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COMMERCIAL IN CONFIDENCE

NOT FOR PUBLICATION

COMMITTEE ON SAFETY OF MEDICINES

WORKING PARTY ON BOVINE SPONGIFORM ENCEPHALOPATHY

PAPER

SURGICAL CATGUT

UK sourced product, derived from bovine small intestine. Large scale production and extensive clinical use.

Advice is sought on Company proposals for action.

154

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CATEGORY 3: DENTAL AND SURGICAL MATERIALS

SURGICAL CATGUT SUTURES -

1. Introduction

Surgical Catgut represents the most immediate problem arising from the review of tissue implants, wound dressings, dental and surgical products containing material of bovine origin. The reasons for concern are:

i. UK origin of the source material

ii. nature of the source material (serosal layer of bovine small intestine) and proximity to lymphoid tissue

iii. large scale of production and use of product.

The aim of this paper is to outline relevant aspects of manufacture and clinical use of surgical Catgut, and to present the proposals for action put forward by the Company in response to the Letter and Questionnaire from the Department of Health 'Bovine Spongiform Encephalopathy: Guidance on good manufacturing practice and request for information', March 1989.

2. Licensing Background

Surgical sutures which are capable of absorption by the body are licensed under the Surgical Materials Order 1971 (SI No 1267). Surgical Catgut received a product licence of right in 1973, and a reviewed product licence was granted in April 1984. An application for renewal was submitted in April 1989, and has not yet been determined pending the outcome of consideration by the Working Party on BSE. SI 1267, MLA 231 and Data Sheet are at Annex 1.

3. Surgical Catgut- BSE Questionnaire

Of the 9 product licences for surgical catgut, Limited, is the only UK sourced product - see accompanying review of replies to BSE questionnaire for Category 3 surgical products.

Thus the product is in a unique position compared with other marketed products. The completed questionnaire received from is at Annex 2.

219

4. Assessment of Response

Following discussions between the Company and members of the Secretariat, Limited has submitted a detailed position paper on the issues concerning BSE and surgical catgut (Annex 3). This will be considered in detail since it sets out all aspects of the problem, in the context of the large scale of manufacture of the product and the equally large scale of clinical usage.

4.1 Scale of Production and use of Surgical Catgut

18.5 million metres of catgut are produced annually by of which 3.5 million metres (4.7 million product units) are used annually in UK. The balance is exported world-wide.

90% of catgut is manufactured from bovine serosal tissue, the balance being ovine sub-mucosal material. The requirement for raw material is 25 million metres per annum, originating from 550,000 cattle (13% of the UK cattle kill from 18 abattoirs distributed throughout the UK). One animal yields about 45 metres of intestine and the catgut manufacturing plant requires the input from 2,500 animals per day.

4.2 Source Animal

4.2.1 Alternative Species

The utilisation of intestinal raw material from other species, for example porcine or caprine, on the scale required by is considered by the Company to be impracticable.

4.2.2 Country of Origin

The Company considers that the only safe material sources which could supply the quantities required are in Australia, and states that plans to change to Australian raw material are now well advanced. This would entail procuring the equivalent of 10% of the annual cattle kill in Australia and 24% of the New Zealand kill, in a competitive raw material market. The current projected date for commencing production from Australasian source material is 1991.

4.2.3 UK Cattle Source

The current raw material used cannot comply with the requirement that 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.

220

153

proposes to operate a limited selection procedure, confining raw material to 'clean beef cattle' having an average age of 18 months to 2 years. By January 1990, 18 month old cattle should not have been exposed to rations containing animal protein, since the Bovine Spongiform Encephalopathy Order 1988 prohibiting this came in to force on 18 July 1988.

The abattoirs utilised by for source material are all EEC licensed. The Company has prepared a survey of suspected and confirmed BSE cases in the 6 months to December 1988, and from January-June 1989 (see Appendix 2 of Company paper).

4.3 Collection Techniques

Penetrative brain stunning is the slaughtering method used in all abattoirs. The scale of production would render impracticable sterilisation of the stunning bolt.

With regard to the sterilisation of equipment the Company states its concern that no validated method for sterilisation of BSE is available.

4.4 Tissue Source

The Company acknowledges that it would be impossible to exclude lymphoid tissue from the raw material source. Although the serosal layer is anatomically distinct from the submucosal Peyer's patches, the strong crushing forces used to split the gut wall along the tissue planes and enable separation of the layers would rupture lymphatics and inspissate lymphoid tissue between muscle fibres.

Knowledge of the pathway of infection with scrapie increases concern about contamination of the raw material with gut lymphoid tissue.

4.5 Catgut Manufacturing Process

A flow chart is provided at Appendix 3 of Company paper. The catgut manufacturing process is basically a cleaning process involving a combination of physical and chemical operations. The Company contends that although no one step is known to be capable of inactivating BSE, there may be a cumulative effect against the BSE agent. The Company draws attention to

i. Proteolytic enzyme treatments (enzyme of bacterial origin).

ii. Alkaline cleaning solution (pH 9.5-11).

iii. Tanning with chromium salts and formaldehyde solutions in acidic conditions (pH 3-4).

iv. Packaging of catgut in alcoholic conditioning fluid (pH 10.9).

v. Terminal sterilisation by a minimum of 25KGys.

The Company recognises that using the scrapie comparison, terminal sterilisation with the present minimum 25KGy is likely to be ineffective against BSE. However, autoclaving would cause collagen denaturation and irreparably damage the catgut suture. The Company has proposed reintroducing a heat sitting process which involves heating the product in gradually increasing temperatures over a 10½ hour period culminating in 149°C for one hour (dry heat). The Company considers that reintroduction of this process may add a further small safety factor.

4.6 Clinical Usage

An alternative to the use of catgut, in the form of synthetic absorbable sutures, has been available since 1972, and conversion of the surgical profession to the use of synthetic materials would circumvent the BSE problem.

The Company suggests that a short-term step could be to advise the surgical profession that catgut should not be used in certain specialties, namely neurosurgery and paediatrics. Catgut is only rarely used in neurosurgery, but is in extensive use in paediatrics, in an estimated 16% of operations in children (150,000 cases per annum).

5. Proposals

The Company proposals are divided in to short-term and long-term objectives.

5.1	Short Term	Completed By
a.	Source material - Feasibility studies - operation of abattoir selection procedures - change over to Australasian raw material	 End Aug 1989 End Oct 1989
b.	Manufacture - reintroduction of heat setting	End Dec 1989
c.	Clinical - contraindicate in neurosurgery and paediatric surgery.	?
5.2	Long Term	
a.	Commence production from Australasian sourced raw material	? 1991
b.	Conversion of surgical profession to use of synthetic absorbable sutures rather than catgut.	? date

152

6. Medical Comment and Recommendation

6.1 The Company position paper summarises the relevant issues, and the proposals for action are clearly defined with sensible time estimates for implementation.

6.2 The Working Party may wish to endorse the change over to Australasian sourced raw material as the preferred option in the mid to long term.

6.3 The opinion of the Working Party is sought on the reassurance offered by the short term safety measures proposed.

i. Use of 'clean beef cattle' ie 18 months to 2 years.

ii. Procedures specified by Company in current manufacturing process, as in para 4.5 (enzyme, alkali, tanning, alcohol packing, terminal sterilisation 25KGys).

iii. Reintroduction of heat-setting step (149°C for 1 hour)

iv. Contraindications in neurosurgery and paediatric surgery.

6.4 In the light of 6.3 above, the advice of the Working Party is sought on the renewal of the surgical Catgut product licence.

J M RAINE