4. Initial response on human medicines

4.1 Chapter 3 reviewed the initial response on veterinary medicines. We now turn to the way the parallel issues arising for human medicines were identified and handled by DH over the same period.

Early knowledge of BSE within Medicines Division

4.2 Before the MAFF Permanent Secretary wrote to the Chief Medical Officer about BSE in March 1988 (see vol. 3: The Early Years, 1986–88), Medicines Division had only indirectly been alerted to the new bovine spongiform encephalopathy. They were not members of the Biologicals Committee (BC) and had not been informed of the consideration already given to it by the MAFF veterinarians, nor indeed was that to happen until some months later.

July 1987

4.3 One official in Medicines Division who learnt early on of the emergence of BSE was Mr Sloggem, a Principal Pharmaceutical Officer in the Biologicals Unit, who reported to Dr Purves. In the late 1970s he had been involved with the procurement and quality control of pituitary gland hormones made for the NHS, and had become aware of potential CJD contamination.

4.4 In July 1987 Mr Sloggem was asked to assess an application for a Clinical Trial Certificate (CTC) for a drug made from bovine brain extract containing phospholipids. In the Clinical Trial Exemption (CTX) file he found that Medicines Division had as early as 1984 asked for evidence that ‘slow virus’ contamination was not a problem, in view of the bovine brain source, a question which showed remarkable prescience.

4.5 Seeking more information, Mr Sloggem telephoned Dr David Taylor, a researcher into transmissible spongiform encephalopathies (TSE) at the Neuropathogenesis Unit (NPU) with whom he had previously worked, who told him that a bovine spongiform encephalopathy had recently been recognised. At the end of August 1987 Dr Taylor wrote two letters to Mr Sloggem. In the first he confirmed that a disease newly reported in bovines was ‘scrapie-like’ and in the second, in response to a query from Mr Sloggem, he summarised what was known about oral transmissibility of scrapie, kuru and CJD.

4.6 Mr Sloggem also wrote to Mr Batho in the Animal Health Division of MAFF on 7 September 1987 in relation to the application for a CTC. He wanted to know
about standards for certifying healthy cattle, with a view to placing such conditions on the grant of a CTC. Mr Sloggem told us that his enquiry resulted in a telephone call from Mr Batho at the end of September, in relation to the health criteria for the selection of cattle for food consumption, which he thought might have relevance to the product he was assessing.  

Meeting of the Biologicals Sub-Committee of the CSM on 9 September 1987

4.7 When he attended the next CSM/BSC meeting, on 9 September 1987, Mr Sloggem was therefore aware of the existence of BSE. The product Mr Sloggem was considering was not on the agenda for that meeting. However, one of the products that was discussed was composed of human dura mater. This was the meeting attended by Dr Little of the CVL (see Chapter 3).

4.8 Dr Little and Mr Sloggem have different recollections of what happened at, and immediately after, the meeting on 9 September.

4.9 Dr Little told us that he made a mention of the occurrence of BSE in cattle. He believed this was during the course of the formal meeting, possibly during discussion about the dura mater product. When he gave oral evidence, Dr Little explained that he made a very simple statement that there was a ‘condition in cattle, called BSE, which we, CVL, were involved in investigating’.  

4.10 We asked a number of those present at the meeting about this, but neither Professor Collee, the CSM/BSC Chairman, nor any of the Medicines Division officials, among them Mr Sloggem, had any recollection of the matter being raised, nor was it recorded in the minutes.

4.11 Dr Little also recalled that he had an informal discussion about BSE at the end of the meeting. Someone from DH had approached him and told him that a product consisting of an extract of bovine brain was currently under review. This person had said that he was aware of the BSE problem. Dr Little, after considering documents for the purposes of our Inquiry, inferred that the person was Mr Sloggem.

4.12 Mr Sloggem had no recollection of any such informal conversation. He explained to us why he believed he would not have said the things Dr Little recalled. He thought that if the discussion had taken place, Dr Little’s evidence would have jogged his memory:  

I had, by 9.8.87, formed the impression from my contact with Dr Taylor that the bovine slow virus issue was a matter which was not widely known and should not be publicised. I do not believe that I would, therefore, have felt it open to me to approach someone I had not met before, ie Dr Little, to tell him what I knew. Neither . . . would it have been open to me to suggest that either I or someone else within DH would write to MAFF about the subject in

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226 S454A Sloggem para. 9
227 S331 Little para. 14
228 T99 p. 51
229 S454 Sloggem para. 42; S423 Collee para. 55; S422 Rotblat para. 42; S419 Jefferys para. 57; S465 Adams paras 26 and 27
230 YB87/9.9/1–1.12
231 S331B Little para. 19
232 S454A Sloggem para. 5
general. I had already involved NPU and obtained the information I needed from Dr Taylor to put the issue to BSC in my paper on the bovine brain extract. Furthermore I agree with Dr Little that an issue of this significance would have been expected to have been dealt with at a more senior inter-departmental level.233

4.13 Mr Sloggem’s reference to DH writing to MAFF on this issue arises because, following the meeting, Dr Little reported to Dr Watson his understanding that DH was aware of the problems associated with BSE. Dr Watson, knowing that Mr Rees was preparing a progress report for Ministers, minuted the CVO on 10 September to inform him that:234

DHSS are aware of the problem. Concern is being expressed about the possible human health risks due to products for human use which contain an emulsion of bovine brain.

4.14 By way of explanation Dr Watson added:

This matter was discussed by Dr Little with DHSS colleagues attending the Committee on Safety of Medicines Sub-Committee on Biological Products on Wednesday 9 September, and I understand that they will be writing to us.235

4.15 Dr Watson had one of a series of meetings at the NPU in Edinburgh on 14 September 1987 to discuss BSE developments and research.236 He made a note indicating that one of the issues discussed at the meeting was the use of lecithin in treating patients with neurological disease.237 This related to the product Mr Sloggem was considering.

4.16 On 16 September Mr Rees sent a progress report on the handling of BSE to Mr MacGregor and Mr Thompson (see vol. 3: The Early Years, 1986–88). He incorporated Dr Watson’s material and added his own gloss:

DHSS are aware of the problem and have informally expressed some concern about any possible human health risks due to products for human use which contain an emulsion of bovine brain. However, there would be no risk provided the brains are from clinical healthy cattle.238

4.17 Mr Rees told the Inquiry that he believed the last sentence must have represented advice that had been given by Dr Watson.239

4.18 Memories are a poor guide to what took place as long ago as 1987. It seems to us unlikely that Dr Little referred to BSE in the course of the formal proceedings in such a way as to register with any of those present for no mention of it is made in the minutes. Equally, however, we believe that there must have been some informal conversation between Dr Little and Mr Sloggem after the formal meeting was over, in which Dr Little learnt that Mr Sloggem, at least, was aware of the existence of

233 S454A Sloggem para. 12
234 YB87/9.10/1.1
235 YB87/9.16/3.1
236 S70 Watson para. 57
237 YB87/9.16/6.2
238 YB87/9.16/3.1
239 T54 p. 72, line 13–p. 73, line 2
BSE and possibly also that he had written to a MAFF colleague. Such a conversation could be expected having regard to Mr Sloggem’s current concern with the matter, and would explain what Dr Little told Dr Watson. If Dr Little simply confirmed what Mr Sloggem had already been told by Dr Taylor, it is, perhaps, not surprising that Mr Sloggem did not record it and no longer recollects it.

4.19 The unfortunate consequence of the exchange that took place between Dr Little and Mr Sloggem was that MAFF gained the impression that DH staff concerned with medicines were reacting to the potential dangers associated with the use of bovine materials in medicines. However, as we shall see, beyond the limited scope of Mr Sloggem’s work in respect of an individual CTC, this was not in fact the case. In addition, MAFF Ministers were given the false impression that there was communication between MAFF and DH officials in relation to BSE.

Consideration of BSE in Medicines Division from January 1988 to March 1989: a chronological account

January 1988

Meeting of the CSM/BSC on 6 January 1988

4.20 The product that Mr Sloggem was reviewing was considered by the CSM/BSC four months later, in January 1988. Mr Sloggem cited in his paper for the meeting recent reports of a slow virus syndrome in cattle. This was the time at which a number of those in Medicines Division learnt of the new disease, and Professor Collee told us that this reference was the first he, too, had seen to what subsequently became known as BSE. The BSC recommended that a CTC be refused for a number of reasons, including concern about possible infection with transmissible agents. The BSC considered that spiking experiments with suitable hardy viruses should be carried out. This involved contaminating the material in the product with the Hanta virus; if it was eradicated or inactivated by the production process, then ‘this was a useful marker for other resistant viruses’. In fact, as indicated in vol. 2: Science, later work was to show that the inactivation of such hardy viruses does not guarantee the inactivation of BSE.

March 1988

The Chief Medical Officer’s reaction to BSE

4.21 As described in Volume 3, Mr Derek Andrews, Permanent Secretary of MAFF, notified the CMO, Sir Donald Acheson, of the existence of BSE in a letter dated 3 March 1988. The CMO called a meeting on 17 March 1988, attended by officials from DH and MAFF, including Mr Alistair Cruickshank, the Under

240 YB88/1.06/2.3
241 S423 Collee para. 56
242 At its meeting on 25 February 1988 the CSM endorsed this recommendation and refused the CTC application (YB88/2.25/2.2–2.3)
243 YB88/1.02.3
244 T112 pp. 46–47
245 YB88/3.3/4.1–4.2
Secretary for Animal Health, and Dr Watson, Director of CVL. A subsequent note from Mr Cruickshank to Mr Andrews recorded that while all those present found it difficult to give any clear advice on the subject, they tended towards the view that there was probably no risk in drinking milk or eating the flesh from infected animals. However, the position was far less clear in relation to brains, spleens and other organs, which raised questions about the safety of human vaccines prepared using bovine material.

4.22 The DH note of the meeting records that concern was expressed over bovine insulin and the use of bovine serum in the manufacture of many vaccines. Dr Harris, DCMO, agreed to speak to the director of the National Institute for Biological Standards and Control (NIBSC) about biological products.

4.23 Mr Cruickshank’s note records that the CMO concluded the meeting by saying that he suspected there was no risk, but that it could take 30–40 years to prove this. He proposed that a group of experts should be set up to provide advice to Agriculture and Health Ministers. The group might be asked as a priority to advise on the use of bovine material in manufacturing vaccines and on the disposal of carcasses of affected animals.

4.24 Following this meeting, on 21 March 1988 Sir Donald Acheson sent a submission to Health Ministers notifying them of the existence of the ‘new’ disease and seeking agreement to the proposed setting up of an expert group to advise on the human health risks. Sir Donald said:

The condition which was first recognised in 1985 has been brought to my attention in a letter from the Permanent Secretary of MAFF dated 3 March 1988 . . . I have subsequently held a meeting of officials of MAFF, the PHLS and DHSS. Their unanimous view, with which I concur, is that, although a risk to human health through the consumption of milk or meat from infected cattle or through the use of bovine tissue-based biologicals in the pharmaceutical industry is likely to be low, in view of the lethal nature of the virus and its uncertainties, further expert advice is needed as soon as possible.

4.25 The Ministers agreed with the CMO’s proposal, which led to the establishment of the Southwood Working Party. Their establishment and meetings are discussed in detail in vol. 4: The Southwood Working Party, 1988–89. Later in this volume we consider the Working Party’s involvement with medicinal products.

April 1988

Medicines Division learns about BSE

4.26 Senior officials in Medicines Division who had not already learnt of the existence of BSE did so through receiving copies of the CMO’s submission of
21 March 1988. According to Dr Jefferys, Mr Hagger sent him a copy on 4 April and Dr Jones told us that he thinks he saw the minute some time in April. 

**4.27** On 11 April 1988 Mr Wilson, the Administrative Head of Medicines Division, sent a minute to Dr Jefferys about BSE. It has not been possible to find a copy of that minute, but Dr Jefferys recalled that Mr Wilson asked ‘for some immediate comments on the possible implications of the appearance of BSE in cattle for the use of bovine tissue based biologicals in the pharmaceutical industry’. Dr Jefferys replied on 13 April 1988:

I would have thought that the risk of infection and the transmission of BSE from ‘the use of bovine tissue based biologicals in the pharmaceutical industry’ is likely to be less than that from infected food products. I base my views on the facts that much smaller quantities of biological materials are used in pharmaceuticals than would be ingested, and secondly that since the virus particles are resistant to heat, then they will not be inactivated by cooking, etc. For recent products we have taken a very stringent view on the quality control to avoid the risk of transmitting infection. We have demanded ‘spiking’ studies with hardy viruses (these are rather similar to the scrapie virus).

There are still a significant number of older products which are subject to the review procedure. I understand that these are likely to be reviewed in the next year. It might be worth asking Dr Wood to comment on the approach that will be taken to the review of these products.

Probably the most widely used bovine preparation would be bovine insulin. As you will be aware the current trend is to develop highly purified animal insulins and increasingly to switch patients to recombinant DNA (human) insulin. The purification process should considerably reduce the risks of transmission of any virus for the monocomponent highly purified bovine insulin.

A further final thought is that recently we have required certificates that the animals from which biological products are derived are healthy.

I would be happy to look into this matter further if you wish but my view at present is that we should await the deliberations of the proposed expert group.

**4.28** Neither Dr Jefferys nor Dr Jones could recall any particular discussions and meetings over this period, although Dr Jefferys thought the matter must have been discussed at senior management level at one of their monthly Divisional Management Group meetings, co-chaired by Dr Jones and Mr Wilson. Dr Jones and Dr Jefferys agreed that the Divisional view, however arrived at, was to await the deliberations of the Southwood Working Party.
4.29 Mr Wilson wrote a manuscript note to Dr Jones on a copy of Dr Jefferys’s minute, on 15 April. He suggested that Dr Jones might want to show the minute to Dr Wood, the head of MB3B, the branch reviewing older medicinal products. Subject to that Mr Wilson would go along with Dr Jefferys’s view.257

May 1988

A meeting arranged by the NIBSC

4.30 A meeting was convened at the NIBSC on 16 May 1988 to discuss BSE. Dr Schild, the Director of the NIBSC, and Dr Minor, Head of the Division of Virology there, told us that the decision to organise the meeting, drawing on the NIBSC Viral Products Advisory Panel, had arisen out of a discussion between them.258 It is not clear what prompted this discussion; it might have been a result of Dr Harris’s undertaking on 17 March 1988 to raise the matter of BSE with the NIBSC, or alternatively the communications between Dr Little and his colleagues and the NIBSC in the preceding months.259 Mr Wilesmith, the CVL epidemiologist, was among those who attended the meeting. Dr Schild told us that the purpose of the meeting was:

> to obtain the advice and comments of scientists outside the NIBSC on the nature of the epidemic and its implications for biological medicines. Although questions of licensing are for the MCA (which sets out the conditions under which manufacture of biological substances is permitted) we have an obvious professional interest in the safety and efficacy of biological medicines, and an advisory role in that respect.260

4.31 Dr Minor explained:

> The meeting . . . was only ever intended to be a ‘one-off’ session in which knowledge would be pooled and a paper produced which would offer a synopsis of the state of knowledge on the issue for the benefit of those working on biological medicines.261

4.32 The participants, besides Mr Wilesmith, and staff of the NIBSC, were Dr Richard Kimberlin, an expert in TSEs from the NPU; Dr A Beale and Dr A Garland of Wellcome Biotechnology; and Dr R Ridley and Dr H Baker of the Clinical Research Centre. Dr Minor told us that he invited Dr Jefferys, but that he did not attend.262 However, Dr Jefferys did not recall receiving such an invitation. He told us it was strange that no formal invitation was sent to Medicines Division, together with a copy of a discussion paper, in the same way as the invitations sent to others. He also indicated that he would have expected to find a written response from himself to any invitation.263 We have not felt it necessary to seek to resolve this question so many years later.

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257 YB88/4.13/5.1
258 S575 Schild para. 39; S576 Minor para. 14
259 S331 Little para. 8
260 S575 Schild para. 39
261 S576 Minor para. 14
262 S576 Minor para. 16
263 S419E Jefferys paras 2–6
4.33 Dr Minor produced a report of the meeting,\(^{264}\) including the following conclusion:

Bovine spongiform encephalopathy presents features suggesting that it is caused by a scrapie like agent although this is not yet unequivocally proven. The incidence varies geographically with a lower incidence in the North. In the absence of data on transmission the properties of the agent are expected to be similar to those of the causative agents of scrapie and Creutzfeldt-Jakob disease, which are, in practical terms, undetectable by existing technology and cannot be selectively destroyed, although they may be removed. If BSE is held to be a problem, the only option is to ensure that bovine materials for manufacture of biological medicinal products are derived from cattle in areas free of the disease.

It is possible that transmission to humans may not be readily effected under existing conditions. This statement is based on experience with scrapie which is unlikely to cause a disease in humans under natural conditions, and in particular has been shown to be epidemiologically unlinked to Creutzfeldt-Jakob disease. There is no evidence for transmission of scrapie to occupational groups such as shepherds and veterinarians which have high exposure to sheep and scrapie infected sheep. This is true for research workers and abattoir workers or butchers, where there may be exposure to brain tissues. The tissue distribution of infectious agents may also act against ease of transmission. In particular serum is a poor source of infectivity in animals affected by scrapie. Vertical transmission of acquired Creutzfeldt-Jakob disease, kuru or BSE has not been demonstrated. Transmission of scrapie from infected ewes to their lambs occurs with relatively high frequency, however, implying possible transplacental spread or transmission via milk. It is thus possible that BSE poses no real threat to human health provided the main exposures are either as a contaminant of food stuffs which will be minimised by inspection of animals, or from products which are not contaminated with nervous tissue. The information on which to base a decision is however extremely sparse.\(^{265}\)

4.34 Those at the meeting recommended that studies should be set up involving NIBSC, Wellcome Biotechnology and other parties to test for the presence of scrapie-like agents in calf serum by inoculation into mice, hamsters and other species. Such experiments would be very lengthy.\(^{266}\) Dr Minor told us that the studies were actually carried out independently by Wellcome Biotechnology. However, he does not recall actually seeing the research itself and he cannot recall when the results were brought to his attention.\(^{267}\) The company has told us in correspondence that it can find no record of Wellcome carrying out such experiments. It does, however, note that Dr Minor was involved in a critique of experimental protocols for other experiments being investigated by Wellcome at the time.

4.35 The meeting also recommended that consideration should be given to a survey of licensed products using bovine or ovine material in their manufacture and the origin of these materials.\(^{268}\)
Sir Richard Southwood and Dr Pickles become involved

4.36 On 19 May 1988, a few days after the NIBSC meeting, Sir Richard Southwood met Mr Andrews and the CMO. The CMO suggested that urgent advice on the question of the manufacture of biologicals from cattle material would be needed from Sir Richard’s working party. 269

4.37 The next day Dr Pickles sent a minute to Dr Jefferys:

Bovine Spongiform Encephalopathy

I believe you know that there is a joint MAFF-DHSS group looking at this problem. I have now been roped into the secretariat.

We would like to be sure that possible transmission through medicinal products can be ruled out for both humans and animals. Some positive evidence that it appears not to have been so transmitted would be nice. Since we know so little about BSE, we may have to look at scrapie, which is endemic in UK sheep. Is this a problem you should put before biologicals sub-committee?

Questions for them might be:-

– are there any products prepared from bovine or sheep brain which need to be looked at? If rabies vaccine has been made using sheep/goat brain, are there adequate human follow-up data to be sure no viral infections might have been transmitted?

– Can we assume that the ‘dose’ of any infectious agent administered in non-parenteral medicinal products would have been so small in comparison with doses from food that such products need not be considered further?

– Are there any bovine (or sheep) materials used in production processes of parenterals that might be capable of introducing an infectious agent (eg bovine serum albumin in vaccine production, or bovine insulin)?

We have no evidence that BSE can be a risk to humans. If, however, we could identify a group of people who might have received parenteral ‘BSE agent’ through medicinal products then they would be a group that might warrant special study.

I note in your minute of 13 April you take some reassurance from recent requirements that animals used in production of biological products should look healthy and be certified as so. With a long-incubation infection (currently thought to be 2 to 6 years) lack of physical signs cannot be taken to signify freedom of disease. So we cannot be sure.

Maybe you would like to discuss this with me. If you do put the problem to Biologicals Sub-Committee, please involve me if you can. 270
4.38 The same day Dr Pickles sent a minute to Mrs Alderman, an information scientist in MB1B where the Medicines Division data was kept, asking for information about licensed products for human and veterinary use made from bovine material.\textsuperscript{271} Mrs Alderman replied on 23 May 1988 attaching print-outs listing products containing active ingredients or excipients of bovine origin from Medicines Division’s NORSK database. Mrs Alderman had compiled the results by searching for constituents containing ‘bovine’ in their name, which was the only way she could do it.\textsuperscript{272} Following this up in early June Dr Pickles noted that the list had not included any bovine insulins.\textsuperscript{273} Mrs Alderman replied the next day with a further list that did include these products.\textsuperscript{274}

4.39 Dr Jefferys replied to Dr Pickles on 24 May 1988. He said that the CSM/BSC had not formally discussed the matter but had done so informally while assessing an individual application. This appears to be a reference to the January BSC meeting which he had attended. He added: ‘For some months now the Sub-Committee have been requiring appropriate “spiking” studies to be undertaken with hardy viruses and these would include bovine products.’ Therefore he felt ‘reasonably confident about taking appropriate action for the new products’. He thought that the major concern was with the parenteral products. Dr Jefferys continued:

With regard to previously licensed products, then we have no evidence of hazard, but clearly we cannot provide reassurance given the timescale for possible incubation and infection.

As you will be aware from your previous work with the Review, many of the older products are PLRs [Product Licences of Right] (since many of the biological PLRs still have not been reviewed). I am therefore copying this minute to Dr Wood since she will need to take account of this during the review of these products.

\textit{Oral Products}

As I previously stated, I would have thought that the risk from oral medicinal products must be very small in comparison to the risk from food. I base this on the assumption that the infectious agent is probably not heat-sensitive and therefore will not be removed by normal cooking.

\textit{Parenteral Products}

I accept that there may be a different consideration of parenteral products. I presume that the major agents would be bovine insulin, and bovine serum albumen in vaccine production. If you were looking for a group of people to study, then I would have thought that those who have received bovine insulin might be the most appropriate group. I suppose it might be possible to undertake a retrospective study comparing those who have received bovine insulin versus those who have received porcine or ideally human insulin. I presume the endpoint would have to be the development of an encephalopathic syndrome. The danger in constructing such a study would
be the scientific risks of confounding, etc. and the political risk of worrying large numbers of diabetic patients.

These thoughts are very preliminary ones. It also occurs to me that this is more of a long term issue and that it may well involve William Jenkins since this is rather more an ADR [Adverse Drug Reaction] problem than a New Drugs Group issue. I am therefore copying your minute to him. It may be appropriate for Sue Wood, William and I to have a discussion with you at a mutually convenient time.  

June 1988

A minute from Dr Pickles

4.40 The Southwood Working Party held its first meeting on 20 June 1988. Following that meeting, Dr Pickles wrote both to Dr Lewis, private secretary to the CMO, and to Dr Jones. Dr Harris, Mr Wilson and Dr Jefferys were among those to whom the latter minute was copied. This seems to us again to have been an important minute, and we set it out in full:

BSE, Spongiform Encephalopathies and Medicinal Products

1. You will have heard of this new disease of British cattle which is thought to be due to scrapie agent, introduced via sheep offal in cattle feeding stuffs. I am part of the secretariat of a working party, chaired by Sir Richard Southwood, which is looking into the implications of this disease. This group had its first meeting yesterday.

2. We are clearly concerned that ‘BSE-agent’ may be transmitted in medicines. Whilst the epidemiology does not suggest that the current cases in cattle are causally linked with the use of veterinary products, we are concerned about veterinary as well as human medicines in case we facilitate yet more species jumps. Much of the relevant information about ingredients and production processes is not accessible to us so we will look to the section 4 committees (and the Biologicals Sub Committee) to review this problem. All of them, including the VPC and CDSM, might have an interest. Dr Martin is a member of Sir Richard’s working party, and might raise the problem informally at a Commission pre-meeting.

3. I have been in correspondence with Dr Jefferys and others about this. I understand the pharmaceutical industry are also concerned: they had been using bovine not sheep products in various processes because scrapie is endemic in British sheep. Now they need to worry about possible dangers to their workers handling bovine materials as well as possible infection in their final products.
4. Questions we might want to have answered are:

- The highest risk would be from parenterals prepared from brain (e.g., rabies vaccine). Any species in which transmissible spongiform encephalopathies have been described would be suspect (‘natural’ infections in sheep, goats, cattle, deer, mink, but can be transmitted to hamster, mouse, guinea-pig etc.). Are sterilisation processes adequate for the most resistant strain of scrapie agent, or for CJD agent? Should companies be asked to include investigation for inclusion of scrapie agent (e.g., mouse inoculation) in at least some batches?

- If BSE behaves like scrapie, then we might expect other nervous tissue, spleen, lymph nodes and placenta to be contaminated. Infection has been described in other tissues too, e.g., gut wall, and we cannot be sure blood is free. Do we know what bovine materials are used in which products, both as the active ingredient and in production? Bovine active ingredients in human products include insulin, vasopressin, bone, immune globulins, fibrin, dermal collagen, albumin. Bovine serum albumin and fetal calf serum must be used in preparation of very many products. For each of these products would any ‘BSE agent’ be destroyed or eliminated in processing? If not, and the product is administered parenterally or topically into an open wound, might there be a risk? (For oral products, there would only be a trivially increased load on top of that taken in food in omnivores/carnivores including man. But for some herbivores, this might allow the agent to be introduced into yet another species).

- Would it be appropriate to arrange for monitoring of cases who have received any of these suspect products in the past? Could studies be undertaken in recipients of bovine insulin without causing alarm? Would recipients of collagen or fibrin implants be another group for study? Perhaps some animal recipients of suspect products should also be studied.

- Should we restrict our concern to products manufactured in the UK, since BSE has not been described elsewhere?

- Should we step up the physical examination of animals involved in medicine production, ensuring a neurological assessment is included and only healthy animals are used?

- Pending results of further investigations, should we insist all ruminants used for the production of human or veterinary products are not fed at any time since birth supplementary animal protein as in meat and bone meal? Should the same rules apply to any other animals involved in production of human or veterinary medicines? This seems to me to be an easy option for the industry (assuming bovine serum albumin can be bought in from countries overseas where such supplementation is not used) and would be a responsible step. It would provide reassurance if, as I suspect, it is not possible to come up with answers to the other questions.

5. Is this a topic you will want to raise with the FDA at the forthcoming Tripartite?
6. As you know, BSE is of particular concern to CMO. He has asked me to keep him fully posted as to progress. Following yesterday’s meeting of the working party, I have let him know I am writing to you to suggest this potential problem is discussed by your expert committees. Please let me know if there is any further information I could provide for you. I would value the chance to be present as an observer when the issue gets discussed in committee.  

4.41 Copying this minute to Mr Lawrence on 21 June 1988, Dr Pickles described it as ‘an attempt to galvanise Medicines Division into action’. 

The response within Medicines Division

4.42 Dr Pickles’s minute had the desired effect. It prompted a decision within Medicines Division that the issue of BSE should be referred, in the first place, to the CSM/BSC. Neither Dr Jones nor Dr Jefferys could recall, when we asked them, exactly how this decision came about. Dr Jones thought it likely that he would have discussed Dr Pickles’s minute with Dr Jefferys, and that Dr Jefferys would then have met with his staff and pharmaceutical colleagues. When he gave oral evidence, Dr Jefferys thought it was likely that the issue would have been discussed by a team including the three Principal Medical Officers reporting to Dr Jones, the pharmacists and administrative colleagues. He was ‘pretty confident’ that it would have been discussed at the Divisional Management Group meeting. Unfortunately, the minutes of those meetings have not survived.

4.43 In any event, Dr Frances Rotblat, an SMO working to Dr Jefferys, who was medical assessor to the CSM/BSC, and Dr Purves, the pharmaceutical assessor to the CSM/BSC, were asked during the summer of 1988 to prepare a paper on BSE for the Committee. Dr Rotblat told us:

I believe that Dr Jefferys had asked us to prepare this paper. However, I am unable to recall when he first asked us to prepare it. I have some recollection that a decision was taken to prepare the paper so that it could be put before the November meeting of the Biologicals subcommittee and Dr Jefferys probably told Dr Purves and I to work towards completing it in time for that meeting. I believe that when Dr Jefferys asked us to prepare it, he probably told us to prepare it as soon as we could given our existing workloads. I do not believe that Dr Jefferys either told us to drop all our other work and concentrate exclusively on BSE or told us that the paper was a low priority. I imagine that the paper was probably put together over the course of about 3-4 weeks.

Dr Rotblat said that it appeared the paper was completed by 20 September and referred to her minute to Dr Jefferys of that date.

4.44 On 11 July 1988, about the time we imagine Dr Rotblat and Dr Purves were asked to prepare their paper, Dr Pickles contacted Dr Minor at the NIBSC in an
apparent effort to ensure that prompt consideration was given to BSE by the CSM/BSC. She sent him copies of her minute of 21 June 1988 to Dr Jones and of a note she had prepared for the press office, and said:

As we discussed today on the phone, I have lead responsibility for BSE here in DHSS. For your information, here is a copy of the note I prepared for our press office. Also, in confidence, a note about the implications of BSE for biological products I sent to Dr Jones. You had better not let Medicines Division know you have seen this, but there will be no excuse for not having a proper discussion at the next Biologicals Committee. Perhaps you could let me know if it does not appear on the agenda when you receive the papers. 286

4.45 That same day, Dr Minor sent copies of his report of the NIBSC meeting on 16 May to Dr Jefferys. 287 As we have noted in the previous chapter, he was also instrumental in Mr Wood’s despatch of the draft MAFF guidelines on 12 July to Dr Harris, the DCMO.

August and September 1988

4.46 During August, the CMO corresponded with Mr Andrews and Sir Richard Southwood about the proposed advisory group on BSE-related research (which became the Tyrrell Committee). 288 In his letter to the CMO of 30 August 1988 Sir Richard said that he considered serum in pharmacological work the ‘only outstanding practical matter’ and asked whether something could be done through ‘the usual channels’ to check the policy of pharmaceutical companies on its use. 289

The CMO passed Sir Richard’s letter on to Dr Harris, who in turn passed it on to Dr Jones. Dr Jones replied to Sir Richard on 22 September 1988. He told him that the use of bovine serum in pharmaceutical manufacture was one of a number of issues currently being examined by Medicines Division, and promised to let Sir Richard’s working party have all the information relating to medicinal products as soon as it became available. 290

4.47 Meanwhile, when the CSM/BSC met on 7 September 1988, Dr Purves had told them that a paper on BSE was being prepared and would be submitted to them at a later date. 291

4.48 Dr Pickles was not satisfied with Dr Jones’s reply to Sir Richard. In a minute to Dr Jones of 26 September 1988 she pointed out that she had been asking for comments from Medicines Division for some months and had several suggestions as to ‘pertinent questions’ that could be put before the expert committees:

... I understand that the topic has only been raised informally at Biologicals. You explained to me that it has lower priority than other work before you at the moment.
The next meeting of Southwood’s group is on the 10 November. Will I have something positive to report at that meeting from Medicines Division? 

4.49 Evidently the CMO asked Dr Jones about the timing of the Medicines Division consideration of BSE. Dr Jones told him on 29 September 1988 that a draft paper had been prepared and would be considered by the CSM, the Committee on Dental and Surgical Materials (CDSM) and various subcommittees in November. A considered view on the whole issue would be available in late November. The CMO passed this information on to Sir Richard in early October.

November 1988

The Rotblat and Purves paper

4.50 The paper on BSE had been completed by Dr Rotblat and Dr Purves by 20 September 1988 but was not considered by the CSM/BSC until its meeting on 2 November 1988. Dr Jefferys told us:

In addition to the time actually spent preparing the paper there was and remains about a 3–4 week ‘lead period’ in that a paper has to be completed more than three weeks before a subcommittee meets so that it can be checked, photocopied, distributed to the members so that they have adequate time to read it and prepare for the meeting. It was the practice to issue papers two weeks before a meeting to committee members. This would have meant that if a paper was to be put to the September meeting of the subcommittees, it would have had to be available no later than the middle of August.

4.51 Dr Rotblat told us that the two standard principles underlying the paper were, first, ensuring the safety of the raw ingredients, and, second, the use of sterilisation or inactivation procedures in the manufacturing process to minimise any remaining risk. Dr Purves told us the purposes of the paper were to:

1. summarise the current information on BSE;
2. identify the issues that BSE raised for biological products – to consider the possible risk of transmission of the disease to humans through biological products containing or consisting of bovine materials; and
3. present draft recommendations for the Committee's consideration.

4.52 He added:

It was designed to be a discussion paper for the Committee. As was our practice, we presented specific, but draft, recommendations to the Committee to assist in giving focus to the deliberations. Additional recommendations would be included as a result of discussion at committee.
We were very aware that the Southwood Working Group had been set up, given its expert advice in this area and that before implementing industry wide measures, we would need further guidance from our group of experts. However, in the interim we did not hesitate in examining the issue and formulating proposals for action. These could be reviewed in the light of the subsequent recommendations that came from the Southwood Working Party including that Party's assessment of the possible risks associated with biological products.\(^\text{299}\)

4.53 In the paper itself the authors noted that little was known about the disease or the causal agent, although the limited information available indicated that it could be caused by a scrapie-like agent. At the time the total number of reported cases was said to be 510. The paper stated that the lack of hard information made it difficult to see what positive action could be taken by the Division, at least in the short term, but it was thought prudent to consider the following:

i. The animal species from which tissue might be sourced for use in the manufacture of medicinal products.

ii. The significance, if any, of the various types of tissue that might be used.

iii. The ability of the manufacturing and purification procedures to destroy or remove viral or virus-like agents.

iv. The products involved, the type of tissue they contained and the relative risk to the patient on administration of a contaminated product, parenterally, topically and orally.\(^\text{300}\)

4.54 In relation to the fourth issue, the paper said:

It is clear there is a need to know which products contain bovine tissues, along with details of the type of tissue used in manufacture, so that a database is available for discussion later. In addition, consideration may need to be given to the risks associated with parenteral, topical and oral administration, should the product be contaminated by the BSE agent . . . Some questions we may wish to ask are:

1. which products include bovine material and, therefore may contain the BSE agent;

2. what follow-up action is required especially in the absence of definitive information on the properties of the BSE agent;

3. what could be asked of companies in answer to concerns about BSE in addition to our current policy, where, in the last year or so, we have been asking for details of the quality of starting materials and the ability of the manufacturing and purification procedures to remove or inactivate hardy viruses.\(^\text{301}\)

4.55 The second part of the paper set out data from Medicines Division’s existing computer records for licensed products. The list showed 53 product licences for
preparations containing bovine material, of which 42 were for insulin. It was not clear how complete the computer list was; it did not show material used in the process of manufacture such as bovine serum albumin (BSA) and foetal calf serum (FCS).

4.56 Dr Rotblat and Dr Purves had then divided products into those for oral and parenteral use and those derived from brain, tissue and blood. There were no licensed products derived from bovine brain, but there were three products for parenteral use derived from bovine tissue: insulin, bovine collagen implants and bovine fibrin implants.302

4.57 They concluded by putting forward the following recommendations for consideration by the BSC:

i. No licensing action should be taken against oral products.

ii. All bovine products should come from cattle from healthy herds, which have not been given food supplements containing material of animal origin. No brain or lymphoid tissue should be used in parenteral products.

iii. Manufacturers of parenteral products should show that their manufacturing processes are capable of inactivating scrapie-like agents.

iv. All licences for new products from bovine material should comply with the above.

v. The Review/CDSM sections should carry out a search for preparations containing bovine material.

vi. There should be an article in MAIL [Medicines Act Information Leaflet] requesting manufacturers to identify bovine preparations used in the manufacturing process. Bovine albumin and foetal calf serum should come from healthy herds.

vii. The ADR [Adverse Drug Reactions] database should be searched for ADRs to bovine products.

viii. The Committee is asked to consider whether to take any action against bovine insulin or whether the risk/benefit ratio is appropriate.303

4.58 Annexed to the paper were a number of documents, including Dr Minor’s report of the NIBSC meeting of 16 May 1988 and what appears to be Mr Wood’s paper of 6 July, which had been sent to Dr Harris on 12 July. This is annotated ‘MAFF Report’ and referred to in the cover note as ‘suggested action by Ministry of Agriculture’. There is no explanation of its status nor any other reference to it in the paper for the Committee (see Chapter 3).

302 S422 Rotblat para. 55
303 YB88/9.00/3.9
The CSM/BSC meeting on 2 November 1988

4.59 Professor Collee chaired the CSM/BSC meeting on 2 November 1988; those present included Dr Pickles, Dr Jefferys, Dr Purves, Dr Adams, Dr Schild, Mr Sloggem and Dr Minor. No representative of MAFF attended. Professor Collee described to us his thinking, and that of the BSC, at the time:

I recall reading the Purves/Rotblat paper with admiration. I thought that it was balanced and well researched. I recall that my preliminary feeling was that it seemed unlikely that the BSE agent would be transmissible to man, but that the possible consequences of transmission were potentially alarming.

Everyone who attended the Biologicals Sub-Committee meeting on 2nd November was exercised by the issue of BSE. At the meeting, there was a very full discussion of the Purves/Rotblat paper, which was used as a baseline; we then had a wider, general discussion of the issues raised and I would have summarised this discussion. We then went on carefully to discuss each of the recommendations which had been made. It appears that Dr Purves attended the meeting although Dr Rotblat did not. Dr Purves may well have introduced the paper; he certainly answered questions on it. Dr Pickles would almost certainly have contributed to the discussion.

We faced considerable uncertainty at this time. I was aware from my knowledge of other models of infectivity that parenteral delivery of similar agents was likely to be more effective than other potential routes of transmission, such as an oral challenge. I was also aware the infection could ‘home onto’ particular organs or tissues; that brain was likely to be such an organ and that there might also be risks from the use of nervous tissue. The Purves/Rotblat paper had additionally drawn attention to possible risks from lymphoid tissue; I believe that I was unaware of the possibility of lymphoid tissue posing a particular risk before reading this paper. However, I believe I was alive to the concept of sub-clinical infection.

4.60 Following its discussions, the CSM/BSC made the following recommendations:

a. No immediate licensing action should be taken against oral products, in which bovine material has been used.

b. All bovine materials should come from cattle from appropriately certified healthy herds, which have not been given food supplements containing material of animal origin. No brain or lymphoid tissue should be used in parenteral products.

c. Manufacturers of parenteral products should show that their manufacturing processes are capable of eliminating scrapie-like agents.

d. All licences for new products from bovine materials should comply with the above.
e. There should be an article in MAIL requesting manufacturers to identify products in which bovine materials had been used. Bovine albumin and foetal calf serum should come from appropriately certified healthy herds.

f. The above should be drawn to the attention of the review/CDSM sections along with the need to search for preparations containing bovine material.

g. The above should be drawn to the attention of the ADR Section and SEAR [respectively that part of Medicines Division and the CSM subcommittee concerned with adverse reactions to medicinal products] along with the need to search the database for reactions to bovine products.306

4.61 Following the meeting of the BSC, Dr Pickles sent a minute to Mr Alan Lawrence, her MAFF counterpart in the Southwood secretariat, enclosing her own summary of the comments and recommendations from the meeting. In respect of information available about licensed products, she recorded:

There is incomplete information on the licensed products potentially affected, as many products with licences of right (PLR’s) do not have even active ingredients correctly identified on the computer records. Non-active ingredients/materials of bovine origin may also be missed out. Some collagen implants of bovine origin as used by cosmetic clinics are not even licensed. 307

4.62 Dr Pickles also recorded:

The subcommittee’s recommendations could form the ‘framework’ on which specific proposals for specific products could then be formulated by the secretariat and then brought back to the committee. Further information would be sought from MAFF and other experts on how disease-free herds, procedures and countries might be identified.308

4.63 In her covering minute Dr Pickles told Mr Lawrence how matters stood in the other advisory committees (including forthcoming discussions at the SEAR subcommittee and the CSM). She added:

I hope we can persuade Sir Richard that the issue is now being looked at in depth by the appropriate experts who also have the executive power to do something about it. This means that Sir Richard needs only a passing reference in his own report.309

4.64 She said she had seen Mr Wood’s draft paper of 6 July and asked Mr Lawrence to find out what was happening with veterinary products in the Veterinary Products Committee (VPC).310

4.65 When SEAR considered the issue of BSE two days later, it endorsed the recommendations of the BSC.311
Sir Richard Southwood’s first letter to the CSM

4.66 At their second meeting, on 10 November 1988, the Southwood Working Party were told about the preliminary discussions of the VPC and the CSM/BSC (refer to vol. 4: The Southwood Working Party, 1988–89). This prompted Sir Richard to write to Professor Asscher, the Chairman of the CSM, on 14 November 1988:

I understand that the Committee on Safety of Medicines is shortly to consider whether bovine spongiform encephalopathy presents a hazard in those medicinal products for human use that have been manufactured from bovine sources. At a recent meeting of the expert working party which has been set up by MAFF and DH to consider the implications of this disease, we were informed of the provisional conclusions of the Biologicals Subcommittee.

We were pleased to hear of the detailed consideration that was given to this issue. As you may know, we have already identified the pressing need for more research in this area. We understand that in due course you may be considering whether licensing action of some sort is appropriate in relation to any specific products. We trust that any steps that are thought necessary to safeguard new medicinal products will be applied also to existing products. There are various measures that manufacturers could take to reduce or eliminate the risk of contamination by BSE agent in pharmaceuticals and which could be introduced by agreement with relative ease and with no detriment to the product. Those steps include using material only from healthy herds not fed ruminant-derived protein; avoiding use of brain or lymphoid tissue directly or in culture media; and reducing nervous tissue contamination of serum by ensuring animals are not destroyed by brain-penetrative stunning. You may like to consider whether informal advice on these lines to the pharmaceutical industry might be helpful. Other steps, such as ensuring the manufacturing processes are such as to eliminate any scrapie or similar agent, seem likely to prove more problematic.

We look forward to hearing your considered view when you have completed your deliberations.312

Consideration by the CDSM and CSM

4.67 The CDSM discussed the recommendations made by the CSM/BSC on 16 November 1988. Of particular interest to the CDSM was the use of sutures derived from bovine intestines. Its view was that at that stage synthetic materials should be used in surgery wherever possible and materials of bovine origin should be used only where essential. It noted it was to be kept informed of further developments.313

4.68 Professor Asscher told us that his first involvement with BSE occurred in the course of preparing for the CSM meeting on 17 November. He added:

312 YB88/11.14/6.1 (a spelling error in the original text has been corrected)
313 YB88/11.16/6.5
The CSM was, however, aware of the issues involving CJD and human growth hormone at this time and of the occurrence of CJD following dura mater implants. They had come to our attention in the course of considering product licences for dura mater. These experiences made us particularly wary of parenteral, as compared to oral, medicinal products. At the time, the fact that scrapie had not transmitted to man also gave us reassurance that BSE was unlikely to be acquired by the oral route.314

4.69 The CSM considered and endorsed the CSM/BSC and SEAR recommendations at its meeting on 17 November 1988. It also noted Sir Richard’s letter and agreed that Professor Asscher should write to him ‘detailing the view of the Committee and referring to preliminary consideration of this matter by the CRM and CDSM’.315

4.70 Professor Collee was present at the CSM meeting. He recalled that Sir Richard’s letter was seen as constructive and that his points guided the further discussion after the CSM meeting over the coming months.316

Further correspondence between Sir Richard Southwood and Professor Asscher

4.71 On 24 November 1988 Professor Asscher replied to Sir Richard’s letter. He enclosed the recommendations of the CSM. His letter concluded:

Preliminary discussions have also taken place within the Committee on the Review of Medicines and Committee on Dental and Surgical Materials to consider what action needs to be taken in relation to specific existing products.

I hope you will agree that we now have in progress the appropriate action to safeguard both new medicinal products and existing products.317

4.72 Sir Richard replied to Professor Asscher on 7 December 1988, saying that he would put his letter before the Working Party. He offered two initial comments on the CSM’s recommendations:

My colleagues and I are most anxious to ensure that existing products were identified and manufacturers ensured that they conformed to the safety recommendations. The second point is that I believe in practice ‘the certification of healthy herds’ is going to be more difficult, because as you know, this disease may be present for many years in an asymptomatic condition; thus certification would have to depend on evidence that food supplements containing material of animal origin have not been fed to the herds for as long as six or seven years or the lifetime of the animals concerned. I am not sure what arrangement the Ministry of Agriculture has in mind for certifying herds as healthy from this point of view, but as you will appreciate, the absence of a case of BSE would not be a sufficient condition.318
4.73 We were unsure what Sir Richard meant by existing products. Was it products with existing licences, or was it existing stocks of such products? We asked the Working Party when they gave oral evidence. Sir Richard told us he thought they meant products that were already licensed and stocks of those products.\textsuperscript{319}

4.74 In a letter to Sir Richard on 8 December 1988, Dr Pickles commented that she was not entirely happy with Professor Asscher’s reply of 24 November. She saw nothing in the CSM’s recommendations that gave her any confidence that it would be taking any necessary action on existing products, or indeed would be taking note of any of the points raised by Sir Richard in his letter.\textsuperscript{320} The Working Party agreed. At their third meeting, on 16 December 1988, it was felt that Professor Asscher’s response was ‘somewhat complacent, particularly in relation to the problem of existing medicinal products’. It was agreed that a further letter should be sent to Professor Asscher, and that Sir Richard would also write to Dr Little to establish what measures the VPC was adopting.\textsuperscript{321} The latter correspondence is dealt with in Chapter 5.

4.75 Accordingly, on 23 December 1988 a further letter was sent to Professor Asscher conveying the Working Party’s continued concerns.\textsuperscript{322} Sir Richard wrote: ‘We interpret your recommendations as drafted to mean that conditions that may be impossible in practice will be demanded of new products of bovine origin, and yet, other than for the insulins, we see no firm commitment to look at existing products.’ He sought reassurance that appropriate action would be taken against relevant parenteral products other than insulins and heparin. Sir Richard identified a number of other points including:

i. the difficulty, mentioned in his own earlier letter of 7 December, of introducing ‘certification of healthy herds’ if this meant herds never fed ruminant protein;

ii. the problems of ensuring manufacturing processes were capable of eliminating the scrapie agent; and

iii. the question whether the exclusion of brain and lymphoid tissue covered only active tissue, or also material used as intermediates and culture media in the manufacturing process.

4.76 Professor Asscher suggested to us that Sir Richard’s comments on existing products appeared to be based on a misunderstanding:

the CSM had always intended that its recommendations should be applied to both existing and new products. It was for this reason that the CSM ensured that BSE was also considered by the CRM.\textsuperscript{323}

4.77 It remains unclear to us whether Professor Asscher understood that the Southwood Working Party’s concern extended to existing stocks of medicinal products. We consider in Chapter 6 the response to this letter and the action that was taken in relation to existing stocks.

\textsuperscript{319} T106 p. 61
\textsuperscript{320} YB88/12.8/1.1
\textsuperscript{321} YB88/12.16/1.1
\textsuperscript{322} YB88/12.23/1.1
\textsuperscript{323} S441 Asscher para. 48
Giving effect to the CSM recommendations

4.78 According to Professor Asscher, following its 17 November meeting the CSM, together with its subcommittees and officials from Medicines Division, worked at formulating an overall policy on the issues raised for human medicinal products by BSE. This work took place alongside the work of the Southwood Working Party.\[sup]\textsuperscript{324}\[/sup] Professor Collee told us that this period was one of intense activity with a steep learning curve during which new information and ideas were regularly coming to light.\[sup]\textsuperscript{325}\[/sup]

4.79 Dr Jefferys said of the period:

All of [the] issues needed to be debated and required considerable technical expertise. They were not questions which admitted of simple straightforward answers; indeed this was leading edge science. It was felt that the guidelines which were eventually to be approved had to be capable of withstanding scientific scrutiny and possible legal challenge. The guidelines would have to be seen to be proportionate. If the eventual guidelines were clearly justifiable and practical the chances of universal compliance would be greatly increased.

A further consideration during this period was that we were all waiting for a sight of the \textit{Southwood Report}. This was of particular importance not simply because it was felt that it would be the most authoritative consideration of the issues raised by BSE but also because it needs to be remembered that any action taken in respect of individual pharmaceutical products had to be justified on an evidential basis. It was felt that the \textit{Southwood Report} would provide such a basis and that action taken in advance of a report might well be criticised as premature.\[sup]\textsuperscript{326}\[/sup]

4.80 One of the points that had emerged at the November 1988 meeting of the CSM was that its recommendations were to be regarded as initial proposals, which might need to be amended in the light of increased knowledge about the disease. The CSM recognised that more advice was needed from officials at MAFF about the veterinary aspects of their proposals, to ensure that there was a consistency of approach towards human and veterinary medicinal products. In particular, in light of the Southwood Working Party’s concerns, the concept of a healthy herd and the type of inactivation process likely to be effective had to be addressed.\[sup]\textsuperscript{327}\[/sup]

4.81 A meeting was therefore held between Dr Adams, Dr Jefferys and Dr Purves of Medicines Division and Dr Little, Mr Kidd and Mr Bradley, from the CVL, on 3 January 1989. Its purpose was to discuss BSE and medicines licensing.\[sup]\textsuperscript{328}\[/sup] What transpired at this important meeting and afterwards is considered in Chapter 5.

\[sup]\textsuperscript{324}\[/sup] S441 Asscher para. 29
\[sup]\textsuperscript{325}\[/sup] S423 Collee para. 39
\[sup]\textsuperscript{326}\[/sup] S419B Jefferys paras 51 and 52
\[sup]\textsuperscript{327}\[/sup] S419B Jefferys para. 49; S441 Asscher para. 44
\[sup]\textsuperscript{328}\[/sup] YB89/1.03/2.1–2.2
Discussion

4.82 At the end of the previous chapter we noted the limited flow of information about BSE from medicines licensing officials in MAFF to those in DH prior to January 1989. We discuss below the events surrounding the mistaken impression Dr Little gained, when attending the CSM/BSC meeting on 9 September 1987, that Mr Sloggem’s investigations were part of a wider DH Medicines Division response to the emergence of the disease. We also look at what was actually discussed as a result of Mr Sloggem’s paper.

4.83 We go on to consider the adequacy of the initial response by Medicines Division after the MAFF formal approach to the CMO in March 1988 and his identification of biologicals used in human medicines as a specific concern.

4.84 We conclude with discussion of the general state of communications about BSE between the two licensing divisions at this time.

The communication gap between MAFF and DH prior to March 1988

4.85 We discuss in vol. 3: The Early Years, 1986–88 our concern about the failure of those in MAFF dealing with BSE to involve DH in discussion of the risks it posed to human health generally, prior to March 1988. This delay affected the speed with which potential routes of infection were identified and measures could be considered to block them. Had there been better communication between MAFF and DH, one of the matters that might have been recognised earlier is that the concerns emerging within CVL about bovine material in veterinary medicines had similar implications for human medicines.

4.86 In theory, the links that operated between the professional staff in the two licensing authorities might have acted as a channel for informal communication about BSE. For example, although the CVL had their own unit for testing materials, they relied on DH toxicologists. DH professional staff also regularly attended both the Scientific Secretariat and the VPC meetings. Their main interest was in the effect that veterinary medication, including hormones and antibiotics in feedstuffs, might have on humans who ate animal products, or handled them. Dr Little told us that although CVL received CSM/BSC agendas there was not the same veterinary interest in human products and he did not normally attend the corresponding DH meetings: ‘Medical products have very little interest to veterinarians because there is no immediate connection.’ We discuss those links in greater detail at the end of this chapter. However, they did not lead to sharing of information about BSE prior to September 1987, when Dr Little did find something of interest in the agenda of the CSM/BSC meeting: the discussion of a product containing human dura mater.

Dr Little’s attendance at the CSM/BSC meeting in September

4.87 As we have already noted, Dr Little’s attendance at this meeting left him with the mistaken impression that DH knew about BSE and was considering it in relation to human products.
Dr Little told us that he went to the meeting with BSE in mind. He wanted to see how the CSM conducted its safety assessment of a product using human brain, given the risk of CJD. This was his first attendance at the CSM/BSC as an official observer. His thinking on BSE at that time was still highly tentative. Given his awareness that the topic was being handled with kid gloves by his senior officers (see Volume 3) and the fact that there had as yet been no referral to the VPC, we think it was natural that he adopted a low profile at the meeting. Indeed had he wished to notify his counterpart in Medicines Division about the disease and the concerns it raised, an unscheduled contribution at an advisory expert committee on human health would not have been the appropriate way of doing so.

It appears his contribution was, however, so low key that it failed to register with any of those present. This in itself might not have mattered, since it was open to him to contact Medicines Division thereafter through regular channels. However, his unexpected conversation with Mr Sloggem at the close of the meeting intervened. Given the apparent extent of Mr Sloggem’s knowledge of BSE, obtained via the NPU in Edinburgh, and the nature of the product that Mr Sloggem was assessing, it was not unnatural, though extremely unfortunate, that Dr Little concluded that professionals in DH now knew about the disease and were considering it more widely than was in fact the case.

After the meeting

Dr Little told us that his responsibility after the meeting was to report relevant information to his senior officer, Dr Watson, or directly to the CVO Mr Rees. In this instance he reported back to Dr Watson what he perceived he had learnt at the BSC meeting.

Should Dr Little, believing as he did that DH knew about and was considering the disease, also have taken steps to follow up his contact with Mr Sloggem or with his opposite number at DH to establish what was happening next? Dr Jefferys told us what he would have expected: ‘If mention was made of an emerging problem in the margins of the meeting one would still have expected this to have been followed up with a formal letter.’ Alternatively Dr Little might have raised the matter with the DH Medical Assessors, with whom he met at least twice a month at the VPC or Scientific Secretariat meetings.

We explored the question of follow-up with Dr Little when he gave oral evidence.

Q: Did you, Dr Little, think at all about whether anybody should follow up the question of whether the Department of Health had written to MAFF or the CVL?

A: Well, that would have been my view on 10th September, but when Dr Watson returned –

Q: Sorry your view was that they would be writing?
A: Yes. When Dr Watson returned from Edinburgh, from the NPU, and told me they were already in correspondence with the NPU, I was no longer concerned, because they were actually contacting the very group of experts that I would have put them in touch with, i.e. the people who dealt with scrapie inactivation and the growth hormone problem. So if someone, say, John Sloggem had written to me, I would have said, ‘Yes, and have you contacted David Taylor at the NPU?’ I mean, they had, if you like, leapfrogged that process; they had already got to the right place. Not surprising really, when you consider the history.

4.93 Dr Little explained that he did not think at the time that it might be useful for him to see whether the Department of Health was considering the matter on a general level, because he and his colleagues at the CVL dealing with biologicals had not yet produced their own internal documentation: ‘They would immediately have wanted to ask a great deal of questions we would not have had answers to.’ Nor did he think at the time that it would be particularly useful to raise the matter with the chairman or members of the BSC. He told us that he understood that they were dealing with this in a proper manner, and therefore did not see any need to raise it with them: ‘Sure enough it went through the process, as you can see from the minutes. They discussed it at the full meeting in January.’

4.94 We accept that once Medicines Division had recognised the potential risk from the use of bovine materials in the manufacture of medicines, as Dr Little believed, responsibility for considering how that affected human medicines rested with Medicines Division. It was not for Dr Little to check up on what they did.

4.95 However, it seems to us that even if it appeared that Medicines Division was in touch with the NPU, it would have been highly desirable to establish and maintain close communication on BSE directly between MAFF and the Division. Indeed, the fact that the NPU had been approached independently by the two Departments for advice was a clear signal that direct liaison was needed. The question of how best to ensure the safety of medicinal products in the light of the emergence of BSE raised similar issues in relation to human and animal health – for example, which were the most infective parts of the animal? Was it possible to certify herds as BSE-free? Was the disease transmissible via foetal calf serum? Consideration of common measures to deal with these was likely to be appropriate. These were questions on which each of the Departments, including the scientists in the CVL who had been working on BSE, might have had valuable expertise that could be brought to bear. In our view, this called for liaison between those responsible for considering the safety, efficacy and quality of all products, both human and veterinary, covered by the Medicines Act.

4.96 As we have indicated, Dr Little reacted promptly and appropriately in addressing the implications of BSE for veterinary medicines. Two months after the September meeting, Mr Luff was commissioned to write a paper on the subject. This was discussed by the BC, a MAFF committee, on 6 January. In our view this would have been an ideal early opportunity for joint consideration of the issues raised by BSE on the part of MAFF and Medicines Division. There would have been much to be gained by inviting the Division to attend the meeting, and sending them a copy of Mr Luff’s paper.

332 T99 pp. 68–9
333 T99 p. 69
334 YB88/01.06/1.4
4.97 Dr Little told us that if DH staff had concerns there were plenty of opportunities to discuss them with him at the VPC and Scientific Secretariat meetings every month. Indeed, he added: ‘I am sure there were further discussions on BSE with the Medical Assessors outside formal meetings, but I cannot recall them now.’ If there were such discussions during this period they apparently made as little impact on Medicines Division thinking as did Dr Little’s reference to BSE at the September CSM/BSC meeting. It is a pity that no record appears to have been made of any communication between CVL and Medicines Division officials. This might have ensured that there was a clear understanding in each Department of the activities of the other in relation to BSE.

4.98 We do not think that Dr Little is to be criticised for not doing more – his response was not unreasonable – but we do think it regrettable that the opportunity was lost for joint consideration of BSE at an early stage by those responsible for the safety of human and veterinary medicines.

CSM/BSC discussion of Mr Sloggem’s paper

4.99 The position in Medicines Division was wholly different, given that DH had not been formally notified of the existence of BSE. At the time of his conversation with Dr Little in September 1987, Mr Sloggem, in his role as a pharmaceutical officer, had for his part been carrying out an admirably thorough investigation of a specific bovine brain extract in order to offer pharmaceutical advice on an application for a CTC. He had learnt about this new bovine disease only by chance during August. He perceived it as a ‘slow virus’. In our view it was not incumbent on him to share the information more widely at that stage.

4.100 The CTC application came before the BSC on 6 January 1988. On that occasion, nobody from MAFF was present. Mr Sloggem’s paper, based on his diligent research, referred to the emergence of the new slow virus syndrome in cattle. Dr Rotblat told us that Dr Taylor’s letter to Mr Sloggem was included in the material before the BSC. This prompted some discussion of the subject at the meeting. Should this have led officials in Medicines Division who were present at the meeting to instigate action in relation to the use of bovine material in medicinal products generally following the meeting?

4.101 We raised this question with Dr Purves and Dr Jefferys, respectively the Pharmaceutical and Principal Medical Assessor to the CSM/BSC, both of whom were present at the meeting on 6 January 1988.

4.102 In a written statement to us, Dr Purves explained that he did not now believe that the tentative quality of the information in Mr Sloggem’s paper and Dr Taylor’s letter about the new ‘slow virus syndrome in cattle’ could be said to form a proper basis for instigating action of any type in respect of the use of bovine material in medicines. He pointed out, as we have already noted, that no information had been supplied to Medicines Division by the VPC or MAFF. Dr Purves added:

The information contained in Mr Sloggem’s paper was placed before the Biologicals Sub-Committee, whose breadth of experience and expertise was

335 S442 Rotblat para. 44
336 SS35A Purves paras 7 and 9
337 SS35A Purves para. 12
much greater than mine and who would be expected to address any issue of wider significance to which a particular product application gave rise. The sub-committee made no recommendation that any action should be instigated in relation to the use of bovine materials in medicinal products generally.

4.103 Dr Jefferys agreed with this point.338

4.104 We have noted that none of the leading experts present at the meeting suggested, during the course of it or afterwards, that the information in Mr Sloggem’s paper had broader general implications that called for action. We do not consider that those experts are to be criticised for that. They advised that the CTC in question should be refused in part because of the concern about slow viruses and it was reasonable that they went no further.

4.105 Given that the advisory committee did not raise any wider considerations, and that they were unaware of MAFF’s actions on veterinary medicines, our view is that it was not unreasonable for Medicines Division officials not to have raised any wider implications either.

4.106 Nevertheless, although we do not consider that any individuals are to be criticised, it was unsatisfactory that the information discovered by Mr Sloggem was lost from sight, and that its broader implications were not spotted. There was an element of circularity in the system – the officials did not take action because the experts had not raised concerns, but the experts advised only on the matters officials identified. We believe that had there been a system in operation in Medicines Division at that time for identifying, reviewing and recording information which raised concerns of potentially broader application, Mr Sloggem’s information about the new bovine disease would have found a natural home there. Establishing such a system was certainly not part of Mr Sloggem’s remit. We note that at the time the Medicines Division database was in disarray. Our understanding is that, despite the improvements that have been made to the Division’s databases, it is still the case that no such system exists.

4.107 We consider that a working database of concerns and queries not arising from adverse reactions should be established. It might be rather like the Adverse Drug Reactions On-Line Information Tracking (ADROIT) database (see Chapter 2), but would record information provided by, and be accessible to, both the MCA and the VMD. The database would include all materials used as ingredients in, and during the manufacture of, medicinal products. Any new concern identified in the course of the licensing procedure in relation to any such material would be recorded in the database, and the relevant official would be responsible for drawing this and its implications to the attention of all who needed to know. We believe that this would assist the Licensing Authorities and their advisory committees in addressing any issues of potentially wider significance to which a particular licence application gave rise. Queries and doubts from advisory committees about a material might also be logged in for future reference. A shared data series of this sort would facilitate early identification where a range of existing products needed examination, or general guidance might be required.

338 S419B Jefferys para. 26
The Medicines Division response after March 1988

4.108 When the CMO, Sir Donald Acheson, received Mr Andrews’s letter of 3 March 1988 he not only understood the concern of MAFF about the potential human food threat, but also immediately perceived that there might be a risk from contaminated medication. He was unaware that this was already being considered by Dr Little and his team in relation to veterinary medicinal products. His immediate reaction was that an urgent expert assessment of the safety of biological human medicinal products should be carried out. He was particularly concerned about material used in preparing vaccines. No doubt he had vividly in mind his own knowledge of the tenacious infectivity of CJD and the disastrous story of contaminated human growth hormone. He promptly set the wheels in motion to secure advice.

4.109 At the meeting with MAFF on 17 March, called by Sir Donald, it was agreed that the use of bovine material in manufacturing vaccines would be a priority issue for the proposed expert group (which became the Southwood Working Party). The minutes of the meeting do not record any mention by the MAFF representatives, Mr Cruickshank and Dr Watson, of the consideration given so far to this by veterinary medicines licensing staff. Dr Harris, the CMO’s deputy, who had extensive experience in medicines licensing, undertook to take up the biologicals aspect with the NIBSC. Ministers were told in Sir Donald’s submission of 21 March that although the risk to human health through the use of bovine tissue-based biologicals in the pharmaceutical industry was likely to be low, in view of the lethal nature of the virus and its uncertainties, he felt further expert advice was needed as soon as possible. Medicines Division was brought into the picture by being sent copies of this submission.

4.110 Both Sir Richard Southwood, as soon as he was appointed, and Dr Pickles, to whom Sir Donald gave the role of coordinating action within DH and assisting the Southwood Working Party, were left in no doubt about the importance the CMO attached to this matter. Having taken all these steps to secure authoritative advice, the CMO quite rightly stood back to await results. We consider Sir Donald’s initial response with regard to human medicines was prompt and appropriate.

The response of Medicines Division to the CMO’s concerns

4.111 We examined closely the initial response from Medicines Division in order to assess whether it reacted with sufficient urgency after the CMO had set the framework for action. We looked separately at the periods before and after Dr Pickles’s minute of 21 June 1988, on behalf of the Southwood Working Party, pressing for the section 4 committees to be consulted on a number of matters. Dr Jones told us that the receipt of Dr Pickles’s minute was the ‘first time’ Medicines Division realised it was going to be ‘expected to do something’.

4.112 We discussed in Chapter 2 the deficiencies described in the Evans–Cunliffe report, which had been published in December 1987. In particular Medicines Division was overloaded and short-staffed, the database was in disarray, and the management structure was divided and had weak lines of responsibility. These
difficulties are factors we have borne in mind in considering the adequacy of the response in Medicines Division to the emergence of BSE.

Obtaining expert advice

4.113 The CMO’s submission to Ministers identified the need for further expert advice as soon as possible. When we discussed the submission with Dr Gerald Jones, the Senior Medical Officer in Medicines Division, he told us that the state of knowledge about BSE in the Division at that time was ‘virtually zero’, although there was a steep learning curve over the next few months as its knowledge increased. By the end of June it had become clear it had ‘a serious problem’. 340

4.114 Dr Jefferys, who was the branch head responsible for new drugs and biologicals, told us:

> my scientific knowledge of BSE and other spongiform encephalopathies was at the time extremely limited – I had learnt about kuru as a medical student, had seen one patient with classical CJD during my years in clinical practice and was aware of the problems relating to dura mater and iatrogenic CJD. I believe that the other officials within Medicines Division had similarly limited knowledge about BSE and other spongiform encephalopathies and there was not available within the Division the necessary expertise to consider the issue. 341

4.115 Clearly then, Medicines Division was in no position to form its own judgement about the issues raised by the emergence of BSE until it obtained expert advice. We think it was a natural and reasonable reaction of the Division to await the informed advice that the CMO had commissioned from the new working group of experts. The CMO clearly envisaged that the expert advice he required would be provided by the Working Party, and it was anticipated that the Working Party would report within a relatively short period of time. Dr Jones told us that is how he read the CMO’s submission:

> I do not think anyone should read this as saying we need urgent action to examine medicinal products, exposure of people in abattoirs or vets. It does not say that at all. The urgency is for him to get advice to understand what the disease means. It means nothing more in fact, in my opinion. 342

4.116 However, there remained the question of what, if any, preliminary steps should be taken in the interim to ensure the Division was well informed and well placed to take action, should that be necessary.

Searching the database

4.117 Perhaps an obvious preliminary step would have been to obtain a foundation of knowledge about which products contained, or had been manufactured using, bovine materials. The principal sources available to provide such information were Medicines Division’s NORSK database, and its paper files. Unfortunately, as we noted in Chapter 2, the database had severe limitations.
4.118 In addition to those limitations, there were shortcomings relevant to the issues raised by a disease such as BSE. Dr Jefferys told us that the NORSK database was theoretically intended to be able to inform users of the nature of both active ingredients and excipients (ie, non-active ingredients) in licensed medicinal products. However, it was not capable of informing them of the source of these ingredients, nor of the nature of the ingredients used merely in the manufacturing process.343 This was a problem because bovine albumin, foetal calf serum and bovine nutrient broth were extensively used in the production of medicines such as vaccines. Dr Rotblat told us that during preparation of their paper she and Dr Purves had discovered that the database was inadequate; in particular they had no data on materials used as excipients or in the production process.344

4.119 We also described the difficulties with the paper filing system in Chapter 2. The difficulties that would have been involved in discovering the use of bovine material in manufacture by reading the copious gold files are self-evident. Furthermore, manufacturers at that time did not necessarily keep records of sources of raw materials, which were frequently bought from specialist companies, and were not required to advise the Division of any changes in this. Files might therefore have been inaccurate in those respects.345

4.120 In short, the Division could not rely on the information it held to identify comprehensively those products that used bovine materials at some stage in their manufacture, and the source of those materials. We recognise the difficulties to which these shortcomings must have given rise. The new database (the Product Licence User System or PLUS database) was introduced only in 1993. We have been careful to bear in mind the technological advances that have been made since 1988. However, it might be said that the very existence of these difficulties should itself have prompted early thought about what steps might be taken to address them.

4.121 We discussed with Dr Jefferys (to whom Mr Wilson’s minute in April and Dr Pickles’s first minute in May had been addressed) and with Dr Jones, the steps that might have been taken. Dr Jones explained that awaiting the deliberations of the proposed expert view was ‘clearly and obviously’ what they would want to do.346 He did not consider the possibility that the proposed expert group might ask for information about the extent to which bovine tissue based biologicals had been given licences:

Before that expert group met, you are referring to Southwood, my view about what they would say can only be at one extreme they might say that this disease in cattle will have no implications whatever for human health. At the other extreme they might say we are going to face a very serious epidemic of infectious disease, or they could have expressed a view intermediate between those two extreme positions.

That was my position before, as any normal man would have towards a committee that has not started work.

4.122 We noted with interest the contrasting and commendable response of Dr Pickles prior to the first meeting of the Southwood Working Party. At the same...
time as she contacted Dr Jones, she also contacted Mrs Alderman, one of the information scientists in MB1, to request some information from the database. It appears that the database was not entirely uninformative: Mrs Alderman was able to supply some answers to her questions, although these were far from comprehensive.

4.123 It seems to us that this was a logical preliminary step. It might, for example, have identified any products that were of particular concern, assisted in the preparation of the paper for the BSC, or revealed the deficiencies in the information available and enabled thought to be given to the best means of obtaining the information that the database was unable to provide. If a time came when action was called for, Medicines Division might have been better placed to take it promptly.

4.124 While it would have been creditworthy if Dr Jones and Dr Jefferys had taken the initiative in the same way as Dr Pickles, we do not consider that their failure to do so ranks as a shortcoming which calls for criticism. Given their perception in April/May that the Southwood Working Party would be advising on this subject, and their other preoccupations, we think it was within the range of acceptable responses to take no such preliminary steps prior to receipt of Dr Pickles’s minute of 21 June, but rather to await the views of the Working Party.

Action after Dr Pickles’s minute of 21 June – advice from the section 4 committees

4.125 Dr Pickles’s minute of 21 June 1988 was important in changing the Medicines Division perception. She made it clear that the Southwood Working Party were looking to the section 4 committees to consider the issue of BSE and medicinal products. In effect, the Division was expected to advise the Working Party, and not vice versa. There could be no doubt that the ball was now firmly in the Division’s court; it had very little real alternative to referring the matter to the section 4 committees for advice, which it did.

4.126 However, we were concerned whether the matter was put to the section 4 committees sufficiently promptly. We considered first who was responsible for assigning an appropriate degree of priority to the matter.

Who in Medicines Division was responsible for deciding what should be done about BSE, and when?

4.127 The witnesses who gave evidence from Medicines Division told us that there was no obvious lead responsibility in the Division for a topic, such as BSE, that raised issues affecting several branches. The existing structure of the Division had evolved to handle a certain range of applications and issues relating to individual medicinal products. By contrast, BSE was an unusual problem, which had implications across all branches of the Division and potentially affected both new – and as yet unlicensed – drugs, and drugs already on the market.347

4.128 We discussed with Dr Jones and Dr Jefferys whether in practice lead responsibility for BSE naturally fell to a particular individual or branch within the existing structure of Medicines Division. In particular, we noted that concern had

347 S419B Jefferys paras 16–17; S190B Jones G paras 4–5
been expressed by the CMO in his submission of 21 March 1988 about ‘bovine tissue-based biologicals’. Was MB3A, with its responsibility for new drugs and biologicals, the natural branch to address these concerns? And was Dr Jefferys, as head of that branch and as Principal Medical Assessor to the BSC, the individual to whom lead responsibility naturally fell?

4.129 Dr Jefferys explained that MB3A was responsible for the medical assessment of new applications for medicinal products including biologicals, but not dental and surgical materials. He did not accept that it was for MB3A to lead on policy advice concerning the potential impact of BSE on biological products in the first phase of the Division’s consideration of the issue. Its responsibility was for assessing new drug applications. Others in the Division had responsibility for the older products and for dental and surgical materials. A number of people within different branches would be involved. Dr Jones agreed that there was no particular branch with a general responsibility for biological matters, or which would be the automatic point of reference if a problem were to arise with regard to a drug with a biological component.

4.130 Similarly, the issues raised by BSE had implications for each of the section 4 committees and subcommittees.

4.131 We accept that responsibility for BSE did not naturally fall solely to a particular branch or individual in the existing structure of Medicines Division, but raised issues relevant to the different medical and pharmaceutical branches. Although MB3A and Dr Jefferys clearly had some relevant responsibilities, so too did other branches.

4.132 But we also consider that good management called for a lead responsibility to be assigned. It would have been for Dr Jones to do this. He told us:

I think we have to get away from this idea that there was someone beneath my level who would be allocated lead responsibility across Medicines Division. That did not happen in the small number of items which did not automatically belong to one of the Medical Groups, but did involve work by all of them. At some point it would clearly emerge that somebody was going to do the work.

4.133 That being so, it was ultimately for Dr Jones, having discussed the matter with senior staff, to decide the priority to be accorded to BSE in relation to other work within Medicines Division, and set in hand appropriate action.

Was the matter put to the section 4 committees with sufficient urgency?

4.134 The BSC was asked to consider the implications of BSE in November 1988. Dr Jefferys told us that the first available opportunity for BSE to be considered by the BSC was September. The July meeting was only days away in June 1988, and
the section 4 committees did not meet in August, save in an emergency.\footnote{355} We agree that the urgency of BSE was not such as to justify convening the BSC in August. However, we question whether the section 4 committees should have been asked for advice earlier than they were.

4.135 Dr Jefferys suggested that priorities were changed in order to meet the deadline.\footnote{356} Dr Rotblat agreed with Dr Jefferys, although she recalled that, rather than dropping other work, she managed by working longer hours.\footnote{357}

4.136 In oral evidence Dr Jones indicated that Dr Rotblat was not told that BSE was a high priority matter, nor that the paper was to be prepared in time for the September meeting. If the matter had been given a higher priority it could have been put to the committees before November:

She was not told, ‘This is priority, make sure it is done for the next available meeting’, which I take it could either have been September . . . or October. It could have gone in October if you had insisted. Biologicals would not have met in October, as you know. We must not get caught up in bureaucracy. If the Biologicals Sub-committee does not meet, you ask the Chairman and two or three of his colleagues to come to the CSM.

The system is flexible enough to deal with anything if it is identified as of high priority. In this particular case it has obviously been done in an ordered professional way, not with low priority but in an ordered professional way, and the next meeting was going to be November, of the various committees.\footnote{358}

4.137 Clearly much depended on the priority given to BSE at the time. When we asked Dr Jones about this, he said that the risk from medicinal products, although a potentially very serious issue, was considered to be remote and had to be balanced against a number of other extremely urgent priorities:

On the food side we knew in June there was, whatever the words are, remote theoretical risk to human health on the food side. Our perception was the risk to human health from medicines was, if anything, even lower . . . But it was not regarded with the pressing concern of, for example manufacturing defects with medicines, that could lead to the deaths of patients overnight; serious adverse reactions which were collected by the Division at the rate of 15 to 20,000 a year.\footnote{359}

4.138 He did not think that anybody seriously expected an infectious agent that could pose a risk to be present in a final product of a vaccine produced in culture with foetal bovine serum:

If it were a risk it would either be zero or so close to zero that it could never be detected. That was the view.\footnote{360}
4.139 Others, among them the Southwood Working Party and Dr Pickles, did not share Dr Jones’s assessment. Dr Jones told us that he did not inform his colleagues of his view at that time. None the less, it is hard to avoid the conclusion that his opinion influenced his assessment of the priority to be afforded to BSE.

4.140 The evidence we have heard suggests to us that a full paper could have been prepared for the September meeting of the BSC had the task been assigned a somewhat higher priority. In our view, Dr Jones should have asked that such a paper be prepared. Two further months were allowed to elapse during which progress might otherwise have been made.

4.141 Dr Jones accepted that Dr Jefferys did not have the lead responsibility for BSE in Medicines Division and in written communication with the Inquiry accepted that it was for him, Dr Jones, to decide the priority to be accorded to it. As such we do not think that any criticism attaches to Dr Jefferys.

**Publication of a request for information in MAIL**

4.142 On 2 November 1988 the CSM/BSC recommended that there should be an article in MAIL requesting manufacturers to identify products in which bovine materials had been used. No such request was issued until March 1989, in the event by means of a questionnaire rather than an article in MAIL. In considering whether Medicines Division should have acted with greater urgency in response to the emergence of BSE, we questioned whether this lapse of time was appropriate.

4.143 When we asked Dr Jones about it, he pointed out that if urgent communication were required a letter would be sent, rather than an article being published in MAIL. This would be costly but was possible if appropriate. The very fact that the recommendation from the section 4 committees was for an article in MAIL was an indication that they did not consider this to be of that degree of urgency.

4.144 Professor Collee explained to us, in a written statement, that the BSC and CSM did not intend that an article should be placed in MAIL immediately following the November 1988 meetings. They were consulting and progressing with necessary care. In order to determine how many and what questions should be asked, it was necessary to go through a process of careful scientific evaluation. Professor Collee explained why he did not believe it would have been possible for a comprehensive questionnaire to have been administered before March 1989.

4.145 We ascertained that there was an issue of MAIL in November 1988, and that the next issue was not published until March 1989. In those circumstances, it seemed to us unrealistic to suggest that an article should have been included in MAIL immediately following the November meetings of the BSC and CSM. Moreover, we were persuaded by the reasoning, set out by Professor Collee and others, that it was acceptable that no general request for information was issued to licence holders before the guidelines and questionnaire were sent in March 1989.
Communication between Medicines Division and MAFF

4.146 We have discussed above some of the problems that arose because of the weight that was subsequently put within MAFF on Dr Little’s incorrect impression of how matters stood in DH. Joint consideration of the implications of BSE might have prevented the misunderstanding from arising, or from persisting. However, the lack of communication between the two medicines licensing divisions of the Departments continued even after the CMO had asked for the question of bovine biologicals in human medicines to be urgently considered.

4.147 As we have noted earlier, there were arrangements for contact between those in MAFF and Medicines Division responsible for medicines licensing. There was a degree of cross-attendance at the meetings of the VPC, CSM and other section 4 committees. Dr Jefferys told us that Dr Adams and Dr Diggle from the Division were the official contact points with the VPC, who might have brought information across. Dr Adams explained:

I attended these meetings on occasion between 1986 and 1988 (when I was promoted to Principal Medical Officer) as part of my responsibilities as Senior Medical Officer. My purpose in being at the meetings was to encourage consistency of approach with regard to particular drug substances in respect of which there was an application before the VPC, when those substances had already been licensed for human use.

4.148 There were no official MAFF observers at the meetings of the CSM and other section 4 committees; Dr Little told us that VMD officials were not regular attendees at human health committee meetings as ‘medical products have very little interest to veterinarians because there is no immediate connection’.

4.149 Professional staff from Medicines Division also attended meetings of the Scientific Secretariat of MAFF. In addition, Dr Little told us of the ‘good working relationship’ between himself and other CVL staff and the DH medical assessors who attended the VPC meetings and the Scientific Secretariat meetings. He elaborated:

I would also note that as part of my responsibilities as Deputy Director, I met the relevant Department of Health Medical Assessors at least twice a month at either the VPC or its Scientific Secretariat meetings (see paragraphs 19 and 20 of my statement dated 18th December, 1998 . . .). If Department of Health staff had concerns, there were therefore plenty of opportunities to discuss them with me at these meetings. I am sure there were further discussions on BSE with the Medical Assessors outside formal meetings but I cannot recall them now.

4.150 However, it did not seem to us that in practice there was real and constructive communication between the two Departments about the implications of BSE for medicinal products. The narrative in Chapter 3 reveals the consideration that was given to BSE and veterinary medicinal products by MAFF from late in 1987.

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364 T112 p. 106
365 S465 Adams para. 23
366 T99 p. 36
367 S331 Little paras 19–20
368 S331A Little para. 15
onwards. However, it was not until July 1988 that it was suggested that DH should be kept informed of any developments with BSE. Mr Wood’s paper with draft guidelines on veterinary medicines was sent to Dr Harris in July 1988, following a suggestion from Dr Minor of the NIBSC.

4.151 For their part, Medicines Division seem to have initiated very little contact with MAFF: Mr Wood’s paper was one of the annexes to Dr Rotblat’s and Dr Purves’s paper. In a note dated 12 October 1988 commenting on that paper, Dr Pickles said:

5. But there are also other recommendations on the MAFF list that could be looked at and easily incorporated into any recommendations of your own eg not using serum from cows killed by brain-penetrative stunning. Perhaps it would be wise to find out what has been happening in VPC before you put the problem to CSM and its sub committees (different recommendations about acceptability of non-British bovine sources could be embarrassing and would give legitimate grounds for appeal to the MC).369

4.152 Dr Purves referred to this comment in a written statement to us:

One comment Dr Pickles made about our draft recommendations was that we should have looked at, and incorporated into our recommendations, those made by MAFF on veterinary products with bovine materials. We had most certainly considered the MAFF own recommendations and indeed had appended them as Appendix 3 to our own report.370

4.153 Dr Purves did not suggest that he and Dr Rotblat had been in touch with colleagues in MAFF to discuss the issue. His evidence was that Dr Jefferys and Dr Adams were responsible for such liaison:

They were in charge of liaising with those senior people in other organisations, including the lead officials for BSE in DoH and MAFF and the CMO about what was being done in Medicines Division and what could be done.371

4.154 However, Dr Rotblat thought that Dr Purves had been in contact with MAFF colleagues:

I presume that Dr Purves and Mr Sloggem framed the concept of ‘healthy herds’ and specifically mentioned brain and lymphoid tissue following discussions between them and MAFF.372

4.155 Dr Jones told us that it would have been desirable for the people dealing with the issue of BSE to communicate with MAFF. He said that if someone needed to suggest to those individuals that they should contact MAFF, it would be for the appropriate branch head to do so but not himself. He could not recall having had any contact himself with MAFF over this period.373 Dr Jones told us that it was a commonplace practice when preparing a paper for the CSM that was likely to have

369 YB88/10.12/2.1–2.3
370 S535 Purves para. 69
371 S535 Purves para. 33
372 S422 Rotblat paras 56, 69
373 T136 p. 68
It is not clear to us what, if any, real liaison had taken place prior to November 1988. Dr Pickles’s report of the discussion of the BSC meeting that month noted that further information would be sought from MAFF and other experts on how disease-free herds, procedures and countries might be identified. It seemed to us that this was the first occasion on which real consideration was given to the need to work in conjunction with MAFF. Dr Adams told us that he went to talk with Mr Bradley about this in December 1988.375

We wondered whether the requirements of the Medicines Act inhibited such communication. However, Dr Jones told us that the confidentiality requirements of the Medicines Act would never inhibit him or his staff from communicating across the whole branch, all the branches in DH, or indeed all Government. If they wanted to communicate something with MAFF then section 118 of the Medicines Act would not matter at all.376

We were surprised by the tenuous nature of the working relationships between the two Licensing Authorities at this time. Veterinary and human medicines, particularly vaccines, drew on the same or similar raw materials, sterilisation procedures and production processes. A single piece of legislation applied across the board, imposing the same assessment criteria: safety, quality and efficacy. Parallel systems of quality proofing and enforcement were operated through the licensing processes. A family of statutory committees advised under the same section of the Medicines Act. The Medicines Commission spanned both human and veterinary medicines and had an overview of the workings of the system as a whole.

Moreover, as we noted above, the question of how best to ensure the safety of medicinal products in the light of the emergence of BSE raised similar issues in relation to human and animal health on which each of the Departments might have valuable expertise that could be brought to bear.

We were therefore puzzled by the communication gap between the two Departments – both the passiveness of MAFF in relation to informing and discussing matters with DH, and the failure of Medicines Division immediately to open up discussions to ascertain what knowledge the CVL already held. The licensing authorities would appear to have shared interests, shared criteria and shared powers. One possible explanation was the perception, described in Mr Cunliffe’s management report on veterinary licensing in early 1988, that animal health was the smaller ‘poor relation’ of human health and would usually take its cue from human health considerations.377

Whatever the reason, it seems to us that the lack of communication at this stage between the two Licensing Authorities contributed to a delay of several months in putting in hand action and consultations to address the potential risk to the population of the UK through medicinal products manufactured with or containing bovine materials. It meant that officials in Medicines Division were

374 T136 p. 69
375 S465 Adams para. 42
376 T136 p. 84
377 M11D tab 18 p. 14
some months behind their counterparts in MAFF in beginning to address the
problems, and that further delay ensued once the two Licensing Authorities began
to work simultaneously on the matter.

4.162 We do not know what improvements have been made since that period in the
communication arrangements between the two Licensing Authorities. We
understand that the process for passing information between them is for it to be
referred from one section 4 committee to another, via their respective secretariats.
These matters seem to us to fall within the remit of the Medicines Commission to
investigate. However, some of them may be wider than that and raise questions
about the way the Medicines Commission, the Health and Agriculture Departments
and the agencies that now exist relate to one another and where policy assessments,
as distinct from individual product assessments, are made.

4.163 If the suggestion we have made at paragraph 4.107 above for a register of
concerns is followed up, its contents at any given time would provide an obvious
core topic for regular meetings.

4.164 We would also see merit in a formal concordat about information sharing
between the two executive agencies that now exist to handle licensing matters. If a
piece of information rings warning bells with officials on one side, it would be
preferable for this to be shared freely and more speedily than through the formal
processes and paperwork of the advisory committees. There also would appear to
be a departmental ‘need to know’ on matters that might have wider repercussions.
Consideration might be given to whether other aspects of the relationship between
human and animal medicines licensing would similarly benefit from a concordat.