DATE OF SUMMARY : APRIL 2001

SUMMARY OF THE MEETING OF THE COMMITTEE ON SAFETY OF MEDICINES HELD ON 30th APRIL 1998

Committee Members:

Present

Professor M D Rawlins (Chairman)
Professor A M Breckenridge (Vice Chairman)
Professor T R E Barnes
Professor J H Darbyshire
Professor D S Davies
Professor G W Duff
Professor S J Eykyn
* Professor R G Finch
Professor A T Florence
Professor E C Gordon-Smith
Professor H S Jacobs
Mrs E A Kay
Dr M J Kendall
Dr B J Kirby
* Dr S Kumar
Dr A V P Mackay
Professor B L Pentecost
Professor J C Petrie
Professor L L Smith
Dr K Verrier Jones
Professor M P Vessey
Professor I V D Weller

Apologies

Dr K L Costeloe
Professor H J Dargie
Dr A M Douglas
Professor K Gull
Professor M J S Langman
Professor J M Midgley
Professor B K Park
Professor K Sikora

Mr L R Whitbread (*Secretary*)
Mr E M Hazell *(Secretariat)*

Others continued

Dr E Lee	MCA/PL
Dr A McGregor	MCA/PL
Ms C Packman	(Press Office)
Dr J Raine	MCA/PL
Dr R Shah	MCA/L
Dr R Turner	MCA/L
Dr D Woodings	MCA/L

* part meeting only

Professional Staff of MCA

Principal Assessors

Dr A Nicholson (New Drugs)
Dr P Raptopoulos (Abridged)
Dr F Rotblat (Biologicals)

Licensing Division

Dr A Fench
Dr M Jahanshahi
Dr D Jones
Professor J Lewis
Dr C O'Leary
Dr R Patel
Dr M Powell
Dr D Rogers
Dr S S Singh
Mr J Slattery
Dr C Speirs
Dr C Steele
Mr H Stemplewski
Dr J Warren

Post Licensing

Dr E Major
Dr S Millican
Mrs G Williams

ES Division

Mr R Alder
Mr P Dunlevy
Mrs A Thyer

Training

Dr A Caldwell	MCA/L
Ms D Mthumkhulu	MCA/L
Mr M Wilson	MCA/L

Others

Dr M Ali	MCA/L
Dr J Dunne	MCA/L
Dr A Eyre-Brook	MCA/L
Dr S Eisen	MCA/L
Mr C Gardner	SoL C5
Dr G Haase	MCA/L
Baroness Jay of Paddington - MS(L)	
Dr D Jefferys	Director of Licensing, MCA
Dr K Jones	Director and Chief Executive MCA

NOTE: MCA STAFF MAY BE PRESENT FOR ALL OR PART OF THE MEETING OR FOR SPECIFIC AGENDA ITEMS

1. **Announcements and Apologies**

1.1 The Chairman reminded the Committee that the papers and proceedings were confidential and should not be disclosed. Members were also reminded to declare their personal specific, personal non-specific, non-personal specific and non-personal non-specific interests in the agenda items.

1.2 Apologies were received from Professors Dargie, Gull, Langman, Midgley, Park, Sikora, Drs Costeloe and Douglas for the day, and Professors Finch, Smith and Dr Kumar for the afternoon.

1.3 The Chairman informed the Committee that Mr Hazell was retiring, they thanked him for his sterling work for the Committee and wished him a happy retirement.

1.4 The Chairman reminded the Committee at the previous *en college* meeting, the MCA had undertaken to look into having papers dispatched electronically. Contractors had been appointed.

1.5 The Chairman informed members that the Philips Enquiry into BSE would be investigating the BSE Working Party's records from 1988 onwards. It was expected that Professors Asscher, Collee, Rawlins, Jacobs and Tyrrell would be called to give evidence.

1.6 **Subutex Sublingual Tablets - M.A. 00201/0241-3**

The Chairman informed the Committee that the Licensing Authority would be considering both the legal and social consequences of licensing this product.

2. **Minutes of the Meeting held on 26 March 1998**

The minutes were agreed and signed by the Chairman as a true and accurate record of the proceedings.

3. **Matters Arising from the Minutes**

None.

4. **Freedom of Information**

4.1 Members discussed the Government's White Paper "Your Right to Know: Freedom of Information" in relation to the Committee's procedures. In his introduction the Chairman emphasised that:-

- the White Paper envisaged, as a general principal, that the papers and proceedings of public bodies (such as the Committee) should be publicly disclosed subject only to specific exemptions. He reminded the Committee that such exemptions were required to be tested against the criterion of "substantial harm" arising from disclosure.

- the Committee had been specifically requested by the Minister of State for Health to provide her with its views on the implementation of FOI in respect of the Committee's business. This would be done via the Medicines Control Agency.

- the Committee should express its views in relation to its own responsibilities, and should not be constrained by either precedent or by the implications for other government advisory bodies.

4.2 The Committee welcomed the opportunity, presaged by the White Paper, to allow its proceedings and advice to be more transparent. For example, The Committee sometimes had access to information, which it was currently prohibited from disclosing, that might be of assistance to health professionals, health purchasers, and health providers. The Committee believed that the more complete disclosure of its advice, and the reasons for its advice, would increase the confidence of the professions and the public in its activities. The Committee considered that, subject to the exceptions considered below, the objectives of its FOI strategy should be to make publicly available its decisions and advice and the reasons for its decisions and advice.

4.3 The Committee considered the exceptions to public disclosure, described in the White Paper, that might impinge upon its business and procedures:-

4.3.1 *National Security*: The Committee occasionally considered applications for the authorisation of medicinal substances that concerned national security. These would require to be exempt.

4.3.2 *Law Enforcement*: The Committee occasionally considers matters relating to law enforcement. These would require to be exempt.

4.3.3 *Personal Privacy*: The Committee receives reports of suspected adverse drug reactions from health professionals relating to named individuals. In accordance with the undertakings previously given to the public and the professions, details that might allow the identification of patients and reporters would not be permitted to be publicly available.

4.3.4 *Information Supplied in Confidence*: The Committee sometimes receives, in confidence, prepublication reports or data that relate to the quality, efficacy or (most commonly) safety of medicinal products from sources that are independent of marketing authorisation (license) holders. If the information requires either regulatory action, or public comment, the Committee makes every effort to ensure that this occurs at the time of, or after, publication. The Committee would therefore wish such information to be exempt from public disclosure until after publication.

4.3.5 *Commercial Confidentiality*: The Committee recognised three components to commercial confidentiality which might be compromised by disclosure of its advice, and the reasons for its advice:-

4.3.6 *Trade Secrets*: In its consideration of applications for marketing authorisation the Committee has access to legitimate "trade secrets" of applicants (e.g. manufacturing details). The Committee would wish to take appropriate steps to protect such information from disclosure for an indefinite period. A precise definition of "trade secret" will need, however, to be developed.

4.3.7 *Significant Intellectual Property*: The Committee, in its consideration of applications, also has access to applicants' significant intellectual property (e.g. formulations) which it would seek to protect, indefinitely, from disclosure.

4.3.8 *Share-price Sensitive Information*: The Committee recognises that its advice may be share-price sensitive. The Committee's understanding is that the financial institutions expect companies to reveal share-price sensitive information, at the earliest opportunity. The Committee therefore proposes to delay disclosure of such advice, and the reasons for the advice for a period of time after its meetings.

4.3.9 *Advice to Ministers*: The Committee gives advice to Ministers on a wide range of issues related to the quality, safety and efficacy of medicinal products. The Committee also noted that the public disclosure of such advice was intended, in the White Paper, to be based on a "simple" harm test. The Committee, however, did not consider that its advice to Ministers fulfilled even a simple harm test and would not therefore seek exemption from disclosure. Nevertheless, the Committee felt that Ministerial advice should be disclosed after a delay in order that, where necessary, other government of departmental interests could be consulted prior to disclosure.

4.4 The Committee considered various options for ensuring disclosure of its advice, and reasons for its advice:

4.4.1 The Committee did not believe that the public interest would be served by its meeting in public. Public meetings would diminish the debate between members and the candor of discussion. It would be impossible to ensure, even if meetings were partially held in public, that the exemptions from disclosure discussed in paragraph 4.5 would be sustained and pressure on individual members could be intense.

4.4.2 The Committee did, however, believe that it might be useful for it to hold an Annual Meeting in public to allow interested individuals and organisations to learn more of its activities. Such a meeting might be most appropriately arranged at the time of the publication of the Committee's Annual Report.

4.4.3 The Committee propose that its Minutes be disclosed, after an appropriate delay and after removal of exempted items.

4.4.4 At the same time as the Committee's Minutes are disclosed it would also make available those relevant papers that were its own to release. In this context the Committee noted that company submissions, and MCA assessment reports, were not its property and therefore not its [property] to disclose.

4.4.5 The Committee's Minutes, by custom and practice, only usually indicate the Committee's decisions and advice and do not normally include details of the discussion or the reasons for the advice. The Committee would not wish to change this. It would, however, wish to make available a document, explaining the reasons for its advice at the time of disclosure of its Minutes. The format of such documentation will require further consideration.

4.4.6 The Committee believed that the provisions outlined in the White Paper would allow it to produce a more informative Annual Report and to develop a more useful web-site.

4.5 The Committee did not believe that public disclosure of its previous Minutes would be appropriate. First, it included material that (in its view) should remain exempt from disclosure. Second, past members had served on the Committee with an presumption of confidentiality, and present members felt that it would be dishonourable to change this retrospectively. Members were aware, and always had been aware, that the Committee's Minutes and papers would ultimately (after 30 years) be available for inspection in the Public Records Office.

4.6 The Committee agreed that any arrangements for the disclosure of its advice, and the reasons for its advice, would also apply to its Subcommittees and Working Parties. The Committee agreed that this issue should be considered further at their meetings in May before finalising their views.

5. **TSE/nvCJD Working Party - Report and Recommendations**

5.1 The Chairman introduced this item and gave the background. The Chairman of the TSE/nvCJD Working Group then gave the background in relation to the last meeting of the Working Group. The Committee noted:

5.1.1 That there is currently no evidence that nvCJD can be transmitted by blood transfusion. However, given that the prion proteins associated with this disease can be detected in the lymphatic system it is possible that they are also present in white cells in the blood.

5.1.2 At present there is no test which can be applied to individual donors to detect whether or not the prion protein is present. There does not appear to be the possibility that such a test will be developed in the next two years.

5.1.3 Although it is possible that the manufacturing process used to produce plasma products may cause the putative agent of nvCJD to partition or even to be inactivated, it is not possible to validate this. Particularly in the case of partition into separate fractions it is not known whether this would be complete.

5.1.4 Plasma products are manufactured from large pools of plasma and therefore the risk of prions being present in the pool much greater than when a single unit of blood is transfused. Patients who receive these products such as haemophiliacs and patients with immunodeficiency disorders are treated on a long term basis regularly and may be exposed to plasma from many hundreds of thousands of donors in a year.

5.1.5 The Committee was mindful of the need to maintain a secure supply of these often life saving products. As it is not possible to transfer production over night to plasma from a non-UK source a period of time where UK products remain on the market will be necessary. For most of these products an alternative licensed supply is currently available, which is manufactured from plasma from outside the UK.

5.1.6 Several months will be required to secure a safe supply of blood from outside the UK. The collection sites will have to be inspected by the UK Medicines Inspectorate and reassurance will be required on the testing procedures for

viruses that have been previously transmitted by plasma products (such as HIV and Hepatitis). Only when assurance is available that the stringent safety standards applied to the new sources of plasma are equivalent to those currently available in the UK will plasma be imported. There will also need to be a close-down and cleaning of the two manufacturing plants before fractionation of the new source of plasma can begin.

5.2 Following a discussion and questions from the Minister relating to the Working Group's recommendations, ***[see note 1 below]*** responded by saying he felt it unlikely that a test for nvCJD would be available within the next five years that would be suitable to identify donors at risk. The Committee then recommended that the following amendments be made to the Working Group's report:

- in 6.1, in the first line after source add, "foreseeable future"
- in recommendation 6.3, second line, the word "withdrawn" should be replaced by "recalled".

5.3 The Committee asked that ***[see note 1 below]*** and the Secretariat should generate a document elaborating the reasons for the Committee's advice. The Committee might wish to consider how this could be made public.

5.4 The Committee's revised recommendations are detailed below:

5.4.1 That manufactured blood products should not be sourced from UK plasma. Although it was accepted that some parts of the manufacturing process for blood products may separate prion proteins, the present state of the art means that these processes cannot be validated. Therefore the theoretical risk that nvCJD could be transmitted by blood products cannot be discounted.

5.4.2 BPL and PFC should move to sourcing products from plasma derived from outside the UK in a time frame to be agreed with the Committee and giving regard to the effects on the supply of all products, but especially of vital but less readily obtainable products such as some rare and life saving specific immunoglobulins. The latter may have to stay on the market for a longer period of time if replacement products could not easily be found. BPL and PFC should be asked to give a date by which non UK products could be made available. In the future when a test is available to identify the agent of nvCJD in blood donors or when a validated inactivation process is developed it is hoped that there will be a return to the use of UK donor plasma.

5.4.3 In the interim period clinicians who do not wish to use products derived from UK plasma have a choice of licensed products from other source plasma to replace all the commonly used products.

5.4.4 A date after which no products from UK plasma could be released for use should be agreed. It is not intended that products should be recalled. The group recognised that a period of several months would be required to establish satisfactory sources of plasma, to clean equipment and to produce products from the new source plasma.

5.4.5 All CTXs for blood products derived from UK donors should be suspended.

5.4.6 The BPL and PFC should be encouraged to undertake research into validating processes for the identification and removal of nvCJD agents in source plasma, so that the use of UK plasma may be re-established safely in the future.

5.4.7 A need for clinicians to be educated in minimising the use of blood products where alternative treatments were available, for example the use of steroids in children with ITP and the use of Hepatitis A vaccine for travellers. The Committee will consider how to take this forward.

6. **Consideration of the Applications - New Products**

The Committee considered seven applications. In addition, the Committee were also made aware of two applications received via the European centralised licensing system. Details as follows:

Applications 1 and 2: one member declared a non-personal non-specific interest in both applications but that did not debar them from taking part in the proceedings. Regulatory action continues at the date of this summary - ***[see note 2 below]***

The Committee recommended the granting of marketing authorisations to the following four applications:

MA 00025/0369-72:	MAXALT TABLETS 5 and 10mg MAXALT RAPIDISC 5mg and 10mg: (Rizatriptan benzoate)	MERCK SHARP & DOHME

Professors Vessey and Weller declared non-personal non-specific interests, but this did not debar them from taking part in the proceedings.

Applications 7 and 8: The European Commission – ***[see note 3 below]*** - subsequently granted Marketing Authorisations to:

EM 12443/0001-2:	CETROTIDE 0.25mg & 0.3mg: (Cetrorelix)	ASTA MEDICA

Members had no interests to declare

The nineth application was subsequently withdrawn – ***[see note 4 below]***

7. **Consideration of the Applications - Abridged Products**

The Committee considered three applications and advised the grant of Marketing Authorisations to the following:

MA 00426/0099:	BOTOX: (Chostridium botulinum toxin)	ALLERGAN

Members had no interests to declare.

MA 00057/0393:	LUSTRAL: (Sertraline Hydrochloride)	PFIZER ITALIANA

Professor Barnes declared a personal non-specific interest and left the room for this item. Professor Davies declared a non-personal non-specific interest, but this did not debar him from taking part in the proceedings.

MA 00015/0231:	RINATEC NASAL SPRAY: 0.06% (Ipratropium Bromide)	BOEHRINGER INGELHEIN

Professor Davies declared a non-personal non-specific interest, but this did not debar him from taking part in the proceedings.

8. **Pre-Hearing** ***[see note 5 below]***

The Committee considered one application. Members had no interests to declare. The Committee agreed that the company should address the outstanding points at the Hearing scheduled for 28 May 1998. Regulatory action continues at the date of this summary – ***[see note 2 below]***

9. **Aspirin - Proposed Changes to the Restrictions of Sale and Supply of Aspirin**

The Committee considered the paper and recommended as follows:

- The restrictions should be amended so that products containing up to 500mg of aspirin should remain exempt from POM when sold in packs of up to 32 tablets.
- No amendments to the restrictions are required regarding the sale and supply of low dose aspirin preparations.
- No amendment should be made to the definition of 'effervescent'.

10. **Sertindole - Sudden Death/Cardiac Arrhythmias**

Professor Barnes declared a personal specific interest and left the room for this item. The Committee were informed that concern had been raised about the number of reports of sudden death/cardiac arrhythmia associated with sertindole treatment. Various sources of information were reviewed and the main findings showed that the reporting rate for these reactions appears to be higher for sertindole than for the other atypical neuroleptics. – ***[see note 6 below]***

[**Note**: The marketing and use of Sertindole was voluntarily suspended by the manufacturers on 2 December 1998, pending full evaluation of the risks and benefits in collaboration with the CSM/MCA and other European Regulatory authorities. In February 2000, the European Commission reached a decision on the Europe-wide suspension of the Marketing Authorisation for Sertindole for a year – see item on http://www.mca.gov.uk/mca/mcainternet/index.htm]

11. **Review the Working Arrangements of the Committee and its Sub-Committees**

The Committee agreed that, in the light of the current ongoing appointments exercise regarding the Committee, that membership of the three Sub-Committees should be extended for a further three months until the end of March 1999. This is because it would give enough

time for the new members of the Committee to appoint the Sub-Committees. It was agreed that the Chairman should write to the Sub-Committee membership to this effect.

12. **Policy on Disclosure of Information - Requests for Information Under the Code of Practice on Access to Government Information (the Code)**
The Committee had received a request under the Code for certain of its past and current papers. Members considered, as their policy on disclosure was currently under review, that the Agency should refuse that request. [**Note**: that refusal subsequently became the subject of a report by the Parliamentary Commissioner for Administration (the Ombudsman) – see report A.16/99 in volume 4 of the Ombudsman's second report for the 1999-2000 session]

13. **Adroit Statistics**
The Committee noted this item.

14. **Any Other Business**
None.

15. **Date and Time of Next Meeting**
The next meeting will take place on **Wednesday 13 May 1998 at 10.00 a.m.**

note 1: the identity of individuals is being withheld under exemption 12 of the Code of Practice on Access to Government Information

note 2: information about these applications is being withheld on the grounds that this advice remains confidential as at the date of this summary and publication would be premature while regulatory action continues. The advice will be published in due course. Exemption 10 of the Code of Practice on Access to Government Information applies

note 3: the application would have been considered by the Committee for Proprietary Medicinal Products (CPMP). For further information about the product(s), see the website of the European Agency for the Evaluation of Medicinal Products - http://www.emea.eu.int/index/indexh1.htm

note 4: information is being withheld on the grounds that, as the application(s) was withdrawn before regulatory action was complete, details of the application(s) should remain confidential (exemption 13 of the Code of Practice on Access to Government Information)

note 5: for information - at a pre hearing the CSM considers the company's written data and decides whether or not its concerns have been addressed by that data. If not, the company is invited to attend the Committee the following month to present its data orally.

note 6: further information about this item or product is being withheld on the grounds that this advice remains confidential as at the date of this summary and publication would be premature while regulatory action continues. The advice will be published in due course. Exemption 10 of the Code of Practice on Access to Government Information applies