

- INTERIM GUIDANCE -

**MINIMISING THE RISK OF TRANSMISSION OF TRANSMISSIBLE
SPONGIFORM ENCEPHALOPATHIES VIA UNLICENSED MEDICINAL
PRODUCTS FOR HUMAN USE**

INTRODUCTION

- 1) The Unlicensed Medicinal Products for Human Use (Transmissible Spongiform Encephalopathies) (Safety) Regulations 2003 [S.I. 2003/1680] came into force on 30 July 2003. From this date all manufacturers and importers/exporters of certain unlicensed medicinal products will have to comply with the provisions of the Regulations. To help with this requirement the Medicines and Healthcare products Regulatory Agency (MHRA) has produced this interim guidance on the Regulations.
- 2) The main categories of unlicensed medicines to which these Regulations apply are:
 - a) **“Specials”**. These are relevant medicinal products which are exempt from licensing, supplied in response to the unsolicited order of a doctor or dentist to meet the special needs of an individual patient on his direct personal responsibility. They are exempt from the need to have a marketing authorisation by virtue of Schedule 1 to the Medicines for Human Use (Marketing Authorisations Etc.) Regulations SI 1994/3144.
 - b) Unlicensed relevant medicinal products imported in accordance with the Medicines (Standard Provisions for Licences and Certificates) Amendment Regulations 1999, SI 1999/4 and supplied in accordance with Schedule 1 to the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994, SI 1994/3144.
 - c) Medicines (excluding herbal remedies) which are exempt from licensing because they are mixed, assembled and supplied by someone who is not a doctor or dentist, (known as a **“non-orthodox practitioner”**), to a patient who has consulted him about his health. They are exempt from the need to have a marketing authorisation by virtue of Article 2 of the Medicines (Exemption from Licences) (Special and Transitional Cases) Order [SI 1971/1450].

- 3) Compliance with the guidance by products prepared under the supervision of a pharmacist in a pharmacy will be ensured under the existing professional arrangements and these products are exempt from the requirements of the Regulations. There is no equivalent arrangement or exemption for products prepared by doctors or dentists. In addition, the Regulations also apply to any other substance which, although not requiring a product licence, is treated as a medicine under the Medicines Act. The Regulations do not apply to investigational medicinal products that are undergoing clinical trials, which are dealt with through the Clinical Trials Regulations.

BACKGROUND

- 4) The Commission Directive 1999/82/EC requires all licensed medicines to comply with the European Commission's "Notes for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products" and future updates.
- 5) All licensed medicines are required to comply with these guidelines. Applicants and existing licence holders have demonstrated compliance by submitting to the MHRA for each starting material used:
 - a) either a TSE Certificate issued by the European Directorate for Quality of Medicines (EDQM);
 - b) information on its source and processing, obtained from the starting material manufacturer, which has been made the subject of an application to vary the product licence, or
 - c) confirmation that their products do not use any materials of animal origin in their manufacture.
- 6) The Regulations are intended to ensure protection of patients from the same risk arising from certain unlicensed medicines. The arrangements differ in some respects from those applying to licensed medicines and are set out below.

SCOPE OF THE REGULATIONS

- 7) The Regulations apply the European Commission's '*Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human medicinal products*', and any future updates of this guidance, generally to unlicensed medicines. This excludes all unlicensed herbal remedies, Traditional Chinese and Ayurvedic Medicines.
- 8) The Regulations place responsibility for compliance with the EC Guidance on the person or business first placing the unlicensed medicine on the UK market. Consequently this responsibility will normally not fall on anyone buying unlicensed medicines from manufacturers, importers or wholesalers in the UK. However, the licensing authority has powers under the Regulations to take action against any wholesale dealer dealing in unlicensed medicines. This is to prevent

the situation arising where necessary enforcement action becomes impossible because the product has passed through more than one wholesale dealer.

- 9) The responsibility for demonstrating compliance with the EC Guidance under these Regulations will fall on:
- a) **UK manufacturers**;
 - b) **practitioners** other than *pharmacists* who prepare remedies (excluding herbal remedies) for individual patients during the course of a business;
 - c) those who during the course of a business **import** unlicensed medicines (excluding herbal remedies) **directly from countries outside the European Economic Area (EEA)**, i.e. the EC plus Norway, Iceland and Liechtenstein;
 - d) those who source unlicensed medicines directly from other countries within the **EEA**. It is likely that some wholesalers will fall into this category; and
 - e) **exporters** who sell medicines not covered by a UK product licence outside the UK.
- 10) Note that herbal remedies are only permitted to contain active ingredients of plant origin. Any medicinal product which contains an active ingredient of animal origin could not legally be placed on the market as a herbal remedy.**
- 11) Please see Annex 1 for a summary of the EC Guidance. The current complete EC Guidance is available at the EMEA website:
www.emea.eu.int/pdfs/vet/regaffair/041001en.pdf

EVIDENCE OF COMPLIANCE

- 12) There is no requirement to provide documentation routinely to the MHRA to demonstrate compliance. The person or business responsible for compliance should ensure they are in a position to give an assurance that the starting materials used in the unlicensed medicine comply with the TSE guidance before the product is supplied. This evidence should be produced for inspection by officers of the MHRA on demand.
- 13) Where starting materials are of **animal origin** the person or business responsible for compliance should have a written statement from the suppliers of the starting materials or of the imported product giving a reasoned assurance that the materials comply with the guidelines. The person responsible for compliance should satisfy themselves that there is a reasonable basis for accepting the validity of this assurance.
- 14) In cases where compliance has already been demonstrated for the purposes of a licensed medicine, evidence of this will be regarded by the MHRA as acceptable, for example:
- a) when a starting material is a licensed medicinal product;
 - b) when a starting material has been certified by the EDQM; and

- c) when a starting material, although not certified by the EDQM, has been assessed and found acceptable by the MHRA in relation to its use in a licensed medicinal product.
- 15) Where starting materials are clearly of **non-animal origin** it is acceptable for the person or business responsible for compliance to give an assurance to that effect. Given this arrangement, particular care should be taken to establish the origin of any ingredients, which could be derived either from animals or from other sources such as plants (examples are listed in Annex 2). It would be open to MHRA to challenge this assurance if it has reason to do so.

Keeping Records

- 16) Manufacturers and suppliers of many unlicensed medicines are already required to maintain records of the medicines they market for a period of five years from the date of supply, or one year from the expiry date for the product, whichever is the longer. The Regulations extend these obligations as follows-
- a) the person who imports an unlicensed product into the UK or (if the product is manufactured or assembled in the UK) the person who manufactures or assembles the product in the UK, will become the designated record-keeper for that product. This will be so, whether or not they are already required to keep records in respect of that product under other legislation. If an import is modified in the UK such that it becomes a new product under the Medicines Act 1968 both the original importer and the person modifying the product are designated record keepers for the purpose of these Regulations;
 - b) if materials to which the EC Guidance applies (examples are listed in Annex 2) were used in the course of the manufacture of the product, the designated record-keeper is obliged-
 - i) to establish records in English that demonstrate that the product has been manufactured in accordance with the EC Guidance and
 - ii) to maintain those records for five years from the date on which he imports or markets the product, or one year from the expiry date for the product, whichever is the longer;
 - c) if materials to which the EC Guidance may apply have been used in the course of the manufacture of the product, e.g. Stearic Acid Salts that may be of animal or vegetable base, it is the designated record-keeper's responsibility to establish whether or not the Guidance does apply. The Regulations will deem the Guidance to apply, unless the designated record-keeper is able to demonstrate otherwise.

NON COMPLIANCE

- 17) Paragraphs 19 – 30 describe the proposed arrangements where the MHRA has concerns that an unlicensed medicinal product has not been manufactured in accordance with the EC Guidance.
- 18) In summary the MHRA may serve a notice on someone who imports or markets the product requiring him to demonstrate that the product has been manufactured in accordance with the Guidance. If the MHRA then makes a provisional determination that the product does not comply with the EC Guidance the company or individual concerned will have a right to make representations to the Committee on Safety of Medicines (CSM) before a final determination is made. A final determination that there has not been compliance may result in a prohibition on the supply of the product in question. While this procedure is underway, the licensing authority is prevented from issuing a suspension notice under section 14 of the Consumer Protection Act 1987 suspending marketing of the product immediately, unless it is in the interests of public safety to do so.

THE STATUTORY PROCEDURE.

Notice of Compliance.

- 19) In all cases where the MHRA has concerns that an unlicensed medicinal product has not been manufactured in accordance with the EC Guidance, the MHRA may serve on any person a notice of compliance requesting, within 21 days, evidence that it has. The MHRA may extend this deadline depending on the complexity of the case. If evidence is not provided within the time limit the MHRA will in any event, after further consideration of the matter, provisionally determine whether or not the unlicensed medicine has been manufactured in accordance with the EC Guidance. Evidence that is provided in time will be considered before a provisional determination is made.

Provisional Determination

- 20) If the MHRA considers the unlicensed medicine has not been manufactured in accordance with the EC Guidance a provisional determination notice, giving the reasons, will be issued.

Right of Review and Oral Hearing.

- 21) Any person who is issued with a provisional determination and disagrees with the reasons may, within 14 days, request a review. The review can include an oral hearing before the CSM if one is requested within the 14 days.
- 22) If no notice of intention to seek a review is received within the time limit, after further consideration of the matter the MHRA will determine finally whether the unlicensed medicine has been manufactured in accordance with the EC Guidance. The person will be notified in writing of the final determination and of the reasons for it.

- 23) If a review is requested but there is no request for an oral hearing, the MHRA will set a deadline within which any additional material is to be submitted prior to the final determination. In such cases, the MHRA may decide to submit the matter to CSM for their advice. After further consideration of the matter and taking advice from CSM, MHRA will then notify the appellant in writing of the final determination and the reasons for it.
- 24) If an oral hearing is requested, at the hearing the person who has been issued with a provisional determination will be expected to present his case to the CSM. At the same hearing the MHRA will present its case. The CSM will then consider all the evidence presented and provide advice.
- 25) After considering the CSM's advice the MHRA will make a final determination whether or not the unlicensed medicine has been manufactured in accordance with the EC Guidance and issue a final determination notice. If the MHRA's determination is contrary to the advice of the CSM the reason will be stated.
- 26) Following the issue of a final determination notice, the person may provide new material for consideration. If the MHRA is satisfied that this new evidence may demonstrate that the product has been manufactured in accordance with the EC Guidance, they may go back and start the determinations procedure again – or if the evidence satisfies the MHRA without the need for a further procedure, they may simply issue a new decision letter stating that, in the MHRA's opinion, the product has been manufactured in accordance with the EC Guidance.

Restriction Notice

- 27) If it is determined that the unlicensed medicine has not been manufactured in accordance with the EC Guidance, the MHRA may decide to issue a restriction notice. This may do one or more of the following-
- (i) prohibit further importation or supply of the product, from a date specified.
 - (ii) require the person on whom the notice is served to inform others of the MHRA's determination, by a date specified.
 - (iii) require him to recover possession of any of the product that he has supplied to others, by a date specified.
- 28) The notice may at any time be withdrawn by the MHRA, and there is a right of appeal against the notice through the lower courts. It is important to note that a restriction notice could be served on any person supplying the product, although the likelihood is that it will be served on the person on whom the original notice to show compliance was served.

Suspension Notice

- 29) Suspension notices are notices under the Consumer Protection Act 1987 which allow the MHRA to suspend further supplies of products which breach Regulation

2 of these Regulations for a period up to 6 months. There is a right of appeal against such notices through the lower courts.

30) While the determinations procedure is underway, the Regulations will prevent the MHRA from issuing a suspension notice, taking the product off the market immediately, unless it is in the interests of public safety for them to do so. Therefore, unless there are safety concerns, appellants will not formally be barred from marketing their products pending the outcome of the review. However, appellants should be aware that, if they continue to market their products and their products do not in fact comply with the EC Guideline, an ongoing offence would be committed. There is nothing in the Regulations that prevents the appellant from voluntary suspension of marketing of their product while the concerns about it are being considered, and any such action will not in any way prejudice the determination.

LEGISLATION

31) The EC Guidance is applied to certain unlicensed medicinal products by these Regulations, made under the Consumer Protection Act 1987, which will be enforced, in Great Britain, by the MHRA, and in Northern Ireland by the Department of Health, Social Services and Public Safety in conjunction with the MHRA.

32) Copies of The Unlicensed Medicinal Products for Human Use (Transmissible Spongiform Encephalopathies) (Safety) Regulations [S.I. 2003/1680] are available from The Stationery Office (ISBN 0-11-046735-3) price £2.00, or via their website at <http://www.hmsso.gov.uk/stat.htm>.

Medicines and Healthcare products Regulatory Agency
October 2003

Summary of the CPMP/CVMP Notes for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products.

1. The CPMP/CVMP note for guidance is available from the EMEA Website: www.emea.eu.int/pdfs/vet/regaffair/041001en.pdf or the MHRA Eurodirect Publications Service Tel 0207 273 0352. The underlying scientific principles in this guideline can also be found in a General Notice of the European Pharmacopoeia 'Minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products [Chapter 5.2.8 of the 2001 supplement].
2. In Summary the Guidance considers the implications of TSE for human medicinal products arising from the starting materials used in their manufacture and recommends measures to minimise the risk of transmission of TSE via medicines. The risk arises only from materials of ruminant animal origin and materials derived from other animals, which are susceptible to infection with transmissible spongiform encephalopathy through the oral route. Materials that are used for the preparation of active substances, excipients, raw or source material and reagents used in the production of medicines, fall within the scope of this guideline. It is also applicable to materials, which come into direct contact with the equipment used in their manufacture.
3. Where manufacturers have a choice of using materials derived from ruminant or non-ruminant animals, the use of non-ruminant material is preferred. Use of materials of vegetable origin avoids the risk entirely. An illustrative list of examples of starting material that may be of ruminant animal origin is provided at Annex 2. This is not intended to be a complete list and does not mean that other materials need not be demonstrated as complying with the guidelines
4. Further information on the TSE certification requirements for starting materials and on applying for certification may be obtained from the Certification Unit, EDQM, 226 Avenue de Colmar, F-67029 Strasbourg Cedex, France.

**EXAMPLES* OF STARTING MATERIALS
THAT MAY BE OF RUMINANT ANIMAL ORIGIN**

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| <p>Amino Acids (1). Animal based. Animal Based Charcoal. Aprotinin. Azelaic acid. Bacto-casitone. Bile Salts. Bone (used in Herbals). Bovine Serum Albumin. Calcitonin (Porcine usually). Calcium Phosphates. Cetomacrogol. Cetostearyl Alcohol. Cholecalciferol. Cholesterol. Cholic Acid. Chymotrypsin. Collagen. Chondroitin Sulphate. Cortico-Steroids (2). Desoxycholate Na. Emulsifying Agents (3). Emulsifying Wax BP. Fermentation. Fermentation Product (4). Foetal Calf Serum. Gelatin. Gelatin and Polymeric derivatives. Glucagen. Glycerin/Glycerol.</p> | <p>Glycerophosphates. Glyceryl Esters. Glyceryl Trinitrate. Gonadorelin. Heparins (inc low Molecular Wt) And salts. Homeopathic Products of Bovine Origin. Lanolin and derivatives (5). Media. Non Human Insulins (may be porcine/bovine). Oleic Acid Esters and Derivatives. Pancreatin Pepsin/Trypsin. Peptone/Tryptone (6). Pituitary Extracts. Polysorbates ('Tweens') (7). Recombinant Product. Sera. Sorbitan Esters. Sorbitan Mono Stearate. 'Spans' Stearic Acid. Stearic Acid Salts. Thioglycolate. Thyroid & Derivatives. Triglycerides. Vitamins (inc Retinols). 'Witepsol'</p> |
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** these examples are provided for purposes of illustration only and do not substitute for definitive information required on individual starting materials.*

Notes

(1)&(2) Amino Acids & Cortico-Steroids may be prepared synthetically, or by fermentation procedures or from animal sources.

(3) Emulsifying agents can be prepared from stearic and oleic acids of animal or vegetable origin.

(4) Fermentation products should in general include all antibiotics. While innovator methodology may make use of vegetable based media and there may therefore be specific exceptions, current information is that fermentation processes, including those used in the Far East and other third countries, may often utilise animal based media e.g. "Lard Water" or other hydrolysed tallows.

(5) Lanolin and derivatives obtained from wool are not subject to the current TSE guidelines if it is demonstrated that the wool is obtained from living animals.

(6) Peptones etc are mostly encountered as constituents of fermentation and media and will not usually be encountered in non-biological products.

(7) It is understood that **Polysorbate 20** is manufactured by polymerisation and condensation of lauric acid, generally from vegetable source. However **Polysorbate 40, 60 & 80** are usually prepared from oleic and stearic acid which may derive from either vegetable or animal sources.