COMMERCIAL IN CONFIDENCE

NOT FOR PUBLICATION

COMMITTEE ON SAFETY OF MEDICINES

WORKING PARTY ON BOVINE SPONGIFORM ENCEPHALOPATHY

PAPER I

Category 2.2.1 and 2.2.2 : Products with bovine/lymphoid tissue and products with bovine material other than brain/ lymphoid tissue, as ingredients or used in manufacture and administered by injection.

Review of positive responses to questionnaire

Overview of BSE position

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BOVINE SPONGIFORM ENCEPHALOPATHY: OVERVIEW.

Introduction:

1. On 3 February 1989, the Working Party on Bovine Spongiform Encephalopathy (BSE), chaired by Sir Richard Southwood, published its report (the Southwood Report). A summary of the recommendations is attached at Annex A.

2. The Committee on the Safety of Medicines (CSM) considered the Southwood Report and its implications for human medicines at its meeting on 23 February 1989. After taking account of the views of the Chairmen of Committee on Review of Medicines (CRM) and the Committee on Dental and Surgical Materials (CDSM) they agreed with the Working Party (recommendation 7.2) that the risk to man of infection via medicinal products was remote.

3. Under recommendation 8.2 of the report, the Licensing Authority (LA), the CSM, the CDSM and the Veterinary Products Committee (VCP) were asked to take account of the BSE agent in relation to medicinal products and to take appropriate action. The CSM decided to set up its own Working Party to advise on the implications for human medicine.

Guidelines:

4. The CSM and the VPC also agreed as a purely precautionary measure to produce joint guidelines for the manufacturers of human and vetinary medicines who use bovine, or other animal materials either as an ingredient or in the production process. These were issued in March of this year by the Department of Health (for human medicines) and the Ministry of Agriculture Fisheries and Food (MAFF) (for animal products). A copy of the guidelines is at Annex B.

Questionnaire:

5. In order to obtain the additional information needed by the advisory committees and the LA, questionnaires were sent at the same time as the guidelines. A copy of the questionnaire is at Annex C. Approximately 2,700 questionnaires were distributed by the Medicines Control Agency (MCA) to the recipients of MAIL (the Medicines Act Information Leaflet) asking for a response by 1 May 1989. Since then two reminders have been sent. To date 1,131 valid and 76 invalid (ie unanswered) returns have been received.

6. Of the valid returns received, 122 (11%) indicated that they made some use of animal material (574 products). A summary is attached at Annex D. Of these products, 17 contained bovine ingredients of UK only origin and a further 40 contained bovine ingredients of an origin including the UK.

7. The MCA professional Secretariat sub-divided the valid responses into the following categories, in decreasing order of concern:

	Category.	No of Products.
7.2.1.	Products with bovine brain/lymphoid tissue as ingredients and administered by injection.	111

7.2.2.	Products with bovine ingredients (other than brain/lymphoid tissue) and administered by injection.	135
7.2.3.	Tissue implants, open wound dressings, surgical materials, dental and opthalmic products with bovine ingredients.	27
7.2.4.	Products with bovine ingredients and administered topically.	5
7.2.5.	Products with bovine ingredients and administered orally.	9
7.2.6.	Products with other animal/insect/ bird ingredients and administered:	
	a. by injection	a:117
	b. topically	b: 6
	c. orally	c: 8
7.2.7.	Products with materials produced from animal material by chemical processes, eg stearic acid, gelatin and lanolin.	156

With two exceptions, the replies to date have not given any immediate cause for concern, although 176 products do not conform to the CSM/VPC guidelines.

8. The first exception was from which gave very limited information about a very large number of homoeopathic medicines with material obtained from cattle and a number with material from the brain. Of these, 53 were injectable products of which 20 were derived from cattle brain. A list of these products is attached as Appendix 1 to Annex D. The second exception relates to the product, 'Surgical Catgut', which is sourced from UK bovine intestines and will contain lymphoid material.

9. The National Office of Animal Health Limited (NOAH) who represent the manufacturers of animal medicines, have expressed concern over the relevance and practicality of certain aspects of the guidelines. A copy of NOAH's letter plus the Department's response is attached at Annex E.

Research:

10. Recommendation 8.5.1 to the Southwood Report called for rese rch to improve the understanding of the disease. As a result, an expert Consultative Committee on Research was established under the chairmanship of Professor Tyrrell. Its report is expected shortly.

Analysis of Returns:

11. The MCA professional Secretariat have undertaken an analysis of the valid returns.

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Manufacture

- The manufacture of products containing bovine material and a raw material or where bovine ingredients have been used in-process.

1. General Observations

1. In the manufacture of any pharmaceutical product it is essential to establish 'in the broadest of terms' the quality of all starting materials and, in particular, the quality of the active principle. For chemically synthesised drug substances this is relatively straight-forward, because of the predictability of chemical syntheses and the control afforded by such manufacturing processes. This is not necessarily the case for active principles where the raw material is biological in origin. With such substances there is a greater scope for unpredictable variability in quality, including microbial and other contamination. With the recognition of the Bovine Spongiform Encephalopathy agent as a potential contaminant of bovine material, the issue of contamination has been raised and the question posed on how to deal with it.

2. It is common practice in the manufacture of biological products for manufacturers to carry out stringent controls on the quality of starting materials and to validate the various stages of the manufacturing procedure. The emphasis placed on these will depend upon a number of factors including the nature and quality of raw material used, the type of product being produced etc.

3. Although tests may be undertaken to control the quality of starting materials or in-process materials, these may not necessarily be adequate in situations where new agents such as BSE are identified. In such instances, when there is little known about the agent, it would seem prudent to avoid the use of materials in which the agent may be present, so as to minimise the need for additional in-process control.

4. In cases where the raw material or in-process reagents are unavoidably contaminated, or potentially contaminated, manufacturers need to decide whether,

   4.1 to obtain such materials from a source known to be free from the agent, or,

   4.2 to use potentially contaminated material and depend upon the manufacturing procedure to remove or inactivate the agent.

   If the decision is made to use contaminated material then it is essential that the manufacturer proves, by validation studies, that the manufacturing procedure removes or inactivates the contaminating agent.

To prove that the method of manufacture of the active ingredient removes or inactivates the contaminating agent requires scientific information to confirm that the agent present at given levels is eliminated by a stage, or stages, in the manufacturing procedure. In order to do this detailed information is required about the properties of the contaminant agent and about the processes used to inactivate or remove it.

4.2.1. If scientific information is available about the characteristics of the agent (its physico-chemical properties etc) and how it may be removed or inactiviated and such treatment does not adversely effect the product then it may be feasible to use contaminated material.

4.2.2. However, when such information about the agent is not available, it would seem desirable, if not essential, to use material free of the agent if the agent is likely to pose a real risk to patient safety.

2. Specific observations regarding current problem

The above general and theoretical considerations must also take into account,

2.1 the findings of Southwood Report in which it was stated that "the risk to man of infection via medicinal products was remote". It is important not to undermine this considered advice by demanding unnecessary assurances and information from manufacturers.

2.2 the paucity of hard scientific information on the nature of the BSE agent.

2.3 the type of bovine material used in the manufacture of products (brain, lymphoid tissue sera etc).

2.4 the type of product containing bovine material (injection, topical, oral etc).

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CONSIDERATION OF THE PRODUCTS

1. Introduction

The use of bovine tissues as starting material for manufacture and in the process of manufacturing is widespread in biological products.

The products in Section 2.2.1 - those containing bovine brain or lymphatic tissue and 2.2.2 other bovine tissue for injection, have been analysed in an attempt to assess the country of origin of the tissue.

A number of homeopathic products produced by contain bovine tissue, including brain. The source of these tissues is unknown and the range of products considered elsewhere.

Apart from this, the majority of products considered are of proven efficacy and have a major role to play in medical practice.

The use of bovine material of UK or Irish origin is declared for a minority of products only, and many manufacturers are changing to material sourced from New Zealand.

Clearly the production procedures vary and the amount of manipulation given to bovine material in manufacturing differs.

Given the current state of scientific knowledge, it may be felt that control of the starting product is the only reasonable basis for proceeding, at present.

2. Products including bovine brain and lymphatic tissue

Apart from the homeopathic products, no bovine brain is used as an active ingredient.

2.1 Use of Bovine Brain in process

2.1.1 uses a Rosenow medium containing bovine brain in process for their tetanus vaccine. This is marketed as and also as a component of and Dip/Tet/Acellular pertussis - the latter being a CTC.

The brain was a single piece from a French cow sourced in 1982 and used for the initial preparation of working seed lots.

Comment

There is unlikely to be any risk to this product.

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2.1.2 Allergy Products

uses culture media obtained from in process for a wide range of Diagnostic allergies. Calf Brain and Ox heart is incorporated into these media, sourced from UK cattle.

This relates to and diagnostic ranges, and

Comment

These products do not comply with the guidelines.

2.1.3 England Ltd) contains bovine heart and brain sourced from USA.

This is an oral product which declares a number of bacteria as active ingredients and is said to use bovine brain and heart in process, sourced from the USA. (It also uses UK derived equine blood.)

This product holds a PLR, and is indicated for the prevention and treatment of bronchial catarrh, sinus and antrum infections and bacterial infections following virus colds. There are no efficacy data.

2.2 Other Hormones

Growth hormone

and use bovine spleen in process.

Both source from Germany.

2.3 Heparin

Most heparins are declared on data sheets as being of porcine origin. Most companies have returned forms indicating that bovine and ovine material is processed together with porcine and most products are blended.

Companies	Source Country
	Cattle from Scandinavia. Hog from Scandinavia, UK and Ireland. Sheep from UK.
	Cattle and hog from "predominantly Austria".
	Cattle and sheep, Italy, Switzerland, New Zealand.

Comment

UK source material declared only for sheep gut, but UK bovine material cannot be excluded, from the product.

3. Products for injection using bovine tissue

This category includes tissue derived products, other than from brain or lymphoid tissue and excludes bovine blood.

3.1 Bovine Pancreas

3.1.1 Insulin

The following companies hold licences for bovine insulin.

	Source Country
	Denmark
	USA
	USA
	Denmark, Sweden, USA, Italy, Canada, Portugal, Netherlands

In 1988 a sample consignment from UK was used. UK source material is no longer used.

Comment

There are no bovine insulins manufactured from UK sourced material.

Bovine insulin is not widely prescribed, but has a niche in the market for diabetics unable to tolerate other products.

3.1.2 Glucagon

- bovine pancreas from USA.
- as for insulin - Scandinavia, USA, Italy, Canada, Portugal and Netherlands.

3.1.3 Miscellaneous products containing Bovine Pancreas

3.1.3.1 Zonulysin (Chymotrypsin) -		- sourced from Canada.
3.1.3.2 Streptokinase		- culture medium, containing bovine muscle and pancreas are used in process - all sourced from Germany.
3.1.3.3	- Fibrinogen + Desoxyribonuclease	- bovine pancreas sourced from Canada and S Africa.

3.2 Vaccines using Bovine Products in process

3.2.1	DTP vaccine (CTC) (acellular pertussis)	- Beefheart from USA
3.2.2	- tick-born encephalitis vaccine (named patient use, unlicensed)	- USA source
3.2.3	- Meningitis Vaccine	- Muller Hinton medium containing beef - source not known
	Tuberculin -	- Beef heart and peptone
	Typhoid -	- source not known
3.2.4 PHLS	- Anthrax Vaccine	- Peptone, casein and meat of bovine origin - source "probably N.America"
	Adult diphtheria vaccine	- bovine muscle - source Swizterland

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3.2.5	-	Tetanus vaccine	- bovine cardiac muscle
		Diphtheria vaccine	- previously sourced from UK and Ireland now New Zealand
		Dip/Tet	
		Schick Test	

3.3 Allergens

The following products contain bovine material.

3.3.1	-	meat and hair from UK source	
3.3.2		bovine pelt	- USA and Scandinavia

There are numerous other animal materials in all the marketed allergen products, in particular the testing kits.

3.4 Other Bovine Tissues

3.4.1 for bovine lung

3.4.1.1	-	- Denmark and W.Germany
3.4.1.2	-	- France and W.Germany
3.4.1.3	-	- W.Germany

3.4.2	-	Interleukin-2 (CTX)	Casein and Tryptone from USA and New Zeland
3.4.3 PHLS	-	Erwinase (Asparaginase)	- Robinson's cooked meat medium from UK source intending to change to a soya based medium
3.4.4 Consolidated Chemicals	-		- injectable gelatin from UK source
3.4.5	-		- Gelatin from USA source

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4. Bovine Blood

This section covers the use of foetal calf serum and bovine serum albumin in process. This is a common practice for a wide variety of vaccines and rDNA products.

Some of the UK sourced material comes from herds of cattle kept specially for the purpose. Cows are bled serially and not at death, thus there is no problem from brain penetrative stunning. It is not clear which products use material derived from these sources and the information is derived from telephone conversations with the farmer responsible for the herd. These herds have not been fed on ruminant derived protein since they were acquired, but cattle are not bred on the farm.

4.1 In process use of FCS and BSA

19 companies have declared the use of foetal calf serum (FCS) or bovine serum albumin (BSA) during manufacture of their products.

4.2 Serum sourced from the UK is used in the following products:

(tissue plasminogen activator (TPA))

-

Erythropoeitin)

-

Measles Vaccine and MMR

-

rDNA human growth hormone)

- - (now changed to New Zealand source)

Flu vaccine, Mumps, measles and rubella and MMR vaccines

-

(rDNA interferon)

- (due to change to New Zealand source in 1992)

- CTX not licensed

4.3 The following companies did not know the source of some or all of the serum they used

-

(Factor VIII)

-

(Rabies Vaccine)

- Measles, Rubella, MMR and rabies vaccines.

The other companies all sourced their FCS and BSA from non UK sources. No sera from Ireland were declared.

RECOMMENDATIONS

1. That no licensing action is required at present in regard to products produced from bovine material other than brain, and sourced from outside the UK and Ireland.

2. No licensing action at present regarding use of prepared bovine brain in nutrient media.

3. The CRM should review the PLR for in view of the bovine brain used in manufacture.

4. The Joint CSM, VPC guidelines should apply to all UK and Eire sourced bovine material. Companies which at present cannot comply should be encouraged to do so as soon as possible. The time-scale should be agreed with the Licensing Authority for each individual product.

5. No licensing action is required at present in regard to products containing material from animals other than cattle.

6. The Licensing Authority should continue to review scientific progress in the field of BSE, so as to be in a position to take licensing action in the future should this be necessary.