The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

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**SUMMARY OF THE
PROVISIONAL CPMP REPORT: MEDICINAL PRODUCTS FOR HUMAN USE
AFFECTED BY COMMISSION DECISION (97/534/EC)**

1. BACKGROUND

The Commission, referring to its Decision 97/534/EC, in its letter dated 11 August 1997, identified a number of tasks for action by the European Medicines Evaluation Agency (EMEA), the Scientific Committees and Member States. These tasks included:

1.1 EMEA and its scientific committees 'to check with the companies concerned to determine how centrally authorised medicinal products will be affected by the Commission Decision and to inform the Commission of the necessary arrangements planned by companies to comply in due time with the Commission Decision'.

1.2 EMEA 'to collect all available data regarding medicinal products which will be affected by this Decision and to co-ordinate at Community level the different implementation measures that Member States may wish to adopt'.

1.3 revision of the draft "Note for guidance for minimising the risk of transmitting animal spongiform encephalopathies via medicinal products"

Pharmaceutical products are subject to very extensive EU control both in terms of strict, harmonised legislative requirements and specific Marketing Authorisations to assess the safety, quality and efficacy of each, individual product. Guidelines have been prepared to cover the testing of quality, safety and efficacy of such products, to convey more detailed information, to applicants of Marketing Authorisations (MA's), on the scientific and technical requirements to support applications for MA's.

This summary report addresses on the following pages the outcome of the review to identify human medicinal products affected by Commission Decision (97/534/EC), the revision of the CPMP "Note for guidance" and the CPMP observations and recommendations on the outcome of the review.

2. OUTCOME OF THE REVIEW TO IDENTIFY HUMAN MEDICINAL PRODUCTS AFFECTED BY COMMISSION DECISION (97/534/EC)

In order to respond to the request from the Commission, a review was undertaken by the EMEA and its scientific committees. The objective of the review was to identify human medicinal products, both centrally and nationally authorised, which may be affected by the Commission Decision (97/534/EC). The EMEA secretariat examined the status of centralised Marketing Authorisations (granted and pending). As a result of this review they determined which products were implicated due to the use of Specified Risk Materials (SRMs) as active ingredients, the use of reagents derived from SRMs used in manufacture of active ingredients and the use of gelatin. National Authorities responded to Committee on Proprietary Medicinal Products (CPMP) questionnaires, sent out by the EMEA, which also addressed these issues. During the review and subsequent discussions, gelatin and tallow derivatives were also discussed. The review has taken into account the legal interpretation by the Commission of 29th September 1997 and used a broad scope in its definition of products which could be affected by the Decision. Details of the outcome can be found within the body of this Report.

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2.1 Specified Risk Materials

2.1.1 No medicinal product contains in the final formulation put on the market crude specified risk material (SRM) as an active ingredient.

2.1.2 No medicinal product was identified to contain in the final formulation put on the market an active ingredient derived from SRM. There is one vaccine in which cholesterol derived from bovine brain is used as an excipient: this is being considered by the Member State concerned.

2.2 Products using Reagents derived from Specified Risk Materials

Biological reagents derived from SRMs (e.g. brain-heart infusion), are used in the production process of many bacterial vaccines and certain biotechnological products. In addition, many bacterial vaccines, some viral vaccines, recombinant proteins, steroids, vitamins, and antibiotics are reported as being prepared on culture media containing protein hydrolysates the starting materials of which may have come in contact with SRMs. These reagents are used during manufacture but do not remain in the final product put on the market, therefore, the potential risk of contamination is, if any, very significantly reduced for the finished product.

2.3 Gelatin and tallow derivatives

2.3.1 Some medicinal products contain gelatin or gelatin derivatives as active ingredients (used as plasma expanders), the starting materials of which may have come into contact with SRMs. As such they could be classified as products derived from SRM's.

2.3.2 A number of medicinal products derived from blood or plasma, however, utilise tallow derivatives (e.g. polysorbate) during manufacture in a key viral inactivation step to eliminate enveloped viruses. This reagent is used during manufacture and is not in the final product. It should be noted that tallow derivatives are considered safer than tallow due to the further processing to which they are subjected.

2.3.3 Most tablets and capsules contain gelatin and tallow derivatives as excipients and would, therefore, be affected by the Commission Decision.

3. NOTE FOR GUIDANCE FOR MINIMISING THE RISK OF TRANSMITTING ANIMAL SPONGIFORM ENCEPHALOPATHIES VIA MEDICINAL PRODUCTS

3.1 The original version of this "Note for Guidance" was prepared in 1991, following extensive discussions on the steps required to minimise the risk of transmission of Bovine Spongiform Encephalopathy (BSE) via medicinal products. Since then it has been kept under regular review and was used when the CPMP came to its opinion on the potential risk associated with medicinal products in relation to Bovine Spongiform Encephalopathy (BSE) on 16 April, 1996.

3.2 The most recent version of the guideline was enlarged to cover all Transmissible Spongiform Encephalopathies (TSE) and also cross refers to the Commission Decision (97/534/EC). The purpose behind the "Note for Guidance" is to set out the key scientific principles which minimise the possible risk of transmission of spongiform encephalopathy via medicinal products. These principles include three additional precautionary measures, the geographical sourcing of starting materials, the selection of tissues and the design and control of the manufacturing procedures to minimise the risk of transmission. When properly implemented, these measures reduce as far as possible the risk of transmission of TSE.

4. CPMP OBSERVATIONS AND RECOMMENDATIONS

4.1 Risk of a Major Shortage of Human Medicinal Products

If the Commission Decision were to be implemented in its current form, a large number, perhaps three quarters, of human medicinal products might have to be taken off the market on the 1st of January, 1998 with a major adverse consequences for Public Health. This would create a major

disruption in the supply of medicinal products. On the basis of available information contained in the present report, the CPMP considers there is no reason why there should be specific safety concerns about medicinal products currently on the market.

For many groups of patients essential medicines would no longer be available. For others, there would need to be a drastic change in medication. When patients have to change to alternative formulations of medicines, there can be serious effects particularly for patients suffering from epilepsy, cardiac disorders and endocrine dysfunctions. In addition, the Decision would also undermine public confidence in the safety of all medicinal products. The implications for vaccination programmes, for example, would be catastrophic.

Since no crude SRM is used and the risk from reagents is so remote the CPMP recommends that the Commission Decision should not be retroactive and serious consideration should be given to the following points on the future certification scheme, the time needed to make changes to manufacturing processes and the need for multi-disciplinary scientific discussions before the Decision is redrafted.

4.2 Uncertainties about Future Certification Scheme

The requirement for certification under Article 6.3 of the Decision raises major uncertainties for the operators. Marketing Authorisation Holders would be unable to obtain, from the relevant competent authorities of third countries, certificates that bovine materials to be exported are in compliance with the Commission Decision. The CPMP, therefore, recommends to the relevant Commission Services that a functional, certification scheme should be either proposed or introduced and that full details be conveyed to the EMEA, National Authorities and the Industry informed accordingly.

Because it will not be possible for manufacturers to provide certificates as required under Article 6.3 for products produced before the 1st of January 1998, the CPMP recommends that the Commission Decision should apply prospectively and only when a rigorous certification system is put in place and made well known to interested parties.

4.3 Time needed to make changes to manufacturing processes

For products manufactured using derivatives of SRM's, or other bovine derived materials used as reagents, it would take manufacturers well into 1999 to change their production processes, in order to eliminate the use of such materials. The reason for requiring this amount of time is due to the necessary product development and validation of manufacture of the new product to ensure the safety, quality and efficacy of the modified product. Hence, a substantial transition period of at least 18 months should be provided for any necessary changes.

4.4 Need for Multi-disciplinary Scientific Discussions

For gelatin and tallow derivatives, the switch to other providers or manufacturers is difficult due to the world-wide trade and circulation pattern of the starting materials. The CPMP and its BWP have met representatives of gelatin and tallow derivatives manufacturers, but have not been able to get a good overall picture of how individual manufacturers prepare their products and control their processes. To develop a rigorous European position on these materials, the CPMP recommends the pooling of European expertise from other Sectors including food and cosmetics. CPMP is prepared to contribute to the general debate to provide its specialist knowledge on medicinal products to experts in other Sectors and to gain from their experience. This approach should involve all scientific committees with a similar interest. It would allow the establishment of a common understanding of the data available and, thereby, facilitate the development of comprehensive and rigorous European standards, which could be implemented for gelatin and tallow derivatives across all Sectors e.g. food, cosmetics and pharmaceuticals. For tallow derivatives, the temperatures and pressures referred to in the EMEA Opinion of 16 April 1996 were only one example of process conditions used and does not preclude other quality standards which could be agreed across Sectors in Europe.