work. Having been graduated from the Institute of Political Sciences in Paris in 1981, he passed the exam to study at the Ecole Nationale d'Administration. In 1988, he became a senior administrator in the French Ministry of Health. During his time there he was in charge of surveillance, control and prevention of communicable diseases i.e. immunization programs and epidemiological surveys. He joined the European Commission in 1992.

Monsieur Robert is currently Principal Administrator in the Directorate General ENTERPRISE (former DG-III) of the European Commission in Brussels. Having joined the Pharmaceuticals and Cosmetics Unit in July 1997, he is now in charge, *inter alia*, of the revision of part of Community legislation on Pharmaceuticals, post approval changes to Marketing Authorizations of medicinal products, in particular. He is also dealing with biological medicinal products, plasma derivatives and products of gene therapy and cell therapy in connection with the European Medicine Evaluation Agency in London. Before that, he was working with the DG SANCO, Health & Consumer Protection (former DG-V), Public Health Unit, in Luxembourg, on dossiers dealing with communicable diseases, in particular, the recently adopted European Parliament and Council Decision for the setting up of a European network for the surveillance and control of communicable diseases at Community level.

Dr. Sol Ruiz obtained her degree in Biology from the Universidad Complutense de Madrid (UCM), Spain. She studied and did the research work for her Ph.D. thesis both at the UCM, Spain, and at the University of California Irvine (US). She obtained her Ph.D. in Immunology in 1997.

Since then, she has been the Biotechnology Section Head at the Spanish Medicines Agency and the Spanish representative at the Biotechnology Working Party (EMEA).

Dr Jean-Hugues Trouvin – graduated in Pharmacy and received his Doctorate in Pharmacology from the University of Paris. He is currently Professor of Pharmacology and Pharmacokinetics at the Faculty of Pharmacy, University of Paris. Concurrently with his work at the university, Dr. Trouvin has been involved, since 1986, as Rapporteur for the French Marketing Authorisation Commission, in charge of reviewing the Quality Aspect of Biotechnology-derived medicinal products and biological products such as vaccines or plasma –derived medicinal products. He

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was chairman of the French Biotechnology working party (including viral safety aspects) from 1989 to 1993.

He is currently at the “Agence Française de sécurité sanitaire des produits de santé” (AFSSAPS) (French Agency for products for human health) Director of the Direction des Laboratoires et des Contrôles (Directorate for Laboratories and Controls), and in charge of all the aspects dealing with biological products.. This department is in charge of co-ordinating the review of biological and biotechnological applications, covering a wide range of products from conventional vaccines to plasma-derived medicinal products, recombinant proteins as well as gene therapy and cell therapy products.

At a European level, he has been participating to the European Biotechnology working party since 1989. He acted as rapporteur on several topics such as “Biotech headings” and the format of part II-V of the Notice to Applicants, and the revision of EC guidelines on “Production and Quality Control of Medicinal Products Derived by Recombinant DNA Technology”. Since 1992, he has also been involved in the ICH (International Conference on Harmonisation) discussion for the Biotechnology topics.

He was appointed as a French CPMP member in January 1995 and January 1998. He has been appointed as ICH co-ordinator for Biotechnology topics.