HUMAN & VETERINARY MEDICINES BRIEFING GROUP RE. BSE

MINUTES OF MEETING HELD ON 22.2.89 AT 10AM IN THE 19TH FLOOR CONFERENCE ROOM, MARKET TOWERS, TO AGREE ADVICE TO CSM (ON 23.2.89)

Present: Biologicals Subcommittee
Professor Collee (Chairman)
Dr. Minor
Dr. Schild

Invited Experts
Professor Asscher
Professor Sir J Badenoch
Dr. Kimberlin
Dr. Martin
Professor Rawlins

Department of Health Medicine's Division
Dr. Adams
Mrs. Alderman
Mr. Bewley
Mr. Hagger
Dr. Jefferys
Mr. Love
Dr. Purves
Dr. Rotblat
Mr. Sloggem

Department of Health (Other)
Dr. Burton
Mr. Colman
Mr. L. Wilson
Ms. Nash
Dr. Pickles
Dr. Salisbury

MAFF
Mr. Bradley
Mr. Kidd
Dr. Little
Mr. Scolan
Mr. Wilesmith

Apologies for absence were received from Dr. Tyrrell and Dr. Sutton

1. Information Exchange

1.1 It was thought that the Southwood Report would be published on 24.2.89, when a press conference would be held, attended by CMO. CVetO, Sir Richard Southwood, and possibly representatives from MAFF.

1.2 The Southwood Committee considered that the most likely cause of BSE in cattle was feeding with protein derived from scrapie infected sheep. Although man has eaten scrapie infected sheep meat for many years, no incidence of BSE has been reported in humans. Because of the lengthy incubation period, no cases of BSE have been seen in humans arising from bovine sources and the Southwood Committee were of the opinion that cattle will prove to be "dead-end" hosts for the BSE causing agent, and it is unlikely that there will be any implications for human health.
1.3 Because of the above, clarification is needed on the acquisition of BSE by cattle via the oral route, which by analogy with scrapie is relatively inefficient. Although it is probably the primary route in cattle, there may be special factors involved eg. damage to the gut from roughage, causing an "injection" of BSE. It was felt that the oral route need not be of undue concern at this stage.

1.4 The slight theoretical risk of BSE being transferred to humans was considered to be more likely from products used parenterally or by implantation than by the oral route. The implications of this for the vaccination programme (vaccines using bovine ingredients in manufacture) could be very serious and result in epidemics if public reaction turned against vaccination.

1.4 The annual incidence of BSE in the UK at 31.12.88 was cited. It represents 1 case per 1000 adult cattle (total population 4 million) but cases have not occurred uniformly throughout the UK.

1.5 Despite the research and investigative studies already carried out on BSE, the cause of the relatively recent appearance of the disease in cattle has not been established and it may be the result of a mutant strain of scrapie being transmitted by the feedstuff. There is a need for more research into BSE and a consultative research committee chaired by Dr. Tyrrell has been set up to carry research initiatives forward.

2. CSM paper

2.1 Joint proposed DH/MAFF draft guidelines

2.1.1 Draft guidelines covering products for use parenterally, in the eye or on open wounds and the source of bovine materials used in their manufacture had been drawn up.

2.1.2 Normally, in matters where there is as little knowledge as there is in the case of BSE, CSM would have been advised to take no action but to monitor the situation. Due to the publication of the Southwood Report, this option is not open. It is not feasible to go to consultation with industry on the matter due to lack of time, and the fact that this might be seen as our being led by industry. VPC had given broad approval to the draft guidelines.

2.1.3 The guidelines themselves were discussed. These are to be seen as a "gold standard", and may be modified in the light of experience. It is intended that they should be parallel with those issued on the veterinary side, but not identical because they have more difficult problems to handle (BSE being a speculative hazard in man).

2.1.4 It was agreed that it would be better to try to eliminate BSE at source. The possibility of the identification of risk-free herds and their certification was discussed. Ideally, bovine materials obtained from calves should be taken from animals less than 6 months old, which have not been fed on ruminant-derived protein. The question of "BSE-free" countries was raised, but there are other pathogens which also need to be taken into consideration in selecting a source.
2.1.5. It was felt that to issue rules on oral products would challenge our concepts on foods and cause problems with regard to gelatin capsules. The guidelines are a balance between flexibility and standards of ideal practice, and an attempt has been made to major on the question of source.

2.1.6. VPC had expressed anxiety about animal vaccines, and it was felt that in future we may need to ensure that bovine ingredients are not obtained as by-products of abattoirs. The possibility of herds being maintained specifically for this purpose was mentioned.

2.1.7. The question of excluded tissues was discussed. In the case of the intestine, this would eliminate heparin (although most of this is porcine sourced) and catgut. It was felt that the pancreas should not be excluded as this would eliminate bovine insulin.

2.1.8. The section headed "sterilisation" was clarified to refer to equipment used in production, and not to products themselves.

2.1.9. Anxiety was expressed over problems with availability of supply of vaccines if companies could not comply with the guidelines, as failures of supply could lead to epidemics. Drs. Adams and Rotblat had, at the request of the CMO, contacted companies holding licences for vaccines, asking for information on the use of bovine ingredients. Most of the companies were aware of the problems of BSE and some have begun to take action. It was felt that most companies would welcome guidelines on this subject.

2.1.10. The question of unlicensed products involving bovine ingredients was raised. These are not subject to the Medicines Act and are controlled by Supplies Technology Division. Some preliminary screening of these products has taken place, and P0 will follow the lead of CSM and issue similar guidelines.

2.2. Letter to licence holders

2.2.1. The draft letter was discussed. MAFF and Department of Health are sending letters separately, those sent by MAFF being 5.44 letters.

2.3. Questionnaires

2.3.1. The background to the need for data was discussed, the problem at present being that we cannot identify products using bovine ingredients during the manufacture. The intention is to develop a full database of the use of bovine ingredients in human medicines, and companies will be asked to respond to the questionnaire by 1st May 1989. The questionnaire was seen to be adequate.

3. Consideration of particular product groups

3.1. Product groups likely to use bovine ingredients were listed. An assessment of the theoretical risk involved in the use of vaccines and products in the other groups is required.
4. **Proposal for a Working Group on BSE**

4.1 It was agreed that a Working Group, associated with the Biologicals subcommittee should be set up, and a proposal of this was to be made to CSM. Suggestions for a core membership were made, with other experts being brought in as needed.

5. **Form of statement and briefing for press**

5.1 The draft prepared by Medicines Division was discussed, and some amendments suggested.

6. **Other business**

6.1 Dr. Burton asked to be kept informed as to CSM decisions, and also requested that a letter, guidelines and questionnaire be sent to him as holder of the Secretary of State licences.
MEDICINAL PRODUCTS USING ANIMAL MATTER

1. Company Name

2. Do you make use of animal materials in any way in any of your products
   Yes [ ] No [ ]

   If your answer to Q2 is 'No' please sign and date this form below and return it as shown in the letter.

   If your answer is 'Yes' please complete the remainder of this form (using a separate form for each product with continuation sheets if necessary).

3. PL/CTC/CTX Number and Product Name

   If more than one animal ingredient

   | 1 | 2 | 3 |

4. Animal material (specify type of tissue)

5. Animal species (eg bovine, ovine etc)

6. Purpose of inclusion or use (eg active, excipient, in-process use)

7. Country(ies) of origin of collected material

8. Does this medicinal product conform to the guidelines?
   Yes [ ] No [ ]

9. If not, by when (calendar month/year) do you expect to apply the guidelines to this product?
   Month/Year

10. Based on known usage patterns, by what date (calendar month/year) do you expect present stocks (ie. bulk stocks and finished product) to be exhausted?
    Bulk Month/Year
    Finished Product Month/Year

11. Other comment (if any) - please use the reverse of this form

12. Please give company contact person (Name, Position, Address, Telephone No.)
    Name in block capitals
    Position in Co.
    Address
    Telephone No.

Signed [ ]

Date [ ]

* Tick appropriate box

89/2.22/11.5
PROPOSED MEMBERSHIP OF CSM WORKING PARTY ON BSE

Professor Asscher/Professor Rawlins
Professor Berry
Professor A Campbell
Professor Collee
Dr Kimberlin
Professor Lawson/Dr Kirby
Dr Schild/Philip Minor
Dr Taylor
Dr Tyrell
Dr Watson
Dr Will

- Chairman, CSM/Chairman SEAR
- Chairman, CDSM
- Chairman, JCVI
- Chairman, Biols Subcommittee
- Committee on Research (BSE)
- Chairman/Vice Chairman, CRM
- Director/Divisional Head, NIBSC
- MRC Neuropathogenesis Unit
- Chairman, Committee on Research
- Director, Central Veterinary Lab.
- Consultant Neurologist

Terms of reference:

To advise the Section IV Committees on the implications of BSE to human medicinal products.

1 Safety Efficacy Adverse Reactions Subcommittee
March 1989

Dear Licence holder

Bovine Spongiform Encephalopathy: Guidance on good manufacturing practice and request for information

The Secretary of State for Health and the Minister for Agriculture have received Report of the Working Party on Bovine Spongiform Encephalopathy, chaired by Sir Richard Southwood ("the Southwood Report"). One of the recommendations was that medicinal products licensed under the Medicines Acts 1968 and 1971, and the licence authority has been asked to take account of the BSE agent and to take appropriate action.

The Committee on Safety of Medicines (CSM) in consultation with the Chairman of CSM has considered the Southwood Report and agrees that the risk to man of infective medicinal products is remote.

As a precautionary measure, the CSM and the Veterinary Products Committee have agreed joint guidelines for the manufacturers of human and veterinary medicinal products. These guidelines are as follows:

1. A copy of the guidelines is overleaf. It is felt that the guidance represents a standard that is deemed to be "best practice" for the future, and steps should be taken to implement it. However, it is realised that this guidance may not be fully applicable in all circumstances.

2. In order to update and complete our records on medicinal products, you are asked to fill in the attached form giving information about animal materials used in any of your medicinal products as specified in the guidelines (para 1). Information should be given in the guidelines as a percentage of the total material or as an active constituent.

3. If animal material is used in the manufacture or as an ingredient of a medicinal product, a separate form should be filled in for each product. Where necessary, a continuation sheet should be attached to this form.

4. If your company does not use any animal ingredient in a human medicine or veterinary medicine, then a NIL RETURN should be made.

The completed forms should be returned by 1 May 1989 to:

Mrs Judith Alderman, Room 1904
Department of Health, Market Towers
1 Nine Elms Lane
Vauxhall
London SW8 5NQ

Any professional enquiries should be made to Dr Rothblat (medical) Ext.3216, and Dr (pharmaceutical) Ext.3219.

Yours faithfully

D O HAGGER

* Letter distributed on the basis of the 'MAIL' address list. Consequently, companies with multiple sites may receive more than one copy. Please ensure that the letter is drawn to the immediate attention of the senior person in the company responsible for regulatory affairs.
The following guidelines are addressed to PL/CTC/CTX holders and applicants.

1. **Scope**
   It is recommended that all products licensed under the Medicines Act 1968 for human or veterinary use, that are administered parenterally or to the eye or to open wounds, should in general conform to this guidance if they contain material from a bovine source, or if bovine material has been used during their manufacture.

2. **Tissues excluded**
   No brain or neural tissue, spleen, thymus and other lymphoid tissue, placental tissue or cell cultures of bovine origin should be used in manufacture.

   **Cattle source for all other tissues**
   Bovine material should come from animals, taken from a closed herd in the female line since 1980, in which no animal has been clinically suspected of having BSE, and which has not been fed rations containing ruminant derived protein during that period.

3. **Collection techniques**
   All possible measures should be taken to avoid contamination of the bovine material with BSE agent, in particular:
   - No tissue is to be used in relevant medicinal products when collected postmortem from a bovine animal after brain penetrative stunning.
   - All tissue collected from the bovine animal should be taken using sterile equipment. Needles, syringes, scalpel blades etc should be disposable items.
   - It is recommended that whenever possible, source animals should be calves up to 6 months old.
   - For serum: all cellular components must be removed.
   - For foetal calf serum: great care should be taken to avoid contamination by placenta and foetal fluids. All cellular components must be removed.

4. **Sterilization of equipment**
   When sterilization procedures are used, they should be demonstrated to be capable of inactivating scrapie-like agents - at present thought to be autoclaving using a porous load cycle at 134°C-138°C for 18 minutes at 30 psi.

5. **Product**
   Whenever possible, the product should be terminally sterilised by a validated method.

Although these guidelines relate to BSE and materials of bovine origin, they should also be considered as generally applicable to material from sheep, goats, deer, and other animals susceptible to scrapie-like agents. These guidelines may need to be updated in the light of further scientific knowledge.
POSITION STATEMENT BY THE CSM AND LICENSING AUTHORITY ON THE IMPLICATIONS OF BSE FOR HUMAN MEDICINAL PRODUCTS

The Committee on Safety of Medicines (CSM) has considered the safety of human medicines in the light of the report of the Working Party on Bovine Spongiform Encephalopathy (BSE) - the Southwood Report. The CSM agrees with the Southwood Working Party that the risk to man of infection via medicinal products is remote. As a precautionary measure, and for the sole aim of seeking to guard against what is no more than a theoretical risk to man, the CSM and the Veterinary Products Committee (VPC) have agreed joint guidelines on good manufacturing practice for the manufacturers of human and veterinary medicines who use bovine, or other animal, materials either as an ingredient or in the production process. This guidance will be issued by the Licensing Authority to the manufacturers early in March. Manufacturers will also be asked for further details about any animal materials used in their products and, where appropriate, to state how they propose to implement the guidelines in the future. The need for further action will be considered by the Licensing Authority in the light of further information from the industry and expert advice.