7. The Tyrrell proposals for research into pharmaceuticals

Introduction

Why did this research matter?

7.1 The unanswered question that plagued decisions on vaccines was whether serum and other materials used during production of medicinal products could transmit the BSE agent. In this chapter we review what happened to research proposals to establish clearer evidence about this.

7.2 In particular we look at recommendations made in the Interim Report of the Tyrrell Consultative Committee on Research into Spongiform Encephalopathies (the Tyrrell Committee) in June 1989. This report recommended a variety of research projects to be carried out in relation to BSE.862

7.3 The Tyrrell Report described the main purpose of its proposed research agenda as to ‘seek reassurance that the Southwood group was correct in their belief that this disease would not have implications for human health, say through food, through occupational exposure or through medicinal products that use bovine ingredients’.863

7.4 Section 5 of the Report contained two proposals for transmission studies relating to pharmaceuticals, proposals C2a and C2b. We trace the story of these proposals in this chapter.

BSE-related pharmaceuticals research: a chronology

Research proposal for calf serum prior to Tyrrell

7.5 We noted in Chapter 4 that the National Institute of Biological Standards and Control (NIBSC) organised a one-off meeting about BSE, which took place on 16 May 1988.864 The NIBSC was charged with securing high standards of quality, safety, efficacy and consistency of biological substances used in medicine.865 Dr Schild told us that this meeting on 16 May was to obtain advice and comments from scientists outside the NIBSC on the nature of the BSE epidemic and its implications for biological medicines.866 Participants were Mr Wilesmith from the CVL; Dr Ridley and Dr Baker from the Clinical Research Centre; Dr Beale and

862 Information on the framework for commissioning and funding scientific research generally, can be found in Volume 2. This includes details of how DH organised research into transmissible spongiform encephalopathies
863 IBD1 tab 4 para. 2.2
864 S575 Schild paras 39–40
865 S575 Schild para. 4
866 S575 Schild para. 39
Dr Garland from Wellcome Laboratories; and Dr Schild, Dr Minor and Dr Ferguson from the NIBSC.  

7.6 One of the four recommendations resulting from this meeting was:

Studies are to be set up involving NIBSC and Wellcome Biotechnology and other parties to attempt to demonstrate the presence of scrapie like agents in calf serum by inoculation into mice and hamsters and other species. Such experiments are very lengthy.  

7.7 Dr Minor told us that the studies were actually carried out independently by Wellcome Biotechnology. However, he does not recall actually seeing the research itself and cannot recall when the results were brought to his attention. The company has told us in correspondence that it can find no record of Wellcome carrying out such experiments. It does, however, note that Dr Minor was involved in a critique of experimental protocols for other experiments being investigated by Wellcome at the time.

Southwood Working Party discuss biological products

7.8 At their first meeting on 20 June 1988, the Southwood Working Party discussed the use of bovine tissues in the preparation of biological products. The minutes of that meeting note that the use of foetal calf serum was mentioned as a potential health risk. The Southwood Working Party recommended that ‘an expert Working Party on Research should be established’. Subsequently the Tyrrell Committee was set up for this purpose.

7.9 In a minute to the CMO later that day, Dr Pickles summarised the points of interest in the discussion at the meeting including the fact that ‘laboratory workers might be exposed to infected tissue through the widespread use of fetal calf serum in tissue culture work’.

Early questions of funding

7.10 While the Tyrrell Committee was still in the process of being set up, Dr Pickles had raised the question of how any proposals it might make were to be funded. On 22 November 1988 she sent a minute to Dr Metters, at that time Director of Research and Management Division, saying:

I spoke with CMO about the BSE research committee yesterday . . . CMO did not seem to have thought about the funding of any research proposed and seemed to have assumed the research committee would have money to hand out, and MAFF money at that. Agreeing that MAFF could hardly expect to fund any human work, he suggested this was something we could discuss with Sir Richard, MAFF Ministers and officials on Thursday.
7.11 Dr Metters replied the following day:

Unless I have totally misjudged the type of research envisaged, it will fall entirely in the basic biomedical or clinical areas. For both of these the Department would look to MRC to organise and fund appropriate research. MRC would of course consider BSE related research against other priorities, but they cannot overlook their interest in the Neuropathogenesis Unit.

Whether or not MRC decide to place human BSE research with this Unit, there is no doubt in my mind that it would be better managed through the Council’s mechanisms than funded direct from DH.

I find it hard to envisage any BSE research that could properly be described as ‘Health Services Research’ and hence for direct funding by DH. 874

**Tyrrell Committee discussions**

7.12 At its second meeting on 11 April 1989, the Tyrrell Committee was presented with a paper that outlined research questions of immediate interest to the Medicines Control Agency (MCA) and the pharmaceutical industry:

– can freedom from BSE-contamination be demonstrated in existing stocks of products at theoretical risk (many years’ supply of some vaccines, for example)?

– for what processes/products are the risks sufficiently high to be worth subjecting to experimental test, eg with mouse inoculation?

– how can BSE-free herds in the UK be demonstrated and material collected from these herds?

– what overseas sources of bovine material are acceptable?

– are there any products for which the risk-benefit is now unacceptable (considered for the bovine insulins and heparin, but further action not thought appropriate at present)?

– should there be similar concern about other animal species used in pharmaceutical manufacture? 875

7.13 Other papers outlining potential problems and action taken to date were appended, including:

i. a list of medicinal products for human use that used bovine ingredients; 876

ii. a position statement by the CSM, saying that the risk to humans of infection via medicinal products was remote, but that guidelines on good manufacturing practice had been produced as a safety measure; 877

874 YB88/11.23/5.1
875 YB89/4.00/1.1
876 YB89/4.00/1.3
877 YB88/4.00/1.4
iii. a copy of the guidelines and letter sent to all manufacturers of human and veterinary medicines; and

iv. a question and answer briefing prepared by DH in response to the Southwood Report, indicating the line taken up to then.

The Committee’s response

7.14 Dr Tyrrell told the Committee that the papers were mainly for its information, but still raised questions relevant to research needs. Although the CSM’s position statement correctly claimed that the risks from BSE were small, there was still a need to conduct research. Dr Kimberlin told the Inquiry that although the words ‘remote’ and ‘theoretical’ were used, they were not taken to mean that no work needed to be done in this area.

7.15 In discussion of the paper that was to be used as the basis of the Committee’s report, the Committee noted that:

Some pharmaceutical manufacturers were looking for validation of existing stocks. In particular vaccines were a cause for concern. Bovine materials for use in bovines should not be overlooked.

Proposals C2a and C2b

Clearing the final draft

7.16 On 24 May 1989, Dr Pickles, who was the DH member of the Tyrrell Committee secretariat, minuted Mr Hagger of the MCA about a draft of the Committee’s Report. She attached a copy of the draft pharmaceutical section (C2). In Chapter 6 we have discussed the concerns relating to bovine materials in vaccines. Two of those materials, bovine serum albumin (BSA) and foetal calf serum (FCS), were singled out for transmission studies in the draft report. The draft stated:

2. Pharmaceuticals

Part of the justification for using bovine rather than ovine material in pharmaceutical manufacture was because of uncertainty about the significance of scrapie in sheep. Whilst there is no evidence of hazard in those biological medicinal products made using bovine ingredients or intermediates, the industry, drug regulators, the professions and the public naturally seek complete reassurance.

a. bovine serum albumin and fetal calf serum and other common media that involve bovine material: ic to mice. Concern has been expressed about these materials not only by those involved in pharmaceutical manufacture.

---

878 YB89/4.00/1.5–1.7
879 YB89/4.11/2.5
880 YB89/2.24/2.1–2.4
881 T6 (Kimberlin) pp. 103–4
882 YB89/4.11/2.5
883 YB89/5.24/6.1–6.2
884 intracerebrally (ie, into the brain)
but also by laboratory workers in immunology and microbiology, for example. If procedures adequate to contain CJD agent had to be employed, much valuable experimental work would cease. Artificial alternatives have been sought in recent years, mostly for economic reasons. This trend will continue, although complete replacement of bovine material will not be possible and in pharmaceutical manufacture would have a lead-time of several years. Titrations of the kind described in C1a are needed.*** 885

b. similar attempts at transmission with various intermediates and perhaps also final products of pharmaceutical manufacture, chosen on theoretical grounds as plausibly contaminated with BSE including some when starting materials have been spiked or from known contaminated animals. An expert standing group of the CSM and VPC will be considering with the Medicines Control Agency, NIBSC and the Industry whether work in this area might be appropriate. 886

7.17 On 5 June 1989, Mr Hagger replied to Dr Pickles and attached a copy of ‘the proposed membership and terms of reference of the CSM Working Party on BSE’ 887 He commented that the status and role of the Working Party were quite different from the description in the draft; the membership included representatives of the Joint Committee on Vaccination and Immunisation (JCVI), NIBSC and the veterinary profession but the Working Party had no formal links with the Veterinary Products Committee (VPC) or the NIBSC. He continued:

We believe we have understood the gist of item C2 b (bold print) although we did not find it clear. We would expect the working group to comment willingly on relevant research protocols and perhaps to make its own suggestions for fruitful topics in this field. However we were not expecting the working group to be asked to undertake the task described at b. In fact this is the sort of issue on which the CSM’s working group was expecting to look to the Tyrrell group for information – it is of course very helpful that Dr Tyrrell is in both groups. 888

7.18 Mr Hagger suggested a change of wording for the end of paragraph C2b and also passed on some detailed comments on the rest of the section, which were reflected in the final version. 889

The final version

7.19 The final wording of the relevant parts of section C is set out below. We have included C1a for ease of reference as C2a refers back to it. This relationship was to prove important to the way work subsequently developed.

C. TRANSMISSION

C1. of BSE
Infectivity can only be measured using bioassay methods in susceptible animals. There is an urgent need to determine BSE infectivity titres in a large variety of bovine tissues. Titrations in cattle would be prohibitively expensive on a routine basis and, in any case, could be difficult to interpret if cattle carry a gene that influences susceptibility. At present, the only practicable alternative is to perform bioassays in genotypes of mice which are already known to be susceptible to BSE. Each of these studies will be expensive in terms of animals and time. To execute just some of them will put a serious strain on existing animal house facilities and the necessary pathological resources. Nowhere else has the decision on priorities been more difficult.

a. Primary titrations of various tissues, organs, and secretions from BSE animals by inoculation into mice. To include colostrum, milk, semen, embryos, muscle, placenta, blood, buffy coat, spleen, lymph node, thymus, heart, liver, kidney, pancreas, lung, intestine. Whilst available scrapie data allow assumptions to be made about levels of infectivity at various stages of the disease, it is essential to measure BSE infectivity, particularly in those tissues relevant to possible transmission to other animals and to man. For some tissues, such as blood and milk, the expectation is of low infectivity, quite possibly below the sensitivity of the bioassay. If the route and conditions of experimental exposure, mimic those found naturally, say the oral route for milk, negative results would be reassuring. [Rii, Niv] ***

C2. Pharmaceuticals

Whilst there is no evidence of hazard in those biological medicinal products made using bovine ingredients or intermediates, the industry, drug regulators, the professions and the public naturally seek reassurance.

a. Bovine serum albumin and fetal calf serum and other common media that involve bovine material: ic to mice. Concern has been expressed here not only by those involved in pharmaceutical manufacture but also by laboratory workers in regular contact with these materials, in immunology and microbiology for example. Artificial alternatives have been sought in recent years, mostly for economic reasons. This trend will continue, although complete replacement of bovine material will not be possible and in pharmaceutical manufacture would have a lead-time of several years. Titrations of the kind described in C1a are needed.***

b. Additional transmission studies specifically relevant to pharmaceutical manufacture. We recommend that the Medicines Control Agency, with expert advice, considers the need for work in this area. 890

7.20 Each area of research identified was given a star rating from one to three according to the priority afforded to it by the Committee. Proposal C2a was given a three-star rating, the highest priority. C2b was unstarred and we note that it recommended the Medicines Control Agency (MCA) consider the need for work in
this area, not that it actually undertake such research. The related project C1a was also a three-star item.

7.21 Dr Pickles sent a copy of the report to Mr Hagger on 8 June 1989. In her cover minute she said of this version: ‘I hope you find it more acceptable.’

7.22 The next day Mr Hagger sent a minute to Mr Wilson in which he referred to the publication of the *Tyrrell Report* and to Dr Pickles’s minute of 8 June. In the circumstances he said:

... I think that the draft of C2b would be acceptable, but if anyone disagrees please let me know immediately.

7.23 Mr Hagger’s minute was copied to, among others, Dr K Jones, Dr Adams, Dr Jefferys, Dr Rotblat and Dr Purves of the MCA.

**Allocation of responsibility for C2a and C2b**

**Joint responsibility for MAFF and DH**

7.24 Both MAFF and DH focused on the Tyrrell recommendations in the two highest priority categories, ie, with two- and three-star ratings. On 13 June 1989, Sir Donald Acheson minuted Mr Clarke, the Secretary of State for Health, about the Report:

> A large number of research areas are allocated high priority and this work will be laborious, time consuming and expensive. Almost all the recommended work is directly for MAFF (at the Central Veterinary Labs) or for the AFRC: the relatively small amount for DH/MRC (section A2a on page 12) is being taken care of.

7.25 We look in Chapter 9 at how Dr Shannon and Dr MacOwan (Chief Scientists Group, MAFF) were working out a handling strategy to provide resources for the two-star and three-star proposals in consultation with Mr Meldrum and Dr Watson. In advice to Mr Andrews on 30 June 1989, Dr Shannon observed, ‘The parts of the overall programme that might fall to industry involve an element of judgement and at some point would require a Ministerial view on just where the division of responsibility should lie.’

7.26 When Mr Gummer, who had become MAFF Minister a week earlier, wrote to Mr Clarke on 1 August 1989 about BSE research, he recommended speedy publication and endorsement of the Tyrrell proposals. He annexed a copy of two tables prepared by MAFF, which indicated responsibility for C2a and C2b as lying jointly with MAFF and DH. This reflected their joint responsibilities under the Medicines Act for the safety of human and veterinary medication. C1a, on the titration of infectivity in mice, was allocated in table 1 as a MAFF responsibility.

---

891 YB89/6.8/10.1
892 YB89/6.9/14.1
893 YB89/6.13/10.1
894 YB89/6.30/3.1
895 YB89/8.01/3.8
The table indicated that this work was already in hand at the Royal Veterinary College (RVC) and planned for the Neuropathogenesis Unit (NPU).

7.27 Dr Metters, now Deputy Chief Medical Officer (DCMO), spoke on 4 August 1989 about BSE research with Mr Woolley of the Research Management Division of DH. Mr Woolley confirmed that if DH research funds were required during 1989/90, the £30,000–£50,000 that Dr Metters had thought might be required could be found within the present HPSS research budget. Mr Woolley confirmed this conversation in a minute dated 7 August.

7.28 On 7 August 1989, Dr Metters sent a submission to DH Ministers (copied to, among others, Mr Hagger and Mr Wilson) about the Tyrrell Report. He referred to proposals C2a and C2b among those studies that fell to DH for consideration:

...with only a small number of studies falling to DH these can be accommodated within the existing HPSS research budget, though further consideration will have to be given to funding in 1990–91 and subsequent years.

7.29 He attached a draft response to Mr Gummer’s letter to Mr Clarke of 1 August 1989 saying that DH supported early publication and commitment to find the money. On the tables, the draft agreed that the pharmacological studies, including C2a and C2b, fell jointly to MAFF and DH. These would need to be considered again once advice had been received from the CSM BSE Working Group, expected in September at the earliest.

7.30 Mr Freeman, DH Parliamentary Under-Secretary, sent this letter to Mr Gummer on 9 August 1989.

7.31 The first meeting of the BSE Working Group took place on 6 September 1989. However, the Tyrrell research proposals on pharmaceuticals were not discussed. Dr Pickles, who was present at the meeting, said in a minute to Mr Hagger the next day:

1. As you will no doubt hear, we had a very useful meeting about BSE and medicinal products this afternoon.

2. One matter not discussed was research... As I think we agreed earlier, we will look to the MCA to provide any necessary defensive briefing over the response to those items affecting them (see C2a and b on p18).

3. The general line is likely to be that we will try to get going all work starred +++ or +++, and if it is necessary and appropriate by direct funding. As a result of today’s meeting, you may want to argue that the pharmaceutical problem is being circumvented by ensuring no potentially contaminated material will ever start into pharmaceutical processing – the line is up to you of course. But if you are going to argue that these experiments are not now necessary, we must make sure Dr Tyrrell at least is willing to back you up.

---

896 YB89/8.01/3.4
897 YB89/8.07/16.1
898 YB89/8.7/4.1–4.2
899 YB89/8.7/4.3–4.4
900 YB89/8.9/4.1–4.3
901 YB89/9.7/5.1
From my preliminary chat with him this afternoon, I think you will find him very supportive of whatever line you want to take.

4. It is of course open to individual companies to demonstrate by transmission experiments that stockpiles of material they hold or B.S.A that went into them are not capable of transmitting agent to mice. They may find that they need this information to satisfy other regulatory agencies, even if the MCA is relatively relaxed in the short term.\(^{902}\)

7.32 The same day Dr Pickles wrote to Mr Woolley concerning his minute to Dr Metters of 7 August 1989:

> ... the Medicines Control Agency, together with the pharmaceutical industry, will be taking care of C2a and b. I think it unlikely that they will be calling on RM’s\(^{903}\) funds, but that is up to them.

> BSE is a new disease, and who knows what we may want to investigate in the future. For now it looks as if we will not be draining RM’s coffers too much.\(^{904}\)

**The MCA will ‘look after’ C2a**

7.33 On 5 January 1990, shortly before the *Tyrrell Report* was eventually published, Dr Pickles submitted a background briefing to the DH Parliamentary Under-Secretary, Mr Freeman. She noted that proposal C2a was one of only two high-priority areas that fell to DH and that:

> The Medicines Control Agency are acting upon this recommendation together with their experts.\(^{905}\)

**Infectivity studies at the NPU**

7.34 Meanwhile, MAFF had been making good progress on recommendation C1a. On 14 December 1989, Mr Bradley had minuted the CVO regarding bovine tissue infectivity studies, which were being carried out at the NPU in Edinburgh with MAFF funding.\(^{906}\) He stated that since his last document (9/11/88) refinements to the list of tissues for potential study were required, resulting from introduction of the offal ban, extrapolation of data from Hadlow’s studies in sheep, requirements of the research programme, additional uses of bovine tissues by the pharmaceutical industry and additional uses of bovine tissues on farm land, in schools, etc.

7.35 Mr Bradley noted that mouse transmission studies at the NPU were limited in years one and two to 30 in each, and in year three to 20. Already 13 of the available transmissions for year one were in progress, including semen, placenta, spleen, buffy coat and others. Four more were proposed and approved (liver, udder, pancreas and milk), which left only 13 available for year one. Mr Bradley noted that the tissues of highest priority for transmission studies should be identified and sent

\(^{902}\) YB89/7/5.1
\(^{903}\) Research Management Division, DH
\(^{904}\) YB89/9.7/3.1–3.2
\(^{905}\) YB90/1.5/3.1
\(^{906}\) YB89/11.14/3.1–3.3; IBD1 tab 13 p. 27
to the NPU for inoculation. He attached a draft list for proposed tissues to complete
the quota for year one. These were: embryos, uterine flushings, semen, testis, ovary,
abomasum, reticulum, rumen, omasum, oesophagus, distal ileum, prefemoral LN,
foetal calf serum.907

7.36 On 12 February 1990, Mr Bradley circulated a further minute about the tissue
infectivity studies.908 This confirmed that foetal calf blood was to be included in the
quota of 30 tissues for transmission studies in the first year. Mr Bradley also
commented that it was ‘important to get these studies underway as soon as
possible’.909

Checking progress on the Tyrrell recommendations

7.37 In March 1990, Mr Lawrence asked Dr Pickles, Mr Bradley and Dr MacOwan
to comment on a draft table to update Ministers on the progress of the Tyrrell
recommendations.910 C1a was indicated as in hand at the NPU, although FCS was
not mentioned. The table suggested that perhaps C2a and C2b might be funded by
industry.911

7.38 Dr Pickles provided comments on this table on 14 March. She observed,
‘Perhaps we should have indicated clearly work not currently started’,912 and
repeated this in her detailed comment on C1a. On C2 she agreed that the
pharmaceutical industry might be the ones to pay for this research. However, she
questioned whether the high priority given to this area in the Tyrrell Report was now
appropriate. On C2a she observed:

The industry are preferring to abandon UK sources so such testing would
carry no purpose for them; they would not be reassured by even negative
results and positives would be disastrous (and entirely unexpected).913

Comments from Supplies Technology Division

7.39 In March 1990 Miss Duncan of the NHS Procurement Directorate’s Supplies
Technology Division (PD/STD) wrote to Dr Pickles offering STD comments on the
Tyrrell Report, and expressing interest in establishing liaison with researchers
working on research projects in PD’s field.914 In relation to the proposal C2a the
note said:

Comment: At the time of writing of the interim report no proposal had been
received although this research was given high priority.

STD considers this work to be of the utmost priority.

STD may be able to help in finding research workers to undertake this work.

---

907 YB89/11.14/3.3
908 YB90/2.12/3.1–3.4
909 YB90/2.12/3.2
910 YB90/3.00/2.1–2.5
911 YB90/3.00/2.4
912 YB90/3.14/4.1
913 YB90/3.14/4.1
914 YB90/3.00/10.2
7.40 In relation to C2b the STD group agreed that this work was needed and asked where the funding for it would come from.\footnote{YB90/3.00/10.4}

7.41 Dr Pickles responded to Miss Duncan on 15 March 1990. She said that a new group might be set up to supervise and coordinate research in this field. Meanwhile, a new BSE group was being set up under Dr Tyrrell and one of its first jobs would be to see how its earlier recommendations had been received and acted upon. STD’s comments could be fed in at that stage. Of Miss Duncan’s comments on proposal C2a she said:\footnote{YB90/3.15/5.2}

> I think perceptions of the importance of this work have changed. The original assumption was that the pharmaceutical industry, as you rightly point out, would be interested in this and this would extend to funding the work. But the industry is taking no chances and in many cases going straight away to overseas sourcing. In any case, the chance of any positives at all is thought so remote that it would be very soul-destroying work. The problem is not of funding ‘research workers’ as such, as of animal houses able to hold enough mice for a couple of years and staff able to do the subsequent laborious neuropathology. These skills and facilities are very limited (and expensive) so the requirement for this work has to be weighed up against all others that involve mouse inoculation. I had rather left the MCA to ‘look after’ this item and if you feel they and I are not giving it the high profile you think it deserves, perhaps you should come up with a specific proposal (and funding).

7.42 On Miss Duncan’s query as to how C2b would be funded she said:

> Discuss with the MCA. The assumption is that the industry funds work of interest to it.

7.43 Dr Pickles copied her reply along with Miss Duncan’s original minute to Dr Purves, who then asked Dr Adams, Dr Jefferys, Dr Rotblat and Mr Sloggem for comments and observations to ‘pull together an MCA position’.\footnote{YB90/3.22/5.1}

7.44 On 9 April 1990, Dr Barnes, Director of DH Research Management Division, sent a minute to Dr Pickles about DH research objectives as a basis for writing to the MRC:

> 4. Another high priority area identified in the \textit{Tyrrell report} which falls within DH’s responsibility concerns certain bovine materials used in pharmaceuticals. Dr K Jones [Dr Keith Jones (MCA)], to whom this minute is copied, is asked to up-date us on the current position on whether this research is going ahead and if so with what sponsorship . . .\footnote{YB 90/4.09/4.1–4.2}

**C2a and C2b: what priority?**

7.45 As discussed in Chapter 6, the MCA and Veterinary Medicines Directorate (VMD) were continuing the exercise of ensuring that manufacturers complied with
the joint CSM/VPC guidelines. The majority of manufacturers had replied to the questionnaire that was sent out with the guidelines. Of those that used UK-derived bovine material in the manufacture of their products, many had switched to sourcing ingredients from overseas, and the MCA and VMD were following up the small number of companies that had yet to comply.

7.46 On 11 April 1990, Mr Lawrence circulated his table summarising the research projects recommended by the *Tyrrell Report.*919 In relation to item C1 on transmission studies it included FCS in the list of items being tested by the NPU with MAFF funding. On C2a it listed work as being carried out on this at the NPU, with industry funding. The associated comment was: ‘Trade restrictions and industry sourcing from outside UK has lowered the priority on this.’920

7.47 On 17 April 1990, Dr Jefferys replied on behalf of Dr K Jones to Dr Barnes’s minute of 9 April.921 He said that the MCA was unaware of any research commissioned or being undertaken concerning bovine material used in pharmaceuticals. He added that the MCA would not be funding any such research and hence others might know of work that had not been brought to the MCA’s attention. He concluded by saying that it appeared that the industry had accepted the guidelines and had made arrangements to switch sourcing so as to comply with the guidelines.922

**Checking suppliers of FCS**

7.48 At its meeting on 1 May, the Spongiform Encephalopathy Advisory Committee (SEAC) considered Mr Lawrence’s table and noted that item C2a was now ‘low priority, as the trade had adjusted of its own accord. The secretariat would enquire where suppliers of fetal calf serum sourced their raw material.’923

7.49 On 3 May, Dr Pickles sent a minute to Mr Burton in PD/STD, seeking his help:

> We are no longer concerned about use in licensed pharmaceuticals, since the MCA is dealing with this, but these materials are used as laboratory reagents in a wide range of laboratories. There could possibly be health and safety issues, particularly if culture systems are used in which spongiform encephalopathy agents might conceivably thrive. If I could find the names of the suppliers, I could make some discreet enquiries.

> We must be careful in making these enquiries to be sure that we are not suggesting these materials in their original form are somehow dangerous (since of course we are not saying this for meat or other parts of the animal). But in experimental laboratories there could be processing which concentrates out or amplifies the very minute amounts of infectious agent that might be present.924

7.50 Mr Burton responded to Dr Pickles on 8 May 1990. He provided her with the names and addresses of four UK suppliers.925
7.51 On 15 May 1990, Dr Pickles sent a submission to Mr Dorrell, the new DH Parliamentary Under-Secretary, with a general briefing note on BSE. With regard to medicines she said:

The Medicines Control Agency (MCA) have gathered information from pharmaceutical companies about use of bovine ingredients in parenteral pharmaceuticals and issued interim guidelines. Many biological products and vaccines use such ingredients, but few still source them in the UK. The MCA are considering whether action on specific products is appropriate.

7.52 On 20 June 1990, Mr Love, an administrator in the MCA, circulated to other officials in the MCA a copy of a Question and Answer briefing for the Agriculture Select Committee, which had been sent to the CMO’s officer earlier that day. On pharmaceutical research the briefing said:

What about the research on pharmaceuticals given high priority by the Tyrrell Research Committee?

In view of the rapid change to overseas sourcing, the Committee has downgraded the priority given to this item. The BSE Working Party of the CSM is continuing to consider developments in this field.

7.53 On 16 July 1990, Dr Pickles sent a minute to Dr Richardson (PD), with copies to Mr Burton and Mrs Shersby. She informed him that all the suppliers of FCS and BSA she had written to asking about their sourcing had now replied. They had all explained that they no longer sourced from the UK and had not done so for some time. Presumably Dr Pickles reported back to SEAC on the results of her survey. However, no mention of this is made in the minutes of SEAC meetings.

SEAC questions the relevance of pharmaceuticals research

7.54 In 1992, SEAC published an interim progress report about the research that had been recommended in 1989 in the Tyrrell Report. Annex 3 of the report summarised the relevant work in progress in the UK and noted that research into the infectivity of cattle tissues (C1a and C2a) was being undertaken. In relation to pharmaceuticals the report said:

At the time the first Interim Report was written it was assumed that additional work would be needed to reassure the licensing authorities of the safety of human pharmaceuticals manufactured from all of these tissues from British cattle. Now that BSE has been reported outside the British Isles, the same issues could arise for biologicals sourced from other countries. However, the pharmaceutical industry, acting in part on the advice of the Committee on Safety of Medicines (CSM) and the Veterinary Products Committee (VPC) has produced guidelines for the medicinal products.
industry and sought information from them via a questionnaire . . . The guidelines 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 the guidance if they contained material from a bovine source or if bovine material was used during their manufacture. In the event the pharmaceutical industry decided to source bovine ingredients or bovine materials used during manufacture from BSE-free animals in BSE-free herds in BSE-free countries . . . In the light of this development the relevance of studies on the safety of pharmaceuticals manufactured from tissues from British cattle is now questionable.932

7.55 Dr Fraser and Dr Foster of the NPU reported the results of transmission experiments for various bovine tissues, including FCS, to the Scientific Veterinary Committee on Spongiform Encephalopathies in Brussels in September 1993. No clinical or neuropathological evidence for transmission by non-nervous tissues and fluids, including serum, was obtained.933 The results were published in 1994.934

Discussion

7.56 Lack of knowledge about whether serum and other bovine blood products could transmit BSE created doubts about the safety of certain vaccines and laboratory materials. Should existing products and stocks continue to be used, in order to maintain the national vaccination programme, if no alternatives were available? What handling precautions were appropriate in laboratories? The need to establish a basis for answering these questions was swiftly recognised.

How this was approached

7.57 We considered in particular the response to the three-star priority Tyrrell recommendation C2a for intracerebral assays in mice of BSA and FCS.

7.58 The second of the proposals made by Tyrrell on pharmaceutical research, C2b, was tentative and unstarrered. There was no apparent sponsor. We were not surprised that this proposal was left fallow while the available mouse resources were used for other high-priority work.

7.59 The first proposal, C2a, however, was a different matter. All acknowledged its importance. It raised laboratory safety issues and we have discussed in Volume 6 how those were addressed in respect of transmissible spongiform encephalopathies generally. For the licensing authorities it was directly relevant to the agonising question of how to balance risks in dealing with existing vaccine stocks.

7.60 The NIBSC was responsible for advising on the safety of biological products used in human medicines and had been an early port of call for advice to DH and MAFF on the implications of BSE. Its seminar in May 1988 had indicated that a precautionary strategy meant switching to overseas sourcing. It recommended that

932 IBD2 tab 13 p. 11
933 M8 tab 12 p. 150
934 M8 tab 12
research into the infectivity of calf serum be undertaken by the NIBSC and Wellcome Biotechnology, but it appears that no such experiments were undertaken.

7.61 FCS was immediately recognised as a potential risk by the Southwood Working Party. The continuing efforts of Sir Richard to ensure that the CSM was getting to grips with the use of biologicals in medicinal products encompassed this concern. The Tyrrell Committee in its June 1989 Report not surprisingly recommended research studies into serum as a top priority. It had earlier noted manufacturers’ concerns over vaccines for both humans and animals.

7.62 To find answers, the first step was to test whether the serum itself carried the BSE agent. This meant using mice as surrogates for cattle and humans and was bound to take years. Meanwhile, money, staff, and in particular sufficient specially bred animals appropriately housed, were all in short supply. Many other cattle and sheep materials urgently needed to be tested in the same way to help establish the safety of food and other products. Which should therefore be done first? As the Tyrrell Report observed:

Nowhere else has the decision on priorities been more difficult. 935

7.63 However, MAFF and the NPU had not been idle. Prior to the Tyrrell Report, they had already begun to establish a programme of research on tissue and blood testing. Following the three-star rating for tissue studies in recommendation C1, they lost no time in pressing ahead with work at the NPU, concentrating on the aspects identified by Tyrrell as the highest priority. In December 1989, Mr Bradley suggested adding FCS to the priority list. This was confirmed in February 1990.

7.64 As predicted, the NPU work on infectivity took years to complete. When the results were eventually available in 1993, those involving FCS, serum and blood were all negative. As discussed in vol. 2: Science, such experiments cannot provide a 100 per cent guarantee. However, these results, and the fact that vaccines contain no FCS in their highly processed end product, must at least provide some assurances.

7.65 On the face of it, therefore, the necessary research was tackled in a businesslike way. Commendably the FCS studies were carried out promptly by MAFF and the NPU, despite the problems of securing funding and getting a slot in the animal testing programmes.

Inconsistencies in the approach

7.66 However, it seemed to us that this outcome was in some respects achieved through inconsistencies in approach and at a degree of cross-purposes. Four features struck us as having complicated the process:

i. The notion that industry might voluntarily sponsor and share the results of this work.

ii. The compartmentalised consideration of the serum testing and other testing work.

935 IBD1 tab 4 p. 13
iii. The detached attitude of the medicines licensing divisions.

iv. The divergent perceptions of MAFF, DH and SEAC about the actual work being done and the purposes it would serve.

We comment on each of these.

1. Was it suitable for industry?

7.67 We consider that research of this type and importance was never suitable for leaving to industry itself to carry out. As Dr Shannon had pertinently observed in his minute to Mr Andrews in June 1989, an element of judgement was involved in looking to industry to carry out research work. If findings were for general application in licensing policy and the issue of advice, then Departments needed themselves to promote the research actively, to satisfy themselves about how it was to be done and to get the earliest possible results.

2. Compartmentalised items

7.68 The Tyrrell recommendations gave top priority ratings to both the general tissue studies (item C1) and the studies of serum (item C2), while noting that the latter would depend on titrations of the same kind as the former. Thus, in practice, both needed to be considered together in allocating available resources. As we have noted, the MAFF-sponsored programme of work on tissue titrations speedily took on board the studies needed on serum, assigned it a priority slot and oversaw delivery.

7.69 However, this was not wholly compatible with the administrative line drawn by MAFF in compiling the tables attached to Mr Gummer’s letter of 1 August 1989, on the basis of which work was subsequently monitored. This had allocated C1 to MAFF as its sole responsibility in table 1. The serum studies, however, were allocated to table 2, to be financed and carried forward by both MAFF and DH as part of their shared responsibilities for the safety of medicines. DH did not demur and earmarked money in its budget for the work. This separate categorisation contributed to a certain amount of confusion about how the work was carried out thereafter and who was calling the shots.

3. Detached attitude of the MCA and VMD

7.70 The cross-purposes were exacerbated by the detached attitude of the medicines licensing divisions, the MCA and VMD, as customers for the outcome. Licensed medicines were not the only products that used serum. Concern about these other uses led Dr Pickles at the behest of SEAC to carry out her own investigations in July 1990 with the four major suppliers of FCS and BSA. In the event, she satisfied herself that they were all by then obtaining their bovine materials from non-UK sources. We thought this was a commendably practical way of addressing matters that did not fall neatly into the MCA remit.

7.71 However, this did not answer the question of what to do about existing products and stocks, licensed or unlicensed, that had used earlier material. It did not provide information on whether there might already have been extensive exposure
to the BSE agent. Nor did it clarify whether in the event of BSE emerging overseas, serum would constitute a continuing source of concern.

7.72 The joint responsibility agreed between MAFF and DH Ministers for work on the safety of serum was specifically linked with their joint responsibilities for safe medication. Dr Metters told Ministers that resources were available and that the C2 studies would be considered once advice had been received from the BSE Working Group in September. However, the BSEWG did not discuss research needs at its September meeting, and Dr Pickles’s subsequent minutes and briefing reflected her understanding that the MCA together with the pharmaceutical industry were ‘taking care of C2a and b’. This was not in fact the case. On the contrary, as Dr Jefferys made clear in his minute to Dr Barnes in April 1990, the MCA had been giving no consideration to the matter and had no intention of funding any such work. We could find no indication of consultation on the studies and the potential application of their outcome between it and VMD reflecting ‘joint responsibilities under the Medicines Act’.

4. Divergent perceptions of MAFF, DH and SEAC

7.73 The main interface between MAFF and DH about the studies, therefore, appears to have been in terms of reports made to SEAC about progress on the Tyrrell recommendations as a whole. We were struck by the apparently divergent perceptions in this process.

7.74 MAFF, as represented by the Central Veterinary Laboratory, had perhaps the simplest and most productive attitude. They decided to fund the serum work at the NPU and gave it a priority slot in their programme in February 1990. They backed it through to its conclusion in 1993.

7.75 DH blew hot and cold. Dr Pickles, after initially supporting the proposal began to swing round to the view that the work was not necessary after all for licensed medicines since they were being tackled through a new sourcing strategy. However, she saw the MCA as being in the lead. By March 1990, only a month after MAFF had taken the work on serum into its programme as a top priority item, and apparently in ignorance of the MAFF action, Dr Pickles was telling Miss Duncan that in her view – though she had ‘rather left MCA to look after this item’ – it rated lower than other studies for the scarce resources available. This was the DH line thereafter.

7.76 SEAC took a continuing interest in what was happening to the NPU’s general clutch of tissues studies under C1a. The findings would be crucial to its assessment of risk. It does not appear to have done other than take note of the successive reports to it about how matters stood on item C2a.

7.77 Its 1992 report set out the reasons why it now thought the C2b studies were of questionable value. After noting the emergence of BSE overseas, it went on to say that, since all the materials now used in the UK were sourced from ‘BSE free animals in BSE free herds in BSE free countries’, the relevance of the additional pharmaceutical studies was now questionable.
7.78 In the event, the work at the NPU on C1a and C2a transmissions was maintained to its conclusion and became part of the set of scientific benchmarks in the difficult field of assessing risks from BSE.

Lessons for the future

7.79 Given that it was eventually completed, did the cross-purposes surrounding this important piece of work matter? They did not, in our view, constitute grounds for criticism of how matters were handled. However, we thought that the way the project was handled indicated three lessons for the future:

i. It is important that government itself takes a lead in promoting and disseminating research work needed to determine safety regulatory action. While cooperation with industry may be valuable, it seems to us unrealistic to expect private sector companies to be enthusiastic about promoting and publicising research that could be to their financial detriment.

ii. As we have seen in other fields, there needs to be a clear policy customer for research work. That lesson, as we have seen, was being increasingly applied by Government Departments during the 1990s. When there is more than one customer, and in particular, more than one customer Department, communication between them and the allocation of lead responsibility is essential.

iii. The detachment of the medicines licensing authorities from decision-taking about the Tyrrell studies was striking. We have noted elsewhere that relationships on policy-making and information exchange between the licensing authorities were not close. We think further thought might usefully be given to the arrangements for ensuring their involvement in decision-taking about desirable research on safety matters where animal materials are involved.