5. Issue of guidelines

Introduction

5.1 As we have seen, up to January 1989 MAFF and Medicines Division worked separately in responding to the emergence of BSE and there was no contact between the work of the Veterinary Products Committee (VPC) and the other section 4 committees. On 3 January 1989 MAFF and DH officials met collectively for the first time to discuss the handling of BSE and medicines licensing. They agreed that it was essential to keep ‘in step’, and issue joint guidelines.

5.2 For the next three months the two Departments worked closely to agree and issue joint guidelines and questionnaires. In this process, MAFF ceded the lead to DH in the way matters were handled. Although there was a more obvious risk of animal-to-animal transmission than of animal-to-humans, it was felt that human safety issues were paramount. In particular, DH fears about creating a vaccine scare were taken into account in agreeing with MAFF how matters should be handled. The outcome was that joint guidelines and a joint questionnaire about the use of products were issued in early March. This chapter reviews these events, how they interacted with the final drafting and perceived message of the Southwood Report, and the action taken immediately after that report was published at the end of February.

Preparation and issue of joint guidelines between January and March 1989: a chronological account

January 1989

MAFF and DH agree to keep in step

5.3 We have seen from Chapter 3 that towards the end of 1988 Dr Adams (PMO in Medicines Division) had various informal conversations with MAFF colleagues about BSE, including a visit to Mr Bradley in December 1988. Dr Adams told us that around this time it occurred to him it would be helpful to set up a meeting between MAFF and DH, so that officials from MAFF’s Central Veterinary Laboratory (CVL) would be on hand to provide advice about BSE and feed into Medicines Division discussions. This was because they needed as clear an understanding as possible of the up-to-date knowledge of the CVL. In addition, MAFF was working on draft guidelines for industry and he felt that the two Departments should keep in touch. He therefore arranged a meeting for 3 January 1989.378

378 S465 Adams paras 43–4
5.4 In addition to Dr Adams, Dr Jefferys and Dr Purves attended the meeting from Medicines Division. From MAFF, Dr Little and Mr Kidd came from the veterinary medicines licensing side, as well as Mr Bradley in the CVL.

5.5 At the meeting MAFF explained what action it had taken on veterinary medicines since November 1987, and provided some background information. Medicines Division described the progress of its consideration, and outlined some of its unresolved questions, for example how to define a healthy herd. The two Departments agreed it was ‘essential to keep “in step” especially as MAFF concerns about animal vaccines would cause DH great difficulties of supply if current stock had to be lost’. They agreed that MAFF would put revised guidelines to the VPC later that month. This had in any event been the intention (see Chapter 3). Following the meeting of the VPC the two Departments would meet again with expert advisers from the National Institute of Biological Standards and Control (NIBSC) to produce joint guidelines for industry. These would then be published in MAIL, together with a request for information on products.379

5.6 Following the meeting, Dr Jefferys and Dr Adams sent a joint minute on 9 January to Dr Harris, the DCMO, to update him on the current state of play. They circulated this widely in Medicines Division and sent copies to Dr Pickles and to MAFF. They noted that the importance of MAFF and the Division keeping ‘in step’ had been recognised, particularly as vaccines were prepared in the same way for humans as for animals and involved the use of foetal calf serum, a potentially infective material. It would, they said, cause great difficulties if current stocks of vaccines were to be lost as, for some vaccines, ‘there may be supplies of up to 5 years’. They also mentioned that Medicines Division’s database was unable to identify products used, not as an active ingredient, but rather as an excipient or an intermediate in the manufacturing process: this created a much greater problem as bovine albumin, foetal calf serum and bovine nutrient broths were extensively used in the production of all vaccines, as well as in that of other biological and biotechnological products. 380

5.7 Dr Jefferys and Dr Adams also told Dr Harris of the plan for a common set of guidelines on the procedures for collecting and using bovine material. The amalgamation of the two sets of guidelines would mean:

a slight change in emphasis since the MAFF proposals concentrate upon the collection of the bovine material, whereas the initial CSM proposals were concerned more with the production of the medicinal products.

This would allow clarification of the definition of healthy cattle and would give clear advice about the collection of foetal calf serum and bovine albumin. 381

5.8 They noted that a proposed joint working group involving NIBSC and BSC members would ensure that the proposals were practicable and capable of implementation in as short a time as possible, and should not damage the supply of important products such as vaccines and monoclonal antibodies for human use. The minute concluded by pointing out that neither MAFF nor Medicines Division had

379 YB89/1.3/2.1–2.2
380 YB89/1.9/2.1–2.2
381 YB89/1.9/2.2
been given sight of Sir Richard Southwood’s interim Report and that it would be most helpful if this could be made available.\footnote{YB89/1.9/2.2–2.3}

**5.9** Within MAFF, the conclusions of the meeting were relayed to Mr Scollen, Head of Animal Medicines Division, who on 13 January 1989 sent a minute to Mr Cruickshank to bring him up to date. Mr Scollen noted the difficulty in ensuring that foetal calf serum and other bovine material used in the preparation of biological products was free of contamination. There were safeguards that could be introduced for the future, but Mr Scollen noted that there was also a potential problem over existing stocks of vaccines, most of which were produced with some kind of bovine material. He told Mr Cruickshank of the plan to combine the two sets of guidelines produced independently by Medicines Unit and by DH Medicines Division, ‘so that the two Departments are seen by the industry to be speaking with one voice, particularly on a matter where they are so interdependent’.\footnote{YB89/1.13/1.1}

**5.10** Mr Scollen noted that there was further work to be done in order to judge the need for more extensive action. While there was potentially a need for ‘radical – and expensive action’ it was also possible, he pointed out, that in the course of a few years they would be able to demonstrate the effectiveness of the action already taken to eliminate BSE:

> Extravagant action now to deal with a contingent risk could then seem to be wholly disproportionate. Moreover, new collection methods would not deal with the problem of existing stocks of vaccine.\footnote{YB89/1.13/1.1}

Mr Scollen concluded:

> In my own view the issues involved centre on an assessment of the risks associated with maintaining or disrupting the supply of vaccines for human health purposes. The issue is therefore one to be addressed first and foremost in the human health context, with MAFF advising on the availability of animal material considered free of contamination. Judgements about what is needed and feasible on the animal medicines front can be more readily taken afterwards. In addition to the meeting on 1 February, I shall be taking up these points with Mr Wilson and his colleagues when they visit Tolworth on 23 January.\footnote{YB89/1.13/1.2}

**VPC discussion of the draft guidelines**

**5.11** As planned, the VPC considered MAFF’s draft guidelines for industry for the first time on 19 January 1989. They requested a full list of products involved, including all the ‘old medicines’, ie, those with Product Licences of Right, to assess the likely effect of various control measures and their practicality. Written comments on the draft guidelines were invited, to be discussed at the next meeting in February.\footnote{YB89/1.19/7.2; YB89/2.13/2.17}
Further correspondence with Sir Richard Southwood

5.12 We noted in Chapter 4 that, following the third meeting of his Working Party, Sir Richard Southwood had written for the second time to Professor Asscher. On 20 December 1988 Sir Richard also wrote to MAFF for the first time to make enquiries about veterinary medicinal products. Sir Richard directed this letter to Dr Little, asking him what steps were being taken by the VPC in its consideration of licence applications for new products. He said that he trusted that any safeguarding steps would also be applied to existing products. He suggested as possible solutions purchase of material from abroad; exclusion of brain and lymphoid tissue directly or in culture media; and avoidance of animals destroyed by brain penetrative stunning. Sir Richard asked if some form of guidance to the industry might be useful.387

5.13 Dr Little replied on 26 January 1989. He outlined the discussions that had taken place during the past year with the VPC, and with MAFF’s Biologicals Committee (BC), the National Office of Animal Health (NOAH) and individual licence holders. Dr Little said that the VPC had asked for a full list of products involved, ‘including all the old medicines to assess the likely effect of various control measures and their practicality’. He explained ‘our philosophy in drafting guidelines for consideration by the VPC has been to concentrate on the source and nature of the materials used in the manufacture of veterinary products’. Dr Little indicated some of the difficulties, and added that those dealing with veterinary licensing were working very closely with colleagues in DH to ensure they issued consistent advice to manufacturers.388

5.14 Professor Asscher also replied to Sir Richard on 26 January. He said that the secretariats of the Committee on Safety of Medicines (CSM), the Committee on the Review of Medicines (CRM) and the Committee on Dental and Surgical Materials (CDSM) had been considering, and seeking to implement, the recommendations made by CSM:

We originally considered the problem of BSE in the light of the 43 products which our computer database showed to include bovine material as an active ingredient. We will now need to consider the possible hazard from the use of bovine material as an intermediate in the manufacture of products. This will include the use of bovine material in nutrient broths, foetal calf serum and the use of bovine serum albumin. You will be aware that these materials are used very extensively in the production of most vaccines, monoclonal antibodies and other biotechnologically derived products.

MAFF are also concerned about such products and they have now produced new draft guidelines regarding the use of bovine material in veterinary medicines: these are currently under consideration by the Veterinary Products Committee.

Following several meetings between Medicines Division officials and their counterparts at MAFF, it is hoped that a joint guideline for the manufacturers of both human and veterinary medicines can now be agreed and published. Therefore a further paper is being produced for consideration by the CSM.

387 YB88/12.20/2.1
388 YB89/1.26/2.1–2.2
and its Sub Committees. We will be reconsidering whether our recommendation that ‘... the manufacturing processes are capable of eliminating the scrapie agent’ is too stringent. It will also be proposed that the CSM uses the definition of a BSE-free herd which has been proposed by MAFF (you will remember that my Committee deliberately chose the words ‘appropriately certified healthy herds’ to allow us the freedom to obtain more expert advice from our veterinary colleagues).

We have to consider the impact on the supply of these important products whilst at the same time seeking to maintain public confidence in the vaccination programme. Many vaccines are stored for up to 5 years before being released and this will therefore have to be considered.

For all these products it will be important to ensure that our recommendations are practicable and can be scientifically justified.

Finally, I want to reassure you that CSM intends to take appropriate action in regard of products within its remit and that CRM and CDSM are being kept fully informed of our recommendations. I hope you will agree that the Secretariats and the Committees are giving considerable attention to this important issue.389

February 1989

The Human and Veterinary Medicines Briefing Group (HVMBG)

5.15 Shortly after the VPC had considered MAFF’s draft guidelines, the two Departments met again, on 1 February 1989. The group, called the Human and Veterinary Medicines Briefing Group (HVMBG), comprised Dr Jefferys, Dr Adams, Dr Purves and Dr Rotblat from Medicines Division; Dr Minor and Dr Schild from the NIBSC; Professor Collee from the CSM/BSC; Dr Pickles on behalf of the Southwood Working Party; and Mr Kidd, Mr Bradley, Mr Taylor, Mr Scollen and Dr Little on behalf of MAFF. The role of the group was to review papers that had been prepared for the forthcoming CSM meeting and to formulate advice to the CSM on BSE as a whole. Mr Hagger told us:

This was an uncommon way to deal with CSM business (i.e. other than through its established sub-committees) but the BSE issue was unusual in that the CSM was normally concerned with licensing issues for individual products and here it was faced with unusual concerns which could have related to any number of licensed products and had serious implications for the continuing supply of all kinds of medicines, and vaccines in particular.390

5.16 In a minute of 2 February 1989 to Mr Cruickshank, Mr Scollen reported the conclusions of the meeting. According to his minute the briefing group agreed the text of the joint guidelines, and a timetable for their clearance by the advisory committees to make publication in MAIL possible before Easter. In addition, it was agreed that further action, especially on current stocks of affected products, should be determined once the scale of the problem had been more precisely identified with

389 YB89/1.26/1.1–1.2
390 S476 Hagger para. 31
the help of the manufacturers. Any such action, it was agreed, would need to be based on a human health risk/benefit assessment. 391

5.17 The briefing group also considered an extract from the current draft of the Southwood Report, shown to them by Dr Pickles. The drafting of the Southwood Report is covered in detail in vol. 4: The Southwood Working Party, 1988–89. In relation to medicines the draft read:

5.3.3 . . . All relevant products are being reviewed by the Licensing Authority. However, the Working Party acknowledge that at least some leading pharmaceutical companies have already made appropriate changes in their production processes. There are various steps which could be considered which might reduce the chance of the BSE agent or those bovine tissues most likely to contain it ever entering into pharmaceutical manufacture. For example, only animals never fed ruminant-protein could be used; or serum only taken from animals killed other than by brain-penetrative stunning which might release nervous tissue into the circulation; and the use of brain or lymphoid tissue directly or in culture media could be avoided. In all cases only healthy animals should be used in pharmaceutical manufacture but in the case of BSE it has to be accepted that infection could be present without clinical disease. The production processes are being examined to determine how these might be modified so as to destroy or remove infectious agents; the scrapie agent must now be included in such considerations. 392

5.18 The reaction of the briefing group to this draft was recorded in Mr Scollen’s minute to Mr Cruickshank of 2 February 1989:

There was general dismay at the drafting, which tends to highlight the (theoretical) risk via medicines and to relegate the qualification that the risk is remote. The paragraphs concerned also imply (mistakenly) that numerous, licensed human medicinal products are affected; that some but not all manufacturers have taken necessary action; that various safeguards could readily be introduced into the production and processing of bovine material; and that the Licensing Authority and its advisory committees need to have their attention drawn to the problems.

The Working Group felt that much of this was, at best, misleading. For example, many manufacturers have been alerted to the problem but there is no reason to believe that they are in a position to take effective, unilateral action. Moreover, the start of MAFF/DH work on the issue comfortably pre-dates the Southwood Committee.

Even if the Report is modified in the light of these reactions, its appearance seems likely to trigger a need for a major public relations job which takes full account of the medicines angle. Consistency between MAFF and DH will be essential and should be achievable. The guidelines themselves could subsequently generate similar pressures since they clearly do not address the issue of current stocks and they could prompt questions – for example – on

391 YB89/2.2/4.1
392 M61 tab 1 para. 5.3.3
the standards applicable in the collection of animal material at slaughterhouses for biological medicinal purposes.

While I have no doubts about the Working Group’s staged approach and the balance being struck between risks and benefits to human health, this will not be the easiest position to present to a potentially critical public prone to seeing the influence of commercial interests.393

Consideration by the Southwood Working Party

5.19 On 2 February 1989 Dr Pickles reported the concerns expressed by the HVMBG in a letter to Sir Richard Southwood:

They have now realised that virtually none of the current essential human or animal vaccines could comply with the CSM guidelines as agreed by their November meeting, and there may be several years of some vaccines in stock to make matters more difficult. Public confidence in the vaccination programme must not be put in jeopardy and yet supplies of some vaccines are very limited. After a late start, it now seems that both human and veterinary sides of the medicines business are working together and putting together a package of measures that seem sensible and workable (and indeed now incorporate all the points you raised with Professor Asscher in your earlier letters, and which I had raised with them separately).394

5.20 She suggested that the draft be amended:

If you are content that all is now in hand, a briefer version of 5.3.3 might be adequate. I attach my suggestions. This treats CSM/VPC like HSE: i.e. the problem has been referred to the body with the statutory responsibility in that area and it is then for them to take appropriate action. I also have suggestions for minor alterations to the summary sections to make it clear that the Licensing Authority has already started addressing the problem.395

5.21 When the Southwood Working Party met on 3 February 1989, Dr Pickles reported on the ‘very satisfactory response’ now being made by both the human and veterinary sides, and also on the potentially grave problems to supply of essential vaccines if foetal calf serum were to be considered at risk of being infected.396 The Working Party adopted verbatim Dr Pickles’s suggested wording for this section of their Report, which eventually read as follows:

5.3.3 The greatest risk, in theory, would be from parenteral injection of material derived from bovine brain or lymphoid tissue. Medicinal products for injection or surgical implantation which are prepared from bovine tissues, or which utilise bovine serum albumin or similar agents in their manufacture, might also be capable of transmitting infectious agents. All medicinal products are licensed under the Medicines Act by the Licensing Authority following guidance, for example from the Committee on Safety of Medicines (CSM), the Committee on Dental and Surgical Materials (CDSM) and their subcommittees. The Licensing Authority have been

393 YB89/02.02/4.1–4.2
394 YB89/02.02/1.1
395 YB89/02.02/1.1
396 YB89/2.03/2.3
alerted to potential concern about BSE in medicinal products and will ensure that scrutiny of source materials and manufacturing processes now takes account of BSE agent.

\[...\]

5.3.5 In these, as in other circumstances, the risk of transmission of BSE to humans appears remote.\(^{397}\)

**A draft submission to the Secretary of State: the CMO’s reaction**

**5.22** Following the completion of the Southwood Working Party’s Report, Dr Pickles prepared a draft submission from the CMO (Sir Donald Acheson) to the Secretary of State. The draft included the following passage:

In Sir Richard’s view the risk to human health is minimal. Nevertheless he has alerted the Licensing Authority and the Health and Safety Executive to potential problems in their areas of responsibility. At the present time, we cannot give any complete guarantee of safety for human medicines that use bovine materials in manufacture, such as most vaccines. However, appropriate action is being taken by Medicines Division following advice from the Committee on Safety of Medicines, the Committee on the Review of Medicines and the Committee on Dental and Surgical Materials and defensive briefing is being prepared for when the report becomes public.\(^{398}\)

5.23 This alerted Sir Donald Acheson to the fact that concerns about the safety of vaccines had not yet been resolved. He contacted Dr Pickles, and their conversation led him to ask Dr Harris to look into the matter:

My attention has been drawn to a sentence in Dr Pickles’ draft of a submission to the Secretary of State on this matter. It reads: ‘At the present time we can’t give any complete guarantee of safety for human medicines that use bovine materials in manufacture such as most vaccines.’ Having looked at the report I am not able to find any statement which supports this statement of concern. I have, however, therefore spoken to Dr Pickles on the telephone and she reports to me that for some considerable time she has had serious concern about the safety of bovine-based vaccines in the light of the fact it has been discovered that contamination with placental material (which is known to be heavily infected with the BSE particle) is a distinct possibility in the preparation of material for human vaccines derived from foetal serum. This matter as described to me by Dr Pickles gives me sufficient cause for concern to ask you to look into it urgently together with Medicines Division. I shall amend the submission to indicate that the question of the safety of vaccines derived from bovine material is a matter which has not been dealt with directly by Southwood’s group, but is one in which I am making urgent enquiries.\(^{399}\)

5.24 Sir Donald told us that this intervention was quite contrary to his normal practice; he was trying to ‘stir up more activity in the Medicines Division’.\(^{400}\)
5.25 Having taken these steps, Sir Donald recast the submission to Ministers to advise:

I am also putting work urgently in hand to satisfy myself that everything possible has been done to ensure . . . that transfer of the BSE agent in human and veterinary medicinal products does not occur. 401

Medicines Division’s response to the CMO’s concerns

5.26 The CMO’s minute to Dr Harris prompted Medicines Division to give urgent consideration to establishing the present situation on vaccines. A meeting was held on 13 February 1989, attended by professionals and administrators from the Division. In Dr Jefferys’s absence, Dr Adams took the lead. 402 A manuscript minute by Mr L Whitbread records that those present agreed that a number of steps should be taken, including:

i. Children’s vaccines and the companies manufacturing them would be identified by Mr Love and Mrs Alderman.

ii. The companies would be telephoned by Dr Rotblat and asked
   i. whether the vaccines contained bovine material;
   ii. the source of the material; eg, country of origin;
   iii. the bulk stock of vaccines post-1980; and
   iv. the length of time it would take to switch to another product.

iii. Mr Love would then write seeking more detailed information.

iv. A working group would be established to consider the Southwood Report and the paper to the CSM. Mr Hagger would clear this with Professor Asscher. It was proposed that the group should comprise Professor Collee, Dr Tyrrell, Dr Kimberlin, Dr Minor, Dr Schild, Dr Martin, Dr Pickles and various MAFF representatives. 403

We discuss the establishment and deliberations of this group in Chapter 6.

5.27 A further meeting was held the next day to discuss the outcome of Dr Rotblat’s enquiries. 404 Urgent telephone calls had been made, enabling Dr Adams to report to Dr Harris that they had contacted all the major vaccine product licence holders whose products were likely to be used in children. 405 He said that many manufacturers used bovine material. The information given was diverse and incomplete; many companies stressed that they could not give an accurate assessment without detailed research. He set out an overview, which we include in full below.

1. SKF have polio, measles, mumps, rubella, rotavirus vaccines. All use bovine serum from a UK source and bovine commercial product from unknown source. Some agent comes from the USA and New Zealand.

401 YB89/2.9/5.3  
402 S465 Adams para. 53  
403 YB89/2.14/7.1–7.3  
404 YB89/2.15/8.1–8.3  
405 YB89/2.14/10.1
2. Wellcome gave us most information (see Appendix 2). All their vaccines apart from yellow fever, cholera and typhoid contain bovine material:

Oral polio; up to 1988, foetal calf serum was used from UK and New Zealand (pooled); since 1988 foetal calf serum only from New Zealand. Large stocks are held.

Rubella; bulk was made before 1979 from foetal calf serum from UK and New Zealand. None has been made as there are some 15 years stock.

Diphtheria; UK bovine beef muscle and ox heart is used but since the end of 1988 this has been sourced from Eire. There are 1,250 litres of stock.

Tetanus; this involves bovine material from the UK mainly Scottish. There are 21,000 litres of stock.

Pertussis; uses bovine material from the UK. There are 63,000 litres of stock.

They consider that to switch to a non-UK source will take a minimum of 6–18 months and to switch to a non-bovine source will take a minimum of five years.

3. Merck Sharp & Dohme have measles, mumps, MMR, rubella vaccines. These are sourced from the USA and the company believes that US material only is used.\textsuperscript{406}

4. Evans Medical have a measles vaccine using bovine serum from the UK. There are 440,000 units of stock.

– They have also got MMR using bovine serum from the UK.

5. Merieux have influenza, rubella, measles, MMR vaccines likely to be used in children. Of those they think that only MMR contains bovine material which is probably a French origin.

6. Cyanamid have diphtheria/tetanus and pertussis on clinical trial [. . .]; These use veal material, some of which has come from the UK and has been made by Wellcome (see above).

7. Duphar Laboratories have influenza vaccines which are made up in egg medium.

8. The Secretary of State has a number of licences. We understand that the inactivated polio vaccine is no longer being used. There is a stock of smallpox vaccine. We have not been able to determine the source material. (Made in sheep very unlikely to contain bovine ingredients).

\textsuperscript{406} Merck & Co Inc have provided the following statement in connection with the statement at paragraph 3: ‘To date our efforts to confirm Merck’s participation in the Department of Health’s telephone enquiries to companies during February 1989 have proved to be unproductive. The essential point of the statement in paragraph 3 is correct; however, we wish to update the information to reflect that to the best of our knowledge the sourcing of raw materials was not limited to just the USA, but that all ruminant raw materials have been sourced from animals originating in countries where native BSE is not known to exist for the history of manufacture of our measles, mumps, and rubella family of vaccines.’
9. *Porton Products* have a cellular triple vaccine in which *Wellcome* material of UK bovine source has been used.

As far as I can see *Wellcome* are the sole supplier of pertussis vaccine which uses bovine casein digest.

You should also be aware that DH has made arrangements for meningococcal vaccine to be available, on a named patient basis, from *SKF* and *Merieux*. Both companies use bovine media in production.\(^{407}\)

**Briefing to MAFF Ministers**

5.28 We discuss in vol. 6: *Human Health, 1989–96* the meeting that took place on 14 February 1989 with the MAFF Minister, Mr John MacGregor, to discuss the recommendations in the *Southwood Report*, the timing of its publication and its handling.\(^{408}\)

5.29 Mr Lawrence had circulated briefing material prior to the meeting, including a briefing note, which said of the risks associated with medicinal products:

> The Working Party concludes that the risks of transmission of BSE to cattle and other species, including man, through the use of medicinal products are remote. However, they recommend that the attention of the Licensing Authority; the Committee on Safety of Medicines (CSM), the Committee on Dental and Surgical Materials, and the Veterinary Products Committee, be drawn to the emergence of BSE so that they can take appropriate action.\(^{409}\)

5.30 The briefing material included a copy of the draft MAFF/DH guidelines. Mr Lawrence’s note indicated that these were currently being considered by the CSM and the VPC, and that they represented a ‘counsel of perfection’. He pointed out a number of considerations:

i. The use of defined, BSE-free sources would be severely restrictive. Although there were undoubtedly farms that could ostensibly meet the criteria, they could not be certain that non-detection of BSE equated in all cases with freedom from the disease. New Zealand and Australia appeared to be the safest sources, but their supply was unlikely to match demand.

ii. Suppliers of primary and intermediate materials, from whom pharmaceutical companies purchased ingredients, were not covered by the Medicines Act. Licence holders would therefore have to obtain assurances from their suppliers that the guidelines were being adhered to. If this could not be satisfactorily achieved then the product licence might have to be withdrawn.

iii. The guidance on collection techniques conflicted with normal practice in abattoirs. This was unlikely to matter if reliable, BSE-free sources were used, although a risk of cross-contamination might remain.

iv. The recommended sterilisation treatment was generally inappropriate to biological medicines, which it would destroy, but would be suitable for some tools and equipment.\(^{410}\)
5.31 Anticipating the likely response from the industry, the briefing note added:

Although NOAH . . . accept the need for guidelines, they have not seen the draft, which they may find more rigorous than expected. They may respond by pressing for assistance in complying with the guidelines (eg. by introducing a BSE-free farm certification scheme, extension of Medicines Act controls to primary source suppliers). Any proposals would need to be considered in relation to their likely effectiveness in improving the supply of BSE-free material. 411

5.32 At the meeting itself, on 14 February, the CMO advised Mr MacGregor that a special working party (HVMBG) was scheduled to meet on 22 February to consider the implications of BSE for medicinal products. It was hoped it would offer some reassurance on this area, and he suggested that it would not be sensible to publish the Southwood Report until after the meeting. There was discussion about whether medicinal material should be sourced from countries with a significant sheep population where sheep material might be fed to cattle. Sir Richard Southwood, while highlighting the lack of certainties, was of the view that they should be careful in sourcing material in this way. Mr Meldrum, CVO, pointed out that the issue was complex: some countries might ostensibly be free of BSE while having an underlying problem with the disease in subclinical form. It was agreed that they would have to wait for the outcome of the meeting on 22 February to be clear on this issue. 412

VPC approves the guidelines

5.33 The VPC met on the following two days. It considered a further draft of the joint guidelines, which had been revised since it saw them on 19 January. These revised draft guidelines provided:

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

Although these guidelines relate to BSE and materials of bovine origin, they should also be considered as applicable to material from sheep, goats, deer, and some other animals susceptible to scrapie-like agents.

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

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

4. Collection techniques
All possible measures should be taken to avoid contamination of the bovine material with BSE agent, in particular:

   a. no tissue is to be used in medicinal products when collected postmortem from a bovine animal after brain penetrative stunning.

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

   c. it is recommended that whenever possible, source animals should be calves up to 6 months old.

   d. for serum: all cellular components must be removed.

   e. for foetal calf serum: great care should be taken to avoid contamination by placenta and foetal fluids. All cellular components must be removed.

5. Sterilisation
When sterilisation procedures are used they should be demonstrated to be capable of inactivating scrapie-like agents – at present thought to be autoclaving using a porous load cycle at 134°C–138°C for 18 minutes at 30 psi.

6. Product
Whenever possible, the product should be terminally sterilised by a validated method.413

5.34 The VPC agreed the guidelines subject to the following specific comments:

   1). Members asked for clarification of paragraph 4a. It was explained that under the BSE Order, the head had to remain intact. Clarification was provided on the methods of slaughter that could be allowed.

   2). It was considered that subject to CSM advice, pancreas should be included at paragraph 3. (‘Tissues excluded’), and this paragraph could apply to material of other species not just bovine origin.

   3). It was considered that paragraph 4c should be expanded to exclude animals fed ruminant derived protein.

   4). With reference to paragraph 2, it was considered that in practice it could not be guaranteed that animals had not been fed rations containing ruminant derived protein.

   5). It was considered that bovine serum albumin should also be included in paragraph 4e.
6). Members also asked for clarification about the recommendation to use calves under 6 months of age.\textsuperscript{414}

\textbf{Second meeting of the Human and Veterinary Medicines Briefing Group}

5.35 The HVMBG met for a second time on 22 February 1989 to agree advice for the CSM meeting on the next day. A number of officials from MAFF, Medicines Division and other divisions of DH, as well as representatives of the CSM/BSC, were present, along with the following invited experts: Professor Asscher, Professor Sir John Badenoch, Dr Kimberlin, Dr Martin (a member of the Southwood Working Party) and Professor M D Rawlins. They considered the \textit{Southwood Report} itself, the proposed joint guidelines, a draft letter to licence holders and a draft questionnaire.

5.36 The group noted that the Southwood Working Party considered the most likely source of BSE to be cattle feed containing protein derived from scrapie-infected sheep and were of the opinion that it was unlikely that there would be any implications for human health. Nevertheless, the ‘slight theoretical risk of BSE being transferred to humans was considered to be more likely from products used parenterally or by implantation rather than by the oral route’.\textsuperscript{415}

5.37 The group noted:

\begin{quote}
Normally, in matters where there is as little knowledge as there is in the case of BSE, CSM would have been advised to take no action but to monitor the situation. Due to the publication of the \textit{Southwood Report}, this option is not open. It is not feasible to go to consultation with industry on the matter due to lack of time, and the fact that this might be seen as our being led by industry. VPC had given broad approval to the draft guidelines.\textsuperscript{416}
\end{quote}

5.38 A handwritten note of the meeting made by Mr Will Burton, attending on behalf of the Supplies Technology Division (STD) of the Procurement Directorate (PD) of the NHS, indicates that the decision to go as far as issuing guidelines was not an easy one.\textsuperscript{417} A number of those present raised concerns, for instance about causing unnecessary alarm and about the difficulty in formulating guidelines. Mr Burton’s note records that the CSM would have preferred to speak of consultations with industry rather than guidelines and would have preferred to approach industry in the spirit of talking to each other.\textsuperscript{418} In considering the draft guidelines, the group noted:

\begin{quote}
These are to be seen as a ‘gold standard’, and may be modified in the light of experience. It is intended that they should be parallel with those issued on the veterinary side, but not identical because they have more difficult problems to handle (BSE being a speculative hazard in man).\textsuperscript{419}
\end{quote}

\textsuperscript{414} YB89/2.15/6.1  
\textsuperscript{415} YB89/2.22/11.2  
\textsuperscript{416} YB89/2.22/11.2  
\textsuperscript{417} YB89/2.22/27.1–27.9  
\textsuperscript{418} YB89/2.22/27.5  
\textsuperscript{419} YB89/2.22/11.2
The group agreed that it would be better ‘to try to eliminate BSE at source’ and discussed the possibility of maintaining or identifying and certifying ‘risk-free herds’. They felt that ‘to issue rules on oral products would challenge our concepts on foods, and cause problems with regard to gelatin capsules.’ The VPC had expressed anxiety about animal vaccines and ‘it was felt that in future we may need to ensure that bovine ingredients are not obtained as by-products of abattoirs’. Herds might have to be specifically maintained for this purpose. In considering excluded tissues, they noted that to exclude the intestine would eliminate heparin (most of which, though, was porcine) and catgut, and were of the view that the pancreas should not be excluded as this would eliminate bovine insulin.

Anxiety was expressed at the meeting over problems with the availability of supply of vaccines if companies could not comply with the guidelines; failures of supply could lead to epidemics. The group noted that Dr Adams and Dr Rotblat had contacted companies holding licences for vaccines, and some had begun to take action. It was felt that most companies would welcome guidelines on this subject.

The HVMBG also recommended that a working group, associated with the CSM/BSC and initially proposed at the Medicines Division internal meeting on 13 February, should be set up.

Dr Martin told us in relation to this meeting:

I was left with the impression that those on the human medicine side regarded BSE as an animal problem and that we . . . were being excessively apprehensive.

Consideration by the CSM

The CSM met the next day, and heard a detailed report on the previous day’s meeting from Professor Collee. It had before it a paper giving it an update on the steps taken since the last CSM meeting on BSE and the action proposed by Medicines Division, together with the relevant documentation.

The paper proposed that the guidelines would be issued in a letter to all licence holders, who would also be requested by means of a questionnaire to supply details to Medicines Division. The Division and MAFF officials had sought to ensure that the guidelines would be practicable and capable of implementation over as short a time period as possible, and that they would not damage the supply of important products such as vaccines and monoclonal antibodies for human use.

On existing stocks of vaccines the paper noted:

A particular problem which will need to be considered is that of products (vaccines in particular) which have been produced and are awaiting distribution. It has to be recognised that for some vaccines there may be supplies of up to 5 years. Thus a question on the stocks of the product has
been included. The Committee’s advice on this issue will be sought at a later date.425

5.46 We consider the action subsequently taken in relation to existing stocks in Chapter 6.

5.47 At its meeting the CSM considered in detail drafts of a CSM position statement, the letter to licence holders and questionnaire, and the guidelines to industry. It also considered proposals for a Working Party, its terms of reference and membership. It approved the various documents, and the proposal to set up a Working Party on BSE. It also recognised ‘the need for research into BSE in relation to medicines manufacture’.426

5.48 Professor Asscher told us that the CSM had now finalised its policy on BSE and medicines and he was pleased that the whole process had taken only three months from the date that the problem was first presented to the CSM.427

5.49 The first part of the position statement read:

The Committee on Safety of Medicines (CSM) has considered the safety of human medicines in the light of the report of the Working Party on Bovine Spongiform Encephalopathy (BSE) – the Southwood Report. The CSM agrees with the Southwood Working Party that the risk to man of infection via medicinal products is remote. As a precautionary measure, and for the sole aim of seeking to guard against what is no more than a theoretical risk to man, the CSM and the Veterinary Products Committee have agreed joint guidelines on good manufacturing practice for the manufacturers of human and veterinary medicines who use bovine, or other animal materials either as an ingredient or in the production process.428

Joint CSM/VPC guidelines

5.50 The approved guidelines read as follows:

1. Scope

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

2. Tissues excluded

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

Cattle source for all other tissues

425 YB89/2.00/2.3
426 YB89/2.23/13.5
427 S441 Asscher para. 56
428 YB89/2.23/6.4
Bovine material should come from animals, taken from a closed herd in the female line since 1980, in which no animal has been clinically suspected of having BSE, and which has not been fed rations containing ruminant derived protein during that period.

3. Collection techniques

All possible measures should be taken to avoid contamination of the bovine material with BSE agent, in particular:

no tissue is to be used in relevant medicinal products when collected postmortem from a bovine animal after brain penetrative stunning.

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

it is recommended that whenever possible, source animals should be calves up to 6 months old.

for serum: all cellular components must be removed.

for foetal calf serum: great care should be taken to avoid contamination by placenta and foetal fluids. All cellular components must be removed.

4. Sterilisation of equipment

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

5. Product

Whenever possible the product should be terminally sterilised by a validated method.

Although these guidelines relate to BSE and materials of bovine origin, they should also be considered as generally applicable to material from sheep, goats, deer and other animals susceptible to scrapie-like agents. These guidelines may need to be updated in the light of further scientific knowledge.

5.51 The questionnaire contained the following questions:

1. Company name

2. Do you make use of animal materials in any way in any of your products?

If your answer to Q2 is ‘No’ please sign and date this form below and return it as shown in the letter.
If your answer is ‘Yes’ please complete the remainder of this form (using a separate [sheet] for each product with continuation sheets if necessary).

3. PL/CTC/CTX number and product name

4. Animal material (specify type of tissue)

5. Animal species (eg bovine, ovine etc)

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

7. Country(ies) of origin of collected material

8. Does this medicinal product conform to the guidelines?

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

10. Based on known usage patterns, by what date (calendar month/year) do you expect present stocks (i.e. bulk stocks and finished product) to be exhausted?

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

Please give company contact person (Name, Position, Address, Telephone No.)

Discussion of the Southwood Report and Medicines with Ministers

5.52 We discuss in vol. 6: Human Health, 1989–96 a meeting of the Minister of Agriculture, Mr John MacGregor, the Secretary of State for Health, Mr Kenneth Clarke, the CMO and officials on 23 February 1989. The meeting was held for Ministers to deal with the two main outstanding issues of concern – vaccines and baby food – prior to the publication of the Southwood Report on 27 February. As to the first of these, Ministers were informed that the CSM and the VPC had concluded that the risk of transmission of BSE through vaccines was remote, but ‘so as to be doubly sure in the future, they intended to take the opportunity to improve standards throughout the field of biologically derived medicinal products’. It was noted that additional guidelines for users of bovine materials had been prepared and would be issued in March.431

5.53 We also consider in Volume 6 the discussion of the Southwood Working Party Report by the Cabinet later that day. We note here that the minutes record that, in the light of the Working Party’s recommendations on vaccines, guidelines were about to be issued recommending that manufacturers of medicinal products use non-bovine sources wherever possible.432

430 YB89/2.22/11.5
431 YB89/2.23/3.2
432 YB89/2.23/9.3
Briefing for public handling of the outcome of the CSM meeting

5.54 Mr Hagger reflected the outcome of the CSM meeting in a note entitled ‘Briefing on Human Medicines’ that went to the CMO’s private secretary on 23 February, along with a copy of the guidelines, the questionnaire, the CSM’s position statement, and a set of relevant questions and answers on BSE and the safety of medicines. The note was circulated widely among officials in DH and also to a few officials in MAFF. The question and answer briefing read as follows:

1. Can BSE be transmitted to patients by medicines?

The Southwood Report suggests that there may be a remote theoretical risk of BSE being transmitted to patients by the use of injectable medicines derived from bovine material. The CSM agreed that the risk is remote.

2. Which medicines are affected?

Bovine material is used as an active ingredient in some medicines, for example, the older bovine insulins. Bovine material is also used in small quantities in the production and manufacture of many biological and biotechnologically derived medicines including vaccines and monoclonal antibodies.

3. Are the risks greater with some medicines than with others?

Theoretically, injectable (parenteral) products might seem to pose a greater risk than oral medicinal products, but the CSM agreed that the risk from either is remote.

4. How are medicines affected?

Bovine material is used both as an active ingredient (for example in products such as bovine insulin) and in very small quantities in the production and manufacture of a wider range of medicines.

5. Are some of the products available over the counter from pharmacies or shops?

A range of products available over the counter may contain bovine material as an active ingredient or an excipient, including oral products and injectable insulin which is obtainable only from a pharmacy. But the CSM agrees that any risk of transmission of the agent by medicines is remote.

6. Are existing stocks safe?

The CSM agreed with the Southwood Working Party that the risk of transmission of BSE via medicinal products to man is remote and there is therefore no reason to question the safety of existing products.

7. Are there alternatives to the use of bovine material in medicinal products (including vaccines)?
Certain products such as insulin are now produced by using genetic engineering techniques. While it might be possible to replace bovine materials by using other ingredients or manufacturing methods in some other products, the Licensing Authority would need to be satisfied about the safety of such products before they could be made generally available. It would take some time to undertake the work needed to introduce such a change.

8. Which patients are at risk?

Although bovine material has been used in a wide range of medicinal products, it is not possible to say that any particular patients are at risk since we have no evidence of transmission of BSE to man.

9. What risks exist to those who have already used these medicines?

There is no evidence to suggest that people who have used medicines containing bovine material are at any risk from contracting BSE.434

10. How long will it be before risks are quantified?

It is very difficult to answer this question since we are talking only about a theoretical risk. It is one of the issues which will be considered by the new Consultative Committee on Research which has been established by the Government. The Committee on Safety of Medicines are also establishing a working party to advise them on BSE and human medicines.

11. What action is the Licensing Authority taking to ensure proper scrutinising of source materials and manufacturing processes?

The Licensing Authority has sought the advice of the Committee on the Safety of Medicines, the Veterinary Products Committee and other outside experts. Guidelines on good manufacturing practice have been produced and are being sent to all manufacturers.

12. Will the guidelines be published?

They will be sent to all manufacturers of licensed products shortly.

13. What is being done to reassure parents and doctors about vaccines?

The benefits of immunisation are well founded and not affected by the remote theoretical risk from the use of bovine material in vaccines. We see no reason to take any special steps to reassure parents and doctors at present. We are also taking the advice of the Joint Committee on Vaccination and Immunisation (the expert Committee which advises the Health Department on immunisation). If it proves necessary, the message about the benefits of immunisation can be addressed generally in the publicity material and the professional advice on immunisation provided for parents and doctors.

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

15. Is the vaccination programme put at risk because of BSE?

No. The measures being taken about the use of bovine material in medicines are merely precautionary against a remote and theoretical risk.

16. Are there any risks from BSE to anyone who has already been vaccinated?

The *Southwood report* describes the possibility as remote (para 8.2) but has alerted the Licensing Authority to the potential concern. This has led to plans to issue guidance to the pharmaceutical industry as a precautionary measure.435

5.55 The following day Mr Hagger sent a minute to the Private Secretary to Mr Clarke, the Secretary of State, referring to the document of the previous day and enclosing an amended set of questions and answers. Q8 was a new addition, the previous Q9 had been deleted, and Q7 now excluded the reference to vaccines and the answer had been shortened. The new Q8 read as follows:

8. Why can’t we eliminate the use of bovine materials in all medicines?

It might be possible to find alternative ingredients and methods but development of this kind takes time and requires careful testing.436

March 1989

Issue of joint CSM/VPC guidelines by DH

5.56 The CSM/VPC guidelines and questionnaire (see paragraphs 5.52–5.53 above), as approved on 23 February, were sent to all licensed manufacturers and product licence holders on 9–10 March, under cover of the letter approved by the HVMBG and CSM. Mr Hagger told us that approximately 4,000 letters were sent out by DH, on the basis of the MAIL address list.437 The covering letter read:

Dear Licence Holder

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

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

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

As a purely precautionary measure, the CSM and the Veterinary Products Committee have agreed joint guidelines for the manufacturers of human and veterinary medicines who use bovine, or other animal, materials as either an ingredient or in the production process. A copy of the guidelines is overleaf. It is felt that the guidance represents a standard that . . . is deemed to be ‘best practice’ for the future, and steps should be taken to implement it. However, it is realised that this guidance may not be fully applicable in all circumstances.

In order to update and complete our data on medicinal products, you are asked to fill in the attached form giving information about animal materials used in any of your medicinal products as specified in the guidelines (para 1). Information should be given on any ingredient of animal origin as an active constituent, as an excipient, or used in their manufacture (e.g. serum, enzymes, broth etc). In particular we are interested in the expected pattern of bulk and finished product where appropriate.438

5.57 Recipients were asked to return the completed questionnaires by 1 May 1989.

5.58 A letter was also sent to suppliers of medical devices. That, and the events surrounding it, are described in paragraphs 5.64–5.79 below.

**Issue of joint CSM/VPC guidelines by MAFF**

5.59 A slightly different covering letter was sent to all licence and certificate holders for veterinary medicinal products on 15 March 1989. It was sent to 248 companies, which marketed between them 3,239 products. The MAFF letter stated:

> Dear Licence Holder

> SPONGIFORM ENCEPHALOPATHIES OF BOVINE, OVINE AND CAPRINE ORIGIN: GUIDANCE ON GOOD MANUFACTURING PRACTICE AND REQUEST FOR INFORMATION

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

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438 YB89/3.00/1.1–1.3
On the 10th March 1989, 2398 farms had at least one confirmed case of BSE, the total number of cases being 3395. This represents an annual incidence in cows of 1 per 1,000 of the population at risk. These figures demonstrate the serious nature of the problem.

As a purely precautionary measure, the Veterinary Products Committee (VPC) and the Committee on Safety of Medicines (CSM) have agreed joint guidelines for the manufacture of veterinary and human medicines which use material of bovine, ovine and caprine origin either as an ingredient or in the production process. A copy of the guidelines is attached. They represent a standard that is deemed to be ‘best practice’ for the future, and steps should be taken to implement them. Where a company will find it impossible to meet the guidelines, or, where an alternative process is in use which is thought to give equivalent or better protection than the guidelines, details should be provided at (11) on the attached form.

Since BSE has been made a notifiable disease it is important that the licensing authority is aware to what extent material of bovine, ovine and caprine origin are used in the manufacture of licensed veterinary products (including products subject to Animal Test Certificates and Animal Test Exemptions and Emergency Vaccines).

In order to update and complete our data on veterinary medicinal products, you are asked to complete the attached form giving information about material of bovine, ovine and caprine origin used in any of your veterinary medicinal products as specified in the guidelines (para 1). Information may be required from the supplier or manufacturer of the ingredient or material, in which case you should arrange for the information to be supplied (Commercial in Confidence) either through you or sent directly to the Medicines Unit. The country of origin of animals used to prepare the ingredient or material should be stated. Any information sent in (from yourselves or your suppliers) must be clearly cross-referenced to indicate the licence/certificate to which it refers.

A separate form should be completed in respect of each veterinary medicinal product and where necessary continuation sheets should be attached. I have enclosed a list of your veterinary medicinal products. Please inform us of any omissions. Nil returns are required.

5.60 The deadline for the return of the questionnaire was the same, 1 May 1989.

MAFF meeting with NOAH on the guidelines: Continued concern about public reaction

5.61 When NOAH and MAFF next met, on 21 March 1989, the BSE guidelines were discussed. The minutes record that Dr Little suggested that the Southwood Report had so far turned out to be a ‘damp squib’, but stressed that care must be taken to ensure that certain elements of the press did not get the wrong impression about the safety of vaccines, both human and veterinary, and cause major problems. He pointed out that the guidelines ‘took into account the fact that a high standard
was being set, and also accepted that certain manufacturers may have other equivalent methods of attaining the required standard’. 440

Guidelines on medical devices

Introduction

5.62 We noted in Chapter 2 that, prior to 1993, medical devices were not licensed under the Medicines Act, but were subject to a voluntary Manufacturers Registration Scheme (MRS). Being unlicensed, they were not covered by the CSM/VPC guidelines. However, the Supplies Technology Division (STD) of Procurement Directorate (PD), which monitored the MRS, identified the implications of BSE for such devices. It was notified in February 1989 of the steps being taken in relation to medicinal products by MAFF and Medicines Division, and obtained at the same time an advance copy of the Southwood Report. Guidelines to MRS members, slightly adapted from those issued by the CSM/VPC, were provided in March 1989.

Responsibility for medical devices

5.63 Medical devices differ from medicines in that their principal intended action is typically achieved by a physical rather than pharmacological, immunological or metabolic means. Certain dental and surgical materials, such as catgut, required a licence under the Medicines Act, and fell within the remit of the CDSM: we are not concerned with such products in this section. Examples of medical devices that were outside the licensing system include heart valves, pacemakers and hip joints. At the time when BSE emerged, such devices were regulated only by the MRS. 441

5.64 As explained in vol. 14: Responsibilities for Human and Animal Health, STD was responsible for promoting and investigating the safety of a wide range of medical devices and equipment. Miss Marilyn Duncan was the Grade 5 in charge of much of this work in STD, reporting to the Director of PD. 442

Issue of guidelines on medical devices: a chronological account

February 1989

5.65 Mr Burton, who was head of the Pharmaceutical Supply and Technology Section (PSTS) of STD, told us that on 17 February 1989 he received a minute from Mr Hagger alerting him to recent developments on BSE. The minute outlined the recent steps taken by DH and MAFF and invited him to attend the HVMBG meeting scheduled for 22 February 1989. 443

440 YB89/3.21/13.1–13.4
441 DH01 tab 13 para. 1
442 SS36 Duncan paras 4, 7, 12–13
443 YB89/2.15/11.1–11.2; S605 Burton para. 6
5.66 Mr Burton told us that immediately upon reading Mr Hagger’s minute he realised that it had implications for his areas of responsibility, namely supplies of pharmaceuticals; the safety of medical devices not covered by the Medicines Act; and product licences for which the Secretary of State was the licence holder, which had historically been held by STD. Mr Burton obtained a copy of the Southwood Report and discovered that it concentrated on food and pharmaceuticals, and appeared to omit reference to the bulk of unlicensed products.444

5.67 Staff within STD met to discuss BSE on 21 February prior to the HVMBG meeting that Mr Burton was to attend the next day. During the meeting three areas of interest concerning BSE were identified: the effect on pharmaceutical supplies including vaccines, named patient supplies and NHS in-house manufactured products; the effect on product licences held by STD on behalf of the Secretary of State for Health; and the implications for control and supply of those medical devices derived from animal sources.445 Mr Burton attended the second HVMBG meeting on 22 February. We have discussed that meeting in paragraph 5.37 above.

5.68 On 22 February, after the HVMBG meeting, Miss Duncan sent a minute to Dr Metters, Senior Principal Medical Officer, MED SEB. She said:

As you will know from Dr Sutton we only became aware of the Southwood Report on Friday and it is clear that those compiling the report were unaware that there are a range of unlicensed medical devices made from or containing material of bovine origin.446

5.69 Miss Duncan explained that STD had already prepared a provisional list of devices that they knew, from their MRS data and from individual specialist knowledge, contained material of animal origin. She said they had considerable information on how the companies sterilised their products, but noted that there was regrettably little scientific information on how effective these processes were against the infective ‘material’ in this case. She was asking Dr Hoxey to consult further on this.447

5.70 Miss Duncan suggested it was clear that the Department needed to take action to complement that to be taken for licensed products; she proposed that a formal letter and questionnaire and guidance notes be faxed to UK companies known to use bovine materials, and sent by post to all medical device companies which might conceivably use animal materials, the majority of which were in the USA.

5.71 Dr Metters agreed with Miss Duncan, and asked that Dr Pickles be kept closely informed.448

5.72 On 23 February, Mr Burton attended the CSM meeting. He told us that insulin, heparin, heart valves and dura mater were considered by the CSM, in addition to other medicinal products using bovine material.449
March 1989

5.73 Guidelines and a questionnaire relating to medical devices were sent on 17 March 1989, under cover of a letter signed by Miss Duncan, to 328 recipients drawn from the membership of the MRS in relation to sterile medical devices and surgical products. The letter stated that ‘in parallel’ with the action taken by the Licensing Authority on medicines, PD/STD was ‘considering the implications of the BSE agent for those surgical implants and blood contact medical devices which fell outside the scope of the Medicines Act’. It continued:

Supplies Technology Division, in conjunction with the UK Committee on Safety of Medicines, has considered the Southwood Report and agrees that the risk to man of infection by BSE and other scrapie-like agents resulting from the use of such devices is remote. As a purely precautionary measure, we have developed the enclosed guidelines for manufacturers of medical devices who use bovine, or other animal materials, either as a component or in the production process. The guidance represents ‘best practice’ for future manufacture and outlines the steps which should now be taken to implement it. It is realised that this guidance may not be fully applicable in all circumstances and it will be further developed in the light of experience.

5.74 Recipients were asked to respond by 1 May 1989.

5.75 The guidelines attached to the letter read as follows:

1. Scope

It is recommended that all products in the following categories, which are supplied to hospitals in the United Kingdom, and which do not fall under the remit of the Medicines Act, should in general conform to this guidance if they contain material from a bovine source, or if bovine material has been used during their manufacture.

Categories:

a). Biological heart valves.

b). Other cardiovascular implants (eg vascular prostheses, cardiac patches etc)

c). Orthopaedic implants such as tendons, bone grafts etc.

d). Single use sterile devices that use such animal derivatives as heparin and gelatin in, for example, coatings.

e). Any other implantable products or products which come into contact with blood or the lymphatic system and which utilise materials of bovine origin.

a. Tissues to be excluded
Brain or neural tissue, spleen, thymus and other lymphoid tissue, placental
tissue or cell cultures of bovine origin should not be used in manufacture.

b. Cattle sources for all other tissues

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

Collection techniques

All possible measures should be taken to avoid contamination of the bovine
material with BSE, in particular:

No tissue should be used when collected postmortem from a bovine animal
if brain penetrative stunning has been used.

All tissue collected should be taken using sterile equipment. Needles,
syringes, scalpel blades etc should be used as disposable items.

It is recommended that whenever possible, source animals should be calves
up to 6 months old.

For serum: all cellular components must be removed.

For foetal calf serum: great care should be taken to avoid contamination by
placenta and foetal fluids. All cellular components must be removed.

Sterilisation of equipment

When sterilisation procedures are used, they should be demonstrated to be
capable of inactivating scrapie-like agents. At the present time the following
autoclave cycles are recommended:

a) A single cycle at 134°C (30 psi) for 18 minutes hold time at temperature.

OR

b) Six separate cycles at 134° (30 psi) for 3 minutes hold time at temperature.

5. Sterilisation of product

Standard methods of sterilisation of medical devices are currently thought to
be ineffective against scrapie-like agents, but further research continues. It
is for this reason that we have adopted the approach of controlling the source
of animal materials.

These guidelines may need to be updated in the light of further scientific
knowledge.
Although these guidelines relate to BSE and materials of bovine origin, they should also be considered as generally applicable to material from sheep, goats, deer and other animals susceptible to scrapie-like agents.\textsuperscript{452}

5.76 The questionnaire for medical devices was almost identical to the questionnaire for licensed medicines (see paragraph 5.53 above). It did not, however, include a question on when existing stocks would be exhausted.\textsuperscript{453}

5.77 Follow-up action taken on medical devices and the adequacy of the response is dealt with in Chapter 6.

Discussion

5.78 We turn now to discuss a number of issues arising out of the preparation and finalisation of the guidelines.

The message contained in the \textit{Southwood Report}

5.79 The view of the Southwood Working Party was inevitably going to be influential in determining the response of MAFF and Medicines Division on medicines. Indeed, those who met as the HVMBG on 22 February expressed the view that only the publication of the \textit{Southwood Report} removed the option of advising the CSM, as normally would be done where there was as little knowledge as in the case of BSE, to take no action but to monitor the situation.\textsuperscript{454}

5.80 It was therefore important that the view of the Southwood Working Party was clearly expressed. We discuss in vol. 3: \textit{The Early Years, 1986–88} the wording of paragraph 5.3.5 of the Working Party’s Report, and our view that this did not, on a natural reading, convey the real concerns of the Working Party.

5.81 It seems to us that those who formed the HVMBG, when they first met on 1 February, were under the impression that the Working Party’s view was that the risk from medicinal products was remote, even before the taking of any precautionary measures. The working draft of paragraph 5.3.3 of the Working Party’s Report, which they had in front of them at that meeting, highlighted the steps that might be taken to destroy or remove infectious agents from medicines. However, as described above, there was among the HVMBG ‘general dismay at the drafting, which tends to highlight the (theoretical) risk via medicines and to relegate the qualification that the risk is remote’.\textsuperscript{455}

5.82 Dr Pickles told the Southwood Working Party of these concerns, and reassured them that the Licensing Authority, as she fairly believed, had appropriate action in hand. As a result paragraph 5.3.3 was amended to include a simple reference to the fact that the Licensing Authority had been informed and would take account of BSE.

\textsuperscript{452} YB89/3.17/10.3–10.5
\textsuperscript{453} YB89/3.00/3.7–3.8
\textsuperscript{454} YB89/2.22/11.2
\textsuperscript{455} YB89/2.2/4.1
5.83 This, it seems to us, led unfortunately over time to a further lack of understanding. The HVMBG had brought about a change in the wording of the Report, on the basis of their mistaken, but in our view reasonable, understanding of the Working Party’s view. In the months and years to come, the circumstances leading to the change in wording naturally faded into the background. Similarly, although the Working Party had in correspondence communicated the importance of taking action, over time this too faded into the background, and it was the actual wording of paragraph 5.3.5 that took precedence. This was reinforced by the wording of the CSM statement of 23 February, and by the covering letters to manufacturers interpreting the Report.

Was it appropriate to issue non-binding guidelines?

5.84 We have discussed in some detail the joint guidelines issued to manufacturers of medicinal products. They were described as ‘a standard . . . deemed to be “best practice” for the future’. Was issuing such guidelines the appropriate step to take, rather than taking formal licensing or regulatory action? We have concluded that it was.

5.85 In reaching this view, we were assisted by evidence from a number of those involved. Professor Asscher explained in a written statement to us the considerations in play:

My own experience of the licensing of medicines is that it is advisable to avoid regulatory action if it is possible to do so. As Chairman of the CSM, my policy was always to attempt to use negotiation and recommendations rather than legal action. Formal regulation was only to be used in cases of extreme urgency or where the pharmaceutical industry had indicated an unwillingness to accept the CSM’s recommendations.

Informal action is invariably both quicker and cheaper than regulatory action. The pharmaceutical industry is highly professional and is normally content to accept the recommendations of the CSM. It is not in the interests of pharmaceutical companies to promote products which are being questioned on safety grounds.

I believe that in the case of BSE, the issuing of non-binding recommendations achieved a result that could not have been obtained through taking regulatory action. Licences cannot generally be revoked merely on the basis of a remote and theoretical risk. Such a revocation would very probably be overturned if legally challenged and we would never advise Ministers to take formal regulatory action in such circumstances. The risk posed by BSE was regarded as remote and theoretical and as such formal regulatory action could not have been scientifically justified. However, it was possible to achieve the same result through the issuing of recommendations because the industry wished to receive advice and was willing to accept it. As far as I am aware, no companies declined to follow the recommendations of the CSM on BSE and medicinal products.  

456 YB89/5. 15/4.1
457 S441 Asscher paras 64–6
5.86 Dr Jefferys and Dr Rotblat echoed these views in their written statements.\textsuperscript{458} Dr Rotblat told us that the climate at the time was such that the industry was very willing to comply with informal guidelines. To the best of her knowledge, no manufacturer refused to comply with the CSM/VPC guidelines on bovine material.\textsuperscript{459}

5.87 We have also noted that even issuing informal guidelines was going beyond what would normally have been done in such a situation. The notes made by Mr Burton, from PD, of the discussion at the HVMBG meeting on 22 February 1989 indicate that this decision was not taken lightly, and that some were concerned that issuing guidelines was going too far.\textsuperscript{460}

5.88 These are persuasive arguments, on the basis of which we concluded that it was entirely appropriate to issue non-binding guidelines to address concerns about BSE and medicinal products. We discuss in Chapter 6 the action taken to achieve compliance with those guidelines.

The scope of the guidelines

5.89 Under the heading ‘Scope’ the joint guidelines read:

It is recommended that all products licensed under the Medicines Act 1968 for human or veterinary use, that are administered parenterally or to the eye or to open wounds, should in general conform to this guidance if they contain material from a bovine source, or if bovine material has been used during their manufacture.\textsuperscript{461}

5.90 All were agreed that parenterals posed the greatest cause for concern, and that action should be taken to safeguard them. Was it appropriate that the guidelines did not apply to medicinal products administered orally, and that, in the case of topical products, they appeared to apply only to those administered to open wounds or to the eye?

5.91 It is worth setting out what the Southwood Report said about the relative risks of administration by the parenteral, topical and oral routes:

5.3.2 Information from several spongiform encephalopathies suggests that parenteral inoculation is much more efficient in transmitting disease than oral or topical exposure and that neural, and to a lesser extent, lymphoid tissue carry the infection whilst the risk is far less with other tissues. The theoretical routes of transmission from cattle to humans can be presented in ‘risk’ order to help clarify whether action is appropriate or research worthwhile.

5.3.3 The greatest risk, in theory, would be from parenteral injection of material derived from bovine brain or lymphoid tissue. Medicinal products from injection or surgical implantation which are prepared from bovine tissues, or which utilise bovine serum albumin or similar agents in their

\textsuperscript{458} S419 Jefferys paras 42–7; S422 Rotblat paras 32–4
\textsuperscript{459} S422 Rotblat paras 33–4
\textsuperscript{460} YB89/2.22/27.1–27.5
\textsuperscript{461} YB89/3.15/4.3
manufacture, might also be capable of transmitting infectious agents. All medicinal products are licensed under the Medicines Act by the Licensing Authority following guidance, for example from the Committee on Safety of Medicines (CSM), the Committee on Dental and Surgical Materials (CDSM) and their subcommittees. The Licensing Authority have been alerted to potential concern about BSE in medical products and will ensure that scrutiny of source materials and manufacturing processes now takes account of BSE agent.

5.3.5 In these, as in other circumstances, the risk of transmission of BSE to humans appears remote. Nevertheless, because the possibility that BSE could be transmitted orally cannot be entirely ruled out, known affected cattle should not enter the human food chain and action now taken ensures this. 462

Products administered orally

5.92 In their paper for the BSC/CSM meeting in November 1988, Dr Rotblat and Dr Purves suggested that consideration might need to be given to the risks associated with parenteral, topical and oral administration, should the product be contaminated by the BSE agent. They recommended that no action should be taken with regard to oral products ‘in view of the widespread consumption of beef by the population at large’. 463

5.93 Dr Rotblat explained to us that their reasoning was that it would have been inconsistent to take action against such products when no action was proposed against food containing bovine material. 464 Dr Purves agreed. 465

5.94 The CSM/BSC recommended that no immediate licensing action should be taken against oral products in which bovine material had been used. Professor Collee explained to us the reasoning that led to this recommendation:

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 that 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.

On the other hand we were conscious that scrapie, which had existed in sheep for more than 200 years, had not been shown to have any implications for human health. It was not merely that people who had eaten lamb or mutton had not developed CJD. The evidence also suggested that those who

462 IBD1 tab 2, Southwood Report para. 5.3.3
463 YB88/9.00/3.7 para. 6.1
464 S422 Rotblat para. 56 l
465 S Purves para. 67
had eaten high-risk tissues (e.g. sheep brain) had not developed CJD. In addition, those who worked in high-risk occupations had not developed CJD from contact with infected sheep, including those who had worked in situations where there might have been a risk of contamination of cuts or wounds.

...  

Recommendation (a): ‘No immediate licensing action should be taken against oral products, in which bovine material has been used.’

Our approach was based on the premise that the disease appeared to parallel scrapie, which had not been shown to be transmissible to man by the oral route. In the absence of further evidence we felt that it would be alarmist to take the view that BSE could be transmitted by the oral route, particularly in the case of orally administered medicinal products where the dose involved would be much smaller than in food. We added the word ‘immediate’ to the recommendation to take account of the fact that the position might need to be changed if further relevant evidence came to light. 466

5.95 The full CSM endorsed that recommendation of the CSM/BSC. Professor Asscher explained that at the time of the November 1988 meeting, the fact that scrapie had not transmitted to man reassured the CSM that BSE was unlikely to be acquired by the oral route. 467

5.96 When the HVMBG met on 22 February, it discussed the views of the Southwood Working Party on the risk of transmission to humans, which were based on the view that the most likely cause of BSE in cattle was feeding with protein derived from scrapie-infected sheep. The minutes of the meeting note that clarification was needed on the acquisition of BSE by cattle via the oral route, which by analogy with scrapie was relatively inefficient. They suggested that there might be special factors involved, such as damage to the gut from roughage causing an ‘injection’ of BSE, and it was felt that the oral route for humans need not be of undue concern at that stage. The minutes also record that it was felt that to issue rules on oral products would challenge concepts on food, and cause problems with regard to gelatine capsules. 468 We note that among those present at this meeting were Dr Kimberlin, who had particular expertise in transmissible spongiform encephalopathies, and Dr Martin, of the Southwood Working Party.

5.97 The CSM endorsed the draft guidelines. In doing so, they noted the view of the Southwood Working Party ‘that the risk to man of infection via medicinal products [was] remote’. 469

5.98 It seems to us that careful consideration was given to the question of oral transmission via medicinal products by the experts who sat on the section 4 committees and by the HVMBG. Nothing in the Southwood Report when it was completed was such as to change the assessments that had been made. No recommendations were made regarding sub-clinically infected cattle entering the human food chain. Indeed, we note that the Southwood Working Party had seen the

466 S423 Collee paras 68, 69, 72
467 S441 Asscher para. 35
468 YB89/2.22/11.2–11.3
469 YB89/2.23/6.4
CSM’s November 1988 recommendations and had not dissented from their approach to orally administered products.

5.99 In our view, it was not unreasonable for the section 4 committees to reach the view that they did, and to assume that if it was safe to eat meat, it must be safe for humans to eat the minimal amount of bovine material contained in medicinal products.

5.100 This reasoning did not apply in the case of animals, particularly for cattle where there was no species barrier. However, the VPC had carefully considered the issue and we believe it was reasonable that MAFF officials took no further action on oral veterinary medicines.

**Products administered topically**

5.101 Dr Rotblat and Dr Purves made no specific recommendation on the appropriate course of action for topically administered products, nor was any explicit recommendation made by the CSM/BSC or the CSM itself in November 1988.

5.102 Professor Collee told us that he could not recall whether the question of topical products was discussed at the November CSM/BSC meeting, but he believed that topical products would have been thought of as very unlikely to pose a hazard to man and that they therefore did not warrant their immediate concern.

5.103 We consider in the next chapter the formation and work of the BSE Working Party. However, it seems to us that what Professor Collee told us about their consideration of the risks from topically administered products is of some relevance to our consideration of this issue:

As to topical products, one of the obvious reasons for our not being concerned about those products was the barrier provided by the skin. I regarded topical products, when applied to intact skin, as involving even less risk than products taken orally, though applications to broken skin would potentially involve a greater risk. I believe that we would also have discussed the possibility of infection being spread by the application of topical products to open wounds. However, the lack of epidemiological evidence of CJD-like illness amongst those occupationally exposed to spongiform encephalopathies (e.g. butchers and farm hands) encouraged us to regard this issue as a very low risk. In addition, the topical products involved appeared to contain low risk bovine material.

5.104 In February 1989, it was decided that products administered to open wounds or to the eye should be included within the scope of the joint guidelines. It is not entirely clear what prompted this extension. Professor Collee believed that the phrase ‘or to the eye’ was added as a result of concerns raised by him and others of the possibility of infection via the conjunctival route.
5.105 We have in mind also the views of the Southwood Working Party on the risk of topical transmission. Again, it seems to us that the views taken by the section 4 committees and the HVMBG as to the risks from topically administered medicinal products were not unreasonable, particularly given that open wounds and the eye were brought within the scope of the guidance.

5.106 We note in Chapter 6 that when further consideration was given to topically administered medicinal products by the BSE Working Group in July 1990, it appeared that the use of bovine material in such products was confined to two manufacturers, who used material from Germany. Although there might have been a case for including all topically applied products within the guidelines, it appears with the wisdom of hindsight that this would have made no difference in the event.

5.107 Again, although the position was somewhat different for animals, for the reasons given above, we do not think that this should necessarily have led to a different approach being taken in the case of veterinary medicines.

**Did the covering letters convey the appropriate message?**

5.108 It was important that, once the guidelines were finalised, information was obtained and compliance was secured as quickly as possible. The covering letters with which they were sent out had a part to play in achieving this. Did those covering letters convey the appropriate message to licence holders?

5.109 In considering this question we noted the difference between the letters sent by MAFF and those sent by Medicines Division. Both described the guidelines as a ‘purely precautionary measure’ and as representing a standard ‘deemed to be “best practice” for the future’. Both indicated that steps should be taken to implement the guidance. However, the letter sent by Medicines Division said that it was realised that the guidance ‘might not be fully applicable in all circumstances’, while the MAFF letter read:

> Where a company will find it impossible to meet the guidelines, or, where an alternative process is in use which is thought to give equivalent or better protection than the guidelines, details should be provided.

5.110 The MAFF letter also referred to the gravity of the situation so far as farmers were concerned. Animals did face a more certain risk than humans: for animals of the same species as the material used in the medicinal product, there would be no species barrier to the transmission of a TSE. Indeed, this point was recognised at the second meeting of the HVMBG. Medicines Division was addressing a more speculative concern that BSE might be transmissible to humans. In doing so, it seems to us that they were entitled to have regard to the views of the Southwood Working Party as they perceived them, and of the experts who sat on the section 4 committees and the HVMBG, as to the likelihood of that concern being realised.

5.111 The HVMBG were of the view that the guidelines should be seen as a ‘gold standard’; they, and the CSM, approved the covering letter that was sent by DH. Professor Collee told us that there was an appreciation that they would have to be flexible as time progressed.

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473 YB89/3.00/1.1 (DH letter); YB89/3.15/4.1 (MAFF letter)
474 YB89/2.22/11.2 para. 2.1.3
41. It is also correct to say that the guidelines were viewed as best practice and we knew that as we progressed, we would have to be flexible... Products were treated on an individual basis, taking into account the considerations set out in paragraph 42 below and balancing those considerations against the benefit provided by the particular product. Action was not taken on all products that did not meet the guidelines issued in February 1989. For example, the guidelines excluded the use of all bovine material of a certain type, regardless of its source. However, it was reported to us that BSE was confined to the British Isles, save some cases which had occurred as a result of export (see the meetings of September 1989 (YB 89/9.6/10.1-10.8) and July 1990 (YB 90/7.4/1.1-1.8)) and accordingly we were able to recommend that no action be taken on certain products using the excluded material if it was appropriately sourced (see recommendation one, September 1989 Working Party meeting). In other cases, however, drawing on the responses to questionnaires, we determined that action was required.

42. The consideration of particular products in relation to BSE involved looking at a number of different questions, namely:

(a) The particular part of the bovine animal which was used in the product;

(b) The way in which that bovine material was used (whether as an active ingredient, excipient, or as part of the manufacturing process);

(c) The way in which the product was administered to the human i.e. orally; by implantation; by parenteral injection or topically.

5.112 We recognise these pragmatic considerations, which the covering letter reflected. We note from Mr Burton’s notes of the HVMBG meeting on 22 February that, given the concerns about issuing guidelines at all, a conscious decision was taken, at Mr Hagger’s suggestion, to accompany the guidelines and questionnaire with a reassuring letter. One consequence of this appears to have been the use of the phrase ‘purely precautionary’. In our view, the addition of the word ‘purely’ itself changed the emphasis, to a much less urgent tone.

5.113 We do not think that the covering letter is to be criticised. However, given its reassuring wording, it was all the more important to ensure that appropriate action was taken to follow-up the letter, and ensure that the guidelines were complied with. We consider this question in Chapter 6.

**Should existing stocks have been withdrawn immediately?**

5.114 If a decision had been taken to revoke or suspend the product licences of medicines containing, or manufactured with, bovine materials, immediate withdrawal of existing stocks of those medicines would have been required. The use of informal guidelines did not have the same consequence, so MAFF and Medicines Division had to make a decision one way or the other about whether to withdraw existing stocks at that stage.
5.115 We noted above our view that the line taken on orally and topically administered products was reasonable. It seems to us that the logical corollary of that approach was to take no action on existing stocks of such products. Accordingly, we focus here on the question whether existing stocks of vaccines should have been withdrawn.

5.116 We saw that in February 1989 Dr Pickles’s draft submission to the Minister alerted the CMO to the fact that concerns about the safety of vaccines had not yet been resolved. This prompted an initial telephone survey of companies manufacturing children’s vaccines. The information obtained indicated that considerable stocks of some vaccines had been manufactured using bovine serum of UK origin.

5.117 The CSM was told that for some vaccines there might be supplies for up to five years, and that a question on stocks of products had accordingly been included in the questionnaire. It was told that its advice on this issue would be sought at a later date. The CSM was apparently content with this approach – it approved the draft guidelines, to be issued shortly, and the setting up of a BSE Working Party. The question and answer briefing circulated by Mr Hagger the next day stated that there was no reason to question the safety of existing products.

5.118 Concerns about vaccines were also discussed by Mr MacGregor, the CMO and Mr Clarke on 23 February, and by the Cabinet later that day. It is not clear whether the question of what, if anything, should be done with existing stocks was expressly addressed. Both the Ministers and the full Cabinet were told that guidelines were shortly to be issued to manufacturers, and it seems to us that it must have been at least implicitly understood, if not expressly discussed, that existing stocks were not to be immediately withdrawn.

5.119 On 7 March 1989, Mr Mellor answered a Parliamentary Question on the dangers to human health from vaccines using material from cattle infected with BSE. He answered:

> The comments in the recent report by the working party chaired by Sir Richard Southwood that there may be a remote theoretical risk of bovine spongiform encephalopathy being transmitted to patients by the use of injectable medicines derived from bovine material, have been carefully considered by the Committee on Safety of Medicines. The committee agreed with the working party that any such risk from injectable medicines including vaccines is both theoretical and remote. We have accepted this advice. As a purely precautionary measure, further guidance on good manufacturing practice in this area is about to be issued to manufacturers of all medicines including vaccines.477

5.120 A question we were anxious to explore was whether, on receipt of the preliminary information about stocks of vaccines using bovine serum of UK origin, DH should have ordered the immediate withdrawal of all affected existing stocks. We are conscious that this is a matter that has excited considerable public interest and concern. There were two principal arguments against immediate withdrawal of stocks – the difficulty of procuring sufficient ‘clean’ stocks to maintain the
vaccination programme, and the danger of causing a vaccine scare that would deter parents from having their children vaccinated at all.

5.121 The HVMBG expressed concern at its meeting on 22 February about problems with the availability of supply of vaccines if companies could not comply with the guidelines. Dr Rotblat told us that existing stocks could not simply be replaced ‘overnight’ because of the long time scale for manufacture of new batches of the vaccines. Professor Asscher explained:

When considering the question of vaccines, it is important to be aware that manufacturing vaccines is an art – it is not easy to manufacture large supplies of effective vaccines. Manufacturers tended to keep large stocks of existing vaccines which, in some cases, were likely not to be exhausted for as much as 5 years.

5.122 In determining the appropriate course of action, the advisory committees had to weigh against the ‘remote’ and ‘theoretical’ risk posed by BSE the consequences of any disruption to the vaccination programme, caused by interruption to supplies of vaccines or by withdrawal from the vaccination programme as a result of a vaccine scare. Professor Asscher explained:

Vaccines were the main group of existing products which came before the CSM for consideration. From my point of view, the risk-benefit analysis of existing stocks of vaccines was comparatively easy, principally for two reasons. The first was that the risk posed by BSE to human health was, during my time as Chairman of the CSM, always regarded as remote; that was certainly the view of the Southwood Working Party in its report. The second was that vaccines are very important to the protection of human health. The CSM’s judgement was that the risks associated with interruption of the UK vaccination programme were far greater than the potential risk of BSE being transmitted. The CSM had learnt from its experience of previous vaccine scares, such as that connected with the whooping cough vaccine, that a potential consequence of any vaccine scare was refusal by the public to take part in the vaccination programme, which could lead to serious public health problems. I recall us advising the Licensing Authority of this.

5.123 Professor Collee, too, explained that in any consideration of vaccines they had also to take into account ‘the obvious risk if stocks of vaccines were withdrawn’.

5.124 Dr Jefferys spoke about the ‘inevitable consequences’ of ‘any damage to the vaccine programme’ and Dr Rotblat referred to the disease that ‘would occur’ if the vaccination programme were interrupted:

It was agreed that the benefits of the vaccination programme outweighed the theoretical risk of transmission and that the current vaccines could be used until new batches became available. The theoretical risk of transmission of BSE had to be set against the disease which would occur if the vaccination

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478 YB89/2.22/11.3
479 S422 Rotblat para. 36
480 S441 Asscher para. 77
481 S441 Asscher para. 32
482 S423 Collee para. 49
483 S419 Jefferys para. 55
programme was interrupted. The vaccines in question had proven efficacy in protecting the public against serious diseases. The fact that low risk bovine material had been used in the manufacturing process in no way outweighed the benefit derived from these vaccines.484

5.125 As we have indicated, there was concern to avoid creating a vaccine scare. Professor Asscher had referred to such concerns in his letter to Sir Richard Southwood on 26 January 1989.485 Sir Donald Acheson had a similar concern a little later in 1989, when consideration was given to introducing a Specified Bovine Offal ban (see vol. 6: Human Health, 1989–96). When explaining that concern to us, he told us of the experience that lay behind it, which it seems to us was of equal relevance in February 1989:486

I had in mind a marked and extended previous reduction in the acceptance of whooping cough vaccine which had followed incorrect public allegations by a scientist that the administration of the vaccine carried a significant risk of encephalitis. On the one hand I was aware that during the period 1980–1988, due to incomplete vaccination of our population of children, there had been 123 deaths from measles and 50 from whooping cough in England, together with a many times larger burden of illness and some long-term complications. Against this I had to balance a remote risk of a fatal disease.

5.126 Of some importance was the way in which bovine sera were used in the manufacture of vaccines. We describe this in Annex 2 to Chapter 2. This underpinned the experts’ evaluation of whether and to what extent vaccines might become contaminated with BSE. Professor Collee explained the process to us.487

Organisms used for vaccine production have to be grown in various nutrient media. Specifically, viruses need to be grown on host cells (tissue culture cells) which in turn are fed by nutrient media in bottles. It is this food which contains the foetal calf serum and/or bovine serum albumin. In due course, the viruses are harvested from the cells by various processes that achieve their separation and the viruses are then purified and further treated to be vaccines.

5.127 We have weighed all of this evidence carefully. It is clear that the overwhelming opinion of the medical professionals was that existing stocks should not be immediately withdrawn. This was accepted by the officials in Medicines Division, and in our view it was reasonable of them to do so. Experience had shown that incomplete vaccination of children led to significant numbers of deaths that would otherwise have been prevented. The experts attached considerable importance to the need to avoid a reoccurrence of this situation. It seemed to us that a responsible approach was adopted, having regard to this known risk and the countervailing potential risk posed by BSE, particularly bearing in mind the nature of the material and manufacturing processes involved. Again, this decision increased the importance of making efforts to ensure that sources were changed and existing stocks replaced. We discuss this in Chapter 6.

484 S422 Rotblat para. 37  
485 YB89/1.26/1.2  
486 S251 Acheson para. 70  
487 S423 Collee para. 45
The decision not to withdraw immediately existing stocks gave rise to a separate but related dilemma: the question of what information should be given to the public about the risks associated with BSE and the decision that had been taken in respect of existing products and stocks. We discuss this general theme in Volume 1.

Ministerial involvement

We also gave consideration to whether the question of continued use of existing stocks of human vaccines was of such a nature that it should have been drawn specifically to the attention of the Minister, and a decision taken by him. It raised ethical and political issues as well as public health ones. We noted at paragraph 5.120 above that it was not clear in precisely what terms the issue was brought to Ministers’ attention, and what express consideration they gave to it. Mr Clarke could not recall that he was aware of the ‘dilemma’ in relation to existing stocks. As we have already noted, it seems to us that it must have been at least implicitly understood, if not expressly discussed, at a ministerial level, that there was an issue regarding existing stocks of vaccines, and that a decision had been taken that they were not to be immediately withdrawn. However, there is no doubt that the decision was not taken at a ministerial level.

We asked Mr Clarke whether he thought that this decision could perfectly appropriately have taken place without any Minister being aware of it, or whether it was something he would have expected a Minister in DH to be informed of at some stage. His reaction was that where people were making a judgement on scientific risk, on which they regarded themselves as the only people, or the main people, qualified to make that judgement, there was probably no need to refer it to the Minister. The CMO was given a wide remit because Mr Clarke had great confidence in him. Where broader public interest considerations, for example the interests of the pharmaceutical industry, came into play, then Mr Clarke suggested that a Minister should be involved. In his view, if the clinical advisers were all agreed that existing stocks were safe, and this was the advice they could properly give to Ministers, they would not bother the Minister.

Mrs Currie indicated that generally Ministers would be alerted if there was a problem. The experts were trusted at a very high technical level to take decisions in as objective a fashion as possible. She did not think, when we asked her, that the question about existing stocks would necessarily have gone to Ministers. She thought the experts would take a decision within their range of expertise and legal responsibilities.

Given the uniform advice of the expert advisory committees, we think it is highly unlikely that any different decision would have been taken. Those expert advisers included the chairman of the Joint Committee on Vaccination and Immunisation, and representatives of the NIBSC and the Southwood Working Party, as well as the members of the section 4 committees themselves. Mr Clarke referred to the clear impression he gained from his various advisers: ‘they were
advising us that we should continue with vaccine components and so on... the risk was so remote that would not justify stopping it." 492

5.133 Mrs Currie told us:

I would not dream of overruling people who were on the various senior medical committees.

...

If it was an issue that was likely to arouse public concern, for example, a dodgy batch of vaccine, then Ministers would be alerted very quickly. 493

5.134 She observed:

What causes alarm is the feeling that they are being sold a pup; that reassurances are being offered that something is safe when perhaps it is not. That causes alarm and that will cause wholesale withdrawal from a product. 494

5.135 In discussion with us about the vaccination programme, Mrs Virginia Bottomley, who became Secretary of State for Health at a later period, described her likely stance:

I hesitate to speak on a subject which was before my time. I think in the light of the great concern on this subject, as I understand it in the press then, I would have wanted, I think, myself, just to know steps were being taken. 495

Earlier, she had described her likely position in relation to a difficult issue of this sort:

I think I would want a little bit more than a bland assurance. I think I would have wanted to know that on 14th October a minute had been sent out and that there had been some effect or that – I would want to know the date upon which there was likely to be a further report, or I might have said, ‘Please send me a report at the end of the year to say what action is being taken’.

5.136 In our view, while there may have been a case for referring this decision to the Minister for approval, we do not consider that officials are to be criticised for not doing so: it seemed to us that Ministers were aware of the general concerns, if not the specific question of existing stocks, and of the different considerations at play. Moreover, the expert advice was unanimous. However, as we shall see, the fact that Ministers had not been a formal part of the decision-taking process meant that they did not ask to be kept informed about the follow-up action.