COMMITTEE ON SAFETY OF MEDICINES

Minutes of the meeting held on Thursday 22 January 1981

Present	Committee Secretariat
Professor A Goldberg (Chairman)	Dr G Jones (Medical Assessor)
Professor D V W Parke	Dr J Calderwood (Pharm. Assessor)
Dr J M Holt	Mr P Allen (Secretary)
Professor A E Read	Dr G Diggle
Professor J W Dundee	Dr G Venning
Professor M Rawlins	Dr N Taylor
Professor H K Weinbren	Dr A Nath
Professor W I Cranston	Dr L Hill
Professor P H Elworthy	Mr S Stewart
Dr M Richards	Mr J S Bird
Professor B M Hibbard	Mrs J Archer
Professor F A Jenner	Dr K Fowler (Hearing 2 only)
Dr F Fish	Dr J Holgate (Hearing 2 Only)
Dr J Smith	Mrs G Harrison
Professor M Vessey	Mrs K Sherrington
Mr W M Darling	
Professor J Crooks	
Dr A M Geddes (Hearing 1 only)	
Professor R H Girdwood	

Also Present
Mr R N Williams
Dr J Griffin (except hearings)
Dr W G Thomas
Dr R Penn
Mr J Long
Mr R Butcher
Mr P Nilsson
Mr I McKinney
Ms K Atwood

1. APOLOGIES AND ANNOUNCEMENTS

1.1 The Chairman reminded members that the papers before them, and the proceedings, were confidential and should not be disclosed.

1.2 The Chairman welcomed Professor Vessey who was attending his first meeting as a member of the Committee.

1.3 Apologies for absence were received from Professor Grahame-Smith, and Professor Lloyd.

2. MINUTES OF THE MEETING HELD ON 18.12.80.

The minutes were agreed and signed by the Chairman as a correct record.

MATTERS ARISING FROM THE MINUTES

None.

4. CIMETIDINE (TAGAMET) Paper 4

4.1 The Chairman explained that at the meeting in October 1980, Professor Weinbren had informed the Committee that he had learned that ICI had discontinued work on an H2 receptor antagonist because gastric lesions had been discovered early in the animal carcinogenicity studies. He has been concerned that the two products already examined (Cimetidine and Ranitidine) may have produced similar effects in animal studies but that the lesions may have been overlooked as they were very difficult to detect. At that meeting it had been agreed that Professor Weinbren would examine further material and that no action should be taken in respect of Cimetidine or Ranitidine at that time. The Adverse Reactions Sub-Committee had also examined the Yellow Card reports in May and October 1980 and concluded that no action need be taken. Recently however a lengthy article on Cimetidine had appeared in the Sunday Times and an item had been included on the agenda at the request of Professor Parke.

4.2 Professor Parke informed members about the discussions with the journalist concerned and that he had made every effort to ensure that the article was 'low key' but to no avail.

4.3 Professor Weinbren explained that he was still engaged in the work described earlier and was not as yet in a position to produce a paper for the Committee.

4.4 It was agreed that in due course a review of both Cimetidine and Ranitidine would be required. It was suggested that Cimetidine in particular was an over-prescribed drug often for vague or undiagnosed indications and that at present the problem appeared to be primarily a matter of apparently widespread long term use.

4.5 It was also agreed that on completion of Professor Weinbren's work the Secretariat would liaise with Professor Weinbren and Professor Parke to produce a paper for the Committee.

5. CONSIDERATION OF APPLICATION

The Committee considered those applications listed on schedules. A record of their advice is at Appendix A to these minutes.

6. Corvaton (Molsidamine) PL/CT 0086/0070 Paper 1

6.1 Dr Venning spoke to this paper and informed members that Hoechst Ltd had withdrawn a product licence application for Molsidamine (PL 0086/0070) because two rat studies (chronic toxicity for 18 months)

and carcinogenicity study for 27 months) had both yielded significant excesses of malignant tumours of the nasal turbinate epithelium. The company also held a clinical trial certificate for this preparation and wished to maintain the CTC for the purpose of completing a particular study to obtain data on 100 patients for a year.

6.2 This matter had been previously considered by the TCT Sub-Committee who had recommended that in the light of the results of the two rat studies referred to above, all clinical trials with this material should cease.

6.3 The Committee endorsed the Sub-Committee's recommendation and it was agreed that in the first instance the Secretariat would approach the company informally to obtain their agreement to the cessation of the clinical trial referred to.

7. ANNUAL MEETING WITH ABPI PAPER 3

The Secretary explained that Paper 3 detailed the items which would be discussed at the Annual Dinner Meeting between representatives of the CSM and the ABPI. A record of that meeting would be produced for the information of members at a later date.

8. HEARINGS

8.1 The Committee held two hearings in respect of

a. Augmentin: PL 0038/0269-0274 Beechams

b. Humanate: PL 3070/0004 Speywood Laboratories

8.2 A record of the Committee's findings in respect of the above is included at appendices B and C to these minutes.

9. WRITTEN REPRESENTATIONS

9.1 The Committee considered eight written representations in respect of

a. seaweed tablets PL 2150/0016
b. Garlic tablets PL 2150/0011
c. special skin tablets 2150/0007
d. Comfreytablets PL 2150/0004
e. Nerve tonic tablets 2150/0001

} Carr's Mendip Herbal Products

f. LM 5008: CT 4140/0001 : MedicoSimbec Ltd
g. SI tablets: PL 2207/0004: Dr Godfrey
h. CPD Anticoagulant PL 1605/0003 Cutter Laboratories

9.2 A record of the Committee's findings in respect of the above is included at Appendix D to these minutes.

10. AMPIM AUTOMATIC INJECTOR Paper 2

10.1 The Committee noted the further three month suspension of the product licence of right in respect of the above product.

11. CLINICAL TRIAL EXEMPTION SCHEME PAPER 5 (Tabled)

11.1 Mr Long spoke to this paper and informed members that an Order enabling the Licensing Authority to introduce the exemption scheme was in the final stages of preparation and was expected to be laid before Parliament shortly. It was hoped that the Order would come into operation towards the end of February.

MEDICAL ASSESSOR AND SECRETARY'S ORAL REPORT

Mr Allen confirmed that pressure of business would mean that an extra meeting of the Committee (at which its business would be devoted to the consideration of hearings and written representations) would be needed. This extra meeting had been arranged for Thursday 19 March.

13. ANY OTHER BUSINESS

13.1 The Chairman informed members that following discussion between the Chairmen of all Section 4 Committees and the licensing authority it had been agreed that members of all committees should be invited to consult their Chairmen or the DHSS in any case where they had been invited to appear on radio or television programmes or contribute to press articles regarding a subject which currently had recently been under discussion by the Committee.

13.1.1. It was also agreed that when an interview or article drew attention to their Committee membership, members should do their best (although it was realised that circumstances might make this difficult) to make it clear that they were giving their personal views and not speaking for the Committee.

13.2 Mr Williams informed members that the Division was shortly to hold a weekend 'Retreat' to discuss the problems associated with the implementation of the Medicines Act. The Chairmen of Section 4 Committees and their Sub-Committees had been invited to attend and it was hoped that the occasion would provide an opportunity to give serious consideration to long-term problems in administering the licensing system established by the Medicines Act. A summary of the weekend's discussion would be put before members in due course.

14. ITEMS FOR INFORMATION

Members received for information those items listed on the agenda.

15. DATE AND TIME OF NEXT MEETING

Thursday 26 February 1981 at 10.30 a.m.

GRO-C

26/2/81

COMMERCIAL IN CONFIDENCE

NOT FOR PUBLICATION

Appendix C Sheet
CSM/81/1st Meeting

COMMITTEE ON SAFETY OF MEDICINES

HEARING 2

PL/3070/0004

HUMANATE

SPEYWOOD LABORATORIES LIMITED

Medical Assessor - Dr Fowler

1. BACKGROUND

1.1 Since 1976, Speywood Laboratories Limited had sold anti-haemophilic globulin (Factor VIII) manufactured by Cutter Laboratories under the name Koate in the United Kingdom. This arrangement had been terminated by Cutter at the end of 1979.

1.2 In February 1980, Speywood had obtained a variation to their product licence which had permitted them to:-

a. continue selling their remaining stocks of Koate for up to one year.

b. import, in bulk, unlabelled vials of anti-haemophilic globulin manufactured by Cutter for relabelling and sale under the name Humanate.

1.3 The material for sale as Humanate was not obtained from Cutter, but through an independent company called Parlier Medical Supply Company of San Francisco, California.

1.4 At the time of granting the Speywood Product Licence for Koate in 1976 a full "stop order" had been routinely applied. This had required the licence holder to supply samples and protocols of tests above on every batch of product and not to sell or supply material from a batch until a certificate of clearance for it had been granted by the licensing authority. Speywood had complied with this requirement for Koate by supplying samples and protocols obtained from Cutter, to the National Institute of Biological Standards and Control (NIBSC).

1.5 The protocol supplied to NIBSC by Speywood for their first batch of Humanate had provided results of tests done on the finished product by a British contract laboratory. These had followed very closely those done by Cutter for Koate, but the protocol had omitted material included in the Koate protocol concerning the Bulk Active Substance Used for Formulation, Formulation and Filling. The Koate protocol had also contained Cutter's statement that the product had been manufactured by them at their plant in Berkeley, California. Although the tests done on the finished product were satisfactory, the protocol had been deemed inadequate, as it was impossible to assess the safety of a blood product by reference to finished product-testing alone. Speywood had repeatedly said that they now had no contact with Cutter, and thus had no access to information relating to the manufacture of the product they were selling.

1.6 Moreover the Product Licence granted to Speywood had obliged the company to ensure that all batches of the product continued to conform to the various specifications contained in the original application. While Speywood had acted as distributors for Cutter they had been able to do this. Now that they had no contact with Cutter they were no longer in a position to guarantee that the product sold as Humanate conformed to its Product Licence specification. If in fact Cutter were the original manufacturers of Humanate as claimed by Speywood they could have changed the source, place or method of manufacture of the product and Speywood would have been unaware of this and unable to communicate such changes to the Licensing Authority.

1.7 The scientists at the National Institute for Biological Standards and Control (NIBSC) frequently had to refer back to the company for clarification or further information concerning the manufacture of the product. Where the Licence Holder was the manufacturer or his authorised distributor, this posed no problem. Where the Licence Holder had no communication with the manufacturer, as in Speywood's case, such a dialogue was impossible.

1.8 As a matter of routine, the additional conditions contained in the Schedule to the Product Licence issued to Speywood referred to protocols but no mention was made therein to the contents required in respect of such protocols. This lack of information was unsatisfactory, particularly in regard to biological products of the type in question. So as to remedy the situation, it had been proposed under Section 29(1) using powers conferred under Section 28(3)(g) of the Medicines Act 1968, compulsorily to vary Speywood's Product Licence in order to require the protocols to include evidence of the source and date of collection of the donor blood from which the product was prepared, the date of manufacture and the results of tests done during and on completion of manufacture. This would have put beyond doubt the nature of the evidence required when the term protocol was used and would have served to bring Speywood into line with the current practice of other manufacturers of anti-haemophilic globulin.

1.9 Following the Licensing Authority proposals a letter had been sent to the Company on 29 July 1980 in accordance with Sections 28 and 29 and Schedule 2 of the Medicines Act 1968. It had informed the company in accordance with paragraph 2 of Schedule 2 that the Committee had had reason to think they might have to advise the Licensing Authority to vary the Product Licence for this product so that paragraph 6 of Part II of the Schedule as applied to PL/3070/0004 provided that:- the licence holder should on request furnish to the Licensing Authority from every batch of the product, or from such batch or batches as the Licensing Authority may from time to time specify, a sample of such amount as the Authority considered adequate for any examination required to be made; and the licence holder should if required by the Licensing Authority, furnish evidence of the source and date(s) of collection of the donor blood from which the product was prepared, the date of manufacture of the product, an outline of manufacturing methods, protocols and results of the tests done, on the donor blood, during manufacture and on the finished product.

1.10 The Licensing Authority had then written to the company on 27 November 1980 stating their proposal to vary the product licence 3070/0004, Humanate, under the provisions of Section 28 (3) (g) of the Medicines Act 1968. They proposed to vary the licence because:-

'Humanate could no longer be regarded as a product which could safely be administered for the purposes indicated in that product licence since evidence of access to data relating to the original manufacture, as evidenced by the absence of protocol data relating to the source of donor blood and in process control, was now lacking. Such evidence had been supplied by Speywood Laboratories Limited prior to 8 February 1980 and was routinely

supplied by other manufacturers. Without this evidence, there was no means of ensuring that the product had been manufactured under conditions which could be shown to minimise the risk to patients of contracting, for example, NON-A and NON-B hepatitis. The action which was proposed would be taken in respect of any product licence for a biological product under similar circumstances."

1.11 On 30 July 1980, the company had written to the Committee giving notice that they intended to avail themselves of the opportunity to appear before the committee to ensure that their position was fully understood.

2. ADDITIONAL INFORMATION

2.1 The Company had submitted a paper giving the background to their case and why the variation to the licence should not be imposed.

2.2 On the day of the hearing, the Company handed in a copy of a notarised statement from Parlier Medical Supply Company which certified that bulk unlabelled antihaemophilic factor (human) shipped to Speywood was:-

(i) manufactured and sold by Cutter Laboratories,

(ii) approved and released for general sale in the USA by the FDA (Bureau of Biologics division)

(iii) derived from human plasma collected in plasmapheresis centres licensed by and conforming to the regulations of the US Bureau of Biologics.

3. PRELIMINARY DISCUSSION

The following points emerged from the preliminary discussion:-

(i) that 4% of the batches supplied for testing in 1980 came from Speywood

(ii) that of 50% of the batches from US sources there had been need to refer back to the manufacturers.

(iii) that Speywood were merely being asked to give information which was routinely supplied by all other manufacturers of anti-haemophilic globulin sold in the UK.

4. HEARING

4.1 The representatives of the Company were as follows:-

Mr D Williams (Spokesman)

Dr P M Jones Director of the Haemophilia Centre,
Royal Victoria Hospital,
Newcastle-upon-Tyne

4.2 The Company's representatives were welcomed by the Chairman, who introduced the Committee, the secretariat and the DHSS officials present. The representatives had no objection to the presence of any of the officials.

4.3 Mr Williams referred to the affidavit from Parlier Medical Supply Company which had been furnished and with the aid of slides explained that the Cutter material was subject to Cutter in-house quality control, before submission to the FDA/BOB for clearance. The material was purchased after clearance and thus its integrity was in his view guaranteed. Following delivery to Parlier Medical Supply Company, all packaging was removed and the product shipped intact to the UK. On arrival in the UK the (unlabelled) material was subject to quality control, carried out in the laboratories of Toxicol and the Oxford Haemophilia Centres. Samples were then submitted to NIBSC together with protocols and following approval, the material was re-packaged as Humanate.

He considered that all Factor VIII products carried a risk of Non-A, Non-B hepatitis, but that the risk was minimised by the monitoring of donors, by the FDA.

Mr Williams felt that any additional data could be obtained from the FDA possibly by NIBSC, under the US Freedom of Information Act.

He explained that his objective, in appearing before the Committee was to seek an extension of the present arrangements to enable the company to make other arrangements if possible for the purchase of Factor VIII and eventually to remove the Company's financial dependence on this imported Factor VIII.

4.4 Dr Jones then explained that he had come to the hearing as an independent consultant (unpaid) to advise the Committee that in his capacity as director of a haemophilia centre, he had satisfactorily treated patients with Humanate.

4.5 In reply to questions Mr Williams stated that he thought that, if necessary, donors of blood might be traced from Cutter's records by means of the Freedom of Information Act.

He had accepted that the batches he imported (unlabelled) were consistent with Cutter batches, because of the assurances given by Parlier Medical Supply.

Mr Williams said that he did not know of any other manufacturer who was asked to provide the information required.

5. FINDINGS

The Committee found that there was insufficient evidence of any firm arrangement which would enable Speywood to obtain the data specified in para 1.9.

6. ADVICE

The Committee agreed to advise the Licensing Authority to vary the Product Licence for this product so that paragraph 6 of part 2 of the Schedule to the licence provided:-

"The Licence Holder shall on request furnish to the Licensing Authority from every batch of the product, or from such batch or batches as the Licensing Authority may from time to time specify, a sample of such amount as the Authority may consider adequate for any examination required to be made; and the licence holder shall, if required by the Licensing Authority, furnish evidence of the source and date(s) of collection of the donor blood from which the product is prepared, the date of manufacture of the product, an outline of manufacturing methods, protocols and results of the tests done, on the donor blood, during manufacture and on the finished product".

8. REASONS FOR ADVICE

8.1 That, because of the risk to patients arising from lack of evidence as to the origins and provenance of the donor blood, the Committee were not satisfied as to the safety of the product.