6. Ensuring medicinal products complied with the guidelines

Introduction

6.1 Officials in DH and MAFF now had the task of dealing with the concerns already identified, and securing replies to all the questionnaires in order to establish whether other products needed urgent action. The advice of expert committees had to be obtained on questionable products, compliance with the guidelines had to be achieved, and decisions taken on potentially contaminated stocks. We look in this chapter at the way these tasks were carried out and whether the response was adequate.

6.2 We also examine the interaction between decisions to exclude Specified Bovine Offal (SBO) from the human food chain and about the application of the guidelines to similar products for medicinal use. The operation of the different regulatory provisions led to differing outcomes.

The agreed policy framework for action in March 1989

6.3 As at March 1989, licensing officials now had the following policy framework within which to work where bovine and ovine ingredients had been used:

i. For oral and topical products the guidelines did not apply. These would continue to be licensed in the usual way.

ii. For products to be injected, or applied to the eye or open wounds:

- Informal contacts and negotiations with companies already in touch about applying the guidelines to identified risk products should continue.

- The guidelines should operate on all new applications for licences, and on products with Licences of Right when they were reviewed by the Committee on the Review of Medicines (CRM) and the Veterinary Products Committee (VPC).

- As information was collected from the questionnaires, existing licensed products (whatever the class of licence) that appeared to hold a risk would be considered on a case-by-case basis.

- No decision had been taken about existing stocks of risk products or how much latitude should be given if firms holding licences argued that finding other source material was difficult.

6.4 To assist decision-taking on human products, it had been agreed that the new BSE Working Group would advise all the relevant section 4 committees on risk. In the case of veterinary medicines that role would continue to rest with the VPC.
**The period covered in this chapter**

**6.5** This chapter spans the seven years 1989–96, a period when two major changes affected the way matters were handled.

**6.6** The first was the reorganisation of the administrative arrangements within the UK for licensing veterinary medicines and human medicines. Preparatory changes were made in 1989, and formal Executive Agencies set up in 1990 and 1991. The Medical Devices Agency followed in 1994. This reorganisation did not affect the basic Medicines Act licensing system and officials’ use of section 4 committees as advisers. It did, however, affect the way the officials were organised, their accounting lines and the performance standards they were expected to meet.

**6.7** The second major change was increasing EU involvement. In 1990 the EC Committee on Proprietary Medicinal Products decided to set up a working party to monitor BSE in medicinal products and this was given impetus as the first cases of BSE were detected in France and Switzerland. Not only were ingredients and products internationally traded, but, as explained in Chapter 2, EC Directives meant that a product licensed in one country was deemed to meet the licensing requirements in certain others. The EU licensing arrangements were carried a stage further in 1995, with the introduction of a single ‘EU licence’ for some products.

**6.8** European guidelines on human medicines came into effect in May 1992 and closely similar guidelines on veterinary products a year later. In addition the World Health Organisation (WHO) offered a formal view in November 1991 that the careful sourcing of material was the best way of securing safety from the remote risk in medicinal products. While the guidelines and the WHO opinion provided a working framework, they did not remove all difficulties from the international scene, in particular in respect of the use of gelatine and tallow. This international dimension dominates the latter part of the chronology in this chapter.

**Chronicling the events**

**6.9** In chronicling events we had great difficulty in pinning down the actual dates when the use of UK-sourced bovine material in manufacture ceased and when stocks manufactured using UK-sourced bovine material ceased to be used. In relation to human medicines Dr Jefferys told us:

> One reason for the lack of documentation may be that in 1993/4 it appeared that Medicines Division’s involvement in BSE had finished . . . In the circumstances, files may well have been weeded and documentation lost as a result.496

**6.10** Dr K Jones, Chief Executive of the Medicines Control Agency (MCA), also told us:

> I am also handicapped by the loss of my BSE files . . . I have no idea who removed them, why or when . . . I am very concerned that my copies are not available . . .497

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496 S419B Jefferys para. 20
497 S447 K Jones para. 17
6.11 This lack of precise information applied to both human and veterinary products, though there was a rather clearer information trail on medical devices. It was neither appropriate nor feasible for the Inquiry to attempt to trace data on individual products, but we wanted to know how the process of coping with identified risk material was managed and monitored. We found that neither MAFF nor the MCA had the data we needed to perform this exercise.

6.12 We did not see any comprehensive submissions to Ministers about the exercise of following up the guidelines and questionnaire, either seeking decisions or giving details of progress. It appears that no reports of this sort were drawn up.

6.13 An audit of compliance with the European Guidelines by manufacturers of human medicines carried out by the MCA in April 1996 focused on the current situation and dealt only sketchily with the history of events. It lacked the details we sought and appeared in some respects inconsistent with the material we had already studied. The parallel audit of veterinary medicines was also unable to provide a complete picture.

6.14 We therefore turned to the individual reports presented by officials to the relevant advisory committees as the only readily available source of contemporary information and apparent form of accountability. These briefed the committees about progress in their allotted field, and sought or suggested recommendations on individual products where officials considered there were special problems. These reports and the associated brief minutes of the committees provided only parts of the story we needed. We were, however, helped by records of meetings by individual officials, in particular those held by Procurement Directorate (PD) on medical devices and other items, and by the observations and papers offered by various witnesses.

6.15 Thus, despite the gaps in the material as officially recorded and available today, we were able to trace events and actions sufficiently to enable us to form a number of conclusions about the adequacy of the response. These are set out at the end of this chapter.

**Structure of the chapter**

6.16 As in earlier chapters, we set out the main features of the chronology of events, then discuss the adequacy of the response. That response was influenced by much that had already happened and the discussion sets it in that context.

6.17 The chapter covers a long span of years, during which significant changes in responsibilities occurred. To assist understanding of how events were handled, we start with a brief résumé of who was responsible for following up the guidelines on human medicines, medical devices and veterinary products and the changes that took place.

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498 DH01 tab 12 Annex D
499 DM01 tab 14 p. 8
Responsibility for managing the process

Human medicines: Medicines Division, MCA

6.18 Officials in Medicines Division were responsible for the follow-up to the questionnaire and guidelines. Administrators working under Mr Hagger handled the collation of replies and chasing up non-responders. They were also responsible for logging material into the database. Those on the professional side provided papers and assessments to the expert committees considering BSE. These people included Dr Jefferys, Dr Adams, Dr Rotblat, Dr Raine, Dr Purves, Mr Sloggem, Dr Boyd, and Dr Winship.

6.19 In April 1989 Medicines Division was renamed the Medicines Control Agency (MCA) and Dr Keith Jones took up the new position of Director. It acquired full agency status in July 1991.

6.20 Later developments were at a European level and European guidelines on human medicines were issued in 1992. Dr Purves, Mr Sloggem and Dr Jefferys of the MCA were involved in this process as well as Dr Schild and Dr Minor of the National Institute of Biological Standards and Control (NIBSC).

Medical devices: PD/STD, MDD

6.21 The Supplies Technology Division of the NHS Procurement Directorate (PD/STD) was involved in the follow-up to the guidelines and questionnaire on two fronts. First, it was responsible for following up the guidelines and questionnaire sent to the medical device industry regarding unlicensed products. Secondly, it had to respond to the CSM/VPC questionnaire, as it held certain medicinal product licences on behalf of the Secretary of State.

6.22 Restructuring meant that the STD was renamed the Medical Devices Directorate (MDD) from August 1991 and then became the Medical Devices Agency (MDA) in September 1994. Miss Duncan, head of the implants and sterilisation areas of STD, and Mr Burton, a Principal Pharmaceutical Officer who attended the BSE Working Group meetings, had the central roles in relation to medical devices follow-up.

The BSE Working Group

6.23 As recommended by the Human and Veterinary Medicines Briefing Group (HVMBG) in February and agreed by the CSM on 23 February 1989, a new working group was set up to advise on BSE, the BSE Working Group (BSEWG). It was a group of expert advisers who reported through the Committee on Safety of Medicines (CSM), the Committee on Dental and Surgical Materials (CDSM) and the Committee on the Review of Medicines (CRM). Its terms of reference were:

To advise the Section 4 Committees on the implications of BSE to human medicinal products.

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500 DH01 tab 6 p.1, S447 K Jones para. 6
501 YB89/2.22/11.6

135
6.24 The BSEWG considered the follow-up to the questionnaire and guidelines on human medicines, although it also received updates on veterinary medicines. The Working Group was important in overseeing compliance with the guidelines and we look at its meetings in some detail in this chapter.

6.25 The Working Group met altogether five times between September 1989 and July 1992. Professor Collee, chairman of the Biologicals Sub-Committee (BSC), was its chairman. Through its high powered membership, which included Professor Asscher, chairman of the CSM, and also the chairmen of other section 4 committees and of the Spongiform Encephalopathy Advisory Committee (SEAC), it had an immediate channel of communication with each of those committees. Other outside experts were from NIBSC, as well as Dr Taylor of the Neuropathogenesis Unit (NPU) and Dr Kimberlin. Medicines Division fielded medical and pharmaceutical staff and Dr Aileen Lee, head of Veterinary Medicines Directorate’s Biological and Recombinant Products team, represented MAFF. Annex 1 contains a table of those attending each of the five BSEWG meetings and their positions.

Veterinary medicines: the VMD and the VPC

6.26 MAFF’s follow-up to the questionnaire and guidelines on veterinary medicines fell to the Veterinary Medicines Directorate (VMD) with assistance from the VPC as expert advisors. The VPC received two reports on follow-up to the questionnaire, in September 1989 and December 1990. These two reports were also seen by the BSEWG. Administrators under Mr Alan Taylor (Head of Administration, Biological and Recombinant Products) processed the responses to the questionnaire, with technical questions being referred to Mr Alastair Gray on the professional side. From late August 1989, Dr Aileen Lee had the central role in VMD for advising on the follow-up to the questionnaire.

6.27 The VMD had been newly created in April 1989 to bring together existing divisions within a single unit, with Dr Rutter as its Director. In April 1990 the VMD became an Executive Agency of MAFF.

March 1989–March 1996: a chronological account

1989

Preparation for processing the veterinary medicines responses

6.28 Shortly before the questionnaires were sent out, Mr Alastair Gray of MAFF’s Medicines Unit circulated a minute stating:


Ensuring medicinal products complied with the guidelines

... it is important to plan now how to process the information that Licence Holders send in. No doubt there can be an initial handsorting, to determine the numbers of positive cases, but computerising the data will be essential for longterm management of the BSE problem.\textsuperscript{505}

6.29 The VMD described to us the manner in which the responses were actually processed:

the first analysis of the returns was carried out by administrative staff who extracted the information contained in the completed questionnaires. A manual record of the returns was made (e.g. noting when a company returned a form and which products were covered). For each company, note was made of the number of Yes’s and No’s to the question on whether or not the product contained substances of animal origin. Scientific staff then carried out further analysis of the questionnaires and the need for follow up action was done on a case by case basis. The totals for the number of ‘positive’ responses were derived manually.\textsuperscript{506}

Meeting of the Joint Committee on Vaccination and Immunisation (JCVI)

6.30 Professor Collee attended a meeting of the JCVI on 21 April 1989. He reported on the HVMBG meeting of 22 February 1989, which he had chaired. With regard to vaccines he informed the JCVI that the risk had been considered by the HVMBG to be remote and speculative, and very much outweighed by the benefits.\textsuperscript{507}

6.31 The JCVI took their lead from this. Professor Campbell, Chairman of the JCVI, told us that they relied on the advice of the Working Group:

In the light of the Working Group’s assessment that the risk to human health from vaccines was remote, BSE had no significant effect on the JCVI’s consideration of immunisation and the immunisation programme.\textsuperscript{508}

Initial consideration of responses to the medical devices questionnaire

6.32 PD met on 25 April 1989 to consider responses so far to the medical devices questionnaire.\textsuperscript{509} Just over 50 per cent of the 330 manufacturers contacted had replied; 28 companies used animal material and 16 of these used bovine-derived material. There was concern at the lack of response by a number of companies, many of whom might use animal materials. It was decided that all English companies would be chased up by phone, while foreign companies would be sent reminder letters.

6.33 The validity of a number of replies was questioned. To check this, a letter was to be sent to a random selection who had replied in the affirmative, requesting
further information on why they stated that they were conforming with the guidelines.\footnote{510}

\textbf{6.34} The minutes also record:

> A meeting with MCA on this subject has not been forthcoming despite attempts from PD to arrange one. Mr Hagger had agreed that a PD representative (Mr Burton) should join the sub-committee in MCA which will be discussing responses to the questionnaire issued by the Agency.\footnote{511}

**Progress in MCA**

\textbf{6.35} Many licence holders had not replied to the DH questionnaire by the deadline of 1 May 1989, and officials of the newly formed MCA had to chase replies. Because of these delays the first meeting of BSEWG, originally fixed for 5 July 1989, was postponed.\footnote{512} Dr Rotblat told us one reason for the delay was that many UK licence holders did not manufacture these products within the UK, and it therefore took them some time to gather the necessary information.\footnote{513} From the telephone calls she received in the few weeks after the guidelines were sent out, it became clear that many manufacturers considered the easiest way of complying with the guidelines was to source from outside the UK, preferably from New Zealand.\footnote{514}

\textbf{6.36} A minute from Mr Burton of PD/STD dated 2 June 1989 warned his colleagues that the MCA were unlikely to consider BSE formally until September.\footnote{515} He explained that this was in part because two meetings of the BSC were to be cancelled, leaving September as the next date when the relevant experts, who would form the BSEWG, would come together. He continued:

> 3. I also understand that they have difficulty in allocating resources to reviewing the responses they have received.

> 4. We may need to re-define our approach to the problem of BSE in the light of the above delay.

\textbf{6.37} Mr Hagger sent a minute to the CMO, Sir Donald Acheson, on 5 June 1989 to report progress. He said that most licence holders had replied and that preparations for a full professional analysis were nearing completion. The exercise had produced a lot of information, which would take time to study before papers could be prepared for the meeting in September. Meanwhile nothing had emerged that appeared to warrant immediate special action. Mr Hagger noted that bovine insulin had previously been mentioned as an area in which precautionary measures might usefully be taken and this was being borne in mind. He added that it might be reassuring to know that such insulin was used in the UK only for a very small group of mainly elderly patients for whom it was difficult to switch to either porcine or genetically engineered insulin. Nevertheless they were on the look out for any such

\begin{footnotes}
\item[510] YB89/5.12/10.2
\item[511] YB89/5.12/10.2
\item[512] YB89/5.8/6.1
\item[513] S422 Rotblat para. 77
\item[514] S422 Rotblat para. 75
\item[515] YB89/6.02/7.1
\end{footnotes}
products. Mr Hagger copied this minute widely, including to Mr Scollen, his counterpart in MAFF.\textsuperscript{516}

\textbf{VMD discussions with ingredient suppliers about the guidelines}

\textit{6.38} As discussed in Chapter 3, MAFF had been in touch with veterinary medicines manufacturers the previous year about its draft guidelines, and discussions had ensued with some firms about the sourcing of ingredients. Copies of the guidelines and questionnaire had been sent to some ingredient manufacturers, as well as to product licence holders. This was because it was anticipated that licence holders would seek information about the sources of material from their suppliers. One of these supply companies had been having meetings with VMD since the middle of 1988. A minute circulated to others in VMD and the Central Veterinary Laboratory (CVL) by Mr Cameron on 12 May 1989 said:

\begin{quote}
Whilst the VMD’s responsibilities are to product licence holders and for them to encourage improvements in the quality of bought-in materials, it would be of advantage for MAFF to stimulate directly the availability of high quality materials from manufacturers.\textsuperscript{517}
\end{quote}

\textbf{Implications for pharmaceuticals of a ban on Specified Bovine Offal}

\textit{6.39} During early June 1989, MAFF and DH were considering the introduction of a ban on bovine offal from food for human consumption. The planned approach was to remove high-risk tissues at the slaughterhouse and treat them as unfit meat to ensure they did not enter the human food chain. DH was concerned that the announcement of an SBO ban might draw attention to bovine material used in pharmaceuticals. Sir Donald Acheson told us that, with one ‘caveat’, he supported the ban as an additional protection for human health without any apparent balancing disadvantage:

\begin{quote}
My ‘caveat’ related to concern that an announcement of the SBO [ban] in advance of the anticipated reassurance concerning the safety of vaccines from the CSM might lead to a marked and unwarranted decline in the uptake of vaccines in children. I had in mind a marked and extended previous reduction in the acceptance of whooping cough vaccine which had followed incorrect public allegations by a scientist that the administration of the vaccine carried a significant risk of encephalitis. On the one hand I was aware that during the period 1980-1988, due to incomplete vaccination of our population of children, there had been 123 deaths from measles and 50 from whooping cough in England, together with a many times larger burden of illness and some long-term complications. Against this I had to balance a remote risk of a fatal disease. A warning was given to Ministers to this effect but in the event although the announcement was not delayed as I wished, it fortunately did not provoke an anti-vaccine scare.\textsuperscript{518}
\end{quote}

\textsuperscript{516} YB89/6.5/3.1
\textsuperscript{517} YB89/6.12/11.1
\textsuperscript{518} S251 Acheson para. 70
6.40 On 6 and 7 June Mr John MacGregor, the MAFF Minister, held two meetings to discuss the proposed SBO ban. The first was with MAFF officials and Dr Metters in preparation for the second meeting the following day with Sir Richard Southwood. These meetings are discussed in detail in vol. 6: Human Health, 1989–96. Dr Metters attended both meetings on behalf of the CMO who was abroad, and raised the CMO’s concerns about refocusing attention on bovine constituents of pharmaceuticals. His minute to the CMO of 9 June reported on these meetings. He noted:

The possibility that MAFF’s action may refocus attention on bovine constituents of pharmaceuticals cannot be ruled out. While I put this point more than once, it cut little ice with MAFF officials.

6.41 Dr Metters told us that he:

. . . was certainly trying to tell MAFF that if we go for a bovine offal ban, there will be further attention into how this was affecting pharmaceuticals. We had already taken action on pharmaceuticals by that point, but it would cause adverse publicity.

6.42 Following the meeting on 7 June, Dr Metters advised the Secretary of State and others in DH about the further precautionary measures that MAFF were proposing. Mr Hagger received a copy of this submission and passed it to others in MCA.

6.43 At an MCA meeting on 12 June 1989, Dr Jefferys reported that Mr MacGregor proposed to ban the use of bovine offal in human food. With an announcement expected the following day, it was thought that undoubtedly the political profile of BSE would be raised again.

Preliminary review of human medicines responses

6.44 The reason for the MCA meeting on 12 June was to undertake a preliminary review of the replies from licence holders to the human medicines questionnaire. Mr Love chaired the meeting as Mr Hagger was on leave. Also present were Dr Adams, Dr Rotblat, Dr Raine, Dr Purves, Mr Armstrong, and Mr Burton from PD/STD.

6.45 By this time approximately 50–60 per cent of those contacted had replied. At the meeting, products were allocated to seven categories (in descending order of risk) for discussion by the BSEWG when it met in September.

1. Products with bovine brain/lymphoid tissue as ingredients and administered by injection.

2. Products with bovine ingredients (other than brain/lymphoid tissue) and administered by injection.
3. Tissue implants, open wound dressings, surgical materials, dental and ophthalmic products with bovine ingredients.

4. Products with bovine ingredients and administered topically.

5. Products with bovine ingredients and administered orally.

6. Products with other animal/insect/bird ingredients.

7. Products with materials produced from animal material by chemical processes eg. stearic acid, gelatin and lanolin.

6.46 It was also agreed that, in the meantime, on the basis of the information provided by licence holders, Dr Rotblat and Dr Purves were to prepare a paper for the BSEWG on the first two categories, and Dr Adams and Dr Raine on the third. No action was to be taken on the remaining products for the present. By the time of this meeting, officials had already had discussions with one manufacturer of sutures (Ethicon), which, it was reported, was producing a detailed submission on the subject.

6.47 Dr Rotblat told us:

My recollection is that Dr Kimberlin’s views were the major influence behind the way in which we chose to categorise the responses . . . Dr Purves and I were asked to prepare a paper for presentation to the working group.

6.48 Those at the meeting discussed several points for action including:

i. The priority was for the MCA to arrange its response data into an easily manipulable form as quickly as possible;

ii. The MCA was still holding off from detailed consideration of oral products for the time being;

iii. The MCA was attempting to draw up a list of common animal-derived raw materials used in non-injectable products in the hope that these could be submitted to the BSEWG and then dismissed from the enquiries;

iv. Non-licensed injectables made from bovine brain and lymph tissue were discussed. It was agreed that PD/STD would provide details of any such ‘named-patient’ products to Mr Love for consideration by the MCA.

6.49 It was also agreed that the MCA would liaise more directly with MAFF in future. According to the minutes this was prompted because:

MAFF had diverged from MCA at the time the Guidelines were sent out and all matters relating to veterinary medicines were being handled directly by MAFF. Concern was expressed that MAFF could be developing independent policies in the face of pressure from their food sections.
This desire for closer contact between the MCA and MAFF coincided with Dr Rutter, the new director of the VMD, making a similar request to Mr Hagger at the end of June 1989. A minute from Mr Hagger to other MCA officials stated:

1. Dr J M Rutter, the Director of the Veterinary Medicines Directorate, asked to be kept in touch with MCA developments on BSE. He has seen my minute of 5 June to [CMO]'s office summarising progress to date and would like the Veterinary Medicines Directorate (VMD) to be involved in any meetings that we hold as well as being kept in touch with other significant developments.

2. The VMD is in a similar position on the BSE exercise to MCA. They have held exploratory talks with 2 companies.530

**MAFF develops detailed proposals for the intended SBO ban**

6.51 In early June Mr Lawrence of Animal Health Division initiated preparation of a statutory instrument to implement the SBO ban.531 Mr Fry took on the task of preparing instructions for the legal department. He proposed treatment along the lines of that required in the Meat (Sterilisation and Staining) Regulations 1982.532 This would require offal to be sterilised or stained and sent to certain specified destinations.533

6.52 Regulation 17(1)(a) of those regulations permitted condemned meat to be sent unstained, under a movement permit to:

a hospital, medical or veterinary school, laboratory or similar institution for instructional or diagnostic purposes, a rennet manufacturer or a manufacturing chemist for the manufacture by him of pharmaceutical products.

6.53 Mr Fry prepared instructions for MAFF lawyers on the basis that a similar exception would need to be provided in the new SBO legislation.534

6.54 However, on 20 June Mr Fry wrote to Mr Lawrence regarding points for final clarification. He said: ‘I understand that whilst it is acceptable for hospitals, medical and veterinary schools etc to receive these bovine offals we would not want them to go to rennet manufacturers or manufacturing chemists.’535 We infer that he was concerned because products from rennet manufacturers and manufacturing chemists might still be able to enter the human food chain.

**Dr Pickles asks which manufacturers use products covered by the ban**

6.55 We discuss in Volume 6 the consideration given to occupational risks and BSE. As part of that process, Mr Maslin sent a list of cattle products to the Health

530 YB89/6.27/7.1
531 YB89/6.7/8.2
532 L17 tab 15
533 YB 89/6.15/2.1 para. 4
534 YB 89/6.15/2.3 paras 5–6
535 YB89/6.20/2.2
and Safety Executive (HSE). This prompted Dr Pickles to write to him on 3 July 1989:

I was interested to see the list of by-products sent to the HSE. Those of particular concern included:

- small intestines: sutures (I thought the source was ovine but you are checking this)
- spinal cord: pharmaceuticals
- thymus: pharmaceuticals

Are you able to give me more information on which UK manufacturers use these materials? Our proposed ban on bovine offal for human consumption would not affect these uses, I assume.536

6.56 Mr Maslin passed the note down the line in Animal Health Division and a handwritten note on Dr Pickles’s minute from Mr Mark Hawkins, one of his staff, reported back:

1. A few companies make sutures out of intestinal linings, worth around £300 k p.a; probably some sheep used as well, but minimal.

2. Virtually all spinal cord goes for rendering, with just a very small amount going for pharmaceutical use.

3. About 30% of thymus production goes for pharmaceutical use (approx £132 K pa).

Incidentally, some spleen also goes for pharmaceutical uses (approx £170 K pa) . . . Is Hilary serious about her final sentence? I would have thought that a) the staining would make these materials unusable (this is also MLC’s view) and b) if they are unfit for consumption, they are certainly unfit for medication. Has she forgotten iatrogenic CJD?537

Preparations for public consultation about the SBO ban

6.57 On 7 July 1989 Mr Cruickshank sent a submission to the Minister seeking his views on certain exemptions from the proposed SBO ban and agreement to a draft public consultation letter.538 The latter sought comments from interested parties and an annex set out the proposals for the new regulations.539

6.58 The consultation letter explained the proposed regulations. paragraph 8.1 included pharmaceutical manufacturers as a destination to which unstained/unsterilised SBO could be sent.540 It stated:

536 YB89/7/3/4.1
537 YB89/7/03/8.1
538 YB89/7/7.1: formal consultation was necessary under s 118 (6) of the Food Act 1984 (L1 tab 2B)
539 YB89/7/7.1:5–1.14
540 YB89/7.07/1.9
8.1 It would be permissible to move *unstained and unsterilised* specified bovine offal from a slaughterhouse, or other place of slaughter, to a pharmaceutical manufacturer or to a hospital, medical or veterinary school, laboratory or similar institution for instructional or diagnostic purposes. Any such movement would however have to be in accordance with a movement permit issued under the Regulations.

6.59 paragraph 8.1 remained in the final consultation letter that was sent out on 26 July 1989.\(^{541}\) We note that the list of organisations consulted did not include any pharmaceutical manufacturers, or their representatives.

6.60 On 7 July, Dr Pickles wrote to Mr Maslin about the content of the consultation letter and questioned the inconsistency in approach of allowing the use of small intestines for sausage casings.

. . . as it is currently worded it looks as if sausage casings are a risk but you are excluding them from the ban because it would otherwise be inconvenient/expensive. I presume MAFF is content that whatever treatment is given to small intestines to prepare casings means that there is no remaining contamination with lymphoid tissue. Unless you can give me that reassurance, a ‘risk’ must remain. Whilst you know that I am not myself persuaded this risk is one we need take action about, the inconsistency with the other steps you are taking cannot be disguised.\(^{542}\)

6.61 Also on 7 July, Mr Maslin wrote to Mr Cruickshank.\(^{543}\) In relation to pharmaceuticals, he noted:

We are permitting unstained unsterilised offals to go to pharmaceutical manufacturers. One product they make is gelatin. The use of this in pharmaceuticals should of course be covered by the guidance issued by DH but I am not clear whether it also goes from this source into the human food chain through jellies, etc. Can Mr Hutchins advise please urgently. If it does, do we know whether gelatin is a ‘risk’ product?\(^{544}\)

**MCA updates VMD on progress**

6.62 Following Dr Rutter’s request to Mr Hagger to be kept informed (see paragraph 6.50 above), Mr Armstrong in the Information Section of the MCA wrote to Dr Rutter on 19 July 1989 to update him on the MCA’s progress.\(^{545}\) He indicated that 65 per cent of product licence holders had replied, of which a large proportion used no animal products. He said that none of the replies examined so far had given any immediate cause for concern. He also set out the seven categories of risk for assessment purposes that had been agreed at the MCA meeting on 12 June (see paragraph 6.45 above). A handwritten note on the minute from Dr Rutter asked Dr Lee to arrange for a similar update on VMD’s progress to be sent to the MCA.

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\(^{541}\) YB89/7.26/6.5

\(^{542}\) YB89/7.7/4.1

\(^{543}\) YB89/7.2.1–2.2

\(^{544}\) YB89/7.7/2.1

\(^{545}\) YB89/7.19/13.1–13.2
Implications of the SBO ban for medicinal products: consideration by Animal Health Division

6.63 The preparation of the SBO ban prompted consideration by Animal Health Division of a number of issues, some of which were relevant to medicinal products. On 27 July 1989, Mr Maslin circulated a minute to MAFF officials asking, among other things, for views on:

i. The production of sutures from bovine intestine; and

ii. The use of spinal cord, thymus and spleen for pharmaceutical purposes.

6.64 On sutures Mr Bradley replied:

It is anticipated that the standard processing of ovine and bovine intestines to produce catgut for surgical, musical and sporting purposes goldbeaters skin and the like removes the mucosa and muscle layers and with it any lymphoid tissue present. Catgut is essentially formed of the collagenous tissues of the gut wall. However I recommend the process is investigated both in regard to the removal of lymphoid tissue and the chemical and sterilising processes used in manufacture. Alternative sources of suture are available but surgeons are likely to be adamant that for certain procedures natural catgut is essential. Human and Veterinary Surgeons are involved in this.

6.65 As for spinal cord, thymus and spleen, Mr Bradley said:

Unless these tissues are collected from unexposed animals there is a potential risk of agent being present and that risk increases with the age of the infected animal. If such tissues are permitted to be used for pharmaceutical manufacture the industrial processes used must be effective in removing infectivity or reducing it to an acceptable level depending on the use of the final product.

It is important also to recognise risks of cross-contamination between tissues in abattoirs before release.

The VMD and DOH have already provided guidelines for preparation of products licensed under the Medicines Act for human and veterinary use. There needs to be some consistency in approach.

6.66 On 24 August 1989, Mr Kyle, Assistant Chief Veterinary Officer for Communicable Diseases, wrote to Mr Meldrum about the draft regulations and stated ‘I am surprised that Article 11(1)(a) appears to permit the unrestricted use of specified bovine offals for the manufacture of pharmaceutical products. It may be that Medicines Directorate are to cater for this in some other regulation and, if so a cross-reference here would be appropriate’. Mr Kyle passed this letter on to Mr Maslin on 1 September 1989 with the handwritten note on the bottom ‘No one else on the veterinary side seems to have commented, so I had better copy this to you to incorporate in any comments you put forward.’
Veterinary medicines progress report

6.67 On 4 August, Dr Aileen Lee, who was to be the VMD’s representative at the BSEWG, wrote to inform Mr Armstrong of the MCA about the BSE questionnaire returns for veterinary medicines.\(^{549}\) She told him that replies had been received from 186 of the 245 licensees. These companies manufactured 3,239 products, and of these 303 had been found to contain material of bovine, ovine or caprine origin. Dr Lee stated that section 44 letters\(^ {550}\) would be sent to the 59 non-respondents, and follow-up letters would be sent to companies which had submitted returns for only some of their products, or where the information given on a positive return was incomplete. She added that initial analysis of the 303 positive responses would begin soon.

6.68 The VMD told us that the follow-up action

\ldots\text{was taken by VMD staff through correspondence with the licence holders and suppliers of media. Telephone discussions were also held to ascertain that appropriate action was being taken.\ldots}

Assessment of compliance with the CSM/VPC Guidelines was based on written evidence from the company. In addition, informal discussions would have taken place at inspections of manufacturing sites with checks on suppliers’ batch certificates in the manufacturing premises as part of the routine audit of the company’s system of records and quality assurance system. Documentation on the source of bovine serum would be checked at these inspections.\(^ {551}\)

NOAH’s concern about the practicality of the CSM/VPC guidelines

6.69 The joint guidelines gave rise to some concerns among veterinary product manufacturers. On 19 July 1989, Miss Green of NOAH wrote to Mr Whitbread of the MCA:

\text{Many NOAH members are concerned over the relevance and practicality of certain aspects of the guidelines and have been advised by MAFF that comments would be useful and are best addressed to the Department of Health as it was you [DH] that fronted the exercise.}\(^ {552}\)

6.70 She said that it was impossible to produce most types of bovine virus vaccines (and possibly some bacterial vaccines) without the use of cell cultures of bovine origin. Miss Green added that the stipulation in the guidelines that bovine material should come from herds which had never had a case of BSE and had not been fed ruminant protein since 1980 would seriously curtail medicines production, as it was unlikely that such herds existed.
On receipt of Miss Green’s letter, Dr Adams sent a minute to Dr Jefferys.\footnote{YB89/7.26/12.1} He observed that all the difficulties raised by NOAH had already been foreseen by the MCA. A reply was eventually sent to Miss Green on 24 August 1989 saying that the Licensing Authority was continuing its study of animal materials used in medicinal products in the light of the replies to the questionnaire and that NOAH’s comments would be taken into account.\footnote{YB89/8.24/9.1} The comments were put to the BSE Working Group’s first meeting in September 1989 (see below) but the Group concluded no action was warranted.\footnote{YB89/9.06/10.6}

Further consideration of ingredient suppliers

Oxoid, one of the ingredient suppliers with whom VMD had been in touch (see paragraph 6.38 above) wrote to Dr Rutter on 14 August 1989 about their recent steps aimed at assessing the risk of BSE transmission by culture media and culture media raw materials.\footnote{YB89/8.14/9.1} They had proposed formulae for assessing risk and had reworked their production schedules. They were also looking at sourcing from low-risk geographic areas.

A handwritten note to Mr Cameron from Dr Lee commenting on this letter noted:

It will certainly be very helpful to us when assessing BSE risk from media ingredients to have available full details of the preparation of these ingredients. I must say, however, that it would be most helpful if Oxoid would supply the information to the product licence holders for them to provide it to us. The product licence holders are, after all, responsible for the quality of the product and I think they ought to know. In addition, it can be very difficult if we have to tell a company that something is not satisfactory but we cannot tell them why or discuss it with them.\footnote{YB89/8.14/10.1–10.2}

Medical devices: following up non-responses

At its regular BSE review meeting on 21 August 1989, PD/STD was told that, despite letters and telephone calls to the companies that had not responded to the questionnaire, the response rate was still only around 66 per cent.\footnote{YB89/8.21/10.1} Many of them were UK companies. It was decided that a definitive list was needed of the companies in the UK and Europe who had not responded. Those companies were to be sent a second reminder.\footnote{YB89/8.21/10.1}

Of the companies who had returned questionnaires, 46 used animal material of some form; 26 used bovine material, of which 2 sourced their material (pericardium tissue) from the UK.\footnote{DH01 tab 11 p. 5}

To check the accuracy of responses, further information had been requested from 10 companies whose initial responses stated that their products conformed...
with the guidelines. Only five had replied to this further request and two of these had changed their responses. The minutes note that the non-responding companies were to be chased. The meeting also agreed that a discussion document on sterilisation procedures, ‘Inactivating scrapie-like agents’, needed further work and that more information should be sought about abattoir systems.

First meeting of the BSEWG

6.77 The BSEWG met for the first time on 6 September 1989. As will be seen from Annex 1, this was a large meeting with 26 people present. In his opening remarks Professor Collee, the chairman, observed that their task was to advise the section 4 committees on the implications of BSE with special regard to human medicinal products but not veterinary medicines, which were the responsibility of MAFF. The minutes continue:

Since the publication of the Southwood Report, no further evidence had come to light to change the original view that the risk of BSE being transferred to humans is considered to be remote and theoretical. Hence the likelihood of the BSE agent affecting humans via medicinal products . . . is also thought to be remote. Nevertheless the Working Group would need to consider this risk and balance it against the obvious and known advantages to health afforded by the current availability of medicines and vaccines incorporating bovine material. To date available evidence has suggested that cattle are likely to be a dead-end host for the BSE agent, but the Chairman sounded a note of caution and stressed the need for further investigative research into the disease, of which little is really known and quoted from the Southwood Report:

‘From present evidence, it is . . . most unlikely that BSE will have any implications for human health. Nevertheless, if the assessments of this likelihood are incorrect, the implications would be extremely serious.’

Responses to the questionnaire

6.78 Around 75 per cent of holders of human medicinal product licences had responded to the March questionnaire by this time. The importance of achieving a total response was emphasised and licence holders who had not replied were to be followed up before the next Working Group meeting.

Ranking the risks: the paper by Dr Rotblat and Dr Purves

6.79 Dr Rotblat and Dr Purves had prepared a paper summarising the questionnaire responses received so far. As had been agreed on 12 June, the 574 products that
used animal ingredients were divided into the following categories, in decreasing
order of concern: \(^\text{565}\)

- Products with bovine brain/lymphoid tissue as ingredients and administered by injection. \(^\text{111}\)
- Products with bovine ingredients (other than brain/lymphoid tissue) and administered by injection. \(^\text{135}\)
- Tissue implants, open wound dressings, surgical materials, dental and ophthalmic products with bovine ingredients. \(^\text{27}\)
- Products with bovine ingredients and administered topically. \(^\text{5}\)
- Products with bovine ingredients and administered orally. \(^\text{9}\)
- Products with other animal/insect/bird ingredients. \(^\text{131}\)
- Products with materials produced from animal material by chemical processes eg. stearic acid, gelatin and lanolin. \(^\text{156}\)

6.80 The paper identified a number of general and theoretical considerations. It noted that these considerations must take into account a number of other factors including:

- 2.1 the findings of the 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. \(^\text{566}\)

The BSEWG considers the risks

6.81 The Working Group concluded that, on the evidence available, products with bovine ingredients in the last four categories gave no cause for immediate concern (ie, no action was required with regard to these products). \(^\text{567}\) The Working Group made four general recommendations in relation to products falling within the first three categories: \(^\text{568}\)

1. That no licensing action is required at present in regard to products produced from bovine material or using prepared bovine brain in nutrient media and sourced from outside the United Kingdom, the Channel Isles and the Republic of Ireland provided that the country of origin is known to be free of BSE, has competent veterinary advisers and is known to practise good animal husbandry.

2. The Joint CSM/VPC guidelines should apply to all bovine material sourced from UK, Channel Islands and the Republic of Ireland and any other area known to have BSE. Companies which at present cannot comply should be encouraged to do so as soon as possible. The timescale should be agreed with the Licensing Authority for each individual product as appropriate.

3. No licensing action is required at present with respect to products containing material from animals other than cattle.

\(^{565}\) YB89/9.06/11.2–11.3
\(^{566}\) YB89/9.06/11.5
\(^{567}\) YB89/9.06/10.3
\(^{568}\) These recommendations were adopted directly from the Purves and Rotblat paper
5. 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.\textsuperscript{569}

\textbf{6.82} The first two of these recommendations varied the CSM/VPC guidelines by allowing bovine material from foreign BSE-free sources. The CSM/VPC guidelines had specified that certain high-risk tissues should not be used in manufacture, whatever the source (refer to Chapter 5 for a list of the guidelines).

\textbf{Identification of high-risk products}

\textbf{6.83} Dr Rotblat’s and Dr Purves’s paper indicated that of the 574 products identified as using animal ingredients, 17 contained bovine ingredients of UK origin only and 40 contained bovine ingredients of mixed origin, including the UK.\textsuperscript{570} The paper noted that, with two exceptions, the replies to date did not give immediate cause for concern, although 176 products did not conform to the CSM/VPC guidelines.\textsuperscript{571}

\textbf{6.84} The paper contained an analysis of these 176 products.\textsuperscript{572} Most of them contained bovine material sourced from outside the UK and, we assume, were not thought to be of immediate concern for this reason. Others fell into the lower four risk categories identified in paragraph 6.78 above.

\textbf{6.85} The first of the two exceptions that gave cause for concern was a range of homoeopathic medicines (including 53 injectable ones) that contained material obtained from cattle, including 20 that used material derived from brain. More information was needed on the source of the bovine material used, and the BSEWG noted that further follow-up action would be needed, with the possible involvement of the CRM.\textsuperscript{573}

\textbf{6.86} The second exception was surgical catgut, made from bovine intestines, which was discussed at length in a separate paper presented to the BSEWG by Dr Raine, Medical Assessor to the CDSM.\textsuperscript{574} We review this below.\textsuperscript{575}

\textbf{Surgical catgut}

\textbf{6.87} Of 27 positive responses in the third category (tissue implants, etc) surgical catgut was the only product that was found to use material from cattle within the UK.

\textbf{6.88} The reasons for concern over catgut, set out in Dr Raine’s paper, were: the source material’s proximity to lymphoid tissue; and the large scale of production and use of surgical catgut. Discussions had already been taking place with the major UK manufacturer of surgical catgut, Ethicon, since it approached MCA officials in June 1989 (Ethicon had applied for a renewed licence in April 1989).

\textsuperscript{569} YB89/9.6/10.7
\textsuperscript{570} YB89/9.6/10.9
\textsuperscript{571} YB89/9.06/10.10
\textsuperscript{572} See YB89/9.06/11.6–11.11
\textsuperscript{573} YB89/9.13/7.1–7.2, YB89/10.00/5.1–5.2
\textsuperscript{574} YB89/9.06/13.1–13.6
\textsuperscript{575} YB89/9.06/10.10
90% of Ethicon 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.576

6.89 Dr Raine’s paper explained to the Working Group that Ethicon’s plans to change to Australasian raw material were well advanced, but noted that this would entail procuring the equivalent of 10 per cent of the annual cattle kill in Australia and 24 per cent of the New Zealand kill. Ethicon had proposed the following course of action and timetable.577

*Short Term*

<table>
<thead>
<tr>
<th>Activity</th>
<th>Target Date</th>
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<tbody>
<tr>
<td>a. Source material – Feasibility studies</td>
<td></td>
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<tr>
<td>– operation of abattoir selection procedures</td>
<td>End Aug 1989</td>
</tr>
<tr>
<td>– change over to Australasian raw material</td>
<td>End Oct 1989</td>
</tr>
<tr>
<td>b. Manufacture – reintroduction of heat setting</td>
<td>End Dec 1989</td>
</tr>
<tr>
<td>c. Clinical – contraindicate in neurosurgery and paediatric surgery</td>
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*Long Term*

<table>
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<tr>
<th>Activity</th>
<th>Target Date</th>
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<tr>
<td>b. Conversion of surgical profession to use of synthetic absorbable sutures rather than catgut</td>
<td>? date</td>
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6.90 In the meantime, Ethicon had proposed some short-term safety measures, on which the Working Group’s views were sought:

i. use of ‘clean beef cattle’ ie, 18 months to 2 years;

ii. procedures specified by Company in current manufacturing process (enzyme, alkali, tanning, alcohol packing, terminal sterilisation 25K Gy);

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

iv. contraindications in neurosurgery and paediatric surgery.578

6.91 The BSEWG was divided. A minority (three members) considered that bovine-derived catgut should be excluded from neurosurgery until or unless it came from a BSE-free country. This was because:

i. of the experience of the agent of Creutzfeldt Jacob Disease;

ii. of an anxiety that the BSE agent may differ in some subtle ways from the classical scrapie agent;
iii. infectivity in various microbial models could be related to the site of inoculation or implantation.\textsuperscript{579}

6.92 However, a majority of those present concluded that the risks did not justify a ban on its use in neurosurgery because:

iv. catgut sutures have been made for many years from sheep intestine which may have been infected with scrapie with no epidemiological evidence of an association with CJD,

v. catgut is seldom used in neurosurgery because of the risk of inflammatory response associated with its dissolution,

vi. to raise this concern amongst doctors at this time, based upon a purely theoretical risk, might hazard the public perception of the safety of other products of bovine origin.\textsuperscript{580}

6.93 The BSEWG advised that Ethicon’s product licence should be renewed and did not require the company to warn against using catgut in paediatric surgery or neurosurgery. In addition, a general recommendation was made that any UK bovine material used for catgut should come from ‘clean beef cattle’ of 18 months to 2 years of age and be subject to certain sterilisation and heat treatment processes.\textsuperscript{581} However, a changeover to Australasian sourced raw material was the preferred option for Ethicon in the medium to long term. The Working Group specified no timetable for this changeover; Ethicon’s proposal had indicated that this could perhaps be achieved by 1991.\textsuperscript{582}

6.94 Professor Collee later added a Chairman’s note to the minutes:

Members of the Working Group will appreciate that they have an advisory role and that the Section 4 Committees will take account of situations in which opinion may be divided.

Accordingly, it is reasonable to record a minority view that bovine-derived catgut sutures should forthwith be excluded from neurosurgery until or unless the materials are sourced from BSE-free countries. There seems to be an implied, albeit remote, risk if present practice is permitted. This worry may be linked with (1) our experience of the agent of Creutzfeldt Jakob disease, (2) our anxiety that the BSE agent may differ in some subtle ways from the ‘classical’ scrapie agent, and (3) our knowledge that infectivity in various microbial models can be related to the site of inoculation or implantation. If this is logical, it is not unreasonable to avoid even a remote outside chance that cerebral implantation of UK-sourced bovine-derived catgut may be harmful.

Three members of the Working Group have registered this anxiety. They understand that the debated point would draw attention to a hazard that the majority feel is non-existent, but it is difficult to escape the logic and scientific consistency of the minority view.\textsuperscript{583}
6.95 Professor Collee told us:

The question of bovine-derived catgut sutures was also carefully discussed at the meeting. On receiving the draft minutes of this meeting, I amended them and added a Chairman’s note (paragraph 9) to reflect our discussion. In light of the Working Party’s advisory function, I was anxious that the comments on the use of catgut sutures in神经外科 should be recorded. I was personally concerned by this issue. Since the relevant sutures were manufactured from bovine intestine, this bovine intestine might be contaminated with bovine lymphoid tissue. Although at this time it was not proven that lymphoid tissue harboured the BSE agent, lymphoid tissue was regarded, on the basis of the scrapie analogy, as being potentially infective.\(^{584}\)

**Medical devices**

6.96 The Working Group also considered a report from PD/STD regarding unlicensed products containing bovine material. They agreed that there was no particular cause for concern, provided the guidelines were followed. PD/STD intended to follow the lead of the MCA in deciding on future action.\(^{585}\)

**Veterinary medicines**

6.97 The BSEWG had before them a paper prepared by Dr Lee of VMD.\(^{586}\) This summarised the replies received so far to the veterinary medicines questionnaire. About 45 different ingredients of bovine or ovine origin had been identified in products, the most common being bovine serum (86 products). However, different companies had interpreted the questionnaires differently and some apparently complete returns were, in fact, incomplete. In particular, on closer investigation, the stated country of origin of the animal material was often the country where the material was purchased, not necessarily the country the animal had lived in. Dr Lee reported that more work was needed to get as complete a picture as possible, but that in the meantime effort would be concentrated on products that ‘can be identified as having a possible risk of BSE contamination. Follow-up letters with specific questions will be required for the licence holders of these products.’\(^{587}\)

6.98 Handwritten notes on a copy of this report from Dr Lee’s files indicate that some of the products contained bovine ingredients sourced from the UK.\(^{588}\) The handwritten notes continue:

> When we have as full information on these products as possible, we can then judge the degree of risk, in consultation with experts, as required, and in the light of this a course of action for each can be worked out – such as setting a timetable for compliance with the guidelines, as you have suggested, or if necessary, suspension of the licence. VPC will of course need to be consulted & we will of course keep you informed of progress.

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583 YB89/9.06/17.5
584 S423 Collee para. 109
585 YB89/09.06/10.6 para. 9.5
586 YB89/09.06/10.5 para. 9.3
587 YB89/8.30/6.1
588 YB89/8.30/8.1. It is unclear who this note was being sent to.
6.99 The BSEWG noted that 75 per cent of recipients had responded to MAFF’s questionnaire, and that the Working Group would be kept informed of progress with the remaining licence holders who had not responded. The minutes record: ‘considerations relating to veterinary medicines are not the same as those relating to human medicines.’ It is not clear whether this reflected the collective view of the Working Group or was part of the MAFF presentation.

VMD report to the VPC

6.100 Dr Lee’s report on veterinary medicines, although presented to the BSEWG, had been prepared as the first VMD progress report for the VPC meeting on 20 and 21 September. The report had earlier been discussed by the Biologicals Committee at its meeting on 4 September 1989.

CDSM and CSM consider the BSEWG advice

6.101 At the CDSM meeting on 20 September 1989, the Committee received a report of the BSEWG meeting earlier in the month. It also considered the licence renewal application for surgical catgut. The Committee advised that the catgut product should be granted a renewed licence on two conditions:

(i.) when bovine material from the UK, Channel Islands or Eire was used, it should come from ‘clean beef cattle’ (18 months to 2 years of age);

(ii.) current manufacturing procedures (as specified by the manufacturer) should continue to be used.

The Committee remarked that a change to Australasian material was the preferred option in the mid to long term. Professor Berry, Chairman of the CDSM, reported this to the BSEWG when it next met in January. At that time, he commented on the reservations expressed by the minority of the BSEWG in September, and wished to make it clear that the selection of materials other than those established in use by clinical experience exposed patients to potential hazards that might be greater than those posed by catgut.

6.102 When the CSM met on 28 September 1989, it noted Professor Collee’s report of the BSEWG meeting and endorsed the recommendations made by the BSEWG earlier in the month. (See paragraph 6.80 above.)

Further consideration of tissues to be covered by the SBO ban

6.103 Meanwhile MAFF officials were reviewing the scope of the proposed SBO ban in the light of responses to their consultation document received by the deadline of 13 September 1989 (refer to paragraphs 6.56–6.58).
6.104 A meeting called by Mr Meldrum took place on 18 September between DH and MAFF to discuss details of the ban on bovine offal, including possible exceptions to it. Attendees were Mr Bradley, Mr Lowson and Mr Lawrence from MAFF; Dr Metters and Dr Pickles from DH; as well as Sir Richard Southwood, Dr Tyrrell, and Dr Kimberlin. Of relevance to medicines were the potential risks from catgut and from foetal calf serum. During discussion it was indicated that the CSM was looking at the issue of sutures and that DH would decide on action following that advice. Those at the meeting regarded foetal calf serum as low risk provided that care was taken when it was collected.

6.105 After the meeting, Dr Metters contacted Mr Hagger, and asked whether, if bovine offal was to be excluded from human consumption, it was consistent to continue to allow the use of catgut derived from bovine intestines. He also raised the issue of foetal calf serum. He asked for confirmation that these were to be discussed at an MCA meeting that was to be held soon.

6.106 On 25 September Mr Maslin circulated to MAFF officials and to Dr Pickles a summary of the comments on the SBO ban that had been received through the consultation process. Although few of the comments were relevant to medicines, one respondent, the Royal Environmental Health Institute of Scotland, had suggested:

If it is intended that these regulations are to prevent the risk of material infecting the human population then it would be appropriate to remove pharmaceutical manufacturers from this section.

6.107 This was considered at a meeting on 27 September 1989 called by MAFF to reach decisions in the light of responses to the consultation. Nobody from DH attended. However, Dr Lee from VMD attended, as did representatives from Northern Ireland, Scotland and Wales. It was concluded that: ‘[t]he current exemption for pharmaceuticals should be maintained. The Regulations were not the correct vehicle to control these products and we should rely on the Medicines Act. A possible amendment to apply the exemption specifically to those covered by the Medicines Act should be considered.’ The minutes of the meeting also noted that a further provision should be made to allow offals that were used in pharmaceuticals to be stored frozen at abattoirs (or removed unfrozen). The minutes of the meeting were copied to Mr Taylor of VMD and Dr Pickles of DH.

Medical devices

6.108 The BSEWG’s views were discussed at the PD/STD meeting on 21 September 1989 and it was agreed to follow the BSEWG’s lead by taking no steps in relation to bovine material sourced outside the British Isles.

6.109 The meeting was told that a ‘definitive list of companies which had not responded to the PD questionnaire had been produced and a second reminder letter
[had been] sent to all UK and other European companies.\(^{604}\) It was thought important to get replies from the few UK companies that were still to respond by a deadline of 30 October 1989.

6.110 Of the 10 companies sent follow-up letters after indicating compliance with the guidelines, eight had now replied. Four of these companies had changed their response and the others stated that their animal materials were not susceptible to BSE. It was noted that:

No company which claimed to fully comply with the draft guidelines could therefore be identified.\(^{605}\)

6.111 It was decided to consult Miss Duncan about the paper on ‘Inactivation of scrapie-like agents’, ‘as such an action would raise the profile of BSE contamination and may not accord with the action of the MCA.’\(^{606}\)

**Inconsistency between the SBO ban and BSEWG advice**

6.112 Dr Metters continued to question the possible inconsistency between the terms of the SBO ban and advice from the BSEWG (refer to paragraph 6.104). He asked Dr Pickles on 4 October whether MAFF’s proposed 6-month age limit, above which SBOs would be banned for human consumption (see vol. 6: *Human Health, 1989-96*) was inconsistent with the BSEWG’s 18-month-to-2-year limit on bovine material used to manufacture sutures.\(^{607}\) Dr Pickles replied on 9 October, explaining that the 18 month to 2 year limit was interim action to reduce the risk, while Ethicon made arrangements to source from overseas.

[Ethicon] volunteered to reduce the ‘risk’ by using beef not milk cows (sensible, since BSE is less common in the former) and animals under two years (their rationale being that such animals are unlikely to be just about to go down with BSE, which usually appears later but also I suspect recognises the usual life span of beef cattle.) The expert working party accepted this interim compromise, knowing neither being beef cattle nor being under 2 years was any real guarantee, but realising there was no alternative.\(^{608}\)

6.113 On 12 October, Dr Metters responded.\(^{609}\) He asked whether the difference could be defended and justified on scientific grounds. Dr Pickles advised ‘the ready defence is that those decisions were taken on expert advice’.\(^{610}\)

**Human SBO ban: consideration of the implications for medical devices**

6.114 On 3 October 1989, Dr Pickles sent a minute to Miss Duncan of PD to bring her up to date with what was happening with the proposed SBO ban.\(^{611}\) Dr Pickles was aware that several unlicensed devices were made from cattle tissues and said

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604 YB89/9.21/14.1
605 YB89/9.21/14.1
606 YB89/9.21/14.1
607 YB89/10.4/2.1
608 YB89/10.9/2.1 para. 3
609 YB89/10.12/8.1
610 YB89/10.12/8.1
611 YB89/10.3/7.1
that she hoped that the way things were going at the moment, no great supply
problems would be caused. She explained that she had ‘argued not to ban collection
of offal intended for pharmaceutical and related use, since more rigorous control
would be applied later’. However, Dr Pickles thought the MAFF rules might be
relevant only to products licensed under the Medicines Act. She therefore asked
whether Miss Duncan had any comments that needed to be passed on to MAFF
without delay.

6.115 On 6 October 1989 Mr Burton replied to Dr Pickles on Miss Duncan’s
behalf:

3. We are pleased to note that, as a result of your intervention, the removal
of specified bovine offal from the place of slaughter to a pharmaceutical
manufacturer would remain permissible . . .

4. On the medical device front we are only currently aware of two British
manufacturers using UK derived bovine material. Both make heart valves
using pericardium and this tissue is not included in the definition of
‘specified bovine offal’. Consequently the proposed regulations should not
affect these products. However if 8.1 of the proposals612 could be amended
to read ‘. . . pharmaceutical and other medical product manufacturers . . .’ it
would not then act as a barrier to any further developments. Products made
from such offal would still come under the scope of the PD/STD Guidelines.
We would be grateful if you would pass this view on to MAFF.

5. There may be some unlicensed medicinal products, used on a named
patient basis, which would be assisted by proposal 8.1. This causes us some
concern since rigorous licensing controls would be bypassed in these cases.
I have been passing details of any such products to Mr Love as we become
aware of them.

6. We also find it strange that research is not included alongside
‘instructional or diagnostic purposes’ in 8.1 of the proposals.613

6.116 Dr Pickles passed this on to Mr Maslin on 10 October. She said:

. . . I thought you might be interested in the attached minute from the
procurement directorate who have responsibility for devices etc not covered
by the Medicines Act.

Note in particular:

(1) they are keen to retain the right to remove unstained offal to a
pharmaceutical manufacturer

(2) it would help if this could be amended to ‘pharmaceutical and other
medical product manufacturers’

(3) they suggest ‘research’ could be added to ‘instructional or diagnostic
purposes’.614

612 For paragraph 8.1 of the proposals, refer to paragraph 6.57 above
613 YB89/10.06/5.1
614 YB89/10.10/6.1
We asked Dr Pickles, when she gave oral evidence, whether she was able to remember the circumstances in which the exemption for pharmaceuticals was made. She explained that it was because more rigorous controls would be applied later. If a product could only be made from bovine material, but by a sterilisation process that would make the BSE agent completely safe, for example, it would seem inappropriate for the SBO ban to prevent the product from getting the right source material. Dr Pickles added that she was confident there would be no loopholes in the way regulatory controls were applied to medicines. In a later statement to the Inquiry Dr Pickles clarified this evidence. She said that she found it difficult even on reflection exactly how the request for the exemption for pharmaceuticals originated. However, she thought it unlikely that the suggestion originated with her and unlikely that it was in response to a specific request from a company.

MCA: issues arising from the BSEWG meeting

On 10 October 1989, Mr Love, an administrator in MCA working for Mr Hagger, sent a minute to Dr Jefferys about putting the recommendations of the BSEWG into practice. Among the matters raised by Mr Love were the highly relevant questions of setting timescales for the three high-risk categories, stockpiled products and the need for a coordinated Licensing Authority approach with clear allocation of responsibility. We set this important minute out in full:

1. Following the meeting of the CSM at the end of September and its acceptance of the recommendations of the BSE Working Party, it would now seem appropriate for the LA [Licensing Authority] to consider what action is required to take the exercise forward in line with the recommendations.

2. I have set out below some possible points which may or not be completely relevant and are certainly not exhaustive and I would be grateful for your opinion and those of the copy recipients of this minute [Drs Adams, Purves, Raine and Rotblat, Mr Hagger and Mrs Shersby] on the following:

   a. do the guidelines need updating as a result of the Working Party meeting?

   b. what further action, if any, should be taken re notifying industry of the recommendations of the Working Party? (by means of a possible article in MAIL?)

   c. should active encouragement now be given to those companies which do not meet the guidelines and source material from areas where BSE is known, to change within appropriate timescales to BSE free sources? This would be for all applicable products in the first three categories as set out in the Working Party minutes and not merely catgut.

   d. a need to consider further products which may be stock-piled and not meet the guidelines.
ENSURING MEDICINAL PRODUCTS COMPLIED WITH THE GUIDELINES

e. a need to alert the CRM about the Weleda [homoeopathic] products and determine if any special action should be instigated.

3. Some or all of the above points may be unnecessary or are already being taken forward but I believe that the necessity for a coordinated LA role in the BSE exercise should now be considered along with ‘what needs to be done and by whom’ being developed.

6.119 Mr Love also wrote to Mr Burton of PD saying that he had raised these issues with Dr Jefferys and that ‘[a]s soon as the MCA stance on these and other points is finalised I shall let you know’. 618

6.120 On 13 October 1989, Dr Jefferys replied. He stated that he had discussed the matter with Dr Adams, Dr Purves and Mr Hagger and that they agreed that the Working Party needed to meet in January. He did not think that the CSM/VPC guidelines needed updating and thought there was no need to notify the industry further. An in-house procedure would need to be considered for approaching non-complying companies and for establishing an acceptable timetable for them to comply with the guidelines. 619 Dr Jefferys said in a written statement to us that Mr Hagger’s division was responsible for contacting manufacturers who did not respond to the questionnaire. He added that approaching those companies that did not comply with the guidelines and establishing an acceptable timetable for them to do so was the responsibility of the MCA and the Inspectorate rather than the CSM. 620

CRM: considering products of concern

6.121 We noted above that a range of homeopathic products, made by Weleda, was one of two sets of products that gave immediate cause for concern to the BSEWG in September. On 7 November, the CRM considered a paper on these homoeopathic products, prepared by Dr Winship, who had ascertained that the bovine material used was all sourced in Germany. 621 The CRM therefore considered that no further action was required. 622

The Bovine Offal (Prohibition) Regulations 1989 (the SBO ban)


618 YB89/10.16/4.1
619 YB89/10.13/6.1, S Adams para. 85
620 S419 Jefferys paras 123, 126
621 YB89/10.00/5.1
622 YB89/11.07/10.3
624 L10 tab 9, The Bovine Offal (Prohibition) (Scotland) Regulations 1990, No. 112; L8A tab 6, Bovine Offal (Prohibition) Regulations (Northern Ireland) 1990, No. 30
Presentation on veterinary medicines to the Royal Society of Medicine

6.123 Dr Lee of VMD presented a paper entitled ‘BSE: Implications on Production of Veterinary Medicines’ to a meeting of the Royal Society of Medicine on 15 November 1989. Originally the paper was to include a discussion of human medicinal products but the MCA objected to this lest the MCA/CSM or DH stance on BSE be compromised and asked that she restrict her paper to veterinary medicines. The MCA decided not to send a representative to the conference and a briefing minute warning Ministers and officials of possible media interest noted:

The subject is too problematical scientifically and too sensitive politically for officials to speak out at what seems to be a conference with the object of stimulating scientific hypotheses. We have examined the proposed VMD talk, and are satisfied that is should not repercuss on MCA interests.

6.124 The introduction to Dr Lee’s paper to the Royal Society of Medicine gave a reassuring message:

BSE has few implications for production of veterinary medicines. Indeed, there would be no implications at all if the Veterinary Medicines Directorate and manufacturers did not take what is really a belt, braces and pieces of string approach to all aspects of safety and quality of veterinary medicines.

Medical devices

6.125 By 24 November 1989, all the manufacturers of medical devices had responded to the questionnaires sent out by PD/STD in March 1989 (see Chapter 5). Of 76 products that used animal materials, 34 contained products of bovine origin and 13 of those were sourced either from the UK or from Europe. Of those 13, 6 were a minor component (ie, a coating or impregnation of gelatine or collagen), 4 were an aid in the production process (ie, tallow), and only 3 contained bovine material as a major component. Only two of these three products were thought to be of concern; the third was made by a continental manufacturer using bovine pericardium from a closed herd on the continent.

6.126 On 8 December 1989, PD/STD met with these two manufacturers, who were both producers of heart valves. The main purpose of the meeting was to discuss the companies’ current manufacturing procedures, their future plans and their compliance with the BSE guidelines. Their views were also sought as to the practical feasibility of the guidelines with respect to the manufacturing process, and any improvements that could be suggested.

6.127 Mr Burton told us:
I believe the companies were left in no doubt, from our discussion, that their compliance with the guidelines was required, even in the absence of our having any specific statutory power, because we could, if we had felt it appropriate, influence the market for their products due to the fact that the NHS effectively represented a monopoly purchaser.\textsuperscript{632}

\textbf{Update on veterinary medicines}

\textbf{6.128} On 28 December 1989, Dr Lee circulated a further update on replies to the veterinary medicines questionnaire.\textsuperscript{633} Since August four more replies had been received, bringing the total number of companies replying to 190; 302 products had materials of bovine, ovine or caprine origin as ingredients, ie, one less than recorded in August. Dr Lee’s note stated:

Follow-up letters will be sent out soon to those companies who have not yet sent in a return for one or more of their products. Follow-up letters are also being sent out to companies where further information is required due to an inadequate return or to allow better assessment of any possible risk.

The note went on to say that MAFF were aware from the returns, direct contacts and licence variation requests that many manufacturers were making efforts to comply.

\textbf{1990}

\textbf{Second meeting of the BSEWG}

\textbf{6.129} On 10 January 1990, the second BSEWG meeting took place. The key issues for discussion were the responses to the questionnaire, and products not complying with the guidelines, particularly vaccines and surgical catgut.

\textbf{Returns to CSM/VPC questionnaire: human medicines}

\textbf{6.130} By this time, 94 per cent of the licence holders had responded to the questionnaire, those responses had been evaluated and the ‘appropriate action taken’.\textsuperscript{634} It was decided that the MCA should look at the individual licences held by the 6 per cent of companies who had not yet responded. Those companies whose products were likely to be associated with or to use bovine material would be asked for further information, and a report would be made to the next Working Group meeting.

\textbf{Non-complying products (other than catgut)}

\textbf{6.131} A paper produced by Dr Rothlat for the meeting considered products other than catgut, using UK sourced cattle and not meeting the guidelines. The BSEWG reiterated its view that where cattle were UK sourced, companies should be encouraged to comply with the guidelines as soon as possible, the timescale to be

\textsuperscript{632} S605 Burton para. 104
\textsuperscript{633} YB89/12.28/1.1 It is not clear to whom this note was sent
\textsuperscript{634} YB90/1.10/1.4
agreed with the Licensing Authority for each individual product as appropriate.\textsuperscript{535} The majority of the non-complying products in Dr Rotblat’s paper used bovine serum albumin or foetal calf serum from UK sources.\textsuperscript{636} Most were vaccines, which we discuss below. However, the paper revealed that, with one exception, no products sourced from high-risk material (brain and lymphoid material) failed to satisfy the guidelines. We consider the exception, a range of allergen products, below.

\textbf{Vaccines}

\textbf{6.132} In Chapter 5 we discussed the decision taken not to order the immediate replacement of existing stocks of vaccines and the indicative picture of the scale of the problem gleaned from a ring-round of manufacturers. By the time of the BSEWG’s second meeting, Dr Rotblat was able to provide more concrete information about the existing stocks of vaccines made using bovine serum albumin or foetal calf serum from UK herds. She indicated that there were four such vaccines, with stocks as follows.\textsuperscript{637}

i. An MMR (measles, mumps and rubella) vaccine with stocks to December 1990 – not yet licensed;
ii. A measles vaccine with stocks to September 1990 – not used much now;
iii. A Tuberculin PPD with stocks to September 1991 – no other source available;
iv. A line of DTP (diphtheria, tetanus, pertussis) vaccines\textsuperscript{638} with unadsorbed stocks to May 1991 and adsorbed stocks to June 1990 – adsorbed used in preference to unadsorbed (not used much now).

\textbf{6.133} The minutes of the meeting record:

The Working Group discussed the hazard-to-benefit ratio for the vaccines and decided that the benefits accruing from continuance of the vaccine programme outweighed the very remote risk to the population from the use of bovine material in these products.

It was considered after some discussion that negotiations should take place to ensure that sources are changed as soon as possible and to replace existing stocks with new material whenever feasible. Replacement of Wellcome unadsorbed DTP vaccine, by Wellcome adsorbed vaccine should ensure that the former, which is not much used, is replaced earlier than 1991. In the case of the Tuberculin PPD, no other source is available at present, but the company (Evans) should be asked to move over to the new product and replace stocks as soon as this is feasible.\textsuperscript{639}

\textbf{Allergen Products}

\textbf{6.134} The only products sourced from high-risk material were a range of allergens, products for treating allergies. The MCA had received a request for advice from the
ENSURING MEDICINAL PRODUCTS COMPLIED WITH THE GUIDELINES

manufacturer, Beechams, which used UK-sourced bovine material, including calf-brain in media, in the production of certain allergen products. The Working Group decided that alternative sterilisation programmes suggested by Beechams would not be effective, and that effective programmes would destroy the usefulness of the bovine material. The BSEWG considered that it was not reasonable to use calf-brain from the UK if other sources were available and advised that the Licensing Authority should insist upon a changeover to Australasian material, within a reasonable timescale. The MCA were to reply to the company’s request, taking into account the Working Group’s views.

Surgical Catgut

6.135 By January 1990, Ethicon had provided updated information on its progress towards compliance with the guidelines. It had stopped sourcing from UK cattle on 20 November 1989, and the changeover to an Australian source had been moved forward from 1991 to February 1990. The Working Group considered in detail an appropriate strategy for decontaminating Ethicon’s manufacturing facilities before the changeover. It asked for reassurances from Ethicon that existing stocks would be replaced as soon as they had the new stocks available. The Group was ‘impressed’ by the effort being made.

Reviewing the guidelines

6.136 The Working Group considered that the guidelines had served their purpose well and that there was no need to amend them at this stage.

The SBO regulations

6.137 So far as the SBO ban, which was now in force in England and Wales, was concerned, the minutes simply record that a copy of the Regulations was attached. It is not clear to us whether there was any discussion by the BSEWG of whether the introduction of the ban called for any reconsideration of the guidelines.

CSM and CDSM receive reports of the BSEWG meeting

6.138 The CDSM met on 17 January 1990 and noted the draft minutes of the January BSEWG meeting. With regard to surgical catgut, the Committee noted Ethicon’s proposal to change over to Australian bovine intestine from 5 February 1990 and begin the decontamination of the manufacturing plant on 30 January 1990. They wished to place on record their recognition of the speed with which the company had responded to the recommendations of the BSEWG.

6.139 At the CSM meeting on 21 and 22 February 1990 Professor Collee, attending as a member for the second day, reported on the January BSEWG meeting and the Committee noted the minutes of that meeting.
Medical devices

6.140 By 26 January 1990 one of the two companies with which PD/STD had met in December had managed to bring their practices in line with the guidelines by sourcing material from calves under the age of 6 months, or from overseas.646

6.141 The second manufacturer, Bio-Medical Systems, could not comply with the guidelines for the production of its heart valves and was unlikely to be able to do so in the near future.647 PD/STD agreed to organise a further meeting with the company. This took place on 20 February 1990.648 The company was at that stage investigating both the possibility of sourcing from West Germany, and suitable sterilisation procedures. However, on 27 April 1990, at a further meeting, Bio-Medical Systems told PD/STD that sourcing its pericardial material from West Germany would be prohibitive in terms of cost and accordingly the manufacture of the heart valve in question would cease from 30 April. Valves remaining on the shelves would be recalled.649

6.142 In May PD/STD decided to request a check of the Heart Valve Registry to find out whether anybody who had died of BSE/CJD-related diseases had used a heart valve produced by one of the two manufacturers with whom they had been involved.650 Dr Richardson approached Professor Ken Taylor at the Heart Valve Registry and asked him to review causes of death and/or post mortem reports of all registered patients with bovine pericardial valves who had died, to ascertain if there was anything that might suggest encephalopathy. Professor Taylor’s investigation did not find anything that indicated a relationship between encephalopathy and bovine pericardial valves.651

Assurances about bovine insulin

6.143 Following a request on 14 March 1990 from the British Diabetic Association for information on BSE and bovine insulins,652 Dr Jefferys replied on behalf of the CSM. He noted:

The manufacturers of Bovine insulin have responded to our request for information. There are no Bovine insulins sourced from cattle in the UK or Ireland.653

CRM meeting

6.144 The CRM met on 1 May 1990 and noted that the BSEWG had met in January. The Chairman, Professor Lawson, reported that none of the products likely to come before the CRM was involved in potential concerns regarding BSE.654
Spongiform encephalopathy in a cat

6.145 On 10 May 1990 MAFF announced the discovery of a spongiform encephalopathy in a domestic cat. This is discussed further in vol. 6: Human Health, 1989–96.

6.146 Dr Pickles circulated a Question and Answer briefing in relation to the announcement, which included the following:

Q. What about cat gut?

A. This is not made from cats these days. In fact most ‘cat gut’ is synthetic. The Medicines Control Agency, with advice from the Committee on Dental and Surgical Materials, has considered the implications of spongiform encephalopathies for natural ‘cat gut’ and taken any action that was considered necessary.

Q&A briefing: Agriculture Select Committee

6.147 On 20 June 1990, Mr Love circulated to colleagues in the MCA a copy of a Question and Answer briefing on BSE and medicinal products, which had been prepared for the CMO in advance of his giving evidence to the Agriculture Select Committee. In relation to existing stocks, the brief said that the CSM had agreed with the Southwood Working Party’s advice that the risk of BSE being transmitted via medicinal products was remote. It continued:

It was considered essential that existing supplies of medicinal products essential to public health continue to be used whilst companies implemented the guidelines to remove any remote theoretical risk of BSE.

6.148 In relation to the vaccination programme the brief noted:

The immunisation programme for children and adults is vital to individuals and the public health. There are very considerable benefits in the prevention of serious or fatal disease. By any reckoning these outweigh the remote and theoretical risk of BSE.

6.149 The brief noted that guidelines had been issued to manufacturers in March 1989. A further question asked how the pharmaceutical industry had responded to the guidelines:

The guidelines have been well received, and implemented by the industry. Many companies who previously used UK bovine material have voluntarily changed to sourcing overseas, from countries with competent veterinary services and where BSE has not been reported. Many companies have never used bovine material from UK sources in their products.

655 YB90/5.10/2.1
656 YB90/5.10/3.2
657 YB90/06.20/19.1–19.4
658 YB90/06.20/19.2
659 YB90/06.20/19.3
660 YB90/06.20/19.4
Surgical catgut: change to Australasian source

6.150 On 12 June 1990, Ethicon, the manufacturer of surgical catgut sutures, confirmed that by 30 June 1990, 100 per cent of ‘the sterilised surgical catgut products supplied to the United Kingdom market would be manufactured from raw material of Australian and New Zealand origin.’661 This met with time to spare the company’s target as set out in a position paper provided to the MCA in January 1990.662

Third meeting of the BSEWG

6.151 The third meeting of the BSEWG was held on 4 July 1990. The group was given a further update on responses to the questionnaire, and discussed vaccines, foetal calf serum, allergen products, topical medicines, and an update on the epidemiological aspects of BSE.

Returns to CSM/VPC questionnaire

6.152 By this time only four replies were outstanding in relation to human medicines and none of those related to a full product licence; all had approval for clinical trials only. Further information was to be sought from these four and reported to the next meeting.663

6.153 In relation to veterinary medicines, MAFF reported:

. . . most Companies have now changed the source of bovine material and are obtaining it from BSE-free areas for veterinary medicines but there are still stocks held of products that were associated with UK bovine material.664

Update on epidemiological aspects of BSE

6.154 MAFF had provided a paper on epidemiological aspects of BSE. In particular:665

- MAFF’s statistics indicated an increasing incidence since July 1989 that could not be attributed to cattle-to-cattle transmission. The increase had occurred contemporaneously in all regions of Great Britain and there was a greater increase in the number of affected herds than in the within-herd incidence.

- BSE had been confined to the British Isles, apart from cases where cattle were exported. A condition known as ‘Downer Syndrome’ had been identified in the United States. The US authorities planned post-mortem testing for BSE.

- BSE had become a notifiable disease in the EC on 1 April 1990. As long as BSE remained confined to the British Isles, ‘concern about the use of bovine
material in the manufacture of pharmaceuticals is restricted to bovine material originating in the British Isles.\textsuperscript{666}

\textbf{6.155} The BSEWG was reassured by what it was told, but was concerned that:

\ldots where foetal calf serum \ldots or other bovine material is sourced from outside [the] UK, it should come from areas known to be BSE-free and having a good veterinary service and adequate animal husbandry. The availability of bovine material from New Zealand and Australia \ldots is finite and tending to be taken up so that there is no spare supply capacity. Where material comes from a specific source it should be certified as originating in that country and not imported from elsewhere for re-export.\textsuperscript{667}

\textbf{Foetal calf serum}

\textbf{6.156} MAFF reported to the BSEWG that calves under 6 months might be incubating the disease, even though the causative agent or prion was not detectable.\textsuperscript{668} This raised issues concerning the use of foetal calf serum and the possible infectivity of vaccines. Commenting on this Professor Collee told us that the question of infectivity in calves had to be separated from the question of infectivity of foetal calf serum.\textsuperscript{669} Our discussion in Chapter 5 refers to the reasons why foetal calf serum was considered most unlikely to be infected. In Chapter 7 we also review what happened to research proposals to test the infectivity of bovine serum.

\textbf{6.157} Professor Collee told us:

I recall that we considered the risk posed by foetal calf serum and bovine serum albumin in great detail at the time. I believe that I had sought the advice of Dr David Taylor and others in advance of this meeting; I wanted their views on the likelihood of the BSE agent being present in such bovine material. I believe I had also asked about the risk of maternal transmission in cattle and the risk of contamination of the material in the course of its collection. The minutes state that the Working Party regarded the risk from vaccines as very remote. The bovine materials involved were very low risk and, as a result, the risk from vaccines could generally be described as very remote rather than merely remote.\textsuperscript{670}

\textbf{6.158} The Working Group reiterated its earlier view that the risk relating to serum was low. Taken together with the fact that the risk of transmission of BSE was theoretical and the view that the benefit of availability of vaccines outweighed any potential hazard from their use, the use of foetal calf serum was accepted.\textsuperscript{671}

\textbf{Allergen products}

\textbf{6.159} The Working Group returned to the products identified in January as being of concern. Discussion and correspondence with Beecham’s about its range of
products were continuing. Some products used calf-brain and ox-liver in culture media used in the production of allergens, others used animal hides and hair. The BSEWG considered that where bovine material was used it was essential that the licence holder complied with the guidelines, unless the material used was derived from milk or casein. Discussions with the company were to continue and would be reported to the next meeting. 672

Non-complying vaccines

6.160 The BSEWG also reviewed the situation regarding the four non-complying vaccines considered at its second meeting in January, ie, MMR, Tuberculin PPD, Measles and DTP. 673 The Working Group had before it a paper prepared by Dr Rotblat on the current situation with regard to vaccine stocks and the progress being made in manufacturing new batches. 674 The paper included copies of letters from both the manufacturers involved, Evans Medical and Wellcome Biotech, which had been sent to Dr Purves in June.

6.161 The letter from Evans Medical, the manufacturer of the MMR, Tuberculin PPD and Measles vaccines, said: 675

Bovine constituents include serum, peptone and glycerol beef broth. Serum and peptone are used in the manufacture of Measles antigen and Measles Vaccine . . . and also the, as yet unlicenced, Rubella antigen and vaccine and the MMR vaccine. Glycerol beef broth is used in Tuberculin production.

A. SERUM. Undetectable in Finished Product. Aseptic donor serum from New Zealand has been evaluated and is satisfactory. Such serum is now on order . . . and will be used for all future batches.

B. PEPTONE (Ex milk casein, present in Finished Product).

Alternative peptone . . . containing no components of British origin, has been used in preliminary trials with satisfactory results. Results of further trials on freeze-drying following blending with peptone-containing diluent are expected mid July 1990. If satisfactory, we expect to switch to this source of peptone in September 1990.

C. GLYCEROL BEEF BROTH

This is used in Tuberculin Seed Culture and is purchased from local beef supplies (i.e. not certified BSE-free herds). Subject to satisfactory results from current trails we expect to submit a Product Licence Variation to eliminate glycerol beef broth from all future production.
D. **STOCK LEVELS** (at 31/5/90)

<table>
<thead>
<tr>
<th>Product</th>
<th>Quantity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles Antigen</td>
<td>–</td>
<td>approx 3 million doses</td>
</tr>
<tr>
<td>Measles Vaccine (single)</td>
<td>–</td>
<td>Nil</td>
</tr>
<tr>
<td>Measles Vaccine (10-dose)</td>
<td>–</td>
<td>733,536 doses</td>
</tr>
<tr>
<td>Rubella antigen</td>
<td>–</td>
<td>approx 1 million doses</td>
</tr>
<tr>
<td>Rubella vaccine</td>
<td>–</td>
<td>60,000 doses</td>
</tr>
<tr>
<td>MMR vaccine</td>
<td>–</td>
<td>184,029 doses</td>
</tr>
<tr>
<td>Tuberculin</td>
<td>–</td>
<td>300 litres bulk at 100,000 units/ml</td>
</tr>
</tbody>
</table>

6.162 The letter from Wellcome Biotech, the manufacturer of the line of DTP vaccines, said: 676

The sourcing of beef for media preparation was changed to non UK sources in September 1988. Bovine milk is not included in the UK BSE manufacturing guidelines. However, Wellcome has pursued a policy for bovine milk derivatives used in media manufacture to exclude UK sources, with implementation completed during 1989.

Residual vaccine stocks manufactured prior to the changes in media sources are now confined to Diphtheria and Tetanus. Due to the protracted lead times for certain biologicals, component stocks of Diphtheria and Tetanus manufactured prior to the changeover will be incorporated in blends and formulations of Diphtheria, Tetanus and Pertussis combinations until December 1990 to supply the market through to 1992/93, based on average offtake.

6.163 In preparing her paper Dr Rotblat had also obtained from Mr Coleman of PD, via Mr Burton, comments on these letters and information on vaccine suppliers. 677

6.164 The first of the four vaccines discussed by the BSEWG was the unlicensed MMR vaccine. Dr Rotblat had ascertained that other companies had licences for this type of product and were producing sufficient quantities to meet demand. The Working Group decided that the vaccine should be granted a licence only if the components of bovine origin complied with the guidelines. The company had changed to a New Zealand source and future production would comply with the guidelines. However, the Working Group recommended that existing trial batches prepared using UK sourced bovine materials should not be marketed. 678

6.165 The second product was the Tuberculin PPD. No other source of this product was available, and there were stocks to cover up to September 1991. The product was derived from glycerol beef broth made from bovine muscle, but the licence holder had reported that it was changing over to peptone broth as quickly as possible, and that stocks were to be replaced ‘as appropriate’. The Working Group felt that replacement of stocks should be encouraged as quickly as practicable. However, glycerol broth was very low on the list for potential infectivity, and the
hazard of having no stocks outweighed the potential risk from using the product with its current composition.\textsuperscript{679}

6.166 The third product was the measles vaccine. The manufacturer was changing to a New Zealand source. No stocks of single vaccine were currently available and other stocks would be depleted within three months.\textsuperscript{680}

6.167 As for the line of DTP vaccines, the company had changed the source of its bovine media. However, existing stocks of non-complying media were still to be incorporated into the final product. The Working Group recommended that a meeting be held with the company to discuss future plans and bring forward the time by which all bovine components in the manufacture of the vaccines would comply with the guidelines.\textsuperscript{681}

Topical medicinal products

6.168 The safety of topically applied medicinal products was reconsidered at this meeting. The Working Group had before them a paper prepared by Dr Winship. He explained that advice had been given to the cosmetics industry regarding the use of bovine offal (see Chapter 8), and said that in view of this more recent concern it had been considered advisable to look into topical medicinal products again. He had found that the use of bovine offal in topically administered medicinal products appeared to be confined to products from two companies who got their material from Germany. Dr Winship recommended, and the BSEWG agreed, that no further action was required in relation to licensed topical medicinal preparations.\textsuperscript{682}

Medical devices

6.169 Mr Burton had prepared a briefing note on medical devices for the BSEWG, but did not actually present it at the meeting.\textsuperscript{683} His note stated that, of the two remaining companies using UK bovine material, one had changed to a non-UK source and the other had ceased to make its product.

CSM endorses recommendations of third BSEWG meeting

6.170 On 25 July 1990 the CSM received a report from Professor Collee of the BSEWG meeting earlier in the month. The Committee noted the minutes of that meeting and endorsed the recommendations of the Working Group.\textsuperscript{684}

Restructuring of Procurement Directorate

6.171 On 1 August 1990, the Procurement Directorate was reorganised: the procurement role was transferred from the STD to the newly created NHS Supplies Authority. The STD was renamed the Medical Devices Directorate (MDD).\textsuperscript{685}
European working party on human medicines

6.172 Up to now consideration of the implications of BSE for human medicinal products had been at a UK level. On 11 October 1990 the European Community’s Committee on Proprietary Medicinal Products (CPMP) decided that a working party should be set up to monitor the implications of BSE for the circulation of human medicinal products.686

Fourth meeting of the BSEWG

6.173 The BSEWG held its fourth meeting on 31 October 1990. The main issues discussed were the range of allergen products, one remaining non-complying vaccine, and a new development – the transmission of BSE to a pig.

Final returns to CSM/VPC questionnaire

6.174 By this time all outstanding replies to the human medicines questionnaire had been received. The final four replies received gave no cause for concern: none of the companies used bovine material sourced from the UK.687 Annex 2 provides a summary of the responses made to the questionnaires for human medicines, veterinary medicines, and medical devices.

6.175 MAFF reported that where action was still outstanding, measures were being taken to follow-up respondees. They were still waiting for some assurances that appropriate action had been carried through. It was noted that a paper would be put to the VPC shortly.688

Allergens: an update

6.176 The Working Group were told about SmithKline Beecham progress in complying with the guidelines, which now seemed satisfactory. With respect to the specific animal ingredients, they noted:

Cow-hair – The preferred source would be Australia or New Zealand or a closed herd in the UK. It is understood that SKB has a closed herd in the UK, used to obtain sera for the production of their vaccines, and the company should be encouraged to use this source, since they were concerned that decontamination procedures necessary for overseas sources and required by the anthrax regulations could denature the material and alter its antigenicity.

Beef-Veal – from Holland. The licence holder should be advised to specify that the veal is from milk-fed cows.

Mycological Media – containing ox-liver sourced from Italy as a component are acceptable as the source is not UK, provided that the usual assurances are given concerning good animal husbandry and an adequate veterinary service.
Bacteriological Media – A peptone based medium now replaces the brain heart medium used previously. Since this is highly refined and autoclaved at 132°C for 80 minutes, the Working Group considered the use of this material acceptable.  

Vaccines

6.177 The BSEWG again reviewed the situation concerning the stocks of the DTP vaccines. It considered that the secretariat should explore with the licence holder whether the unadsorbed vaccines (which had limited usage) should be replaced with batches that complied with the guidelines, especially where the stock-out date extended beyond 1991. The Working Group recognised that there ‘may be some commercial loss to the licence holder but it is unlikely to be very large’. The adsorbed vaccines, about which the BSEWG made no recommendation, had stocks that would run out between June 1991 and December 1991. These are different stock-out dates for this line of vaccines from those provided to the BSEWG on 10 January 1990 (refer to paragraph 6.131 above). These updated estimates, based on Wellcome’s most recent demand forecasts, had been sent to Dr Rotblat in September.

Foetal calf serum

6.178 The Working Group again discussed foetal calf serum, considering the potential for contamination during the delivery of the calf. It noted that the guidelines might need to be extended should further investigations reveal deficiencies in cleanliness in this area.

The pig

6.179 The Working Group was told of an important new development – BSE had recently been transmitted experimentally to a pig. It considered the implications for medicinal products using porcine material, such as heparin, insulin, a heart valve and heparin-coated blood collection tubes. Professor Collee told us that the Working Group:

. . . noted that the condition had resulted from a massive dose given by an unnatural route; we regarded the likelihood of infection developing as a result of oral ingestion as being extremely remote. The Working Party considered the paper relating to medicinal products containing porcine material. Our unanimous view was that since transmission of spongiform encephalopathy had only been seen under experimental conditions and in a single animal only, no action with regard to human medicines or devices was warranted.
6.180 In a minute to Dr Metters the previous month Mr Hagger had indicated that there were no licensed medicinal products on the UK market with which high-risk porcine tissues could be associated.696

Dural implants

6.181 At the request of the CDSM, the Working Group advised on a licence application for a dural implant derived from bovine pericardium. It was considered that the bovine material would be acceptable provided the selection complied with the guidelines and it was sourced from outside the UK. Validated sodium hydroxide disinfection procedures would also be insisted upon.697 In the absence of an unequivocal declaration by the company that the source herd management met the guidelines, a clear statement that the cattle had never been fed ruminant protein would be required.698

Paper on sterilisation of animal tissues in medical devices

6.182 MDD sought comments from the Working Group on the ‘Control of Harvesting Techniques’ chapter of its paper ‘Guidance on Chemical Methods for the Sterilization of Animal Tissues used in Medical Devices’.699 Minor changes were suggested but it was thought that detailed comment on the content would be more appropriate from some other body such as the BSC and then the CDSM.700

BSE in Switzerland

6.183 On 14 November 1990 Dr Sprang, Director of the IKS (the Federal Swiss regulatory authority for pharmaceuticals), telephoned Dr Jefferys about BSE in Switzerland and the action being taken with regard to pharmaceuticals.701 Later that day Dr Jefferys sent a minute reporting on his conversation to a number of people in MCA as well as Dr Metters and Dr Pickles. That minute said:702

There has been one confirmed case of BSE in Switzerland and the public position is that two cases are under investigation. In confidence Dr. Sprang tells me that there are 12 other likely cases.

. . . The pharmaceutical authorities are considering their response and at one stage were considering banning all pharmaceutical products containing bovine material. I think they have now realised that this would pose very considerable difficulties considering the use of bovine material is widespread as an intermediate in vaccines and other products. The Swiss authorities already have a copy of our guidelines and we are bringing together a package of information which will be sent to them later today which we hope will be of help in their discussions . . .
Pharmaceuticals have been highlighted as a major issue in Switzerland and we will have to watch the position carefully . . . I hope following my lengthy conversation that the Swiss will be following a similar procedure to that which we undertook in the UK.

Mr. Love has already arranged for a search to be made of our new database so that we can identify any products using Swiss material and consider whether any action is necessary.

... The Swiss authorities will be circulating their decisions through the CPMP and PER rapid alert networks. I therefore suspect that this item will appear on the CPMP agenda at its December meeting and this may bring forward the date of the proposed BSE Working Party.

6.184 A note by Dr Metters in manuscript on this minute said that the CMO would wish to know of the cases of BSE in Switzerland and of the action there regarding pharmaceuticals.

**CDSM and CSM consider recommendations of fourth BSEWG meeting**

6.185 The CDSM meeting on 21 November 1990 considered the dural implants that had been discussed at the BSEWG meeting on 31 October.\(^{703}\) The Committee was unable to advise the grant of a product licence for the bovine pericardium implant.\(^{704}\) However, the documents we have seen do not give us the basis of this decision.

6.186 When the CSM met on 22 November, it endorsed the recommendations of the BSEWG. Professor Collee, attending as a guest member, reported to the CSM that, as far as vaccines were concerned:

> We are still worried about this matter, and it is right that we should continue to send signals to CSM and JCVI that present evidence allows us to give no absolute assurance but some relative assurance. Meanwhile, it seems unreasonable to allow vaccines that have some association with UK sourced bovine products to be used when they could be replaced with batches that have been processed in compliance with the guidelines. Accordingly . . . our line of advice to CSM is hardening and I would like you to count me amongst the hawks in this.\(^{705}\)

**VMD reports progress on veterinary medicines to the VPC**

6.187 VMD continued to take follow-up action on the veterinary medicines questionnaire and compliance with the guidelines. Its second progress report, for the VPC’s December 1990 meeting, described the action various manufacturers were
taking to comply with the guidelines and also highlighted decisions that were taken on existing stocks of veterinary vaccines. The report stated:

Most of the companies have now made satisfactory arrangements. The VMD has recently written again to the small number of companies where further information and reassurance on satisfactory progress is required. The replies received to some of these may need to be considered by the Committee in the future. In the meantime, the following are being brought to the attention of the Committee.

1. A number of products for external use contain lanolin from UK sheep. A number of oral products contain gelatin from UK cattle. Such products were defined as outside the scope of the Guidelines and it is proposed that no action is taken with regard to these.

2. Lungworm vaccines are produced by harvesting larvae from the faeces of UK production calves. These calves are less than 6 months of age. Since faecal material is classed as a very low risk tissue for scrapie infectivity and the vaccines are given orally, it is proposed that no action is taken.

3. Three products are manufactured in bovine origin brain heart infusion broth. Two of the three are fish immersion vaccines. The bovine material used for one of these has never been of UK origin and the other manufacturer has indicated that he has now changed to a non-UK source.

Coopers-Pitman Moore have a product licence for a bovine mycoplasma vaccine, Bovulin, which also requires brain heart infusion broth during manufacture. However this product has not been marketed since licensing.

It is considered that the use of any bovine brain material is to be discouraged. The two fish vaccine manufacturers have been trying to find an alternative growth medium. It is proposed that pressure is maintained on these two manufacturers to finalise this work.

It is proposed that Coopers-Pitman Moore is told that an alternative medium should be found before undertaking manufacture of product for sale.

4. Media from Unipath (formerly called Oxoid) is used by a small number of companies to prepare vaccines. Some of the media contain a bovine soup stock of UK origin. . . . The soup stock is prepared from bones from EC approved abattoirs and is autoclaved for 80 minutes at 132°C. It is considered that this is satisfactory treatment for this material.

5. Some of the questions on the BSE questionnaires were interpreted differently by different companies. As a result, it is thought that we are likely to have incomplete data on when all stocks of batches of products made before changes to comply with the guidelines will be used up. Coopers-Pitman Moore and SKF have provided the information.

Coopers-Pitman Moore have some batches of bacterial vaccines which are likely to be used till 1994. Further information is being sought from the company.
SKF have bulk viral vaccines made with serum from the UK which would normally last for another 4 years or so. They do not have the manufacturing capacity to replace all these bulks with new stocks. The company has proposed to give priority to manufacture of fresh bulks of their large animal products and would expect to have this completed by December 1992 at the latest. The UK serum used was filtered and cell free. It consisted of foetal serum or donor calf serum. The latter was collected from calves less than three years old and were thought to have received no animal protein for most if not all of their lives. It is proposed that the company should be encouraged to change to fresh bulks as soon as possible for all products but that no action is taken in the meantime against existing stocks.  

6.188 The VPC considered this report at its 13 December 1990 meeting and agreed that:

i. Bovine brain material must not be used during manufacture (see sub-paragraph 4 of paragraph 6.189 above);

ii. Full information on the herd history of the source of donor calf serum used in manufacture of SKF’s bulk viral vaccines was required (see sub-paragraph 5 of paragraph 6.189 above);

iii. Dr Taylor \(^{707}\) was to be consulted on whether the autoclave treatment of bovine soup of UK origin was satisfactory (see sub-paragraph 3 of paragraph 6.189 above); and

iv. Any action should conform to current EC regulations on BSE.  

6.189 We have not seen any minutes of further meetings at which the follow-up to the veterinary products questionnaire may have been discussed. However, the VMD provided us with a table outlining the 143 products that did not comply with the CSM/VPC guidelines and the outcome of compliance measures taken (see Annex 3). We have also been provided with some supporting documentation.  

6.190 In relation to compliance the VMD told us:

The speed at which the companies concerned were able to move away from the use of bovine/ovine material carrying a potential risk of BSE/scrapie was dependent upon both the complexity of their manufacturing processes and the availability of alternative sources of supply of suitable material which would neither compromise safety/efficacy nor lead to risks from contamination by other agents. With regard to serum used ‘in process’ manufacturers had changed to non-UK sources by December 1990. Where companies needed to make more significant changes to manufacturing processes this required a longer lead time e.g. to make fundamental changes to bacterial growth media. With the exception of 1 fish vaccine, which remains under review, VMD’s records indicate that all manufacturers had complied with the CSM/VPC Guidelines by 1992.  

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706 YB90/11.00/5.1–5.2. The report was prepared in November 1990
707 Principal Research Scientist, NPU, who had done some studies into the inactivation of BSE. See Volume 2
708 YB90/12.13/7.2
709 M74 tab 3
710 DM01 tab 24 para. 2
It is clear from the VMD report to the VPC at paragraph 6.189 that at least some veterinary vaccine stocks that did not comply with the guidelines remained in use until several years after the guidelines had been put in place.

1991–92

**BSE in France**

**6.192** Confirmation of a case of BSE in Normandy was circulated by Dr Matthews to Dr Raine, Dr Purves, Mrs Baker and Mr Sloggem on 4 March 1991. His minute pointed out that two companies sourced raw material for sutures from France. He went on to say: ‘We will presumably need to take urgent action to get the new material sourced from somewhere else, and existing stocks withdrawn from the market.’

**6.193** Dr Purves told us that discovery of BSE in Switzerland and France ‘emphasised that a European wide approach to BSE was needed’.

**Initial steps towards development of European guidelines**

**6.194** On 4 and 5 March 1991 the Biotechnology Working Party (BWP) met in Brussels. The BWP was an ad hoc committee of the CPMP chaired by Dr Schild of the NIBSC. Other UK attendees were Dr Purves, Dr Minor, Dr Kimberlin and Mr Bradley.

**6.195** The German delegation to the BWP put forward a draft guideline on BSE and pharmaceutical products. This document was discussed by the group but discounted as a starting-point because it lacked certain information and agreement on the conclusions and recommendations could not be reached. A further draft was to be prepared by Dr Purves, Dr Minor and the German delegates for the next meeting in May. Many of the other European representatives thought that the UK guidelines could be used until more information was available.

**Second thoughts on the exemption from sterilisation and staining of SBO material used for pharmaceuticals**

**6.196** We consider in vol. 6: *Human Health, 1989–96*, the introduction of the Bovine Offal (Prohibition) (Amendment) Regulations 1992, which extended the ban over material derived from SBOs and introduced regulations regarding bovine brain removal. We review one part of the development of these regulations in this chapter, the question whether the specific exemption for manufacturing chemists should be removed.
The question was raised by Miss Bronwen Jones, of MAFF’s Meat Hygiene Division (MHD), who circulated a draft submission and draft regulations to Ministers on 6 March 1991.\footnote{YB91/3.6/1.1–1.2}

Mr Lawrence, commenting on Miss Jones’s draft, observed:

\ldots\text{ it looks odd to include in the excepted premises a manufacturing chemist for the manufacture of pharmaceutical products. I don’t quite see the circumstances when this should be allowed to happen, particularly in view of the Committee on Safety of Medicines’ clear guidance that pharmaceutical companies source any necessary bovine raw material from countries which are free from BSE and scrapie.}\footnote{YB91/4.02/6.1}

Mr Lewis Baker of MHD, in a minute to Mr Lawrence, pointed out that manufacturers of pharmaceuticals had been exempted originally because the intention of the regulations was to prohibit the use of SBO only in food. He added:

\begin{quote}
In addition, there was no evidence to suggest that use of sbo in pharmaceuticals posed any risk and I understand \ldots\text{ this is still the case.}
\end{quote}

\begin{quote}
In light of this, and taking into account the guidance which has already been issued by the Committee on the Safety of Medicines, I am not sure how much value there would be in amending the definition of excepted premises to exclude manufacturing chemists. There is clearly a danger that such a move would arouse unnecessary public concern about the safety of pharmaceuticals, although if any evidence of a risk to public health were to emerge we would clearly have to act on it.\footnote{YB91/4.11/13.1}
\end{quote}

Mr Lawrence was not persuaded. ‘I cannot see how it would arouse public concern, if such materials are not used anyway. What it would do is remove this rather anomalous exemption’.\footnote{YB91/4.17/17.1} This debate continued in July (see below).

**Further consideration of European guidelines**

As planned, the German representatives to the BWP, assisted by Dr Minor and Dr Purves, prepared a redrafted set of European guidelines for the May 1991 BWP meeting.\footnote{S535 Purves para. 176} Dr Purves told us: ‘Although the document was in a different format to the UK guidelines the salient points of the UK guidelines were incorporated’.\footnote{S535 Purves para. 180}

The draft guidelines were tabled at the CPMP meeting in June 1991 and it was agreed that the document should be put out for consultation to interested parties.\footnote{SS35 Purves para. 180} Dr Purves asked Mrs Shersby to circulate the draft guidelines to other parts of DH, to VMD and to the members of the BSEWG for comments.\footnote{SS35 Purves para. 181}

\footnote{YB91/6.14/1.1}
Assurances about contact lens products

6.203 Following a query from Dr Pickles about bovine material in contact lens products, Dr Raine replied on 10 July 1991 that ‘[c]ontact lens care products containing bovine catalase were scrutinised in 1989 in light of the Joint CSM/VPC guidelines for industry’.

Further meeting of the BSEWG proposed

6.204 A further meeting of the BSEWG had been tentatively suggested for 29 October 1991. However, Dr Jefferys ‘questioned whether there were any new issues or agenda items and expressed the view that, if there were not, there was no need for the working party to meet’.725 Dr Purves confirmed that there were no pressing items requiring advice and therefore a meeting was not required.726

Continuing debate on ‘excepted premises’

6.205 When Miss Jones produced a further draft submission on the proposed amendment to the bovine offal regulations, Mr Lawrence said:

I realise that the intention of the Regulations is to prohibit the use of sbos in food. But I remain convinced (as I said in my minute of 17 April to Lewis Baker) that the premises of a manufacturing chemist which are used for the production of pharmaceuticals should be deleted from the definition of excepted premises, unless there is a legal obstacle to doing this. If we do so I see no reason why such a measure should arouse public concern. It can be explained simply by indicating that we are bringing it into line with current practice and advice from the Committee on the Safety of Medicines that UK bovine materials should not be used in the manufacture of pharmaceuticals.727

6.206 Accordingly, Miss Jones’s submission to Ministers on 31 July said:728

The definition of ‘excepted premises’ currently includes the premises of manufacturing chemists which are used for the production of pharmaceuticals. Such premises are exempted from the main requirements of the Regulations because the intention is to prohibit the use of specified bovine offal in food, (pharmaceuticals do not fall within the definition of food) and because there is no evidence to suggest that the use of such material in the manufacture of pharmaceutical products poses any risk to public health. Nevertheless, the Committee on the Safety of Medicines has, as a precautionary measure, issued guidance that specified bovine offal should not be used for this purpose.

Ministers are asked to decide whether they wish manufacturing chemists to be removed from the list of excepted premises. There is clearly a danger that such a move would arouse unnecessary public concern about the safety of pharmaceuticals which is, in fact, not in question. On the other hand, it could...
be explained by indicating that we are simply bringing the Regulations into line with current practice and advice from the Committee on the Safety of Medicines that UK bovine materials should not be used for this purpose.

6.207 The submission was copied widely, including to DH.

6.208 The Parliamentary Secretary, Mr Maclean, decided that the exemption for manufacturing chemists should be removed. This was reflected in revised draft consultation documents circulated by Mr Baker on 19 August 1991, and in the consultation letter and draft amendment regulations circulated by Miss Jones on 21 August 1991. The amendment regulations, which came into force in March 1992, did not include a manufacturing chemist in the definition of ‘excepted premises’. However, manufacturing chemists may still have been covered by the general exemption for premises used for the manufacture of products other than food.

Consideration of TSEs by WHO

6.209 On 12–14 November 1991, the WHO met in Geneva to discuss transmissible spongiform encephalopathies and concluded that the careful selection of source material was the best way of securing safety from the remote risk posed by bovine materials in medicinal products and medical devices. Those present were of the view that the measures being taken in the UK were sufficient at that time to minimise the risk to all species including humans.

Finalising European guidelines on human medicines

6.210 The draft European guidelines on BSE and medicinal products were amended following comments from interested parties, and the revised document was approved by the BWP at its meeting on 25–26 November 1991. The guidelines were endorsed by the CPMP on 11 December 1991.

6.211 On 1 May 1992, the CPMP guidelines, entitled ‘Minimising the Risk of Transmitting Agents Causing Spongiform Encephalopathy via Medicinal Products’, came into effect.

6.212 The CPMP guidelines applied to:

all medicinal products which contain active ingredients and/or excipients derived from bovines, as well as medicinal products for which the production process involves bovine materials.

6.213 They also covered:
the use of such materials in procedures which are indirectly associated with the manufacturing process, for example, in test media used in the validation of plant and equipment to avoid cross-contamination.736

6.214 All products were to be considered on a case-by-case basis taking into account: the selection and processing of source materials; the age and geographic origin of the individual source animal; the intended use of the product; its stipulated dose and route of administration; the production process; and quality control.737

6.215 The main focus of the guidelines was the sourcing of bovine material used in manufacture. Sourcing was allowed from countries ‘which have not reported cases of BSE, if they have an effective veterinary service capable of detecting a low incidence of disease and if BSE is reportable’. Additionally, it was recommended that the risk of BSE from feeding SBO material to ruminants should be avoided.738 Materials could also be sourced from countries with a ‘low incidence’ of BSE if a number of precautionary measures were taken, including destroying all affected carcasses, and not using any progeny of affected animals.739

6.216 Guidance was also given about the relative infectivity of different types of tissue. Category 1, classified as ‘High Infectivity’, included brain, spinal cord and eyes. Lymph nodes, spleen and tonsils were all said to be of medium infectivity.740 The guidelines said that ‘these potential risks, amongst other criteria, should be considered for the selection of source materials’.741 This advice, which allowed for other factors to be taken into account, was somewhat less rigorous than the CSM/VPC guidelines, which stated that ‘[n]o brain or neural tissue, spleen, thymus and other lymphoid tissue, placental tissue or cell cultures of bovine origin should be used in manufacture’.742

6.217 Similarly, the CPMP guidelines stated:

the potential risks will be influenced by the circumstances in which tissues were removed, especially by contact of material of a low-risk group with that of a high-risk group. Thus the contamination of some tissues may be increased if infected animals are slaughtered by penetrative brain stunning, or if the brain and/or spinal cord is sawed.743

6.218 They added:

body fluids should be collected with minimal damage to tissue, and cellular components should be removed; e.g., fetal blood should be collected without contamination from placenta and amniotic fluids.744

6.219 This contrasts with the more specific requirements set out in the CSM/VPC guidelines.745

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736 YB91/12.11/3.4
737 YB92/1.09/3.4
738 YB91/12.11/3.5
739 YB91/12.11/3.5
740 YB91/12.11/3.8
741 YB91/12.11/3.8
742 YB99/3.00/1.2
743 YB91/12.11/3.7
744 YB91/12.11/3.7
745 YB99/3.00/1.2
no tissue is to be used in relevant medicinal products when collected post-mortem from a bovine animal after brain penetrative stunning.

all tissue collected from the bovine animal should be taken using sterile equipment. Needles, syringes, scalp blades etc should be disposable items.

... 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.

6.220 Manufacturers throughout the EC were required to comply with the new provisions. However, Dr Purves told us that the practical assessment of licence applications went on as before because, in his opinion, ‘the [CPMP] guidelines incorporated the principles of the CSM/VPC guidelines’.

6.221 The CPMP guidelines applied only to human medicines at this stage. Before the guidelines could be adopted in relation to veterinary medicines, they had to be approved by the Committee for Veterinary Medicinal Products (CVMP) following a public consultation process. The Working Party on Immunological Medicinal Products, a sub-group of the CVMP, of which Dr Lee was a member first considered the guidelines in May 1992.

Fifth meeting of the BSEWG

6.222 A fifth and last meeting of the BSEWG took place on 8 July 1992. Key issues for discussion at this meeting were sourcing of material for sutures from France and possible infection of foetal calf serum.

Products containing French sourced bovine material

6.223 As noted in 6.194, the occurrence of BSE in France and Switzerland had prompted concerns about sutures sourced from France. The Working Group noted that at least two suture manufacturers sourced from France, although ‘the sutures material was supplied in minuscule amounts to the UK’. Two specific questions were asked:

i. Are sutures sourced in France of concern to the Working Group?

ii. What is the relevance of the BSE guidelines to sutures?

6.224 The BSEWG concluded on the first question that ‘the risk associated with material from France now would appear to be many orders of magnitude less than material [previously] sourced from the UK’. Nevertheless, the Working Group
‘expressed the view that where a demonstrably safer source is available then a company should use it’.753 In drawing these conclusions the BSEWG noted:

The recent cases of BSE in France, and 11 cases in Switzerland appeared to have no link with the UK . . .

. . . it was admittedly unlikely that France and Switzerland would get the same type of epidemic as in the UK . . .

In connection with sutures, it was noted that the BSE Guidelines indicated that a country with a low incidence of BSE [such as France] . . . was suitable as a source of raw material if the other aspects of the Guidelines were complied with.754

6.225 On the second question, the Working Group ‘indicated that . . . the CPMP BSE Guidelines should be applied to surgical sutures although no other member state applied the Guidelines to these materials’.755

Vaccines

6.226 The Working Group was told that the line of DTP vaccines, the only outstanding vaccine of concern (see paragraph 6.179 above), had now been replaced with a new batch using material from New Zealand cattle. This was the last vaccine to be replaced.756

6.227 In summary, four human vaccines did not comply with the CSM/VPC guidelines in March 1989: one measles, one MMR, one Tuberculin PPD and a line of DTP. The MMR vaccine had not yet been licensed and was never marketed. The other three vaccines had achieved compliance by the end of 1990. Non-complying stocks of the measles vaccine were exhausted by September 1990. In May 1991, it was estimated that non-complying stocks of the Tuberculin PPD would last until December 1991. However, the BSEWG encouraged replacement of these stocks as quickly as possible. As for the DTP vaccine, non-complying stocks were estimated to last until the end of 1991 (adsorbed) and at least until September 1992 (unadsorbed). The BSEWG encouraged all stocks to be replaced by the end of 1991. The table at Annex 4 summarises the action taken on non-complying human vaccines.

Medical Devices

6.228 MDD had been working for some time on a paper on sterilisation of animal tissues in medical devices, which was introduced to the meeting by Mr Burton. The content of the paper took account of earlier contributions from the Working Group, and from industry. It was also intended that the CPMP guidelines on the inactivation of viruses would be incorporated. The BSEWG agreed that the paper should now be presented to the CSM and CDSM.757
**Foetal calf serum**

6.229 The Working Group again considered the possible infection of foetal calf serum.\(^{758}\)

6.230 Professor Collee stated that continued vigilance was necessary, particularly given the widespread use of foetal calf serum in a variety of biological products including vaccines and recombinant DNA technologies.

6.231 Recent evidence indicated foetal lambs might be infected with scrapie. However, it was noted that the BSE analogy with scrapie did not necessarily hold good, as there was much less dissemination of the BSE agent in tissue outside the central nervous system than there was with scrapie.

6.232 The establishment of Australasian foetal calf serum as the ‘gold standard’ gave rise to certification problems in relation to products from other areas.

6.233 The BSEWG noted that, as well as sourcing appropriately, the collection of foetal calf serum should be carried out with due care and attention. In this respect, procurement methods in some countries might not have been critically controlled. The method of collection could be improved in some cases because cross-contamination with BSE would be most likely from specified offal.

**Consideration of the safety of gelatine**

6.234 During 1992 concerns arose about the safety of gelatine, which was widely used in oral medicinal products. On 21 July 1992, Dr Minor, Head of Virology at NIBSC, wrote to Professor Collee:\(^{759}\)

> At a recent meeting in Heidelberg a gentleman from a gelatin manufacturing concern presented an account of the process which was very worrying. As you know, the assumption has been that gelatin is produced under such vigorous conditions that it gives no cause for concern, but the process he described was, to me, shockingly mild. Moreover he claimed that any old cow bone went into the production vat, including spine and skull . . .

> A number of other BSE working party members were present at the meeting, including John Purves, Richard Kimberlin and David Taylor, so it is possible that the matter was raised [at the BSE Working Group meeting of 8 July 1992].

There is no indication that this issue had, in fact, been raised at the BSEWG meeting.

6.235 Dr Taylor also wrote to Professor Collee:\(^{760}\)

> Like Philip [Minor], I was not impressed by the reassuring noises made . . . at the Heidelberg meeting. However, I am not really familiar with gelatin manufacturing processes in the UK . . . I would certainly be concerned if it

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\(^{758}\) YB92/7.8/15.2; see also Chapter 7 in relation to results of experiments into the infectivity of foetal calf serum  
\(^{759}\) YB92/07.21/2.1  
\(^{760}\) YB92/07.30/3.1
is produced by a similar procedure to the German process described at the meeting.

6.236 On 31 July 1992, Dr Kimberlin wrote to Professor Collee about Dr Minor’s observations.\textsuperscript{761} He concluded:

(a) The general assumption that gelatin is of very low risk with regard to BSE contamination is still tenable.

(b) Any uncertainty would be if the source material included significant amounts of brain and spinal cord from countries which either had reported BSE or were at risk of getting BSE cases, and which did not have a specified offals ban.

(c) In these circumstances it might be reasonable to require either that these potential risk tissues were excluded from the source material, or that validation studies were carried out which were capable of demonstrating a clearance factor appropriate to the potential contamination.

6.237 On 5 August 1992, Dr Tyrrell wrote to Professor Collee. He had seen Dr Minor’s letter of 21 July and he thought it was ‘necessary to get more details . . .’\textsuperscript{762}

6.238 As a result of these concerns, and acknowledging the help he had received from Dr Minor and Dr Kimberlin, Professor Collee produced a written opinion on gelatine and BSE.\textsuperscript{763} He said:

It is possible that gelatin is of low risk with regard to BSE contamination, but there are justifiable anxieties when the source material includes brain and spinal cord of cattle (or sheep) from countries with known cases of BSE or at risk of having BSE cases.

Validation studies to demonstrate the safety of processing and extraction procedures in this context would be commendable, but there are very significant practical difficulties and such an exercise would take some years.

It is reasonable to press for assurances with regard to quality and sourcing, analogous to those sought with respect to catgut sutures, in relation to gelatin manufactured for use in the pharmaceutical industry . . . Full compliance with the BSE guidelines should be required for the starting material.

6.239 Dr Purves told us: ‘We would have taken Professor Collee’s recommendation into account when we were subsequently assessing applications for product licences for gelatin.’\textsuperscript{764}

6.240 However, Professor Collee’s suggestion was not without difficulties. On 28 August 1992, Dr Minor wrote to him.\textsuperscript{765}
... [there] may be a slight difficulty raised by the sentence in your summary requiring full compliance with the BSE guidelines. In the European version of the document... gelatin is specifically singled out as a product which given assurances of adequate collection and processing is unlikely to present any risk of contamination. The implication to me is that the source animal probably does not matter...

6.241 Dr Tyrrell received a copy of Professor Collee’s paper in September and Mr Lowson circulated it to other members of SEAC as well as to Mr Meldrum, the CVO. It was suggested that a short note be put together on the subject for discussion at the next SEAC meeting. SEAC’s advice in relation to gelatine is considered in detail in Chapter 3 of vol. 11: Scientists after Southwood.

6.242 On 11 September 1992, Mr Meldrum wrote to Mr Lowson about the paper. He said, ‘I am a little concerned at the comment that the raw materials should be sourced from a BSE-free country. I have no difficulty with the definition applying to Australia and New Zealand, but not to other countries where they do not have an active surveillance system.’ He went on ‘I am worried at the possibility that we may be clobbering the UK even though we have got excellent controls in place, but still be ignoring the unknown and unquantifiable risks from overseas.’

CDSM and CSM meetings

6.243 At the CDSM meeting on 15 July 1992 the Committee considered two suture products sourced in France and said that, on grounds of quality and safety, it might be unable to advise the Licensing Authority that licences should be granted.

6.244 When the CSM met in September 1992 the concerns about gelatine were raised, but the CSM deferred consideration of the subject until a later date. At the same time it noted the report of the fifth meeting of the BSEWG, and was told by Dr Rotblat that there was no cause for concern regarding the use of foetal calf serum.

1993–96

European guidelines on veterinary medicines

6.245 Final approval for the European guidelines on veterinary medicines was given by the CVMP in January 1993. These guidelines remained almost identical to the CPMP guidelines on human medicinal products.

Pharmaceutical products: quantitative studies of risk

6.247 In April and May 1993, Dr Richard Kimberlin produced three reports, commissioned by The Wellcome Foundation Limited, to assess quantitatively the BSE and scrapie risk to patients from certain pharmaceutical products. The reports covered:

i. a number of topically applied pharmaceutical products;\(^{772}\)

ii. a number of orally administered pharmaceutical products;\(^{773}\) and

iii. bovine insulin.\(^{774}\)

6.248 The reports were based on ‘worst-case’ assumptions and therefore aimed to calculate the maximum possible risk to a patient using the product.\(^{775}\) The conclusions compared the risk of contracting CJD from the products studied with the risk of an individual contracting non-iatrogenic, sporadic CJD, which occurs at approximately one case per million people per year. Dr Kimberlin’s papers said that this meant the lifetime risk to any one individual of contracting sporadic CJD was about 1 in 10,000.\(^{776}\)

6.249 Dr Kimberlin concluded that the maximum risk of contracting CJD from the topical products was 1,900 times less than contracting sporadic CJD.\(^{777}\) For the oral products the estimate was 38,000 times less likely.\(^{778}\) And for the bovine insulin the estimate was 1,000 times less likely.\(^{779}\)

German guidelines on the use of bovine and ovine material in medicines

6.250 On 28 February 1994, the German Federal Health Office (BGA) issued safety standards for human and animal medicinal products to minimise the risk of BSE/scrapie transmission.\(^{780}\) Dr Purves told us that the ‘new German safety standards had been issued unilaterally without prior discussion at the CPMP and appeared to go further than the existing European guidelines’.\(^{781}\) The guidelines were published in the Federal Gazette in Germany in February but did not come to the attention of UK authorities until some months later.\(^{782}\)

6.251 Mr Sloggem prepared a paper for the CSM/BSC meeting on 6 July 1994 updating the Committee on BSE.\(^{783}\) The German guidelines were covered briefly by the paper and the BSC then asked Mr Sloggem to prepare a detailed paper comparing the CPMP guidelines with the German ones.\(^{784}\)
Other European issues

6.252 In July 1994, Portugal, as rapporteur to the CPMP, requested that all Member States provide a history of action taken on medicines and BSE since the introduction of the CPMP guidelines.\textsuperscript{785} The French had also made a request to MAFF for an update on BSE in the UK with regard to veterinary medicines.\textsuperscript{786} Mr Sloggem was involved in responding to both of these requests.

6.253 While undertaking this review process Mr Sloggem discovered that the MCA’s BSE database was out of date. It had not been updated with information from new licence applications since the UK guidelines came in and still contained only the information received from the original CSM questionnaire.\textsuperscript{787} Dr Purves told us that this discovery prompted improvements to the new MCA database:

By then internal discussions were underway on the new PLUS database which was being set up to record details of product licences and applications. In light of the discovery that the existing BSE database had not been kept up to date, my team put forward a case that the PLUS database should be modified. This modification was requested to allow the input of the bovine materials included in products, not merely as active ingredients but also as excipients or reagents, and the source of such materials. Those discussions went on in early summer 1994. I recall that the administrators in charge of the new Database, PLUS, conceded that it was necessary for the database to be amended as we had suggested.\textsuperscript{788}

Further meeting of the BSEWG proposed

6.254 Dr Purves thought the action taken by Germany on medicinal products raised the question of whether a further meeting of the BSEWG was needed.\textsuperscript{789} Dr Jefferys thought that the precise issues to be discussed needed to be clearly defined before a decision could be made. He also noted a number of practical difficulties in calling another meeting.\textsuperscript{790} No further meeting of the BSEWG ever took place.

6.255 The CSM met on 22 and 23 September 1994 and considered (among other things) the German guidelines.\textsuperscript{791} The CSM decided that the BSC together with a number of invited experts should meet in November to consider the issues further.

Medical Devices Agency

6.256 On 27 September 1994, the MDD became the Medical Devices Agency (MDA).

\textsuperscript{785} S454 Sloggem para. 131; YB94/7.14/11.1
\textsuperscript{786} S454 Sloggem para. 130
\textsuperscript{787} S454 Sloggem para. 131; S535 Purves para. 212
\textsuperscript{788} S535 Purves para. 212
\textsuperscript{789} YB94/7.20/15.1
\textsuperscript{790} YB94/7.22/13.1; S535 Purves para. 221
\textsuperscript{791} YB94/9.22/6.1–6.8
Meeting of the Biologicals Sub-Committee

6.257 The BSC meeting was held on 2 November 1994. At this event Professor Collee, no longer Chairman but attending as an invited expert, was able to raise matters discussed at the BSEWG’s fifth meeting in July 1992.

6.258 As noted above, there were no further BSEWG meetings. However, in his address to the BSC Professor Collee discussed the continuing need for such a group. He said:

When Professor David Lawson, my Chairman on the Medicines Commission, asked me to comment on the present position with regard to our surveillance of BSE, I made the point that the BSE Working Party had not met since July 1992. There was a danger . . . that the gap might be thought to be reassuring (on the grounds that no business was pressing us to reconvene, and that the evolving scene did not justify a further meeting).

. . . our committees need the continuing assurance that a specialist cross-discipline group is able to give at a time when BSE continues to pose worrying questions in relation to human health and to the safety of some of our medicines and biological products. You and your colleagues on Biologicals may well feel that a separate group is unnecessary and that the BSE business can be adequately transacted within this committee. I would ask you, however, to see the amount of paperwork that only today’s discussion has called for on topics relating to BSE. And I would ask you for your indulgence and understanding if my answers to some of the ensuing questions that you will no doubt wish to put to me are answered in guarded, if not evasive terms. By this I imply that I really do need the backing of my scientific advisers on the Working Party and I am uneasily aware of my limitations in such a complex field.

6.259 The BSC also discussed the European situation, in particular the German stance. Dr Purves summarised the key points made by the Committee in relation to the German guidelines:

(a) That the UK should not be singled out for any ban on the use of bovine material from a closed herd, as other countries had indigenous cases of BSE. It was stated that a source material from a BSE free closed herd should be acceptable.

(b) All inactivation methods should be validated rather than assumed. The CPMP classification of tissues and approach was acceptable. The German numerical factor system was not acceptable.

(c) The data requirements of the German Guidelines were not feasible in that it was unlikely that suppliers of bovine materials would be able to provide all the data required. A case by case approach was required.
6.260 The German guidelines continued to be discussed at the CPMP and BWP meetings in December 1994 and thereafter. Although no agreement was reached between the UK and Germany on the issue of revising the European guidelines, the CPMP confirmed that the current European guidelines would remain in force until such time as they were modified through the ongoing discussions.\textsuperscript{795} The impact of the German stance on the export of pharmaceuticals from the UK, and exports of pharmaceuticals generally, are considered in Chapter 7 of vol. 10: \textit{Economic Impact.}

\section*{MCA and VMD audits of manufacturers}

6.261 Following the Government’s announcement on 20 March 1996 that the most likely explanation for vCJD was exposure to BSE prior to the SBO controls,\textsuperscript{796} the MCA undertook an audit of UK medicine manufacturers, in order to reassure itself that proper procedures were being followed.\textsuperscript{797} A letter was written to licence holders seeking written confirmation that the 1992 CPMP guidelines were being observed. In addition, inspection visits were made, between 10 and 18 April 1996, to those manufacturers of medicines that might contain material of bovine origin.\textsuperscript{798} Inspectors visited 166 sites in all.\textsuperscript{799} This audit took place outside the period covered by our terms of reference; however, it is of relevance to that period in indicating what was then thought to be the degree of compliance with the guidelines.

6.262 A report of the audit dated 26 April 1996 said:

The results of the audit:

(a) re-confirmed that no bovine material of UK origin is used in the manufacture of vaccines or other injectable medicines in the UK since 1989. The audit confirms that all injectable products are therefore free from any risk associated with UK bovine materials;

(b) re-confirmed certification of compliance with the 1992 CPMP guidelines;

(c) established that since mid-April 1996 no pharmaceutical product for human use manufactured in the UK uses gelatin derived from materials of UK bovine origin;

(d) established that there are three UK manufacturers of gelatin who supply gelatin certified for pharmaceutical use, and that they do not supply gelatin derived from materials of UK bovine origin to manufacturers of pharmaceutical products for human use in the UK;

(e) established that in respect of tallow derivatives, as a result of a commercial decision virtually all UK manufacturers have moved away from using tallow derivatives which have been refined from tallow of UK bovine origin. However it should be noted that the UK produced a detailed paper on tallow derivatives, which was considered by the special meeting of the
CPMP on 15 April 1996. The EMEA opinion of that meeting emphasised that the processes used to produce tallow derivatives which are used in pharmaceutical products are more than sufficient to render them safe. 800

6.263 VMD carried out a parallel audit in April 1996. On 4 April the Directorate wrote to all marketing authorisation holders asking them to provide information on the source of any ingredients in their products of bovine origin, to ensure continued compliance with the CVMP guidelines. 801 VMD had to follow up responses from eight companies that did not reply immediately. In the end all but three companies confirmed compliance with the guidelines. VMD was unable to locate responses from these three companies and has since undertaken further investigations. 802

Discussion

What needed to be done?

6.264 From March 1989 onwards, officials were in a position to apply the guidelines to all new licence applications and to the review of Licences of Right. They appear to have lost no time in doing this.

6.265 The questionnaire review covering existing licences, though admirably comprehensive for filling in the information gaps, was a different matter. Because of its sheer scale alone it was bound to involve much time and effort. Unfortunately, for reasons we develop below, this process did not run speedily or smoothly. The original six-week deadline for returns proved a pious hope and in the event the exercise as a whole took years to complete.

6.266 What faced officials was a major administrative exercise in order to manage and apply the results. In particular they needed to:

- chase up replies, and decide which required further investigation;
- assess risk and supply considerations where bovine materials were involved and seek the advice of the expert committees on problem cases; and
- take follow-up action to ensure manufacturers dropped objectionable products or found new supply sources, and phased out contaminated stocks as speedily as possible.

6.267 We discuss below the way these tasks were tackled by each of the three groups of officials concerned respectively with veterinary medicines, human medicines, and medical devices. For brevity we generally refer below to bovine products, but many of the actions taken applied also to ovine and caprine products, which were recognised as raising similar issues.

6.268 As stated at the beginning of this chapter we had difficulty in pinning down precisely when stocks of products, particularly vaccines, manufactured with UK bovine material were used up. The MCA was not able to provide us with this

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800 DH01 tab 12 Annex D
801 DM01 tab 14 p. 8
802 DM01 tab 14 p. 8
information and the report of the audit of manufacturers carried out in 1996 did not
deal with the issue of phasing out stocks. We have done our best to piece together
what we could about the use of stocks of vaccines, but the information is still vague.
Although there is no evidence at this stage that vaccines or any medicinal products
were implicated in transmitting the disease, the possibility cannot be ruled out
entirely. Should that be the case, accurate tracing of what happened to products
would then be helpful. We found the overall lack of information concerning the
phasing out of existing stocks of products frustrating.

6.269 We begin our discussion by reviewing three background factors that directly
affected the response:

i. Handling uncertainty.

ii. The management context.

iii. Perceptions about the risk posed through medicines.

(i.) Handling uncertainty

6.270 As explained in Chapter 2, the elaborate licensing system rested on medical
and pharmaceutical assessments of technical data. Tests and trials might take years
to complete and be validated. The actual grant or revocation of licences was
performed by administrative staff acting on behalf of Ministers. They were advised
by professional branches and they consulted expert committees as necessary. Their
decisions had to be founded on proper evidence and were subject to appeal.

6.271 A key function of the ‘Yellow Card Scheme’ for recording adverse reactions
in humans and animals was to alert officials to where licensing action might be
justified. In the case of BSE there were no demonstrable adverse reactions among
users to justify intervention. There were no tests available to detect contamination
and no guaranteed methods of sterilisation to rule it out. On the other hand there
were demonstrable medical benefits from most of the products under suspicion, and
large investments at stake.

6.272 Professional and administrative assessments about the balance of risks and
benefits in allowing existing products using bovine materials to remain on the
market were therefore going to be peculiarly difficult. In the end they could be no
more than value judgements by officials and the expert committees they consulted,
drawing on what was known about other TSEs. It was bound to be attractive to
make the maximum possible use of the flexibility the guidelines allowed if
manufacturers stalled for time to find ‘clean’ sources or dispose of existing stocks.
The alternative might be a time-consuming string of Medicines Act appeals.

(ii.) The management context of the review exercise

6.273 The case-by-case approach of the review exercise meant that each of many
hundreds of returns had to be scrutinised and assimilated with existing material.
Judgements had to be reached on each return’s adequacy and accuracy and if need
be more information obtained. A view then had to be reached on whether advice
should be sought from the expert committees.
6.274 These considerable tasks were being superimposed on a creaking system which, as the management reviews had shown and as witnesses testified, was overloaded and understaffed. The record systems were antediluvian. Parallel hierarchies of professional and administrative staff diffused the management responsibility. To address this state of affairs, agencies were in the process of being set up. While this shake-up in the organisation had admirable goals, it meanwhile was a new factor affecting reporting lines and the priorities of top management, just as the BSE information-gathering exercise was being put in train.

6.275 New Directors had taken up post in April 1989, as the heads respectively of the MCA and VMD. Neither had firsthand knowledge of the previous debate over BSE and medicines safety nor of what lay behind the choice of wording in the Southwood Report, the CSM statement and the letters to companies.

6.276 Dr Gerald Jones’s successor, Dr Keith Jones, whose previous career had been in commercial pharmaceutical management, told us he was heavily preoccupied over the next 18 months in setting up the MCA as an agency, no doubt in the process tackling the matters criticised in the management reports. He told us he had little independent recollection of his involvement with BSE during his early years at the MCA, not only because of the passage of time, but because creating and funding the new organisation was the primary focus of his attention. The BSE review exercise continued to operate as before on a collective basis and old reporting lines – the traditional ‘team effort’.

6.277 Dr Little’s successor, Dr Rutter, who had come from the Institute of Animal Health to head the new VMD, registered his interest in BSE in June 1989 by asking that VMD and the MCA should keep one another informed on progress. Thereafter, follow-up action was handled by Dr Aileen Lee.

(iii.) Mixed messages on the urgency of the exercise

6.278 Dr Keith Jones and Dr Rutter were not alone in assuming the exercise might be allowed to proceed in a routine way. The tight initial deadline of six weeks had been set for the questionnaires to be returned. This having proved unattainable, thereafter there was no set timetable. On the contrary, the wording of the Southwood Report and the message conveyed in the CSM statement and accompanying letters were now being interpreted in both VMD and the MCA as taking the heat off medicines. While follow-up action needed to be pressed ahead, a flexible line on timing and on existing stocks seemed reasonable.

6.279 Thus, the low-key presentation of risk from injected products, which had been so carefully crafted to avert public alarm about the vaccination programme while remedial action was being taken, had the pernicious result of being taken as the message itself. Few of those handling the follow-up, certainly at top management level, would have known about the earlier deep concern of Sir Richard Southwood over injectable products, and his attempts to get assurances that action was being taken on these.

6.280 The gap in perception applied equally to VMD and the MCA. It encouraged a slackening of tempo in delivering the action on which the assessment of remote

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803 S447 K Jones para. 16
804 S499 Rutter para. 2; YB89/6.27/7.1
risk actually depended. Thus the first meeting of the BSEWG was advised by MCA officials that the *Southwood Report* had stated the risk to man via medicinal products was remote and that it was important not to undermine this considered advice by demanding unnecessary assurances and information from manufacturers.\(^{805}\) We discuss in Volume 4 the Southwood Working Party’s assessment of risk.

6.281 VMD had a similar view. Dr Little suggested to NOAH on 21 February that the *Southwood Report* had so far turned out to be a damp squib\(^{806}\) and Mr Kidd told us in his statement how

manufacturers were advised to change the sources of supply of bovine and ovine materials as quickly as possible, where necessary, to minimise the risk of contamination of products. However, manufacturers were allowed to exhaust existing stocks as the *Southwood Report* and the VPC and CVL specialists in BSE had considered that the risk of BSE transmission by medicinal products appeared remote.\(^{807}\)

6.282 The mixed messages on urgency clearly influenced the attitude of the two Departments. Reassurance that action was purely precautionary and that the guidance was a ‘gold standard’ must also have influenced the manufacturers whose cooperation and action were needed.

**The response by the Licensing Authorities**

6.283 We turn now to consider, in the light of these factors, the action taken on veterinary products by VMD, on human medicinal products by the MCA and on medical devices and other matters by PD/STD.

6.284 Given all the background considerations, the way Departments were organised and the message, we do not think individuals are to be criticised for their handling of the response. Each decision taken, viewed in the circumstances of the time, was reasonable. However, unfortunately overall they contributed to a lengthy process, particularly in the case of some vaccines.

6.285 We were and remain concerned about some general aspects of the arrangements that produced this outcome and the light that outcome shed on their weaknesses. It seems to us that some of these persist today. We conclude this chapter with comments on these matters.

1. The response on veterinary products

**The basis for action**

6.286 In theory MAFF already had a head start on veterinary products. Talks with manufacturers had begun in mid-1988 about draft guidance. NOAH had undertaken to provide information and the VPC had urgently reviewed bovine hormone products.
6.287 However, to keep in step with DH, and pending the findings of the *Southwood Report*, MAFF had reined back on its draft guidance and modified it somewhat. It now needed to pick up momentum again and secure action by the industry on the products of concern.

**Whose job was this?**

6.288 It was not the role of the BSE Working Group to advise on veterinary medicinal products, as Professor Collee made plain at its first meeting.\(^{808}\) Expert advice on their safety continued to be the responsibility of the VPC. The VPC held only two discussions about the review, in September 1989 and December 1990. Otherwise matters were dealt with entirely by officials in VMD.

6.289 From August 1989, the lead on following up the questionnaire fell to Dr Aileen Lee, who headed the division responsible for biological products. She acted as VMD link with the BSEWG, attending all its meetings. Her function there appears to have been to report how matters stood on the veterinary products exercise, rather than to engage in discussion of BSE issues vis-à-vis veterinary medicinal products. Likewise she was asked to keep the Biologicals Committee of MAFF informed about progress. The BSEWG papers and discussions on human risk must have been of great assistance to her and to VMD in providing up-to-date material and opinions on risk as background to their own consideration of difficult items.\(^{809}\)

6.290 Dr Rutter told us that Dr Lee maintained contact with Mr Bradley and Mr Wilesmith of the CVL as information on BSE emerged.\(^{810}\) We noted from their written statements that Dr Purves, Dr Adams and Mr Sloggem all looked to Mr Bradley throughout the period rather than to Dr Lee for informal handling advice, in particular in relation to international developments.

**Securing action**

6.291 The starting-point had to be adequate information about products using bovine material. The veterinary products industry had not yet delivered the details MAFF had asked for through NOAH, though discussions had begun with suppliers of biological materials to manufacturers.

6.292 The deadline of 1 May 1989 for all questionnaire returns from the 248 companies approached proved to be unduly optimistic. In the end the review exercise on veterinary products was no speedier than that on human products. The issue of existing stocks was dealt with on a case-by-case basis. Existing stocks were in some cases allowed to remain on the market until exhausted, although manufacturers were encouraged to replace these sooner.\(^{811}\)

6.293 As we noted in Chapter 5, MAFF had already tackled what it saw as the highest-risk item: hormone-based products. In July 1989, it was sent the MCA categorisation of risk. At the first BSEWG meeting in September, when this list was...
discussed and endorsed, Dr Lee reported that VMD was concentrating on products that could be identified as having a possible risk of BSE contamination. 812

6.294 We infer on the basis of various references in the papers we have seen that, as in human medicines, these were items containing brain and lymphoid tissue as ingredients, vaccines and sutures, and that VMD followed *pari passu* the line taken within the MCA. We were not, however, shown any contemporary VMD papers confirming this as a policy line.

6.295 What we did see were the successive reports that Dr Lee prepared for the BSEWG and her two reports to the VPC. These made clear the extent of effort going into letters, telephone calls and meetings chasing up non-responders and seeking further information where returns were inaccurate or incomplete. Unfortunately the reports and associated brief minutes lack details of the items of concern and their usage, the stocks in hand and the dates when these were eventually removed. But it is clear from the final report to the VPC in December 1990 that at least some veterinary vaccine stocks remained in use long after the guidelines were issued. The table at Annex 3 provides the most comprehensive picture, but it too lacks details of the stocks in hand and when they were eliminated. 813

6.296 Should VMD have secured speedier results and taken a tougher line on stocks? Transmission between animals via contaminated medication was a direct and obvious risk and the risk of a vaccine scare with life-threatening consequences did not hold the same force as with human medication. However, VMD believed that the Southwood message was that risk through medicines was remote. Continuity of vaccine supplies was important because intensive farming methods created their own hazards. Non-validated alternative sources of supply of materials might hold other perils. Given what was known at the time, and the background considerations to which we have referred, we consider that its approach was reasonable.

6.297 One point that puzzled us in this story was the apparent tailing off after March 1989 of the earlier close liaison between VMD and NOAH on BSE. It did not appear that VMD sought to enlist NOAH’s assistance in pressing manufacturers to comply swiftly with the guidelines.

6.298 When in July NOAH raised with VMD some of its members’ difficulties over the guidelines, VMD advised it that comments would be useful and were best addressed to DH as it had ‘fronted the exercise’. This too was surprising. NOAH was ‘its’ trade association for consultation purposes and it seemed to us that MAFF was in a better position than DH (or, as it turned out, the BSEWG) to discuss practical problems with ‘clean’ sourcing and harvesting of animal material.

6.299 We draw attention to this aspect of events because other factors in the BSE story suggest that working together with trade associations can be an efficient and effective approach.
Our general conclusion on the handling of veterinary medicines

6.300 We concluded it was not unreasonable of VMD to pace and match its efforts with those of the MCA. As was demonstrated in the disagreement that arose over Dr Lee’s paper to the Royal Society of Medicine, the line had been firmly established at the beginning of 1989 that animal medicines should take their cue from the handling of human medicines.

6.301 That said, we think it was unfortunate that playing second fiddle was one of the factors that led to a less urgent and decisive approach, in particular in respect of existing stocks, than was originally contemplated. This was a contrary outcome. We are in no doubt that a further factor was the falsely reassuring messages that the Southwood Report and the CSM statement were perceived to convey. The overall impact on BSE from veterinary medicines may never be known. It is impossible to say today whether continued use of bovine-based medication may have added to the total of cattle born after the ban on ruminant feed of 18 July 1988 that developed BSE (BABs).

2. The response on human medicinal products

The basis for action

6.302 The three factors we have identified as bearing on MAFF – handling uncertainty, the management context and perceptions of risk – applied with equal force to DH. Over and above that, some of the problems facing MAFF in managing the exercise were writ even larger in DH, in particular:

- the volume of products for review was much greater and the backlogs of work were worse;
- the organisational arrangements, both in terms of officials involved and of committees, were more complex; and
- supplies of products regarded as vital to individual humans’ immediate health and survival (insulin, sutures) had to be maintained while alternatives were sought.

6.303 The MCA did not have the advantage MAFF enjoyed of several months’ prior contact with producers about the draft guidelines. However, it seems to us that it was not starting entirely cold.

- Some firms making human medicinal products were also involved in products for veterinary use and would have been alerted on their MAFF grapevine.
- The February ring-around about children’s vaccines, which we referred to in Chapter 4, would have placed manufacturers on high alert.

6.304 The MCA now had to collect in, as speedily as possible, the information it needed not only in the interests of medicines safety generally, but also to resolve the difficult and politically charged issue of risk through the vaccination programme, which had been left hanging fire.
Whose job was this?

6.305 Although Dr Keith Jones had taken over from Dr Gerald Jones when the MCA was established in April 1989, he told us the triple reporting arrangements and structures were left unchanged for some time.\(^{814}\) It was ‘business as before’. It remained the case that no branch was actually in the lead on BSE within the newly established MCA.

6.306 Various witnesses referred to a team effort. We accept this as a valid description of some of the joint pieces of work and preparation of papers that were put in hand. However, teamwork does not just happen. It needs a leader to prescribe what it is expected to achieve overall and who is to do what and by when. There were both significant processing and judgemental matters to be managed.

The impact of the MCA on handling

6.307 Dr Jefferys told us: ‘Considerable resource and attention was directed during the second half of 1988 and the whole of 1989 to the introduction and establishment of the new Medicines Control Agency from the former Medicines Division.’\(^ {815}\) Mr Hagger told us the division of work became known from about August 1989 and began to influence working arrangements from then. In about February 1990, senior staff started to run shadow businesses as precursors to the distinct MCA organisation.

6.308 Dr Jefferys became head of the new Business A, Licensing, which led on BSE issues.\(^ {816}\) In his new post Dr Jefferys maintained and added to his former MB3A role. He took over responsibility for Mr Bewley’s CSM secretariat branch, in addition to maintaining his role on the CSM and BSC.\(^ {817}\)

6.309 Mr Hagger was initially given a lead role in Business E, Executive Support, but in May 1990 he moved to head Business B, Abridged Licensing. Thereafter he ‘became more detached in relation to the work being done on BSE’ save in respect of the CDSM and as line manager for Dr Raine.\(^ {818}\) Business B did, however, provide some clerical support to Business A, including the administrative secretary of the BSEWG, Mrs Shersby.

6.310 As discussed below, the BSEWG was the key adviser to the CSM and other committees during this period. Mr Hagger told us that Business A would have had primary responsibility for the lead in relation to the BSEWG, although in planning the agenda for such a meeting Business A would have consulted with Business B.\(^ {819}\)

6.311 It appears some confusion reigned during all these changes. Mr Hagger told us he continued to get many papers because the directory was out of date, and he was a ‘familiar name’ and ‘the point of contact in Medicines Division/MCA rather than specifically for my input’.\(^ {820}\) He passed them on as appropriate. ‘The ethos of the Division was such that one continued to provide advisory support if need be to those who might be new to a particular area of responsibility.’\(^ {821}\) Dr Purves told us

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\(^{814}\) S447 K Jones paras 6, 11
\(^{815}\) S419 Jefferys para. 38
\(^{816}\) S476 Hagger para. 22
\(^{817}\) S419 Jefferys para. 12; S476 Hagger para. 22
\(^{818}\) S476 Hagger para. 22–25
\(^{819}\) S476 Hagger para. 50
\(^{820}\) S476 Hagger paras 25, 49
that at the end of 1990 an administrative group was set up to assist in liaison on BSE between the different Departments, and more particularly to circulate relevant papers.\footnote{822}

**6.312** Later, when the focus moved to the EC, with the preparation of European guidelines, the brunt of the DH action was borne by Dr Purves and Mr Sloggem. Together with Dr Rotblat they had been involved throughout in advising on biological products in respect of BSE, first in the ‘triple-line’ arrangement of Medicines Division and then, from 1990, in the Biological Unit, as part of Dr Jefferys’s Business A in the reorganised MCA.

**Identifying and following up the risk products**

**6.313** The MCA, like VMD, quickly found that obtaining full responses to 4,000 letters by May 1989 was impossible. The paper for the BSEWG prepared by the MCA in June to rank risk products was a useful and timely framework for setting priorities. However, it did not discuss timing.

**6.314** As Mr Burton’s minute of 2 June 1989 flagged up, collecting the data was not the only problem. The MCA had resource problems over organising and analysing the data.\footnote{823} For these reasons they postponed the first meeting of BSEWG until September. We did not explore with witnesses how practicable it would have been to stick to the original July date and thus move things along rather faster. It did strike us, however, that there might have been things to discuss even at this stage of the exercise.

**6.315** The paper on risk categorisation gave the ‘initial steer’ to the new Working Group, both about matters where its expert opinion was needed and about the style with which the exercise was to be pursued. It quoted the *Southwood Report* findings, ‘the risk to man via medicinal products is remote’ and added its own gloss: ‘it is important not to undermine this considered advice by demanding unnecessary assurances and information from manufacturers’.\footnote{YB89/9.6/11.5}

**6.316** This bore particularly on the difficult question of items still in production or held as stocks – postponed in February until more was known. As discussed in Chapter 5, the overwhelming opinion of the professionals at that time had been that on the basis of judging between two evils, existing products and stocks should not be immediately withdrawn. As Dr Schild, Director of NIBSC, put it in his statement to us:

> The risk posed by bovine materials to humans was entirely theoretical at the time; the risk posed to the public by the withdrawal of vaccines from the market was, on the other hand, a real one.\footnote{S575 Schild para. 70} 

**6.317** However, the corollary was that injectable medicines derived from suspect bovine material should be replaced as soon as possible. This was already being forgotten.
6.318 The statement in the paper for the BSEWG carried that process a stage further in intimating that there should not be excessive pressure on manufacturers to reply to the questionnaire and to conform.

The role of the BSEWG

6.319 We were particularly interested in the role played by the BSEWG and how it influenced decision-taking within the MCA on human medicines. As the chronology shows, it held four important meetings in 1989–90 to discuss the line to be taken on existing products using bovine material.

6.320 The Working Group’s role was purely advisory. It had no powers to make binding decisions nor any kind of executive role. The members were busy people with many other responsibilities. Information gathering and negotiations with manufacturers rested with officials who proposed the BSEWG’s agendas and prepared its discussion papers with recommendations. The main problem for all the advisory committees was to avoid overload with what the Cunliffe Report described as the norm for the VPC:

unconscionable quantities of paper which it would be impossible to read in entirety in the time available.826

6.321 The BSEWG was a somewhat unusual committee. It was common practice to have cross-membership of the key advisory committees. Dr Purves told us ‘it ensured there was consistency of approach among the different organisations’.827 However, in this case the powerful membership included the chairmen of the CSM, CRM, CDSM and JCVI. It also included Dr Tyrrell and three members of SEAC. The full list of members and observers is at Annex 1.

6.322 Because of its membership, endorsement by the section 4 committees of its recommendations was virtually guaranteed. The complexity and difficulty of the subject matter added to the likelihood of this.

6.323 There were obvious merits in this arrangement. It directly drew on knowledge from experts who were advising government in other capacities, notably Dr Taylor, Dr Kimberlin, Dr Will and Dr Schild. It also fostered shared understanding of issues and concerns, and speedy communication of recommendations between all the committees reviewing the use of bovine materials in medicinal products. This was valuable because official minutes tend to be economical and discreet in what they record and can take some time to circulate.

6.324 There were, however, risks associated with a working group composed in this way. It was in effect a powerful network for delivering its own decisions. Its findings were not being assessed by the committees to which it reported in quite the arms-length way it might appear. Important alternative perspectives and views might be lost.

6.325 It seemed to us that, despite these risks, the BSEWG was an effective device for securing a coordinated approach and quickly sharing information between the various DH advisory committees and beyond that, the VPC. It provided for officials

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826 M11D tab 18 p. 27 para. 4.8
827 S535 Purves para. 25
a convenient collective expert view on priorities, risks and possible solutions, and valuable backing for action.

6.326 However, responsibility for collecting and analysing information and deciding when to seek the Working Group’s advice, then following that up with pressure to conform, all lay with officials. As we have seen, their first paper had signalled that dealings with manufacturers were going to be handled with a light touch, in order not to undermine the Southwood Working Party’s advice.

6.327 The Working Group recommended at its meeting that non-complying companies should be encouraged to comply as soon as possible, but left it to the Licensing Authority, ie, officials, to agree the timescale ‘for each individual product as appropriate’. No overall time horizon for replacing all existing risk material, other than ‘as soon as possible’, appears to have been urged by it.\footnote{YB88/9.00/3.7}

6.328 We examined what happened on the three most sensitive groups of products: (i) those derived from brain and other high-risk material, (ii) sutures and (iii) vaccines.

(i.) How high-risk products were handled

6.329 The March guidance had been categorical that no brain and other high-risk material was to be used. The questionnaires were eventually to demonstrate little current use of these as direct constituents of medicines. We noted that the Working Group immediately recommended (and CSM endorsed) modifying the original guidance to permit the use of materials from outside the British Isles. The formal guidelines were never publicly changed to reflect this (and were overtaken by European guidelines in 1992). However, the change must have informed the way officials dealt with existing licences. This BSEWG advice, by offering manufacturers an alternative to totally changing their formulation, would have enabled clean stocks to be produced more quickly.

6.330 We thought the response on high-risk products was adequate. Only two groups of products caused concern. The first of these, a range of homoeopathic products, was quickly identified as being sourced from Germany and the CRM considered that no further action was necessary as the products complied with the BSEWG’s recommendations.

6.331 The second group was a range of allergens. The BSEWG advised that a changeover to Australasian sources should be insisted upon. Discussions with the manufacturer were continuing at the time of the BSEWG meeting in July 1990 and a report was promised for the subsequent meeting. The report presented to the October 1990 meeting confirmed that the manufacturer had now made satisfactory progress in complying with the guidelines.

6.332 As we saw in Chapter 4, bovine insulin was identified at the CMO’s meeting with MAFF in March 1988 as potentially a high-risk product: it contained bovine material as an active ingredient and was administered by injection. Dr Rotblat and Dr Purves listed 42 licensed bovine insulin products in their September 1988 paper.\footnote{YB88/9.00/3.7} However, no insulin product featured among the products upon which the
BSEWG’s advice was sought following the responses to the questionnaire. We inferred from this that none of the products used UK sourced bovine insulin. This appeared to be confirmed when the safety of bovine insulin was raised with the MCA in March 1990 by the British Diabetic Association. In his reply at the end of April, Dr Jefferys stated that manufacturers of bovine insulin had responded to the request for information and added, ‘There are no bovine insulins sourced from cattle in the UK or Ireland.’

(ii.) How absorbable sutures were handled

6.333 These were a widely used and essential surgical material implanted into patients. Because they were obtained from intestines where lymphoid tissue was located, they were ranked as medium risk.

6.334 As we noted in the chronology, since June 1989 ways of complying with the guidelines had been under discussion between the CDSM team in the MCA and the major UK manufacturer whose licence was due for renewal. A detailed paper was presented to the BSEWG in September 1989, setting out the company’s proposals in the short and long terms.

6.335 The BSEWG did not find this a straightforward matter, and there was evidently a considerable divergence of views. Professor Collee told us of his personal concern about the use of catgut in neurosurgery, which led him to add a chairman’s note to the meeting minutes about the minority view that such use should not take place. We could well understand that concern, based, as Professor Collee’s note said, on logic and scientific consistency.

6.336 Of the three reasons for the majority view recorded in the BSEWG minutes, the first two did not seem to us to be compelling. The first reason, the fact that the use of ovine sutures had not caused CJD, was not an answer; it could not be assumed that BSE would behave like scrapie, and the other action taken by the Government recognised that. The second argument, namely that the material was seldom used in neurosurgery, suggests that a ban would not have caused any great practical difficulty, and was no reason for failing to act in the small number of cases where the risk might in practice arise. The third reason, not damaging the public perception of the safety of other bovine products, was in reality a judgement about presentation, not the merits of the case. It was interesting in demonstrating the continuing preoccupation with avoiding public doubts about bovine products, including among doctors.

6.337 We have noted the further reason identified by Professor Berry, Chairman of the CDSM, which subsequently endorsed the BSEWG advice, namely that the selection of materials other than those established by clinical experience could expose patients to hazards greater than those posed by catgut.

6.338 In the light of what was known at the time and the difficulty of quickly finding the huge quantities of material from a reliable long-term source elsewhere, we consider that the experts’ recommendations on sutures for general use were
reasonable. On the specific question of continuing use in neurosurgery, there was an issue of judgement as to whether the increased risk warranted a different course of action. The issue was not easy; witness the split in views. We do not criticise the judgement that was made at the time, although with hindsight it might have been preferable if the minority view had prevailed.

6.339 Clearly Ethicon made energetic efforts to comply with the guidelines. It ceased to use UK sourced bovine material in November 1989, and by June 1990, 100 per cent of the material it supplied to the UK market was sourced from Australasia.

6.340 As with insulin, we note that there is so far no evidence that neurosurgery using these sutures figured in the history of any of the vCJD victims. Given that introduction into the brain is normally a speedy route for disease transmission, we take the absence of such cases as a hopeful sign that the continued availability of these sutures until June 1990 had no adverse consequences.

(iii.) Vaccines

6.341 The third and most difficult category, making up most of the products of concern, were vaccines. Vaccines were used to prevent a wide range of childhood diseases such as mumps, measles, diphtheria and whooping cough, as well as more exotic diseases.

6.342 As we discussed in Chapter 5, the fear that withdrawal of existing products, or warnings about them, might undermine the national vaccination programme for children had been the main factor in the decision to play matters low key and to allow production and use of existing stocks to continue. We noted that the issue was not the deliberate inclusion of material in the finished product, but the effects of its use as a medium to nourish the growth of cells that in turn would produce an antigen or virus for the vaccine.

6.343 One problem was lack of information; were the growth media infective, and if so was there a possibility that infective material might be present in the finished product despite the ‘washing’ and other production processes? The only way to resolve this was through transmission experiments. The NIBSC seminar in 1988 had identified a need for studies of foetal calf serum, but these do not appear to have been undertaken. The NIBSC interest in doing research work on this was dropped for a number of reasons. The subject was also raised in a recommendation of the Tyrrell Committee Interim Report about studies of infectivity of bovine serum albumin, foetal calf serum and other media using bovine material. We discuss in Chapter 7 how that proposal fared. It was not until 1993 that the results of work at the NPU into the infectivity of bovine serum were reported. These results proved negative.

6.344 The BSEWG therefore had no firm evidence about infectivity to help it decide what to recommend when considering the four vaccines identified by Dr Rotblat from the questionnaire responses as giving cause for concern. It discussed the problem at its second meeting in terms of ‘the hazard-to-benefit ratio’.

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835 YB98/5.16/2.1–2.12 at 2.11; S575 Schild para. 41(1)
836 S575 Schild para. 41(4)
837 S575 Schild para. 41(4), S576 Minor para. 25
838 M8 tab 12 p. 148
This was a purely pragmatic judgement on the familiar lines that the benefits from the vaccination programme outweighed the theoretical risk from BSE. It indicated that negotiations should take place to ensure that sources were changed as soon as possible and to replace existing stocks with new material whenever feasible.839

6.345 By its third meeting in June 1990, Professor Collee, in an effort to obtain some firm evidence, had contacted Dr Taylor of the NPU, who was himself a member of the Working Group. In his statement, Professor Collee told us the BSEWG discussed these materials in great detail and concluded the risk could be described as very remote rather than merely remote.840 One of the Working Group members, Dr Schild, head of the NIBSC, which sets standards for and tests biological products, told us in his statement that calf serum was and still is considered a very low-risk material.841

6.346 These reassuring views must have formed the context in which the BSEWG assessed reports at that meeting about the protracted process of establishing ‘clean’ stocks of the four vaccines that did not comply with the guidelines. As is evident from the chronology, it looked at the position on each of those products in detail, allowing in some cases a certain latitude, depending on considerations such as the availability of alternatives and the nature of the material used. However, as time passed, its attitude hardened about allowing more time. By November 1990, Professor Collee was telling CSM that it was unreasonable to allow vaccines associated with UK bovine products to be used when they could be replaced with new batches. The BSEWG line of advice was hardening and he wanted CSM ‘to count me amongst the hawks on this’.842

6.347 As we indicated above, viewed in the circumstances of the time, which we have explored in this volume, the decisions taken about these four vaccines were reasonable ones. However, it can be seen with the benefit of hindsight that they contributed, overall, to a protracted process of achieving compliance with the guidelines.

Our general conclusions on the handling of human medicines

6.348 It seems to us that taken case by case, the ‘flexible response’ was reasonable. The consequence overall, however, was that existing stocks of some products may have been used until late 1991 and possibly longer. It seems highly unlikely that so long a period of grace was what those who took the decision not to require an immediate withdrawal of stocks had in mind. A key factor, as in veterinary medicines, was the perception shared by MCA staff and BSEWG members alike that the risk was remote. The urgency of removing existing products had become forgotten. Instead, perversely, the reassuring message about low risk undermined the action necessary to achieve it.

6.349 However, the lack of urgency also seemed in part attributable to the somewhat chaotic state of affairs in the MCA already discussed. The reorganisation into businesses added to the turmoil and, as Mr Sloggem and Dr Purves discovered in 1994, the black hole continued in the management of its data system. All this contributed to poor accountability in the arrangements being operated.843
6.350 Matters were being dealt with by a range of different people ad hoc in competition with a great deal of other work. There does not appear to have been an overall management strategy. Officials were seeking views where and when they judged it helpful, but this was obligatory only where sanctions were envisaged, not where latitude was being extended. The pace of action was in their hands.

6.351 The progress reports to the BSEWG appear to be the only form of accountability for progress, and these, as we have seen, were vague on many details. Moreover, the BSEWG was their adviser, not their manager. Because of the closed nature of medicines licensing and the earlier decision to keep as low a profile as possible, there was no external pressure on officials or on companies to defend the slow speed at which matters were moving. We discuss at the end of this chapter some general questions this raised about accountability for medicines matters.

3. The response on medical devices and other matters

The basis for action

6.352 As noted, our interest here was in what were, at the time, unlicensed medical devices. Items to be considered included biological heart valves, bone grafts, disposable products including devices coated with gelatine and heparin, and dressings and adhesives. Even without licensing, the NHS as main purchaser could exert powerful influence on suppliers. This was important because the BSEWG placed tissue implants, open wound dressings, surgical materials and dental and ophthalmic products among the high-risk categories requiring action.

6.353 As noted in Chapter 5, the interest of the relevant DH division, PD/STD, was only belatedly recognised in February 1989. Once that happened those concerned did not allow any grass to grow under their feet. Having read the Southwood Report and collected material on spongiform encephalopathies, they searched their database, reviewed product licences held by the Secretary of State, and decided to mirror the guidance, questionnaires and the letters of the MCA and VMD. Their documents were speedily prepared, and despatched only days after the those of the MCA and VMD. Though only a relatively small number of products and users were involved, none the less the exercise required 330 letters. They also wrote to NHS regional pharmaceutical staff. They are to be commended for this speedy response.

Whose job was it to take action?

6.354 PD/STD showed no reluctance over providing a lead within their triumvirate of pharmacists, doctors and administrators. Miss Duncan, the pharmacist head of Safety and Quality, STD, immediately cleared a line with Dr Metters about action and followed this up.844

6.355 One of her staff, Mr Will Burton, both advised the NHS on pharmaceutical supplies and did audit work for the Manufacturers’ Registration Scheme (MRS) for medical devices. He quickly became the liaison officer between PD and the MCA on BSE, keeping the administrative section informed. We were greatly assisted in

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843 S454 Sloggem para. 131; S535 Purves para. 212
844 YB89/2.22/10.1; YB89/2.23/5.1
our examination of what was done, not only by the statements and documents we received, but also by the careful and detailed support notes supplied by Mr Burton.

Securing action

6.356 It was agreed from the start that the policy line would follow that of Medicines Division (ie, the MCA) as having the overwhelming interest. This affected what followed both in the interpretation of the guidelines and the timing of action.

6.357 As with VMD and the MCA, it proved difficult to secure a 100 per cent response or an accurate one, and PD/STD had to spend months chasing up with letters, telephone calls and successive reminders. However, by 24 November 1989 all the manufacturers had replied.\footnote{YB89/11.27/4.1}

6.358 PD/STD identified two heart valve manufacturers whose products gave particular cause for concern. It met the companies more than once and told us: ‘the companies were left in no doubt . . . that their compliance with the guidelines was required.’\footnote{S605 Burton para. 104} By 26 January 1990 one had complied with the guidelines. The other ceased production at the end of April 1990 because of the expense of alternatives, and at this stage recalled devices on the shelves.\footnote{YB90/1.26/16.1; YB90/4.27/6.1} Thus the timescale for compliance was, in the end, similar to that for sutures.

6.359 We were impressed by PD/STD’s administrative approach, as demonstrated by the documentary evidence. In particular, it set a series of deadlines for different activities; it promptly opened up discussions with known users of bovine products and sought to identify other possible users; it chased to get responses; and it set up a database and arranged for audit check results to be placed on it and for it to be continuously updated.

6.360 It also prepared a draft paper on control of harvesting techniques, designed to reduce risk of contamination, and set out how manufacturers should go about obtaining animal material for use in medical devices.

6.361 To coordinate all this action within its sphere of responsibility, it set up an STD BSE working party of officials. Mr Burton described it as a ‘project team constituted especially for the purpose from those with the appropriate experience or expertise required to contribute to it’.\footnote{S605 Burton para. 49} The group met regularly to monitor and progress matters and to share information. Reading the records of matters it discussed suggests it was an efficient arrangement.

6.362 Mr Burton told us that from the time they got involved, he and his colleagues considered that the risk of transmission might be potentially serious.\footnote{S605 Burton para. 49} From the papers we saw they appeared to have been held back by the tempo of the exercise as a whole and the need to pace themselves with the MCA and advisory committees.\footnote{See for example YB89/5.12/10.2, YB89/6.02/7.1}
6.363 None the less, as agreed initially they faithfully followed that lead and modelled their actions accordingly. In doing so they were following what they saw as the prescribed low-key approach.

**Our general conclusions on the handling of medical devices**

6.364 We recognise that the response required from PD/STD was altogether on a much smaller and more manageable scale than that required of the MCA and VMD. Moreover, the Division did not appear to be labouring under such difficult management and resource problems. None the less, PD/STD’s response illustrates an administrative approach that, had it been mirrored by the MCA and VMD, might have led to a brisker momentum in the important task of phasing out suspect products.

**4. Our general conclusions on follow-up to the guidelines**

**What was handled well**

6.365 Many things were done well in the follow-up to the guidelines. In particular:

- The comprehensive questionnaire approach was a heroic venture to make good the deficiencies in both Departments’ databanks and to bridge the gap between the different sorts of licence in existence.
- Despite their perception that the authoritative view now was that the risk from medicines was remote and action purely precautionary, officials worked diligently to carry the follow-up action to its conclusion.
- The most urgent items were identified and dealt with promptly.
- They successfully achieved the switch-over voluntarily through their case-by-case approach, despite having no evidence to offer of human risk.
- They did so while struggling with the legacy of serious past failings in the running of the licensing system that were still in process of being addressed.

**Where there was room for improvement**

6.366 As we have noted, these endeavours added up to a long-drawn-out process on some items, including some vaccines. There is no means now of finding out whether those products were infective, nor of knowing how many people they were used on. Certainly large numbers of people are vaccinated annually as part of the vaccination programme or prior to overseas travel. Knowing what is now known, a harder line might have been taken, and the window during which people were exposed to potential risk might have been some months or even years shorter.

6.367 One of the main causes of delay was that the Departments believed their own reassuring message. Their overwhelming concern was to avoid a greater public health risk through a vaccine scare. Instead of seeing this as the reason why so reassuring a public line had been taken, they came to believe their own upbeat presentation as a justification for relaxing their efforts. This was only one, but perhaps the most glaring, example throughout the whole of the handling of BSE
where the wish to put the best face on things misled the very people whose understanding and efforts were needed to create the necessary conditions of safety.

6.368 Even within the blinkers of the false impression on risk, there was undoubtedly room for improvement in the way the guidelines were followed up. We think it would have been better if:

i. There had been a handling plan that ‘managed’ the whole process to specific deadlines. This would have required leadership from DH whose priorities determined the overall approach. Ideally this would have happened as soon as the exercise was launched. Alternatively, it might have followed the first meeting of the BSEWG when the criteria were agreed and the measure of the problem was clear. It is a pity that Mr Love’s proposals in October for a coordinated approach with clear responsibilities were not followed up.\(^\text{851}\) This was an opportunity lost.

ii. There had been clear expectations about reporting to top management and Ministers. We were struck by how little Ministers were informed, let alone consulted, about the massive administrative exercise of following up the guidelines. Dr Jefferys told us that ‘Ministers never provided officials with criteria to apply when considering which matters to refer to Ministers. Officials had to apply their own judgement when deciding what matters to refer to Ministers.’\(^\text{852}\) We believe that Ministers should take a lively interest in what is being done in their name, and that there should be clear presentation to them of important policy decisions.

5. General conclusions on medicines and BSE

6.369 It was not part of our remit to carry out a review of the question of medicines licensing at the time and the soundness of its principles. In considering some general conclusions, we thought the view of Mr Cunliffe in 1988 when he reviewed the veterinary medicines licensing system provided a useful pointer on how the handling of BSE might be assessed:

\[\text{The general outline of the UK system ie, a licensing office taking advice from an independent expert body and reporting to the Minister, seems to be correct. The present arrangements allow and, must continue to allow, licensing decisions to be made on science based and defensible judgements about the balance of risk and benefits without undue pressure from industry, politicians, MAFF or Treasury.}\] \(^\text{853}\)

6.370 We have commented above on the importance of ‘reporting to the Minister’. Mr Cunliffe’s assessment also refers to other key elements.

(i.) Science-based judgements and the role of committees

6.371 Mr Cunliffe was of the view that licensing decisions were and should continue to be ‘made on science based and defensible judgements about the balance of risk and benefits’. It seemed to us that the way that ‘risk and benefit’ calculations...
were done on medicines matters where BSE was concerned often owed much more to judgement than to science. The memorandum which DH supplied on risk assessment reinforced this view. 854

6.372 For BSE it was indeed a matter of exercising judgement given the lack of firm scientific evidence. It is not necessarily a bad thing that expert committees should be asked to perform this task, provided that it is clear that is what they are doing. The discussion on sutures was an interesting example of this. We noted that the BSEWG, like the section 4 committees, took into account not only the technical assessments officials provided, but also more pragmatic considerations. Balancing risks about public concern with scientific risks is effectively making a policy judgement. The earlier advice of Professor Collee to the JCVI that the risk from vaccines had been considered by the HVMBG to be remote and speculative, and very much outweighed by the benefits was another example of a value judgement. It was important that the section 4 committees and subsequently MCA officials should be clear about what was a scientific assessment, and what was a value judgement, so that value judgements were not treated as expert assessments of risk. Who was advising whom? It was for the section 4 committees to advise but for Ministers, sometimes acting through officials, to decide.

6.373 This is a general issue about advisory committees that we discuss further in vol. 1: Findings and Conclusions. It is further complicated by other features we have noted such as the cross-membership of committees and the risk that this can create a hidden decision-taking mechanism.

(ii.) Insulation from pressure versus accountability

6.374 Mr Cunliffe also said that those taking decisions must avoid undue pressure from ‘industry, politicians, MAFF or Treasury’. The advisory committee system is one of the devices designed to fulfil that purpose. Another is the deliberate ring-fencing of medicines licensing business from the rest of the work of DH and MAFF. As one witness put it, ‘Medicines Division consumes its own smoke.’ 855 There are respectable reasons for this. A frequent accusation against MAFF was that it acted in the interests of the food industry or farmers rather than of consumers. It was to help create a visible separation between these interests that Mr Gummer initiated the major restructuring of MAFF commands in 1989. Medicines licensing for animals or humans needed to be seen as dispassionate and striking a fair balance.

6.375 The problem with this ring-fencing is that, coupled with the advisory committee system, it reduces the normal accountability of officials taking decisions on Ministers’ behalf. The risk is that those outside the unit concerned may be reluctant to question the competence, speed and judgement of the work of those within it.

6.376 This is exacerbated by the culture of secrecy associated with the provisions of the Medicines Act about non-disclosure of commercially sensitive information. We agree with Mr Cunliffe’s comment: ‘more openness in factors affecting human safety and animal health would instil greater public confidence.’ 856
6.377 We commend the moves made by the VPC during this period to put more matters in the public domain by publishing documents. However, this was only a partial step in that direction.

6.378 Another factor that appears to have left Ministers and senior management in DH in difficulties about accurately tracing and reviewing past actions was defects and gaps in DH record-keeping, ranging from destruction of ministerial papers to the dismal history of its medicines IT system.

6.379 We think it is important that there should be properly reasoned and recorded decision-taking, and that the criteria being applied are made openly available. It should be made plain by whom decisions are actually taken and the basis for these, both on general policy matters and on individual items. And as we have said, important decisions should be validated by Ministers.

(iii.) Liaison between MAFF and DH on medicines

6.380 We discuss in detail in Chapter 4 the question of liaison between MAFF and DH on BSE and medicines. While we expected to find a degree of inter-departmental remoteness, we were surprised at the distance of the gap on medicines policy matters.

6.381 Topics that might have benefited from structured discussions between the two Licensing Agencies in order to establish consistent policies include the SBO Order; testing of sera and other pharmaceutical products for infectivity; testing of stored BSE cattle organs of the type used for implants; identifying and tracking ‘clean’ herds and animals for pharmaceutical use; post-mortem testing of such cattle; organ harvesting and avoidance of contamination; gelatine and tallow.

(iv.) Where medical materials come from

6.382 A number of these topics concerned the source of medical materials. One of the matters that clearly emerged from the response of the MCA and its committees to BSE was the absence of even rudimentary knowledge about how pharmaceutical materials were obtained from animals, and techniques to ensure they were not contaminated in any way. Some of the pharmaceutical manufacturers themselves appear to have been equally uninformed, since they relied on intermediaries to provide them with their raw materials. Thus one manufacturer told us:

The sourcing and processing of these materials is the work of suppliers one or more steps ‘upstream’ from a pharmaceutical company such as [Glaxo Wellcome]. For our company, the details of such activities were traditionally of little concern so long as the substance in question passed regulatory specification tests.

6.383 Even less appears to have been known by some of those advising on biological products. Professor Campbell, Chairman of the JCVI from 1989 to 1996, told us:

\[857\] M67A tab 4 p. 52 (Veterinary Products Committee Annual Report 1996)
\[858\] S608 Wright para. 2.1
For my own part, I had no detailed knowledge about the way in which vaccines were manufactured. Although I was aware that bovine material was used in the manufacture of vaccines, I had no knowledge of the extent of its usage apart from what I learned at meetings of the BSE Working Group.859

6.384 This was an important knowledge gap among those responding to BSE since the fundamental basis of the UK, and later the European and WHO, approach to both animal and human medicinal products was that clean sources were the only way forward. NIBSC had foreshadowed this in 1988:

If BSE is held to be a problem, the only option is to ensure that bovine materials for manufacture of biological medical products are derived from cattle free from the disease.860

6.385 We noted that concerns about its limited knowledge cropped up repeatedly in the BSEWG. It seems to us that thought should be given to ensuring that those dealing with medicinal products deriving from animals are informed about the sources and collection of materials.

(v.) The legislative framework

6.386 Our review of medicines and BSE highlighted the difference between the legislative framework for medicines and that in other areas.

6.387 Where medicines are concerned, unlike the situation on suspected animal contamination of food, it is not possible to turn off the tap at source by destroying the animal or its products. Hence the SBO ban applied to food but not pharmaceuticals. Instead each manufacturer has to validate the legality and safety of its ingredients. Mr Lawrence recognised this and noted in his briefing material to Ministers in February 1989 that manufacturers would need to secure appropriate assurances from their suppliers.861

6.388 It might have been helpful if the legislative powers available to cut off diseased animals or their contaminated products at source, so that they never entered the food chain, could also have been used to ensure they were not available for medicinal purposes. Manufacturers who purchased material from suppliers might have welcomed such action, which could have saved them many later problems over provenance and certification requirements, in particular for products that were not in their original raw state. It could also have dealt with products that were not covered by the Medicines Act.

6.389 We recognise that there are different considerations in play, and that much is dictated by relevant European legislation. However, the different frameworks make it more difficult to achieve a consistent approach. The most glaringly anomalous outcome was the ban on the use of intestines for food purposes while intestines might still be used for sutures – thought to be a higher-risk route of infection.

6.390 We think the current variety of different powers over animal health, food safety, medicines and other products should be reviewed to ensure that they offer a
means of consistent and prompt action in future when an infected product needs urgently to be removed from circulation.
## Annex 1 to Chapter 6: People attending the BSE Working Group

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<tr>
<th>Name</th>
<th>Organisation</th>
<th>Attendance</th>
<th>Position(s) held during membership of BSEWG</th>
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<tr>
<td>Professor J G Collee</td>
<td>(Chairman of BSEWG)</td>
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<td>Also Chairman of BSC</td>
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<td>Professor A W Asscher</td>
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<td>Chairman of CSM</td>
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<td>Professor A Campbell</td>
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<td>Chairman of JCVI</td>
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<td>Professor D Lawson</td>
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<td>Chairman of CRM 1987–91, Member CSM 1987–93</td>
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<td>Professor C L Berry</td>
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<td>Chairman of CDSM, Member CSM 1990–92</td>
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<td>Dr R Kimberlin</td>
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<td>Member of Tyrrell Committee and SEAC</td>
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<td>Dr B J Kirby</td>
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<td>Dr P Minor</td>
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<td>Head of Virology NIBSC 1985 +</td>
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<td>Dr G G Schild</td>
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<td>Director NIBSC 1985 +</td>
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<td>Dr D N Taylor</td>
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<td>Y Y Y Y Y</td>
<td>Principal Research Scientist, NPU</td>
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<td>Dr D A J Tyrrell</td>
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<td>Chairman of Tyrrell Committee and SEAC</td>
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<td>Dr W A Watson</td>
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<td>CVL, Member of Tyrrell Committee and SEAC</td>
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<td>Dr R G Will</td>
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<td>CJD Surveillance Unit</td>
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<td>----------------------</td>
<td>--------------</td>
<td>------------------</td>
<td>-----------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Dr D Jefferys</td>
<td></td>
<td>6 Sept. 89</td>
<td>Y Y Y Y Y MB3A (MD) 1988–89, Licensing (MCA) 1991–95</td>
</tr>
<tr>
<td>Dr P Adams</td>
<td></td>
<td>10 Jan. 90</td>
<td>Y Y N Y N MB3B (MD)</td>
</tr>
<tr>
<td>Dr F Rotblat</td>
<td></td>
<td>4 July 90</td>
<td>Y Y Y Y Y MB3A (MD)</td>
</tr>
<tr>
<td>Dr J Raine</td>
<td></td>
<td>31 Oct. 90</td>
<td>Y Y Y Y Y MB3B (MD)</td>
</tr>
<tr>
<td>Dr K Winship</td>
<td></td>
<td>8 July 92</td>
<td>Y Y Y Y Y MB5A (MD)</td>
</tr>
<tr>
<td>Dr J Purves</td>
<td></td>
<td></td>
<td>Y Y Y Y Y MB5A (MD)</td>
</tr>
<tr>
<td>Dr D Eisen</td>
<td></td>
<td></td>
<td>Y Y Y Y Y</td>
</tr>
<tr>
<td>Mr J Sloggem</td>
<td>DH (MCA and other departments)</td>
<td>Y Y Y Y Y</td>
<td>Pharmaceutical Officer (MD/MCA) 1988–91, R and D Division (DH) 1991–93; Joint Secretary Tyrrell, SEAC observer</td>
</tr>
<tr>
<td>Dr H Pickles</td>
<td></td>
<td></td>
<td>Y Y N Y N PMO (DH) 1988–91, R and D Division (DH) 1991–93; Joint Secretary Tyrrell, SEAC observer</td>
</tr>
<tr>
<td>Mr M Love</td>
<td></td>
<td></td>
<td>Y Y Y Y Y MB1B (MD)</td>
</tr>
<tr>
<td>Mrs E Baker</td>
<td></td>
<td></td>
<td>Y Y Y Y Y PD/STD</td>
</tr>
<tr>
<td>Mr W Burton</td>
<td></td>
<td></td>
<td>Y Y Y Y Y PD/STD</td>
</tr>
<tr>
<td>Mrs B Shersby</td>
<td></td>
<td></td>
<td>Y Y(s) Y(s) Y(s) N Pharmaceutical Officer (MD/MCA)</td>
</tr>
<tr>
<td>Dr I Boyd</td>
<td></td>
<td></td>
<td>N N Y Y Y(s) SMO Health Aspects of Environment and Food Division (HEF(M)1) (DH) 1991–95</td>
</tr>
<tr>
<td>Dr B R Matthews</td>
<td></td>
<td></td>
<td>N N N Y Y</td>
</tr>
<tr>
<td>Dr A Wight</td>
<td></td>
<td></td>
<td>N N N N Y SMO Health Aspects of Environment and Food Division (HEF(M)1) (DH) 1991–95</td>
</tr>
<tr>
<td>Dr A Lee</td>
<td>MAFF</td>
<td></td>
<td>Y Y Y Y Y Biologicals and Recombinant Products 1989–92, Immunologicals and SARS, VMD 1992–93</td>
</tr>
</tbody>
</table>

Y(s) denotes secretary for the meeting
### Annex 2 to Chapter 6: Response to the Questionnaires

#### Human Medicines

<table>
<thead>
<tr>
<th>Date (BSEWG meeting)</th>
<th>Level of response to CSM questionnaire</th>
<th>Analysis of returns</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>September 1989</td>
<td>75% of licence holders had responded.</td>
<td>574 products using animal ingredients; 17 containing UK only bovine ingredients; and 40 containing bovine ingredients of mixed origin. 176 products not conforming to guidelines, but only 2 of concern.</td>
<td>Non-responses to be followed up before next meeting.</td>
</tr>
<tr>
<td>January 1990</td>
<td>94% of licence holders had responded.</td>
<td>No products using high-risk material that did not meet the guidelines; majority of non-compliant products used BSA/FCS.</td>
<td>MCA to consider the 6% non-respondents.</td>
</tr>
<tr>
<td>July 1990</td>
<td>Only 4 companies yet to respond. None of them were full licence holders.</td>
<td></td>
<td>Further information required from these 4 companies.</td>
</tr>
<tr>
<td>October 1990</td>
<td>All outstanding replies received.</td>
<td>Final 4 replies gave no cause for concern.</td>
<td></td>
</tr>
</tbody>
</table>

#### Veterinary Medicines

<table>
<thead>
<tr>
<th>Date (relevant document/meeting)</th>
<th>Level of response to VPC questionnaire</th>
<th>Analysis of returns</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>August 1989. (Letter from Dr Lee to Mr Armstrong)</td>
<td>186 of 245 licensees had responded, accounting for 3,239 products.</td>
<td>303 products contain material of bovine, ovine or caprine origin.</td>
<td>Reminders to be sent to 59 non-respondents. Follow-up letters to be sent to companies where further information required. Initial analysis of responses to begin soon.</td>
</tr>
<tr>
<td>September 1989. (Dr Lee's summary paper to BSEWG)</td>
<td>75% response.</td>
<td>45 bovine or ovine ingredients identified, the most common being bovine serum (86 products).</td>
<td>More information needed from some companies. Effort would focus on products with most risk of BSE contamination.</td>
</tr>
</tbody>
</table>
### Date (relevant document/meeting) | Level of response to VPC questionnaire | Analysis of returns | Follow-up
--- | --- | --- | ---
December 1989. (Dr Lee's update) | 190 licensees had replied by this point. | 348 medicines with animal material, of which 302 contained bovine/ovine/caprine material. |  
December 1990. (VMD report to VPC meeting) | Most companies have now made satisfactory arrangements to comply with the guidelines. | A number of specific products were mentioned that required attention. These are dealt with in the narrative. |  

**Medical Devices**

<table>
<thead>
<tr>
<th>Date</th>
<th>Level of response to medical device questionnaire</th>
<th>Analysis of returns</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>August 1989</td>
<td>66% response.</td>
<td>46 companies used animal material, 26 used bovine material of which 2 sourced from the UK using pericardium tissue.</td>
<td>Definitive list of non-responders to be drawn up and second reminder sent.</td>
</tr>
<tr>
<td>November 1989</td>
<td>All companies who had been sent the questionnaire had responded.</td>
<td>76 products using animal materials, 34 of bovine origin, but only 13 of these from the UK or Europe. Only 2 with UK bovine material as a major component.</td>
<td></td>
</tr>
<tr>
<td>December 1989</td>
<td></td>
<td></td>
<td>PD/STD meetings with the two manufacturers with products having bovine material as a major component.</td>
</tr>
<tr>
<td>July 1990 (Memo by Mr Burton)</td>
<td></td>
<td>1 company had changed to non-UK source material (January) and the other had ceased production (April).</td>
<td></td>
</tr>
</tbody>
</table>

Source: Compiled by the Inquiry from documents referred to in Chapter 6
Annex 3 to Chapter 6: Veterinary medicines that did not comply with the 1989 CSM/VPC guidelines

<table>
<thead>
<tr>
<th>Company</th>
<th>Number of products</th>
<th>Target species</th>
<th>Ingredient (Bovine (b) or ovine (o) material)</th>
<th>Country of origin</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 vaccine</td>
<td>avian</td>
<td>(1) Muscle (b)</td>
<td>France/US/UK</td>
<td>(1)+(2) Changed to US source April 1990</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2) Casein digest (b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1 diagnostic 1 vaccine (Animal Test Certificate only)</td>
<td>1 bovine 1 avian</td>
<td>(1) Muscle (b)</td>
<td>UK</td>
<td>(1) Changed to closed herd April 1990</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2) Casein digest (b)</td>
<td>Various</td>
<td>(2) Acceptable (milk)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(3) Soup stock (b)</td>
<td>UK</td>
<td>(3) Company confirmed source is Oxoid/1</td>
</tr>
<tr>
<td>3</td>
<td>9 emergency vaccines each restricted to use on single farm</td>
<td>2 avian 1 bovine 5 porcine 1 simian</td>
<td>Blood (o) Agar base</td>
<td>UK company</td>
<td>Oxoid/1,3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All products discontinued between 1989 and 1992</td>
</tr>
<tr>
<td>4</td>
<td>7 vaccines comprising 5 emergency vaccines and 2 vaccines (Animal Test Certificates only)</td>
<td>4 avian 1 bovine 2 simian</td>
<td>Soup stock (b)</td>
<td>UK</td>
<td>Company confirmed source is Oxoid/1</td>
</tr>
<tr>
<td>Company</td>
<td>Number of products</td>
<td>Target species</td>
<td>Ingredient (Bovine (b) or ovine (o) material)</td>
<td>Country of origin</td>
<td>Outcome</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------</td>
<td>----------------</td>
<td>-----------------------------------------------</td>
<td>------------------</td>
<td>---------</td>
</tr>
</tbody>
</table>
| 5       | 23 vaccines       | 6 avian 1 bovine 1 porcine 15 small animal | (1) Serum (b)  
(2) Milk Amine (b)  
(3) Hydrolysed gelatin (b/o)  
(4) Casein hydrolysate (b)  
(5) Casein peptone (b)  
(6) Bovine serum albumen (BSA) (b) (b) present in 1 avian vaccine only | UK/NZ  
UK  
Various  
Various  
UK  
UK/NZ | (1) Changed to NZ source January 1990  
(2) Acceptable (milk)  
(3) Acceptable heat treatment  
(4) + (5) Acceptable (milk)  
No documentation located for the BSA component |
| 6       | 18 vaccines including one Animal Test Certificate only | 1 avian 5 bovine 1 equine 11 small animal | (1) serum (b)  
(2) BSA present in 1 dog vaccine | UK/NZ/Australia/US/Canada  
UK/NZ | (1) Changed to non-UK source February 1990  
(2) No documentation located for the BSA |
| 7       | 3 autogenous vaccines | 2 bovine 1 ovine | Lung tissue (b)  
Warts (b)  
Scabs (o) | UK | All production ceased in 1990 |
| 8       | 13 vaccines       | 2 avian 2 bovine 9 small animal | Serum (b) | UK company | Changed to non-UK source August 1990 |
## ANNEX 3 TO CHAPTER 6: VETERINARY MEDICINES THAT DID NOT COMPLY WITH THE 1989 CSM/VPC GUIDELINES

<table>
<thead>
<tr>
<th>Company</th>
<th>Number of products</th>
<th>Target species</th>
<th>Ingredient (Bovine (b) or ovine (o) material)</th>
<th>Country of origin</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| 9       | 1 vaccine          | fish (immersion) | Brain Heart Infusion Broth (b)             | UK/US             | Changed to US source 1990  
<p>|         |                    |                |                                             |                   | Product withdrawn 1994     |
| 10      | 1 vaccine          | fish (immersion) | Brain Heart Infusion Broth (b)             | US                | Remains under review       |
| 11      | 11 vaccines        | 1 bovine       | (1) Brain Heart Infusion Broth (b)         | (1) UK            | (1) Never marketed         |
|         |                    | 1 porcine      | (2) Serum (b)                              | (2) UK/NZ         | (2) No documentation located for 9 small animal and 1 porcine vaccines |
|         |                    | 9 small animal | (3) Soup stock (b)                         | (3) UK            | (3) Oxoid/1                 |
| 12      | 31 vaccines        | 3 bovine       | (1) Serum (b)                              | (1) Ireland       | (1) Never marketed         |
|         |                    | 4 porcine      | (2) Serum (b)                              | (2) UK/NZ         | (2) No documentation located for 1 sheep and 1 bovine vaccine         |
|         |                    | 8 ovine        | (3) Trypsin (b)                            | (3) UK            | (3) No documentation located for 1 sheep vaccine                      |
|         |                    | 1 fish         | (4) Proteose peptone (b)                   | (4) UK/Holland    | (4) Oxoid/2                 |
|         |                    | 15 more than one species | (5) Hydrolysed casein (b) | (5) UK/NZ | (5) Acceptable (milk) |
|         |                    |                | (6) Casein (b)                             | (6) UK/non-UK     | (6) Acceptable (milk)          |
|         |                    |                | (7) Liver Digest (b)                       | (7) UK/non-UK     | (7) No documentation located for 8 multi-species vaccines |</p>
<table>
<thead>
<tr>
<th>Company</th>
<th>Number of products</th>
<th>Target species</th>
<th>Ingredient (Bovine (b) or ovine (o) material)</th>
<th>Country of origin</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 cont'd</td>
<td></td>
<td></td>
<td>(8) Heart (b)</td>
<td>UK/Ireland/NZ/US</td>
<td>(8) No documentation located for 8 multi-species vaccines</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(9) Skeletal muscle (b)</td>
<td>UK</td>
<td>(9) No documentation located for 7 multi-species vaccines</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(10) Pancreas (b)</td>
<td>UK</td>
<td>(10) No documentation located for 8 multi-species vaccines</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(11) Blood (o)</td>
<td>UK</td>
<td>(11) No documentation located for 1 porcine vaccine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(12) Liver (b)</td>
<td>UK/non-UK</td>
<td>(12) No documentation located for 2 multi-species vaccines</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(13) Soup stock (b)</td>
<td></td>
<td>(13) Oxoid/1</td>
</tr>
<tr>
<td>13</td>
<td>11 vaccines</td>
<td>1 bovine, 3 porcine, 5 ovine, 1 avian, 4 more than one species</td>
<td>(1) Soup stock (b)</td>
<td>UK</td>
<td>(1) Oxoid/2</td>
</tr>
<tr>
<td></td>
<td>3 antisera</td>
<td></td>
<td>(2) Gelatin (b/o)</td>
<td>UK</td>
<td>(1)+(2)+(3) Changed to US sourced medium by 1992</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(3) Bile (b)</td>
<td>UK</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(4) Serum (b)</td>
<td>UK</td>
<td>(4) Changed to closed herd source 1992. Replaced by horse sera 1997</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(5) Heart muscle (b)</td>
<td>UK</td>
<td>(5) Changed to milk based medium sourced from NZ/Australia September 1990</td>
</tr>
</tbody>
</table>
### ANNEX 3 TO CHAPTER 6: VETERINARY MEDICINES THAT DID NOT COMPLY WITH THE 1989 CSM/VPC GUIDELINES

<table>
<thead>
<tr>
<th>Company</th>
<th>Number of products</th>
<th>Target species</th>
<th>Ingredient (Bovine (b) or ovine (o) material)</th>
<th>Country of origin</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>8 vaccines</td>
<td>2 avian (1) Serum (b)</td>
<td>(1) Various including UK</td>
<td>(1) No documentation located for 8 vaccines</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 porcine (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 small animal (2) BSA was a component of 3 small animal vaccines</td>
<td>(2) UK</td>
<td>(2) No documentation located for the BSA component</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>1 plasma substitute</td>
<td>equine small animals calf skin (b)</td>
<td>Various</td>
<td>Changed to non-UK source April 1990</td>
<td></td>
</tr>
</tbody>
</table>

*Species to which vaccine administered

Oxoid/1: By April 1990 heat treated to 132°C for 80 mins and considered acceptable

Oxoid/2: Proteose peptone replaced by L85: contains UK soup stock by March 1990

Oxoid/3: Used NZ source of sheep material

Source: The Veterinary Medicines Directorate (M74 tab 3)

Oxoid ensured that it sourced and processed the ingredients it supplied to the various manufacturing companies in such a way as to be acceptable to the Veterinary Medicines Directorate, thus enabling the companies if supplied to comply with the guidelines.
### Annex 4 to Chapter 6: Human vaccines that did not comply with the 1989 CSM/VPC guidelines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Compliance with guidelines</th>
<th>Estimated stocks of non-complying vaccines</th>
<th>BSEWG advice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMR Peptone</td>
<td>Peptone – switched to non-UK source Sept. 1990.</td>
<td>to Dec. 1990</td>
<td>184,029 doses.</td>
</tr>
<tr>
<td>(unlicensed)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberculin PPD</td>
<td>Glycerol beef broth – eliminated from production second half of 1990.</td>
<td>to Sept. 1991</td>
<td>18 months’ supply (ie, to Dec. 1991).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Compiled by the Inquiry from documents referred to in Chapter 6