2. The operation of medicines licensing

Introduction

2.1 In the UK the sale and supply of medicines is subject to a licensing regime, under which the safety, quality and efficacy of both human and veterinary medicinal products is regulated. This licensing regime set the framework in which the implications of BSE for medicinal products were addressed.

2.2 The licensing regime was established by the Medicines Act 1968. After the UK became a member of the European Community on 1 January 1973, EC rules governing the safety of medicinal products became applicable. Until 1995, the principal legislation under which this was achieved remained the Medicines Act 1968.3 We focus here on the system in place in 1988/89, when the implications of BSE for medicinal products were first addressed.

2.3 In essence, a medicinal product could not be sold unless it had been granted a ‘product licence’ by the Licensing Authority. The Licensing Authority was in principle the relevant Minister, although in practice his or her functions were delegated to officials in the Medicines Division of DH (medicines for human use) or in MAFF (veterinary medicines). They received advice from a number of committees of experts, set up under section 4 of the Medicines Act, known as ‘section 4 committees’.

2.4 This chapter begins with a brief explanation of the licensing regime. We then discuss the options that were therefore available to officials and Ministers to tackle the risks posed by BSE to the safety of licensed medicinal products, and medicinal products for which a licence had not yet been granted.

2.5 We then consider the Departments or Divisions within MAFF and DH responsible for operating the licensing regime, outlining the structures in place and identifying the personnel involved. We go on to discuss the findings of two reports published in December 1987 and February 1988, which reviewed the arrangements that were in place for the control of human medicines and veterinary medicines respectively. These reports led to the establishment of Executive Agencies to fulfil the medicines licensing functions, and we briefly describe these agencies at the end of the chapter.

2.6 Medical devices, ie, medical products that work by physical rather than pharmacological means, fell outside the licensing regime. Instead a voluntary manufacturers’ registration scheme was operated by a different part of DH; in

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3 With effect from 1 January 1995, comprehensive provision was made implementing the Community legislation in UK law by the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994 for human medicines and the Marketing Authorisations for Veterinary Medicinal Products Regulations 1994 for veterinary medicines. These regulations provided for applications for marketing authorisations to be made and considered by the licensing authority in accordance with the relevant Community provisions. In addition, in 1993 a central Community procedure for authorisation and supervision of medicinal products was introduced (Council Regulation 2309/93 (L16 p. 3)). This provides a single marketing authorisation to market a product in all Member States and is administered by the European Medicines Evaluation Agency (EMEA). The procedure is compulsory for certain technologically advanced medicinal products, and is optional for certain other novel medicinal products.
1989/90 this was the Supplies Technology Division (STD) of the NHS Procurement Directorate (PD). We conclude with a description of the arrangements for ensuring the safety of medical devices.

The licensing regime for human and veterinary medicinal products

Which products required a product licence?

2.7 We have noted that a ‘medicinal product’ could not be sold or supplied except in accordance with a product licence. Medicinal products were defined as substances or articles, not being instruments, apparatuses or appliances, for use wholly or mainly by being administered to human beings or animals for medicinal purposes. Medicinal purposes are:

a. treating or preventing disease;

b. diagnosing disease or ascertaining the existence, degree or extent of a physiological condition;

c. contraception;

d. including anaesthesia;

e. otherwise preventing or interfering with the normal operation of a physiological function . . .

2.8 The Medicines Act and regulations made under it also placed licensing requirements on certain other substances that fell outside this definition. These included: surgical ligatures; sutures; contact lenses; intra-uterine contraceptive devices; and a wide range of substances, such as heparin, that are used as ingredients in the manufacture of medicinal products.

2.9 Conversely, certain products and substances that did fall within the definition of medicinal products were excluded from the licensing requirements of the Act. For example, the sale of medicinal products intended for human use as foods or cosmetics was excluded, subject to certain qualifications. Also excluded were: medicines made, or imported, for particular patients, sometimes referred to as ‘specials’; in certain circumstances, herbal remedies; and, from 1994, homeopathic medicinal products granted a certificate of registration. Prior to 1994 homeopathic products that satisfied the definition of a medicinal product in the Medicines Act were subject to its licensing requirements.
2.10 Various products fell on the borderlines between foods and medicinal products, between medical devices and medicinal products or between cosmetics and medicinal products, for example vitamin supplements. There were regulations governing whether such products were to be treated as medicinal products or not. A key factor was whether they were sold ‘with indications’, ie, specified their use in treating a particular condition.

2.11 As we have noted above, medical devices, being instruments, apparatus or appliances, did not fall within the definition of medicinal products and were not included in the licensing regime. (Medical devices are discussed at paragraph 2.116 below.)

Who granted a licence?

2.12 Responsibility for the granting, renewal, variation, suspension and revocation of licences was given by the Medicines Act to the ‘Licensing Authority’. Under the Act ‘the Health Ministers’ and ‘the Agriculture Ministers’, ie, the Secretary of State for Health, the Minister of Agriculture, Fisheries and Food and the corresponding Ministers in Northern Ireland, Scotland and Wales, comprised the Licensing Authority, although any one of them acting alone was permitted to perform its functions.

2.13 In practice, the functions of the Licensing Authority in relation to medicines for human use in the UK were, throughout the period 1985–96, performed by the Secretary of State for Health. Similarly, the functions of the Licensing Authority in relation to medicines for animals were performed by the Minister of Agriculture, Fisheries and Food.

2.14 During the BSE period, although formally the Secretary of State for Health acted as the Licensing Authority for human medicines, in practice his or her functions were delegated to officials working in the Medicines Division of DH (and, after April 1989, officials working for the Medicines Control Agency (MCA)), subject to the normal legal principles relating to the extent to which ministerial functions may be delegated. Similar arrangements were in place in MAFF.

2.15 We discuss later in this chapter the way in which those officials operated the licensing regime. The arrangements meant that product licences were physically granted by officials, not by the Minister. The constitutional convention whereby Ministers are accountable to Parliament for their own actions and also for those of their officials is discussed in vol. 15: Government and Public Administration.

Advice to the Licensing Authority

2.16 The Licensing Authority received advice from a number of sources.

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13 L12 pp. A15, A10 Medicines Act, s 6(1), 1(1)
14 L12 p. A15 Medicines Act, s 6(2)
15 DH01 tab 14 para. 9
16 DH01 tab 14 para. 10
17 DM01 tab 14A pp. 3, 5
Medicines Commission

2.17 The Medicines Act 1968 required that Ministers establish a Medicines Commission, made up of professionals with ‘wide and recent experience’ in the practice of medicine and pharmacy. ¹⁸ The Commission was required to advise the Ministers making up the Licensing Authority on matters relating to the execution of the Act and on medicines generally where the Commission considered it expedient or when requested by Ministers. It also acted as an appeal body in respect of advice given to the Licensing Authority by the section 4 committees (see below).

Section 4 committees

2.18 Under section 4 of the Medicines Act, Ministers had power to establish committees (known as ‘section 4 committees’) for any purpose connected with the execution of the Act, after having regard to recommendations of the Medicines Commission and after consultation with appropriate organisations. ¹⁹ The Medicines Commission had a specific duty to advise Ministers with regard to the number of section 4 committees, and to recommend appropriate membership. ²⁰

2.19 Section 4 committees were established to consider particular classes of substances or articles covered by the Act, for the purpose of:

a. giving advice with respect to the safety, quality or efficacy or with respect to all or any two of those matters;

b. promoting the collection and investigation [of] information relating to adverse reactions, for the purpose of enabling such advice to be given. ²¹

2.20 At the time that BSE first came to be considered there existed a well-established network of section 4 committees. These advised on a wide range of different areas of medicines licensing and some took further advice from specialist subcommittees. The following committees gave consideration to BSE:

2.21 The Veterinary Products Committee (VPC): The terms of reference of the committee reflected the purposes described above, requiring it to advise on the safety, quality and efficacy in relation to the veterinary use of any substance or article (not being an instrument, apparatus or appliance) to which any provision of the Act was applicable; and to promote the collection of information related to suspected adverse reactions for the purpose of enabling such advice to be given. ²²

2.22 No subcommittee was established by the VPC to deal with BSE issues.

2.23 The Committee on the Dental and Surgical Materials (CDSM): This committee advised on questions of the safety, quality and efficacy of dental and surgical materials.

¹⁸ L12 p. A11 Medicines Act 1968, s 2
¹⁹ L12 p. A12 Medicines Act 1968, s 4(1)
²⁰ L12 p. A12 Medicines Act 1968, s 3
²¹ L12 Medicines Act 1968, s 4(3)
²² DM01, tab 14 para. 1a
2.24 The Committee on the Review of Medicines (CRM): This committee was established to review the safety, quality and efficacy of medicines that had been on the market before the Medicines Act introduced licensing requirements.\(^23\) At that time these products were granted licences of right (see below).\(^24\)

2.25 The Committee on Safety of Medicines (CSM): The CSM advised on questions of the safety, quality and efficacy of human medicines that fell outside the remit of the CDSM and the CRM. Of the subcommittees reporting to the CSM those relevant to BSE were the Biologics Sub-Committee (BSC) and, after its establishment in 1989, the BSE Working Group (described in Chapter 6).

2.26 The Licensing Authority was required to consult the relevant section 4 committee (or if there was none, the Medicines Commission) in certain circumstances, for example, where it was minded to refuse an application for a product licence\(^25\) or to suspend, vary or revoke a licence\(^26\) (see below). Otherwise officials had a discretion whether to seek advice from section 4 committees in relation to any particular product.

2.27 Dr David Jefferys, Principal Medical Officer, told us:

The Section 4 committees, particularly the Committee on the Safety of Medicines, have a very heavy workload. As a result, the CSM recommended many years ago that a number of advisory subcommittees, such as the Biologics subcommittee, should be set up.

The subcommittees tend to devote more time to scrutinising the details of issues raised for their consideration whilst the Section 4 committees adopt a more general overview. The subcommittees are generally scheduled to meet approximately two weeks before the meeting of whichever Section 4 committee will ultimately consider the relevant issues.

In practice, there is a considerable overlap between the membership of the Section 4 committees and the membership of their subcommittees. This means that it is not necessary for all disciplines to be represented on a Section 4 committee provided that the relevant expertise is available in the subcommittees. In addition the CSM can ask the Licensing Authority to appoint further experts as ‘members for the day’ to provide additional expertise.\(^27\)

**Chief Medical Officer and Chief Veterinary Officer**

2.28 We describe in vol. 15: *Government and Public Administration* the role and responsibilities of the Chief Medical Officer (CMO) and the Chief Veterinary Officer (CVO). The CMO, a Grade 1A official, was:

. . . the principal adviser on medical and public health matters, not only to Ministers in the Department of Health but to the Ministers in other government departments and to the Government as a whole.\(^28\)
2.29 The CMO also had ultimate line management responsibility for the medical and scientific staff in DH. The CVO, a Grade 3+ official, was the chief adviser for veterinary policy for Great Britain as a whole. The CMO played a significant part in the events we describe in the following chapters, the CVO a lesser role.

National Institute for Biological Standards and Control

2.30 Another body that had a role in the BSE story in relation to medicines was the National Institute for Biological Standards and Control (NIBSC). It was established under the Biological Standards Act 1975 in order to secure high standards of quality, safety, efficacy and consistency of biological substances used in medicines. In fulfilling this role it devised standards for the quality, purity and potency of biological substances, tested batches of biological products on behalf of DH, carried out research and advised a number of bodies, including Medicines Division of DH and its section 4 committees. NIBSC staff were members of the BSC/CSM and of the BSE Working Group. The Central Veterinary Laboratory (CVL), rather than the NIBSC, carried out tests on veterinary biologicals.

Licences for medicinal products

2.31 Prior to the introduction of a licensing regime by the Medicines Act 1968, manufacturers of medicines had been able to market products without having to satisfy an independent body as to their safety, quality and efficacy. However, from 1 September 1971, when the relevant provisions of the Act came into force, all medicines had to be licensed before they could be sold or supplied in the UK.

2.32 Manufacturers of medicinal products that had been on the market before 1 September 1971 were able to apply for a Product Licence of Right (PLR) to which they were entitled, subject to certain conditions.

2.33 As we noted above, human medicinal products with a PLR were to be reviewed for their safety, quality and efficacy by the CRM. This involved some 39,000 products. The VPC carried out a parallel review in relation to veterinary medicines and in 1988, 2,600 veterinary medicines were still to be reviewed. This review process became mandatory when the UK joined the EC in 1973 and its completion was required by May 1990. These reviews placed a large extra burden on medicines licensing in both MAFF and DH at the time that consideration of BSE was being undertaken.

2.34 Professor Lawson, Chairman of the CRM, told us:

At the completion of the review in 1990, less than 5,300 reviewed licences had been granted. Licences had either been allowed to lapse by companies or were revoked as a result of the review process.
Product licences, clinical trial certificates and animal test certificates

2.35 As noted earlier, section 7 of the Medicines Act prohibited the sale, supply, export or import of a medicinal product except in accordance with a product licence.37

2.36 Anything done in accordance with a clinical trial certificate (CTC) or animal test certificate (ATC) was exempted from the prohibition set out in section 7.38 Such certificates might be issued where the Licensing Authority had consented, subject to the provisions of the certificate, to a clinical trial of a particular medicinal product on humans (CTC) or animals (ATC).39

2.37 Most product licences were held by pharmaceutical manufacturers. However, certain medicinal product licences were held by the Secretary of State for Health and administered on his or her behalf by the Supplies Technology Division (STD) of the NHS Procurement Directorate (PD). These licences were held by the Secretary of State either for strategic reasons, or because there was no commercial interest in the product, eg, drugs for rare diseases, or because a particular statute required it.40 In February 1989, 33 product licences were held by the Secretary of State for Health. Sixteen of these were antidotes for snake bites and of the remainder eleven were vaccines or biological products.41

2.38 Mr Burton of STD told the Inquiry:

It was a matter of historical fact that Secretary of State product licences had been held by Supplies and Technology Division (‘STD’). Some of these licences related to welfare foods, some had been taken over from the Ministry of Defence and some arose as a result of an expressed public need for pharmaceutical treatments for rare diseases.42

Granting new licences

2.39 Detailed regulations governed applications for the grant of product licences. Until 1993 these were contained in the Medicines (Applications for Product Licences and Clinical Trial and Animal Test Certificates) Regulations 1971.43 Applicants for a licence were required to give the Licensing Authority particulars of all active constituents, all colouring matter, flavouring agents and perfumes and all other constituents.44 They also had to describe the method of manufacture or assembly of the medicinal product, substance or article,45 and the method of manufacture of each active constituent.46

2.40 In dealing with an application for the grant of a product licence the Licensing Authority was obliged to take into consideration several factors, including ‘the

37 From 1 January 1995, section 7 of the Medicines Act ceased to apply to those medicinal products for human use to which Chapters II to V of Council Directive 65/65/EEC apply; instead, they are required to have a marketing authorisation, grant of which is regulated by the Medicines for Human Use (Marketing Authorisations Etc) Regulations 1994; L15 tab U p. 8 [SI 1994 3144, s 9(2)]
38 L12 p. A46 Medicines Act 1968, s 35
39 L12 p. A40 and A46 Medicines Act 1968, s 31(3)(b) and s 32(2)(b)
40 YB89/2.21/13.3
41 S605 Burton para. 26
42 S605 Burton para. 31
43 L13 tab H p. 1. These regulations were replaced by the Medicines (Applications for Grant of Product Licences – Products for Human Use) Regulations 1993 [L13 tab H p. 40A] in respect of medicinal products for human use
44 L13 tab H, Paragraph 12 of schedule 1
45 L13 tab H, Paragraph 16 of schedule 1
46 L13 tab H, Paragraph 17 of schedule 1
safety of medicinal products of each description to which the application relates’. 47
Having done so, the Licensing Authority could: 48

i. grant a licence containing such provisions as it considered appropriate; or

ii. if, having regard to the provisions of the Act and any Community obligation, it considered it necessary or expedient to do so, refuse to grant a licence.

2.41 When a licence application was submitted the administrative divisions responsible for medicines within MAFF and DH, respectively, would first establish that the application was complete. When all necessary information had been received the application would be the subject of assessment by the medical and scientific experts within the Departments.

2.42 We noted above that if the Licensing Authority was minded to refuse a licence on the grounds of its safety, quality or efficacy it had first to consult the appropriate section 4 committee or (if there was no such committee) the Medicines Commission. 49 In other cases, officials exercised their discretion as to whether to refer the application to the section 4 committee. If the application was ‘simple and satisfactory’ it might be granted a product licence at that stage. 50 Such ‘simple’ applications might involve products that were substantially the same as existing products that had been granted licences. Dr Purves, Principal Pharmaceutical Officer in Medicines Division, told us that ‘any new developments where there was not a precedent for action taken by the Licensing Authority, would have been taken to the expert committees for their advice’. 51

2.43 Even in cases where the section 4 committee had given advice, it was the Licensing Authority itself that was responsible for determining the application in question.

Existing licences: renewal, suspension, revocation and variation

2.44 Product licences were not granted indefinitely; they expired either five years after they were granted or last renewed, or at the end of any shorter period if specified in the licence. 52 The licence holder could then apply for the licence to be renewed for a further period of five years and in such cases the Licensing Authority could:

i. renew the licence, with or without modifications;

ii. grant a new licence containing such provisions as the Licensing Authority considered appropriate; or

iii. if, having regard to the provisions of the Act, it considered it necessary or expedient to do so, refuse to renew the licence or grant a new licence. 53

2.45 Before refusing to renew a licence on any grounds relating to ‘the safety, quality or efficacy of medicinal products’ the Licensing Authority was again

47 L2 p. A26 Medicines Act 1968, s 19(1)(a)
48 L12 p. A27 Medicines Act 1968, s 20(1)
49 L12 p. A28 Medicines Act 1968, s 20(3)
50 M1D, tab 15 p. 5
51 S535 Purves para. 13
52 L12 p. A3 Medicines Act 1968, s 24(1)
53 L12 p. A3 Medicines Act 1968, s 24(2)
obliged to consult the appropriate section 4 committee or (if there was no such committee) the Medicines Commission.\textsuperscript{54}

\textbf{2.46} The Licensing Authority also had power to suspend, revoke or vary the provisions of a product licence on certain specified grounds, which included:

\begin{itemize}
\item[(g)] that medicinal products of any description to which the licence relates can no longer be regarded as products which can safely be administered for the purposes indicated in the licence, or can no longer be regarded as efficacious for those purposes; or
\item[(h)] that the specification and standards to which medicinal products of any such description are manufactured can no longer be regarded as satisfactory.\textsuperscript{55}
\end{itemize}

The Act did not specify the kinds of variation that might be made.

\textbf{2.47} Except for suspension in a case of urgency, where the Licensing Authority proposed to suspend, revoke or vary a product licence on either of those grounds, they had first to consult the appropriate section 4 committee or, if there was none, the Medicines Commission.\textsuperscript{56}

\textbf{2.48} Where it appeared to the Licensing Authority that in the interests of safety it was necessary to suspend a licence with immediate effect, then it might do so for a period of up to three months.\textsuperscript{57} In such cases, it had to report the suspension to the appropriate section 4 committee, and the usual procedures were then brought into play.\textsuperscript{58}

\textbf{2.49} Suspension or revocation of a product licence would prevent sale or supply of stocks of the product.\textsuperscript{59} Dr Rotblat, Senior Medical Officer in Medicines Division, commented on action taken on medicinal products utilising bovine material. She told us that maintaining the vaccination programme:

\begin{quote}
would not have been possible had formal regulatory action such as revocation been taken, rather than non-binding recommendations being issued, because revocation of a product licence prevents the use of existing stocks of that product.\textsuperscript{60}
\end{quote}

\textbf{2.50} Similarly, if a product licence were varied, sale or supply of stocks that did not comply with the varied licence would be unlawful.

\textbf{Informal action}

\textbf{2.51} As well as the powers of refusal, suspension, amendment or revocation of a product licence, non-regulatory forms of action were also available to the Licensing Authority. Dr Jefferys told us:

\begin{itemize}
\item \textsuperscript{54} L12 p. A33 Medicines Act 1968, s 24(4)
\item \textsuperscript{55} L12 p. A38 Medicines Act 1968, s 28
\item \textsuperscript{56} L12 p. A39, A151 (Medicines Act 1968, s 29(1) and Schedule 2)
\item \textsuperscript{57} L12 p. A 154 Medicines Act 1968, Schedule 2 paras 10 and 11
\item \textsuperscript{58} L12 p. A 154 Medicines Act 1968, Schedule 2 paras 12 and 13
\item \textsuperscript{59} L12 p. A 15 Medicines Act 1968, s 7
\item \textsuperscript{60} S422 Rotblat para. 38
\end{itemize}
It is important for the Inquiry to understand the distinction between formal regulatory action, such as suspending or revoking a product licence, and informal action, such as the issuing of non-binding guidelines or recommendations. The regulation of medicinal products is effected through a complicated legal framework. This legal framework guides everything that the Licensing Authority and its advisory committees do. Indeed a lawyer attends each meeting of the CSM to advise the Chairman on legal issues. In order to suspend a product licence, which is very rare, a paper has to go to the CSM setting out a risk-benefit analysis of the product in question and the matter then has to go to Ministers. In order to revoke a licence, the Licensing Authority has to make out a case that the risk-benefit ratio for the product concerned is such that it is unsafe (this is a difficult task given that, when the product had been granted a licence it would, by definition, have been found to have proven efficacy). In both such cases the burden of proof is on the Licensing Authority to make out its case. This means that no formal action can be taken against medicinal products unless there is an evidential basis for doing so.

By contrast, informal action, such as the issuing of guidelines or recommendations, depends upon the co-operation of pharmaceutical companies. Such an approach has the added advantage that it invariably produces a quicker result because it involves neither appeals nor legal processes. In the case of BSE, the pharmaceutical companies were happy to co-operate.  

**Options available to deal with BSE**

2.52 When officials were called upon to respond to the emergence of BSE, they had therefore to consider how to deal with medicinal products with existing product licences, including those that had been granted licences of right, and medicinal products for which a licence was sought, then or in the future.

2.53 For those products that were already licensed, they had power to vary, suspend or revoke the licence, if the conditions set out in the Medicines Act were met. Dr Jefferys pointed out the need for such action to be based on proper evidence. Alternatively, it was open to them to take informal action such as that described by Dr Jefferys.

2.54 For new product licence applications, the implications of BSE could be taken into account in assessing the safety of the product and determining whether it should be granted a licence. Conditions might be imposed on a licence, or a licence might be refused, but again only with a proper evidential basis. Informal guidance was also available in respect of such products.

**Adverse reactions**

2.55 One of the ways in which the safety of medicinal products that had been licensed was monitored was through the reporting of adverse reactions to them. This was achieved through the ‘Yellow Card Scheme’, under which doctors, coroners, dentists and pharmacists reported suspected adverse reactions on a voluntary basis,
and the pharmaceutical industry reported them under statutory obligations. These adverse reactions were recorded in an adverse drug reactions database, now known as the Adverse Drug Reactions On-Line Information Tracking (ADROIT) database.

**2.56** ADROIT records against each product details of active ingredients and of excipients. Reports of suspected adverse reactions are also recorded against the product. Reports are reviewed on a weekly basis to assess the causal relationship between the products and reported reactions and to identify possible risk factors contributing to the occurrence of reactions, for example age or underlying disease. Today, if an ingredient might be implicated in a suspected adverse reaction, ADROIT or the Product Licence User System (PLUS) database, used to record licensing data, can be interrogated to identify other products using such material. When a material is used in the manufacturing process but is not present in the finished product it will not be recorded in either the ADROIT or PLUS databases.

**2.57** The Veterinary Medicines Directorate (VMD) also operated a ‘Yellow Card Scheme’ and reports from vets and from industry of adverse reactions to veterinary medicines were recorded in the Suspected Adverse Reactions Scheme (SARS) database. The VMD Annual Report shows that in 1999 there were 1,600 such reports. Potentially serious reactions are reviewed monthly and quarterly reports of all suspected reactions are provided to the VPC. Searches of the system can provide details of other similar authorised products and their ingredients.

**How did the UK licensing regime interact with European regulation?**

**2.58** EC regulation of both human and veterinary medicinal products was introduced with the adoption of Council Directive 65/65/EEC. Its framework was similar to that of the Medicines Act: it was based on the grant of a ‘marketing authorisation’ by the competent authority of the Member State in question (ie, a decentralised system). No product within the scope of the Directive could be placed on the market in a Member State unless an authorisation had been issued by the competent authority of that Member State.

**2.59** When the UK joined the EC, the Medicines Act was already in force and no new legislation was introduced to implement Directive 65/65/EEC. The competent authority of the UK for the purposes of the Directive was the Licensing Authority; the ‘marketing authorisation’ was the product licence; and applications were dealt with under the mechanisms of the Medicines Act 1968, consistently with the relevant EC rules.

**2.60** Additional measures were introduced in 1975 including mechanisms for the recognition by all Member States of product licences granted by any individual state. The Committee for Proprietary Medicinal Products (CPMP), a scientific committee, was also established; this advises the Commission on issues of safety, quality and efficacy in much the same way as the CSM advises the Licensing Authority in the UK. A corresponding body for veterinary medicines, the Committee for Veterinary Medicinal Products (CVMP), was set up in 1981. It

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62 L16 tab 1 p. 65
63 L16 tab 1 p. 65 – Article 3
64 L16 tab 1 p. 95
65 DH01 tab 6 paras 10–11
performs the same functions in respect of veterinary medicines as does the CPMP for human medicines. The CPMP and CVMP are now part of the European Medicines Evaluation Agency (EMEA), which was established to coordinate the evaluation and supervision of medicinal products in the Member States.

2.61 The EU Commission publishes ‘Guidelines on the quality, safety and efficacy of medicinal products for human use’. Since 1975 applicants for a market authorisation of a new product, in assembling a dossier for application, have been required to ‘take into account’ such guidance.

Responsibilities for medicines licensing in 1988/89

Responsibilities within DH for human medicines licensing

2.62 We turn now to consider the Departments and officials who operated the licensing system. At the time when BSE first emerged, the licensing regime for human medicinal products was operated by officials in Medicines Division in DH. This Division was organised in three parallel structures: medical staff, pharmaceutical staff and administrative staff. Responsibility for staff in these structures was essentially divided along professional/administrative lines. The professional staff reported to the Senior Principal Medical Officer (SPMO) or the Chief Pharmaceutical Officer and the administrative staff reported to the Under Secretary.

2.63 Over the period 1984–89 Medicines Division employed some 300 people, 200 of whom were administrative staff and 100 professionals (20 doctors and 80 pharmacists). The three parallel structures in the Division together with some of their key personnel are described below.

(a) Administrative staff

2.64 Mr Clive Wilson, a Grade 3 Under Secretary, was joint head of Medicines Division and head of its administrative branches. He had joint responsibility for supporting and advising Ministers in their statutory responsibilities as the medicines Licensing Authority.

2.65 Mr David Hagger, the Grade 5 Assistant Secretary reporting to Mr Wilson, headed MB1, the branch with administrative and policy responsibilities for medicines licensing. The most relevant section in MB1 in relation to BSE was MB1C. Its responsibilities included providing the administrative lead on policy for medicines licensing issues for which the CSM was the appropriate advisory body; providing the administrative secretariat of the CSM; and managing the product licence database.
(b) Medical staff

2.66 Dr Gerald Jones, a Grade 3 SPMO, was joint head of Medicines Division and headed the medical branches. He was responsible for all professional work concerning drug regulation, new drug applications, adverse reactions, review of existing products, advertising, legal status and the servicing of all the advisory committees. In addition he had responsibility for policy formulation and advice to Ministers.\(^\text{74}\)

2.67 The medical staff were organised into three branches, each headed by a Principal Medical Officer (PMO) who reported to Dr Jones. These branches and their corresponding PMOs were:

i. MB3A: New drugs and biologicals – Dr Jefferys from September 1986 to 1990;
ii. MB3B: Review of medicines and dental and surgical materials – Dr Wood to September 1988 and Dr Adams from September 1988 to May 1990; and
iii. MB4: Adverse reactions and post-marketing surveillance – Dr Jenkins to September 1988 and Dr Wood from September 1988.\(^\text{75}\)

(c) Pharmaceutical staff

2.68 Dr Wills was the Chief Pharmacist at DH (Grade 4 level) until December 1989.\(^\text{76}\) He headed the Pharmacy Division, which was entirely separate from Medicines Division, but he was also professional head of all the pharmacists within DH, including those within Medicines Division. After June 1990 the Chief Pharmacist became part of Medicines Division, reporting to the Under Secretary there.\(^\text{77}\)

2.69 The pharmacists were in Branch MB5 (MB5A, MB5B and MB5C from 1989), headed by a Deputy Chief Pharmacist (Grade 5 level) who reported to Dr Wills. Mr Stewart was the head of MB5A, and Dr Purves (Grade 6 level), who had the lead responsibility for biologicals and was the pharmaceutical assessor to the CSM’s Biologicals Sub-Committee (CSM/BSC), reported to him.\(^\text{78}\)

2.70 Members of each of these three structures – administrators, doctors and pharmacists – were involved in assessing any licence application, or in other licensing action with respect to a medicinal product. As between the two sets of professional staff, the role of pharmacists was to assess the safety of the manufacturing of the product, from the selection of the ingredients, to the end product. The role of doctors was to analyse the data from clinical trials of the product on human patients.\(^\text{79}\)

\(^{74}\) S190 Jones G para. 3
\(^{75}\) S419 Jefferys paras 7–9, T112 pp. 15–16
\(^{76}\) S475 Wills para. 4
\(^{77}\) DH01 tab 21
\(^{78}\) S422 Rotblat paras 8–9
\(^{79}\) S422 Rotblat para. 22
Responsibilities within MAFF for Veterinary medicines licensing

2.71 In 1987 three parts of MAFF shared responsibility for veterinary medicinal products. Animal Medicines Division, part of Animal Health Directorate, at Tolworth, took the lead on policy and regulatory action, including issue of licences, under Mr Wilkes until October 1988, and subsequently Mr Scollen. Professional and scientific advice was provided by two divisions located at the CVL at Weybridge. Their responsibilities were as follows:

i. The Medicines Unit, headed by Mr Alastair Kidd, assessed the safety, quality and efficacy of veterinary medicines and of animal feed additives. It also provided the Secretariat for the VPC, the relevant section 4 advisory committee of independent experts.

ii. The Biological Products and Standards Department (BP&S), headed by Dr Denise Thornton, examined and advised on applications for licences for veterinary immunological products; tested samples of such products; provided British standards for use in quality control; and provided for the inspection of manufacturers of veterinary immunological products.

2.72 Two non-statutory committees of senior officials – the Scientific Secretariat and the Biologicals Committee (BC) – dealt with licence applications and decided, in cases where they had a discretion, which applications should be referred to the VPC. General policy matters were all presented to the VPC for review and advice.

Mr Kidd told us:

At monthly meetings the Biologicals Committee and Scientific Secretariat considered licence applications for veterinary biological and pharmaceutical products respectively and the assessment reports of BP&S and Medicines Unit staff. The Scientific Secretariat of the VPC drew its members from a variety of sources including the Medicines Division of the Department of Health and toxicologists from the Department of Health and from the Chemical Division of Porton Down. As far as the Biologicals Committee was concerned, the Department of Health was not represented and any contact with the Department of Health was on an informal basis. However, as technical documents were invariably submitted to the VPC, Department of Health officials were fully informed through their presence at VPC meetings and were able to comment or pass papers on to appropriate colleagues. The Biologicals Committee/Scientific Secretariat subsequently made recommendations as to whether a product authorisation should be granted or not. The comments of the appropriate committee were incorporated into the reports prior to assessment of licence applications by the VPC.

2.73 Dr Little was Deputy Director of the CVL. His command included the Medicines Unit and BP&S. He told us that he had ‘specific responsibility’ for veterinary medicines and that he was responsible for reacting appropriately to any...
information including on BSE, which might impinge upon their safety. Dr Little also chaired a liaison group between MAFF and the National Office of Animal Health (NOAH) which met every few months. NOAH was the trade association to which most manufacturers of animal medicinal products belonged.

2.74 In April 1989 the three divisions merged to become a new Veterinary Medicines Directorate (VMD) on the CVL site at Weybridge. This was headed by Dr Rutter, who reported to Mr Cruickshank.

Evaluation of the arrangements for the control of medicines

2.75 There was concern during 1987 that Medicines Division was showing signs of overload, and Ministers asked Dr N J B Evans and Mr P W Cunliffe to study the arrangements for the control of human medicines in the UK. The Minister of Agriculture, Fisheries and Food then asked Mr Cunliffe to conduct a parallel review of the licensing and control of animal medicines within MAFF. These reports highlighted significant defects in the handling of medicines licensing and were the catalyst for substantial organisational changes.

Human medicines: Evans–Cunliffe Report

2.76 In December 1987 Dr Evans and Mr Cunliffe produced their Study of Control of Medicines (‘the Evans–Cunliffe Report’). Their terms of reference were:

To examine the issues for DHSS arising from the continued increases in licence applications and other work under the Medicines Act and to recommend ways of dealing expeditiously with this work, while maintaining adequate standards for the safety, efficacy and quality of human medicines in the United Kingdom.

2.77 The Evans–Cunliffe Report stated that the basic framework of medicines control in the UK was satisfactory:

The Medicines Act 1968 has stood the test of time well, as has the general principle whereby a licensing office takes advice from independent expert bodies and reports to Ministers. The high reputation which the UK deservedly holds for medicines control depends upon the excellence of the professional judgements made by staff and those advisory bodies, on the balance of benefit and risk from medicines.

2.78 The professional and expert judgements made by staff and advisers received praise:
. . . W]e are satisfied that the judgemental decisions are generally soundly made. All the evidence, and our own experience and observation, indicate that the quality of the professional and expert judgements made by Medicines Division staff and by the members of the expert advisory committees is very high. This expert competence is in fact the great strength of the UK system, and when recommending change in the present arrangements we have been especially concerned not to weaken its excellence, which has served the public well.93

2.79 The Committee systems were also reported to be working well:

We examined the work of all the Section 4 Committees (except the Veterinary Products Committee, which lay outside our terms of reference) and their subcommittees, and judge them to be well-run and highly expert bodies. Their chairmen and members carry considerable responsibility and a heavy burden of paper-work in preparation for meetings, and the country is much indebted to them for their labours.94

2.80 The Report concluded, however, that there were problems within Medicines Division that needed to be addressed. They identified in particular:

i. delays;
ii. minor documentary errors;
iii. difficulty in recruiting and retaining professional staff;
iv. antediluvian computer support;
v. problems with the paper filing system; and
vi. complex organisational structure preventing effective management.95

They concluded that overall the Division was unduly constrained from without and lacked resilience within.96

Overload and delay

2.81 The Evans–Cunliffe Report discussed problems of overload within the Division and resultant delay, stating, ‘delays and errors are classic indicators of overload’.97

The workload from licence applications received by Medicines Division of DHSS has gone up steadily and is still rising. On the whole, the office has coped surprisingly well with this increase and without proportionate increase in staff, but it is now showing signs of overload. Licences for New Active Substances (ie, the important new drugs) are currently held up on average for as much as two years, compared with the European Community (EC) specified figure of 210 days, and many minor applications are held up almost as long, compared with the EC figure of 120 days.98
And later:

There are . . . sometimes substantial delays in reaching the decisions – delays which are in part attributable to shortage of professional staff though they may also in part reflect the lack of effective management.99

**Recruitment and retention of professional staff**

**2.82** Problems in recruiting and retaining pharmaceutical and medical experts were described as follows:

The other principal area of difficulty relates to staff: because civil service salaries for pharmacists and doctors are uncompetitive and there is too little secretarial and other support, it is difficult to recruit experienced professional staff for this highly specialised work and – once trained and experienced – they leave for posts in industry. Other rigidities compound the problem, for example the control of staff by arbitrary head count, and the dilatory procedures for filling vacancies.100

**2.83** This view was echoed in evidence heard by the Inquiry. Dr Gerald Jones stated:

There was, unfortunately, a considerable turnover of staff. We were recruiting almost permanently. The board recruiting doctors from outside, I called it virtually a standing committee; it had to meet – which I served on – virtually every 3 months. As soon as you were able to appoint a doctor you found that someone had moved on within the Department. The Division stood at about 20 or 25 doctors at that time.101

**2.84** Dr Jefferys also commented on staffing levels in Medicines Division:

At that stage [1988], there were only 5 physicians in MB3A, one of whom was working full time on the Opren litigation. For most of this period we were actively recruiting for a sixth physician. In addition, there were 3 toxicologists in the group. However, for much of this period only one toxicologist was working full time because both the other toxicologists were on extended maternity leave.

By contrast, there are now 27 medical assessors, 8 toxicologists and 4 statisticians in the Licensing Division and 26 physicians in the Post-Licensing Division (including Pharmacovigilance activities). In total there are now approximately 550 staff within the Medicines Control Agency. In 1988 the figure was closer to 220.102

**2.85** He added:

These resource difficulties inevitably had implications for the work of the Division. For example, in 1988, renewals of product licences were handled purely administratively without input from physicians because of the staff

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99 M39 tab 12 p. 15 para. 3.18
100 M39 tab 12 p. 2 para. 5
101 T71, pp. 23–4
102 S419B Jefferys paras 6–7
shortages. In addition, the processing of abridged licence applications was subject to a two year backlog. By summer 1989 the position had started to improve in that the number of physicians within MB3A had increased to 7 and the work on the Opren litigation [which had occupied considerable resources] had decreased, but the major improvement only occurred in the early 1990s with the full establishment of the MCA. 103

2.86 More generally on staff structure the Evans–Cunliffe Report commented:

. . . the staff are structured in separate hierarchies representing the professional disciplines making up the workforce – in this case hierarchies of administrators, doctors and pharmacists respectively. As the structure and subdivisions of the different hierarchies differ from each other, with no common relationship to the several ‘businesses’ into which the work of the Division can be divided, it is difficult to design simple operational policies and almost impossible to engender any feeling that staff are working together to a common purpose.104

Computing and information technology

2.87 The Evans–Cunliffe Report also found that computing and information technology support within the Division was seriously deficient, and that the database used for the processing of applications and the supporting data was almost unusable because it was erroneous and out of date:

There is an urgent need for more and better computerisation of the office processes relating to licence applications, and to the monitoring of adverse drug reactions.105

2.88 Dr Purves, Senior Principal Pharmaceutical Officer, gave the following explanation of the computerised database and its limitations:

The Norsk product licence database used by Medicines Division in 1988 stored information on all product licences and CTC’s. This database recorded information on all active ingredients in products. It did not, however, record whether bovine materials were used as excipients (any other ingredient used in a product i.e. to stabilise the active ingredient) or as ingredients or reagents. (NOTE: - an ingredient106 is a material used in the manufacture of products, which is removed during purification and is not present in the finished product). The most effective way of getting up to date and complete information on which bovine materials were being used in medicines was to consult the manufacturing industry. Getting this information direct from the manufacturers was particularly important because the source of the bovine material was crucial. In some cases only the manufacturing company would have the details of who their suppliers were and from which country their raw materials were derived.107

103 S419B Jefferys paras 9–10
104 M39 tab 12 p. 24 para. 3.22
105 M39 tab 12 p. 24 para. 5.3
106 sic; presumably ‘reagent’
107 S535 Purves para. 37
The paper files

2.89 As a consequence of the computing problems there was heavy reliance on labour-intensive clerical operations and on traditional paper files, called ‘gold files’. However, there was no effective system for keeping track of the files or of the transit of work through the office. The Report stated:

The thousands of current and previous licence applications are moved around the office in cardboard folders, the so-called gold files. It is astonishing that there is no reliable way of finding files within the building. Some months ago, DHSS introduced a file tracking system in which staff read-off bar codes into a central computer, but it is not yet comprehensive nor fully operational. File-tracking is an essential tool not only for finding and linking files but also for monitoring the transit of work through the organisation. We RECOMMEND that a high priority be given to completing and developing the file-tracking system.\(^\text{108}\)

2.90 Clearly the response of Medicines Division to the potential dangers associated with BSE would involve, at some point, establishing the extent to which bovine products were included in medicinal products. Given that applications for product licences involved the submission of detailed data relating to the active ingredients and processes used in the manufacture of particular products, considerable information should have been available to administrators. However, as highlighted by the Evans–Cunliffe Report, neither the computer system nor the paper files were adequate for this purpose.

Structural/organisational difficulties

2.91 Furthermore, the Evans–Cunliffe Report stated that aspects of the running of the Medicines Division indicated a lack of effective oversight of the Division’s work.\(^\text{109}\) The Report stated:

Our scrutiny of Medicines Division showed that it is indeed overloaded and will require more resources – some more staff, and computing equipment.\(^\text{110}\)

2.92 The Report also commented adversely on the organisational structure of the Division, which, it stated:

reflects its historic origins as a headquarters policy division and is inappropriate for the present task; in particular the diffusion of managerial responsibility means that there is no effective overall control of the flow of work, and it is frustratingly hard to bring about change.\(^\text{111}\)

2.93 The Report recommended alterations in the structure and administration of the Division, but fell short of recommending independent status:

We considered carefully whether the Medicines Directorate should be transferred from the DHSS, as has been suggested, into a Special Health Authority or other independent body, but we decided that the balance of

\(^\text{108}\) M39 tab 12 p. 24 para. 5.3  
\(^\text{109}\) M39 tab 12 p. 15 para. 3.20  
\(^\text{110}\) M39 tab 12 p. 15 para. 3.19  
\(^\text{111}\) M39 tab 12 p. 1 para. 4
advantage lies in keeping the Directorate within DHSS under special financial and managerial arrangements to promote a considerable degree of autonomy and flexibility, for example over pay for specialised posts.\textsuperscript{112}

**Veterinary medicines: Cunliffe Report**

2.94 Shortly after the publication of the Evans–Cunliffe Report on the licensing arrangements for human medicines, Mr Cunliffe produced his report entitled *Review of Animal Medicines Licensing*.\textsuperscript{113} In summary the report emphasised that there was ‘little criticism of the general concept and indeed of the correctness of decisions but considerable criticism of the operation of the system’.\textsuperscript{114} Mr Cunliffe noted:

Running through many of the discussions, I detected a feeling that animal health was considered to be a smaller, poor relation of human health. It came through from the industry, from professionals in MAFF and from some members of the [VPC]: in support of this, I was told that the industry was smaller and less profitable, that its professionals in the Civil Service are of a lower grading and that in product assessment, human fears would dominate animal health.\textsuperscript{115}

2.95 In terms of the staffing difficulties and the pressures of workload, the Cunliffe Report’s findings were similar to, though less acute than, those on the human medicines side. It stated:

The present members of the licensing operation have been able to cope with the workload, although at the expense of other activities. Strains are, however, evident and delays are increasing. It is unlikely the present numbers will be able to cope with the future workload unless systems are developed to reduce that workload.

... 

The problem with professional staffing detracts from the licensing operation. The causes appear to be: –

a) restraint on staff numbers eg Treasury head count 

b) difficulty in recruiting because of –

- unpopularity of the Civil Service to professionals
- salaries too low relative to the market
- protracted procedures for advertising and filling vacancies via the Civil Service Commission
- licensing work is highly specialised and hence unattractive in career terms to MAFF veterinary staff.

\textsuperscript{112} M39 tab 12 p. 2 para. 7
\textsuperscript{113} M11D tab 18
\textsuperscript{114} M11D tab 18 p. 14
\textsuperscript{115} M11D tab 18 p. 14
c) dissatisfaction of those in post because of –

- uncompetitive salaries
- inadequate secretarial etc support
- frustration at the inability to bring about change
- lack of career opportunities within the unit.\textsuperscript{116}

2.96 The Report concluded:

The UK approach to the control of medicines appears sound and the intellectual and judgmental qualities stand high. Operation of procedures falls short of effectiveness and would be further adversely affected by the future work load. Computing support is disastrously weak and the whole operation is under-resourced and ineffectively managed. External (ie outside the licensing operation) constraints have prevented any attempts at improvement.\textsuperscript{117}

2.97 The Report recommended improvements in technology; simplification of procedures and removal of unnecessary work; better communications between applicants and the licensing operation; improvements in staffing and personnel; and improved organisational structures.\textsuperscript{118}

2.98 These chronic shortcomings in so many aspects of the arrangements for control of medicines in the UK were identified at the very time when the Licensing Authorities were called upon to deal with the emergence of BSE. Problems with the database and computing support, with the paper files and their management, overwork, ineffective management and complex structures each played a part in shaping the response, as we explain in the following chapters.

2.99 Some of these difficulties were addressed by the establishment of the Medicines Control Agency (MCA), and the Veterinary Medicines Directorate (VMD), as described below.

**New structures responsible for medicines licensing**

**Medicines Control Agency**

2.100 The MCA was created, following the Evans–Cunliffe Report, in April 1989, although it remained at that stage a division of DH. On 11 July 1991 it became an Executive Agency of DH. Crucially, the three parallel hierarchies were replaced with multi-disciplinary teams. The freedoms of Agency status were intended to help it meet the challenges of new developments in medicine; of completion of the EC single market; and of a European system for regulating medicines.\textsuperscript{119}
2.101 In place of the old structure of the Medicines Division, the new MCA had several Business Groups. Management lines were reorganised and the pharmaceutical and medical staff integrated.\textsuperscript{120} The new Business Groups were in place by June 1990, although the reporting lines remained as under the Medicines Division until July 1991.\textsuperscript{121}

2.102 These Business Groups were:

i. Business A: New drugs and European Licensing
ii. Business B: Abridged licensing
iii. Business C: Pharmacovigilance
iv. Business D: Inspection and enforcement
v. Business E: Executive support\textsuperscript{122}

2.103 The Agency was headed by a Director or Chief Executive, Dr Keith Jones, and each Business Group by a Business Manager (of Grade 4 level) who reported to the Chief Executive. The Chief Executive was fully responsible and accountable to the Secretary of State for Health for the efficient management, overall performance and future development of the Agency. Neither Ministers nor DH were involved in the day-to-day management of the MCA. In addition, a Departmental Board made up of Departmental and outside members and a Chairman from DH was set up. It was responsible, after consultation with the Chief Executive, for providing independent advice on corporate planning and strategic issues to the Secretary of State.\textsuperscript{123}

2.104 Dr Keith Jones clarified his role in a written statement:

On my appointment as Director of the MCA all staff within the Medicines Division nominally reported to me. However, in practice the existing lines of command continued and I reported jointly to the Deputy Secretary responsible for medicines policy and to the Deputy Chief Medical Officer (DCMO) until MCA became a Next Steps Agency in 1991.\textsuperscript{124}

... When the MCA became an executive agency on 11 July 1991, my title changed to that of Chief Executive, and I became responsible and accountable directly to the Secretary of State for the efficient management, overall performance and future development of the MCA. My role is primarily that of a medically, scientifically informed manager: I am there to oversee the running of the MCA and since July 1991, to advise Ministers on matters of medicines control.\textsuperscript{125}

2.105 Under the new structure Dr Jefferys was given wider responsibility as the Business Manager for Business A: New drugs and European Licensing. He was responsible for the medical, scientific and pharmaceutical staff involved in the
assessment of new drugs including biological products. In addition he was responsible for the secretariat to the CSM and for the Biological and Biotechnological Unit that was headed by Dr Purves. Dr Jefferys reported to Dr Keith Jones.\footnote{S419 Jefferys para. 12}

2.106 The Biological and Biotechnological Unit was set up shortly after the MCA became operational. Dr Purves was appointed unit manager in late 1990 and Dr Rotblat was the Senior Medical Officer (SMO).\footnote{S422 Rotblat para. 12–13}

2.107 Business B, headed by Mr David Hagger, was responsible for abridged product licensing, variations to existing licences and product licence renewals as well as licensing work and administrative support for the CRM and CDSM.\footnote{S476 Hagger para. 23} Dr June Raine, a Group Manager reporting to Mr Hagger, was Principal Medical Assessor to the CDSM.\footnote{S476 Hagger para. 24}

2.108 Of the other businesses in the MCA structure, Business C was headed by Dr Susan Wood, Business D by Mr Bryan Hartley, Business E by Mr Roy Alder, and Business F by Dr Alan Rogers.\footnote{United Kingdom Medicines Control Agency Annual Report and Accounts 1990/91}

2.109 In the autumn of 1994 there was a further reorganisation of the MCA\footnote{S419 Jefferys para. 13} into the following five divisions:

i. Licensing Division

ii. Post Licensing Division

iii. Inspection and Enforcement Division

iv. Executive Support Division

v. Finance Division.\footnote{DH01 tab 16}

2.110 The Agency was still headed by the Chief Executive, Dr Keith Jones, and each Division by a Grade 4 Business Manager.\footnote{M16A tab 27}

Veterinary Medicines Directorate

2.111 As noted above, in April 1989, just over a year after Mr Cunliffe produced his Report, the three divisions of MAFF responsible for medicines licensing merged to become VMD. A year later VMD became an Executive Agency. An Ownership Board was established consisting of a Chairman from MAFF, senior Departmental representatives and Dr Rutter, as Chief Executive. The Chief Executive reported directly to the MAFF Ministers.\footnote{DM01 tab 4 pp. 6–7; YB90/00.00/10.1–10.2; WS499 Rutter p. 2} VMD was responsible for the licensing of veterinary medicines, post-licensing surveillance (including adverse reactions), the control of animal medicines and medicated feedstuffs, the control of veterinary residues, and for providing policy advice to MAFF.\footnote{M16 tab 21 p. 3; M16 tab 26 p. 2; DM01 tab 15 p. 3; S499 Rutter para. 3} Throughout these
organisational changes, most of the same staff continued in post to operate the established licensing and consultation procedures under the Medicines Act.136

2.112 Within VMD, work was allocated between three multi-disciplinary professional and administrative teams, each headed by a professional (Grade 6 level) and administrative (Grade 7 level) team leader reporting to the appropriate Deputy Director (Mr Kidd on the professional side and Mr Lawson on the administrative side). The three teams which reported to the Deputy Directors were:

i. **Pharmaceuticals** responsible for assessing applications and administering product licences for pharmaceutical products. Also responsible for international and European aspects of market authorisations and legislation for these products. This team coordinated VMD interests on policy developments relating to these matters. Head of the professional team was Dr K N Woodward and head of the administrative team was Mr A F Harvey;

ii. **Biologicals and recombinant products** responsible for assessing applications and administering product licences for biological and recombinant products. Also responsible for administering the Suspected Adverse Reactions Scheme (SARS) for all veterinary products. This team also coordinated VMD interest in policy developments relating to biologicals and recombinant products. The administrative staff in this team provided the secretariat for the Veterinary Products Committee. Head of the professional team was Dr Aileen Lee and head of the administrative team was Mr A J C Taylor; and

iii. Feed additives responsible for assessing applications and administering product licences for all veterinary medicinal products administered in feed or drinking water with the exception of oral vaccines. Also responsible for coordinating VMD interests in policy developments relating to these matters. The Finance team reported to the Head of Administration in this team. Head of the professional team was Mr J O’Brien and head of the administrative team was Mr C Bean.137

### Regulation of medical devices

#### Responsibilities

2.113 We noted above that medical devices such as heart valves and pacemakers fell outside the controls of the Medicines Act. When BSE first emerged, they were the responsibility of the Supplies Technology Division of the NHS Procurement Directorate (PD/STD) of DH. From 1 August 1990 the Medical Devices Directorate (MDD) took over this responsibility.

2.114 Eventually, in 1994, medical devices became the responsibility of the Medical Devices Agency (MDA), an executive agency of DH. It had responsibility on behalf of the Secretary of State for Health for taking all reasonable steps to ensure that medical devices in the UK were of safe design, met appropriate standards of safety, quality and performance and that these standards complied with the relevant Directives of the EU.138

136 S515 Kidd para. 7
137 DM01 tab 15 pp. 7–8
2.115 As noted in paragraph 2.37, PD/STD and its successors also had responsibility for administering product licences held on behalf of the Secretary of State for Health. This function was moved elsewhere in DH in August 1992.  

2.116 Within PD/STD three areas had relevant responsibilities so far as BSE was concerned. These were: implants; sterilisation; and the Manufacturer Registration Scheme (MRS) (see paragraph 2.22). Miss Marilyn Duncan headed both the implants and sterilisation areas, first as a Grade 6 and then as a Grade 5. The other person who had significant involvement in the BSE story in relation to medical devices was Mr Will Burton, a Principal Pharmaceutical Officer in STD.

Ensuring safety of medical devices

2.117 Some medical devices, such as sutures, were expressly brought within the controls of the Medicines Act, by statutory instruments (see paragraph 2.8). They were dealt with under the regime we have described above.

2.118 Those that were not brought within the scope of the Medicines Act were simply covered by general product safety legislation. If there was a need to remove an unsafe medical device from the UK market, powers under the Consumer Protection Act 1987 were the appropriate means of doing so.

2.119 However, PD/STD (and later the MDD) did operate a voluntary MRS on which there were no statutory controls. Purchasers of medical devices (mainly the NHS) were advised to buy them only from manufacturers registered on the scheme. A member of the MRS failing to meet the requirements of the scheme could be removed from the register. A reporting system also operated to encourage manufacturers and users to report details of any adverse incidents involving medical devices.

2.120 Separate regulation of medical devices began on 1 January 1993. Regulations were then introduced which applied to active implants (i.e., relying on a source of power other than that generated by the human body or gravity), partial or whole, left in the body, including pacemakers.

2.121 Regulation of other devices (with some exceptions) was introduced in 1994. Enforcement of these provisions in the UK is the responsibility of the Secretary of State for Health, acting through the MDA. Local authorities have some enforcement responsibilities for medical devices that are also consumer goods. The MDA’s duties include ensuring compliance and evaluating adverse incident reports provided by manufacturers and users under a statutory duty. The Regulations

138 DH01 tab 11 p. 1
139 S605 Burton para. 141
140 DH01 tab 19 pp. 11–12
141 L9 tab 6
142 DH01 tab 13 paras 8–9. With the introduction of European legislation the scheme was gradually wound down and finally ceased in June 1998 (DH01 tab 13 para. 1)
144 DH01 tab 11
146 DH01 tab 11 pp. 1–2
provide for a vigilance system whereby information concerning serious incidents in the UK must be notified by the MDA to the EU and other Member States, so that any necessary action can be taken at European level. 147

2.123 Independent accreditation bodies, known as Notified Bodies, check manufacturers’ claims of conformity for everything except the lowest-risk devices. These bodies are monitored by the MDA. 148
Annex 1 to Chapter 2: Examples of bovine materials used in medicines

Table 1: Active ingredients

<table>
<thead>
<tr>
<th>Bovine By Product</th>
<th>Use</th>
<th>Source &amp; Manufacture</th>
<th>Non Proprietary Medicinal Product (not the marketed trade names)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucagon</td>
<td>Polypeptide hormone – active ingredient</td>
<td>Pancreas. Purified using mild chemical &amp;/or physical conditions</td>
<td>Glucagons</td>
</tr>
<tr>
<td>Aprotinin</td>
<td>Anticoagulant polypeptide – active ingredient</td>
<td>Various bovine tissues, mainly lung. Produced using mild chemical &amp;/or physical conditions</td>
<td>Aprotinins</td>
</tr>
<tr>
<td>Heparin</td>
<td>Anticoagulant – active ingredient</td>
<td>Salts of sulphated glucosaminoglycans prepared from lungs and intestinal mucosa. Highly purified using mild chemical and physical conditions</td>
<td>Heparins, heparin salts (calcium and sodium), low molecular weight heparins (tinzaparin)</td>
</tr>
<tr>
<td>Catgut suture</td>
<td>Surgical sutures</td>
<td>Small intestine. The raw material is processed using harsh chemical washing and irradiation to sterilise</td>
<td>Surgical sutures</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>Calcium supplement – drug substance</td>
<td>Bone (femur). Manufactured using very harsh chemical and physical conditions</td>
<td>Calcium gluconate tablets</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Hormone/steroid treatments – active ingredients</td>
<td>Adrenal glands processed to produce cortisone, hydrocortisone, aldosterone. Mild purification conditions to ensure steroid activity</td>
<td>Various products as individual steroids or mixtures</td>
</tr>
<tr>
<td>Insulin</td>
<td>Hormone – active ingredient for diabetes treatment</td>
<td>Manufactured from pancreas. Highly processed using gentle conditions</td>
<td>Numerous bovine insulin</td>
</tr>
<tr>
<td>Collagen</td>
<td>Implants – drug substance</td>
<td>Processed from hide using harsh physical and chemical conditions. Highly processed</td>
<td>Collagen implants</td>
</tr>
</tbody>
</table>

Source: R Turner MCA DH01 tab 16
<table>
<thead>
<tr>
<th>Bovine By Product</th>
<th>Use</th>
<th>Source and manufacture</th>
<th>Medicinal Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foetal Calf serum</td>
<td>Cell culture ingredient</td>
<td>Calf foetus. Produced using mild conditions and filter sterilisation</td>
<td>Vaccines, antibodies, recombinant proteins</td>
</tr>
<tr>
<td>Serum Albumin</td>
<td>Cell culture ingredient</td>
<td>Blood. Purified using mild chemical &amp;/or physical conditions</td>
<td>Vaccines, antibodies, recombinant proteins</td>
</tr>
<tr>
<td>Adult/Immune Serum</td>
<td>Used as a supplement during cell culture</td>
<td>Blood. Produced using mild chemical and physical conditions</td>
<td>Vaccines, antibodies, recombinant proteins</td>
</tr>
<tr>
<td>Liver digest</td>
<td>Cell culture ingredient</td>
<td>Liver. Produced using harsh chemical &amp;/or physical conditions</td>
<td>Vaccines, multi vitamin (liver extract)</td>
</tr>
<tr>
<td>Trypsin</td>
<td>Pancreatic enzyme used during manufacture</td>
<td>Pancreas. Purified using mild physical and chemical conditions</td>
<td>Vaccines</td>
</tr>
<tr>
<td>Lactalbumin hydrolysate</td>
<td>Hydrolysed milk protein. Cell culture ingredient</td>
<td>Milk. Produced using harsh chemical &amp;/or physical conditions</td>
<td>Vaccines, antibodies, recombinant proteins</td>
</tr>
<tr>
<td>Hydrolysed Casein</td>
<td>Hydrolysed milk protein. Cell culture ingredient</td>
<td>Milk whey. Produced using chemical &amp;/or physical conditions</td>
<td>Vaccines, antibodies, recombinant proteins</td>
</tr>
<tr>
<td>Calcium Caseinate</td>
<td>Cell culture ingredient</td>
<td>Milk whey. Produced using chemical &amp;/or physical conditions</td>
<td>Vaccines, antibodies, recombinant proteins</td>
</tr>
<tr>
<td>Gelatine</td>
<td>Excipient in manufacture. Also used as a blood volume expander</td>
<td>Bones and hide. Highly processed by acid/alkaline hydrolysis - very harsh chemical and physical conditions</td>
<td>Various. Capsules, pastes, pastilles, tablets and suppositories. Blood volume expander</td>
</tr>
<tr>
<td>Peptone</td>
<td>Cell culture ingredient</td>
<td>Meat (skeletal and cardiac muscle). Produced using mild chemical &amp;/or physical conditions</td>
<td>Vaccines, antibodies, recombinant proteins</td>
</tr>
<tr>
<td>Casein</td>
<td>Cell culture ingredient</td>
<td>Milk whey. Produced using chemical &amp;/or physical conditions</td>
<td>Hormones, enzymes</td>
</tr>
<tr>
<td>Lactose</td>
<td>Widely used as a diluent to give bulk to powders and as a diluent in compressed tablets</td>
<td>Milk. Carbohydrate manufactured from milk using relatively mild chemical &amp;/or physical conditions</td>
<td>Various.</td>
</tr>
<tr>
<td>Chymotrypsin</td>
<td>Pancreatic enzyme used in production of medicinal products</td>
<td>Pancreas. Manufactured using mild conditions</td>
<td></td>
</tr>
<tr>
<td>Cholic and deoxycholic acids</td>
<td>Detergent used as manufacturing ingredients (viral inactivation)</td>
<td>Bile. Highly processed using harsh chemical and physical conditions</td>
<td>Vaccines, plasma derived medicinal products, recombinant protein products</td>
</tr>
<tr>
<td>Tryptone</td>
<td>Cell culture ingredient</td>
<td>Meat (skeletal and cardiac muscle). Produced using mild chemical &amp;/or physical conditions</td>
<td>Recombinant protein medicine</td>
</tr>
</tbody>
</table>

Source: R Turner MCA DH01 tab 16
<table>
<thead>
<tr>
<th>Bovine By Product</th>
<th>Use</th>
<th>Source &amp; Manufacture</th>
<th>Medicinal Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oleic acid</td>
<td>Excipient in manufacture</td>
<td>Tallow derivative. Tallow is manufactured from bovine tissue (fat) under high temperature. Derivative production uses high temperature, pressures and concentrations of alkali. Tallow derivatives are all highly processed.</td>
<td>Various, mainly ointments</td>
</tr>
<tr>
<td>Stearic acid and salts (magnesium/calcium)</td>
<td>Excipient in manufacture</td>
<td>Tallow derivative. Tallow is manufactured from bovine tissue (fat) under high temperature. Derivative production uses high temperature, pressures and concentrations of alkali. Tallow derivatives are all highly processed.</td>
<td>Various as excipient/manufacturing ingredient</td>
</tr>
<tr>
<td>Sorbitan monostearate</td>
<td>Excipient in manufacture</td>
<td>Tallow derivative (detergent). Tallow is manufactured from bovine tissue (fat) under high temperature. Derivative production uses high temperature, pressures and concentrations of alkali. Tallow derivatives are all highly processed.</td>
<td>Various as excipient/manufacturing ingredient</td>
</tr>
<tr>
<td>Polyethylene glycol</td>
<td>Excipient in manufacture</td>
<td>Tallow derivative. Tallow is manufactured from bovine tissue (fat) under high temperature. Derivative production uses high temperature, pressures and concentrations of alkali. Tallow derivatives are all highly processed.</td>
<td>Various. Capsules, pastes, pastilles, tablets and suppositories</td>
</tr>
<tr>
<td>Polysorbate</td>
<td>Excipient in manufacture</td>
<td>Tallow derivative (detergent). Tallow is manufactured from bovine tissue (fat) under high temperature. Derivative production uses high temperature, pressures and concentrations of alkali. Tallow derivatives are all highly processed.</td>
<td>Various as excipient/manufacturing ingredient</td>
</tr>
<tr>
<td>Polyoxyl stearate</td>
<td>Excipient in manufacture</td>
<td>Tallow derivative (detergent). Tallow is manufactured from bovine tissue (fat) under high temperature. Derivative production uses high temperature, pressures and concentrations of alkali. Tallow derivatives are all highly processed.</td>
<td>Various. Capsules, pastes, pastilles, tablets and suppositories</td>
</tr>
</tbody>
</table>

Source: R Turner MCA DH01 tab 16

![The Operation of Medicines Licensing](image)
### Table 4: Examples of medical devices utilising tissues or derivatives of animal origin

<table>
<thead>
<tr>
<th>Origin</th>
<th>Start material</th>
<th>Description</th>
<th>End use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Derivative from invertebrate source</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coral</td>
<td>Coral</td>
<td>Porites species</td>
<td>Bone substitute for orthopaedic fractures</td>
</tr>
<tr>
<td>Bees</td>
<td>Honeycomb wax</td>
<td>Beeswax, <em>Apis mellifera</em></td>
<td>Product coatings</td>
</tr>
<tr>
<td>Silkworm</td>
<td>Cocoon filaments</td>
<td>Silk fibres, <em>Bombyx mori</em></td>
<td>Sutures in surgical procedures</td>
</tr>
<tr>
<td>Microorganism</td>
<td>Bacterial</td>
<td>subtilisin enzyme, biofermentation</td>
<td>Enzyme cleanser for contact lenses</td>
</tr>
<tr>
<td>Microorganism</td>
<td>Streptococcus sp</td>
<td>Hyaluronic acid, biofermentation</td>
<td>Viscoelastic gel for ophthalmics</td>
</tr>
<tr>
<td><strong>Derivative of animal exudate or excretory product</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sheep</td>
<td>Wool</td>
<td>Wool, blended from different sources</td>
<td>Range of dressings</td>
</tr>
<tr>
<td>Calf</td>
<td>Calf</td>
<td>Casein, ferment from the stomach</td>
<td>Stabiliser in latex production</td>
</tr>
<tr>
<td>Sheep</td>
<td>Wool</td>
<td>Lanolin, derived from sheep wool</td>
<td>Product coatings</td>
</tr>
<tr>
<td><strong>Derivative of animal tissue</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cattle</td>
<td>Bones &amp; hide</td>
<td>Gelatine, main part of connective tissue</td>
<td>Coatings, impregnations on cardiovascular devices</td>
</tr>
<tr>
<td>Cattle and sheep</td>
<td>Hard fat around kidneys</td>
<td>Tallow, <em>Adeps ovillus</em></td>
<td>Aid to process of manufacture</td>
</tr>
<tr>
<td>Cattle</td>
<td>Bones &amp; hide</td>
<td>Collagen, many structural forms</td>
<td>Impregnations on range of devices, dressings</td>
</tr>
<tr>
<td><strong>Animal tissue as major component</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pigs &amp; cattle</td>
<td>Heart</td>
<td>Valve leaflets, cardiovascular</td>
<td>Heart valves</td>
</tr>
<tr>
<td>Cattle</td>
<td>Intestine</td>
<td>Intestine mucosa</td>
<td>Sutures</td>
</tr>
<tr>
<td>Cock rooster</td>
<td>Combs</td>
<td>Hyaluronic acid</td>
<td>Viscoelastic gels, ophthalmics</td>
</tr>
<tr>
<td>Cattle</td>
<td>Heart</td>
<td>Cardiovascular</td>
<td>Percardium patches</td>
</tr>
<tr>
<td>Cattle</td>
<td>Tendons, ligaments</td>
<td>Tendons, ligaments</td>
<td>Ankle/knee support products</td>
</tr>
<tr>
<td>Cattle</td>
<td>Large bones</td>
<td>Bone structure, cancellous bone</td>
<td>Bone substitute</td>
</tr>
</tbody>
</table>
Annex 2 to Chapter 2: Outline of production processes for vaccines and injectable medicinal products

Vaccines

2.124 Administered to healthy individuals, vaccines protect against infection caused by pathogens, eg, viruses, bacteria, by inducing immunity. Some vaccines contain preparations of an infective agent which are non-pathogenic and do not cause disease. For example, killed vaccines are preparations of a pathogen that has been killed or inactivated. Other vaccines contain attenuated (reduced infectivity) live strains of the agent which do not cause disease but which still induce specific immunity. Some vaccines are produced using so-called recombinant DNA technology where only the antigenic parts of the pathogen, ie, those parts which induce immunity in an individual, are used in the vaccine. Only in this latter class of vaccines are bovine products used during manufacture.

2.125 Recombinant vaccines are produced by isolating the DNA sequence that specifies the particular antigenic (ie, capable of inducing a specific immune response) portion of the pathogen and integrating it into bacterial or animal cells growing in culture. The cells then manufacture the foreign antigenic molecule as if it were a normal constituent of the cell. The antigen can then be purified away from the bacterial or animal cells and used in a vaccine. Alternatively, the antigen can be integrated into a non-pathogenic virus strain, which is grown in animal cells. In this case, the viruses are harvested from the animal cells and suitably treated to become vaccines.

2.126 As illustrated by the examples in Table 2 of Annex 1, various bovine materials are used as ingredients in cell cultures for the production of vaccines. These are most commonly blood products, milk derivatives and peptone.

2.127 In order for animal cells to survive in culture, it is necessary to grow them in nutrient-rich media. These nutrients are generally supplied from bovine serum derived from foetal or new-born calves – foetal calf serum (FCS) and new-born calf serum (NCS) respectively. In these rapidly developing animals, serum is packed with nutrients and important growth factors. Serum from older animals is sometimes used, though it is much less rich. A further bovine blood product, bovine serum albumin (BSA), is often added to serum for nutritional purposes.

2.128 In the production of FCS, blood is removed from the foetus by insertion of a needle into its heart following the death of the dam. Blood is removed under vacuum (rarely by gravity flow) and is drawn directly into a bag to reduce any contamination of the blood. This process occurs at the abattoir. Serum is separated from the blood by centrifugation, filtered to remove large particulates and sterile-filtered to remove particulates 1 micron in size or larger. The serum is then bottled and frozen. NCS is prepared in the same way, except that the animals are between 10 and 14 days old when the blood is removed. Donor serum is removed from animals up to the age of three years old. The animals are not killed, but are periodically ‘tapped’ for blood.149
2.129 When the cells are harvested, the growth medium is removed and the cells washed to remove the serum. Similarly, viruses used for vaccine production are purified away from both the cells and culture medium before being treated further.

2.130 Bacterial cells are not grown in serum-containing media, but in nutrient broths based on peptone. Peptone is obtained through the chemical treatment of milk or beef, which releases the building blocks of proteins that can be utilised by the bacteria. In some circumstances, beef extract is used in a nutrient broth to feed the bacteria in the same way. Unlike serum, these nutrient additives are very stable and can therefore be sterilised by autoclaving. Digests of calf brain and ox liver have also been constituents of special culture media used in the production of allergens. Allergens are similar to vaccines in that they invoke an allergic reaction in an individual as a means of raising general immunity to a particular antigen upon environmental exposure. Whatever the culture medium used, the bacteria are ultimately recovered from the broth and subjected to separation procedures to isolate the component to be used in the vaccine.

2.131 Thus bovine ingredients are not a constituent of the final vaccine product but are used in a peripheral way, for the nourishment of cells used to grow vaccines. The question of risk of transmission of BSE through vaccines was, therefore, linked to the likelihood of any BSE infectivity present in the starting material surviving through to the final product.

**Injectable medicines derived from bovine tissues**

2.132 Unlike vaccines, in which bovine products are used peripherally during manufacture, there are several injectable medicinal products derived directly from a bovine source. Such products include hormones such as glucagon, insulin and corticosteroids or protein products such as aprotinin and heparin. The tissues from which these products are derived are obtained directly from the abattoir. Following slaughter, the cattle viscera, the larger internal organs present in the chest and abdominal cavities, are removed by slaughtermen. These are then passed either to in-house workers in a separate ‘clean’ part of the slaughterhouse called the gut room, or to contractors, who separate the organs according to requirements. The appropriate tissues are cleaned and extraneous material removed in accordance with the specifications of the pharmaceutical company. The tissues are frozen on site before transportation to the pharmaceutical company, to prevent breakdown of the required products.

2.133 The products required from the tissues are extracted in the laboratories of the pharmaceutical companies using purification techniques involving many steps. Initially these steps are crude but increase in specificity as more extraneous materials are removed. These later, more specific purification steps involve stages which are appropriate for only the product of interest, and as such utilise particular physical or biochemical properties that would be shared with few other compounds. In this way it is possible to obtain an homogeneous product free from contaminating molecules.

2.134 It might be expected, therefore, that any BSE present in a tissue would be reduced during purification steps. Indeed, the infective agent of BSE is known to be
‘sticky’ in the absence of detergents, and easily removed from tissue extracts by centrifugation (the process of separating particles based on size and density under centrifugal force) since the agent would remain attached to cellular particles and proteins and be removed in the sedimented material. Filtration is also effective, as the agent absorbs to the filters themselves.\textsuperscript{151}