

MINUTES

of the

BRITISH PHARMACOPOEIA COMMISSION

A meeting of the British Pharmacopoeia Commission was held at Market Towers, 1 Nine Elms Lane, London SW8 5NQ on Monday 24 January 2000.

**Present:** Professor D H Calam (*Chairman*), Professor J A Goldsmith (*Vice-Chairman*), Dr A H Andrews, Professor A F Fell, Mr V Fenton-May, Dr A M T Lee, Professor J M Midgley, Professor A C Moffat, Dr N Randall, Dr G D Rees, Professor A D Woolfson.

**In attendance:** Dr R C Hutton (*Secretary & Scientific Director*), Dr F J Swanson.

An apology for absence was received from Professor D I R Begg.

Also present: Miss M L Rabouhans, Mr R B Trigg, Mrs H J Judd, Mrs M Vallender and Dr A Islam.

Dr D Jefferys attended the meeting for the items dealt with in minutes 687 to 695.

**INTRODUCTORY REMARKS**

687 **Awards** Members were pleased to note that Professor Midgley had been awarded the title of Professor Emeritus by the University of Strathclyde, Dr G. Eccleston (a member of Committee P: Pharmacy) had been designated as a Fellow of the Royal Pharmaceutical Society of Great Britain and Heather Martin (a member of the Secretariat) had been awarded the degree of Doctor of Philosophy from the University of Aberdeen.

688 **Membership of Commission** The term of office of those members whose appointment had been due to expire on 31 December 1999 (Professor Fell, Professor Moffat and Dr Randall) had been extended until 31 December 2001. The terms of office of all members now expired on the same date. It was noted that a press release announcing these re-appointments, together with details of the membership of the other Section 4 Committees, would be issued in due course.

689 **Declaration of Interests** Those members who had not sent in their completed Declaration of Interests forms were reminded to send them to the Secretariat without delay.

690 **Annual Report for 1999 of the British Pharmacopoeia Commission** The Annual Report had been prepared and would be circulated for confirmation shortly.

**I MINUTES**

691 The minutes of the meeting held on 20 September 1999 were confirmed.

**II MATTERS ARISING FROM THE MINUTES**

692 The following matters arising from the meeting held on 20 September 1999 were noted.

**Minute 659 – Review of the Future of the British Pharmacopoeia and British Pharmacopoeia (Veterinary)** Commission would be kept informed of future developments.

On behalf of the Commission, the Chairman congratulated Dr Jefferys on his new post as the Chief Executive of the Medical Devices Agency. Dr Jefferys thanked the Chairman and said he had welcomed the opportunity to work closely with the BP Commission over the past few years.

**Minute 674 – Monographs for Omission from the British Pharmacopoeia 2000** The consolidated list of monographs proposed for omission from the next editions of the BP and BP (Vet) had been published in MAIL as agreed.

**Minute 675 – Review of Membership of Committees and Consultative Groups** Dr Sarah Branch had accepted the invitation to join Committee C: General Chemicals.

**COM(99)54 – Text for the BP 2000: Approved Synonyms (item circulated on 15<sup>th</sup> October 1999)** The list of European Pharmacopoeia Approved Synonyms had been recommended for publication by the Medicines Commission and would be included in the BP 2000.

### III REPORTS AND CORRESPONDENCE

693 **Freedom of Information** COM(2K)1

A copy of a paper that had been presented to the Medicines Commission at their meeting in November 1999 was received for information. In line with the initiatives taken by the other Section 4 Committees in advance of FOI, it was agreed that from this meeting forward summary minutes from all BP Commission and Committee meetings would be made available after they had been formally agreed. The Secretariat undertook to prepare summary minutes for all future meetings. For the purposes of Committee minutes it was agreed that the draft summary minutes should be sent to the Chairman of the relevant Committee for approval. The Secretariat undertook to liaise with MCA colleagues with a view to publishing the summary minutes on the MCA website together with those of the other Section 4 Committees.

694 **British Pharmacopoeia Chemical Reference Substances** COM(2K)2

The list of reports concerning new and revised British Pharmacopoeia Chemical Reference Substances (BPCRS) that had been circulated for approval since the September 1999 meeting was provided for information. Members were pleased to note that the deadline for comment had been increased, usually to four weeks. There were exceptional circumstances, however, when a shorter comment period would need to be given, for example if the Laboratory had run out of a particular material and replacement samples were received late. Dr Islam thanked members for their comments and advice, particularly in difficult cases such as clindamycin palmitate hydrochloride. It was noted that, in the absence of a replacement batch, the material already available had been adopted as the reference material pending further consideration.

695 **New monographs for the BP 2000: BPCRS for Drug Substance Impurities** COM(2K)3

A number of monographs that would be included in the BP 2000 relied on the use of one or more impurities of the drug substance to be supplied as a BPCRS and the Laboratory had not yet received assurance that all of these would be available in sufficient quantities to support the monographs. Members were informed that since circulation of the papers a number of the outstanding reference materials had been received and Commission was invited to consider the appropriate course of action to be taken regarding the remaining affected monographs.

It was pointed out that some of the substances were relatively simple molecules and it was suggested that these might be synthesised by a contract laboratory or as part of a university project. A number of members offered to explore these possibilities.

It was recognised that the continuing changes within the pharmaceutical industry meant that companies had less resources to devote to pharmacopoeial matters. This was one possible reason for failure to provide the necessary reference materials and/or data. Routes of communication within a company could also contribute to the delay and/or lack of a response. It was suggested that for future monographs methods including impurity reference substances should only be included if there was no alternative. However, with the increasing development of monographs prepared

without laboratory work it was recognised that it might not be possible to include different methods. It was agreed that Chairmen should alert their Committee members to the problems experienced in obtaining the necessary BPCRS and to encourage members to offer support where possible.

Commission agreed that assurance that the necessary reference materials to support a monograph would be available should be confirmed at an earlier stage in monograph development. Other aspects, such as cost, also needed to be addressed. The Laboratory undertook to give this matter further consideration in consultation with the Secretariat before a more detailed discussion was held at a future Commission meeting.

It was agreed that since the BP 2000 would not come into effect until 1 December 2000, all the monographs for which reference substances were still awaited should be published as previously agreed. If the necessary reference materials had not been received before the date of implementation, the relevant test(s) would be amended or deleted in an Amendments Sheet which would have the same effective date as the BP 2000.

696 **Homoeopathic Approved Synonyms** COM(2K)4

The comments on the original list of Approved Synonyms for substances included in the European Pharmacopoeia but which are traditionally called by another name in the practice of homoeopathy in the UK had been drawn to the attention of the Homoeopathics Advisory Board. In addition to the points raised by the BP Commission the Advisory Board had recommended that for safety purposes no abbreviations should be included at the present time and that names that were not sufficiently distinctive should not be promulgated. A revised list had now been prepared and was presented for consideration. Members agreed that the remaining proposed synonyms should be included in Appendix XXI B: Approved Synonyms in the BP 2000. These synonyms would be clearly distinguished from the others in Appendix XXI B which were used as the titles or subsidiary titles of monographs in the BP or BP (Vet). The Secretariat undertook to finalise editorial presentation of the list in consultation with MCA colleagues.

697 **Compound Alginate Preparations** COM(2K)5

It was understood that the Joint Formulary Committee (JFC) had agreed to include the name "Compound Alginate Oral Suspension" in the British National Formulary (BNF) subject to confirmation from the Department of Health that the title was required. Reckitt & Colman had sent a letter by fax to the Secretary & Scientific Director which was tabled during the meeting. The Commission noted the company's concerns and agreed that the Secretary & Scientific Director should send a reply to clarify the Commission's position.

Members were reminded to refer any queries they might receive on this, or any other, topic to the Secretary & Scientific Director.

698 **Programme of Meetings for 2000** COM(2K)6

The finalised list of Commission and Committee meetings scheduled for 2000 was provided for information.

#### IV **FUTURE PUBLICATIONS**

699 **Initiated Monographs** COM(2K)7

An updated list giving the current situation with regard to proposed new monographs was received. The figures from the lists presented at the June 1999 and September 1999 meetings had been included for the purposes of comparison and the table had been updated to reflect the decisions taken at the September meeting). Those monographs that would be included in the BP 2000 or BP

(Vet) 2000 and those that the Commission had agreed should not be progressed had been retained for information but would be removed from the list before the next meeting.

**2-Pyrrolidone** In accordance with the decision not to elaborate national monographs for bulk drug substances, unless there was no interest at Ph Eur level, it was agreed that the EP Commission should be asked to add 2-Pyrrolidone to its work programme during the forthcoming priority rating exercise.

**Alfacalcidol Capsules; Betamethasone Valerate and Fusidic Acid Cream; Bumetanide and Amiloride Tablets; Fusidic Acid and Hydrocortisone Cream; Fusidic Acid and Hydrocortisone Gel; Fusidic Acid and Hydrocortisone Ointment; Tinzaparin Sodium Injection** It was agreed that work on Alfacalcidol Capsules should be progressed, subject to receipt of information from manufacturers. Commission agreed that work on all the other monographs should be abandoned but that monograph development could be reconsidered if and when generic products became available.

**Ketoconazole Oral Suspension; Astemizole Tablets** As the sole manufacturer had discontinued these products it was agreed that the monographs should be abandoned.

**Etodolac Preparations** As Etodolac Capsules and Tablets had been discontinued in the UK, and were only sold at low levels abroad, it was agreed that the monographs should be omitted from a future BP publication. A modified-release tablet formulation was available in the UK and members were invited to consider whether this should be added to the work programme. As the formulation was not one of the most widely prescribed items it did not meet the usual criteria for monograph development and so would not be added to the list.

**Fluocinolone Acetonide Cream, Gel & Ointment; Risperidone Tablets & Oral Liquid** Following receipt of the prepublication document containing the list of monographs adopted at the March 1999 session of the EP Commission these preparations had been identified by the Secretariat as possible candidate monographs. However, the items identified were not widely prescribed and it was agreed that monographs should not be developed at this time.

**Veterinary formulations.** It was noted that there was no equivalent form of prescription data for veterinary materials and so the extent of use of such preparations could not be ascertained. It was agreed that monographs for Albendazole Oral Suspension, Albendazole Oral Suspension with Minerals and Morantel Hydrogen Tartrate Ruminal Bolus should be developed. Clarification of the appropriate Standard Term for the ruminal bolus would be sought.

700      **Text for the British Pharmacopoeia 2000: Preliminaries**      COM(2K)8

A copy of the finalised Introduction to the British Pharmacopoeia 2000 was received for information. The draft Preface was accepted and would be submitted to The Medicines Commission for approval.

[SECRETARIAT NOTE Confirmation has since been received that the British Pharmacopoeia 2000 has been recommended for publication by the Medicines Commission.]

701      **Text for the British Pharmacopoeia (Veterinary) 2000: Preliminaries**      COM(2K)9

A copy of the finalised Introduction to the British Pharmacopoeia (Veterinary) 2000 was received for information. The draft Preface was accepted and would be submitted to The Medicines Commission for approval.

[SECRETARIAT NOTE Confirmation has since been received that the British Pharmacopoeia (Veterinary) 2000 has been recommended for publication by the Medicines Commission.]

702 **Text for the British Pharmacopoeia 2000: Supplementary Chapters** COM(2K)10

The new and revised Supplementary Chapters intended for inclusion in the British Pharmacopoeia 2000 were accepted, subject to minor editorial corrections. All other chapters would be brought forward unchanged from the BP 1999. It was agreed that if members had any further points to raise on these texts they should be sent to reach the Secretariat by not later than 4<sup>th</sup> February 2000.

**Chapter I A: Control of Impurities** Reference to the relevant ICH Guidelines had been added at the beginning of the chapter and within the section on formulated preparations.

The statement on Residual solvents had been updated to make reference to the Ph Eur Guidelines incorporated as Supplementary Chapter IV D.

**Chapter I N: Particulate contamination** The draft chapter had been revised following finalisation of the Ph Eur texts. The revised chapter had been accepted by Committee P: Pharmacy in May 1999 and was approved by Commission.

**Chapter II A: Changes in Monograph Title** It was noted that since ciclosporin and ribavirin were now recommended International Nonproprietary Names, these names would replace cyclosporin and tribavirin as British Approved Names. Consequential changes to the relevant monographs would be made in the text of the BP 2000.

**Chapter IV B: Dates of implementation** A paragraph had been added to provide information on the additional Ph Eur texts that had been brought into effect on 1 January 2000. These texts, which would be published in the 2001 Supplement to the third edition of the Ph Eur, would be included in the text for the BP 2000.

**Chapter IV C: Certification** The chapter had been updated in order to make reference to the extension of the scheme in order to provide a mechanism for assessing the risk of transmitting agents of animal spongiform encephalopathies via substances of animal origin.

**Chapter I F: Minimising the risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products (Ph Eur general chapter 5.2.8); Chapter I G: Statistical Analysis of Results of Biological Assays and Tests (Ph Eur general chapter 5.3)** The Ph Eur general chapters would be included in the BP 2000 *verbatim*.

V **COMMITTEES / REPORTS OF COMMITTEES**703 **Committee H: Biological Materials** COM(2K)11

The report of the Committee H meeting (15:10:99) was approved and the following points raised.

**Pyrogen Testing** The Committee had reviewed the list of remaining national monographs which still contained a test for Pyrogens and had contacted manufacturers for data to support a change to the test for Bacterial endotoxins. In addition, an item had been included in MAIL seeking relevant information from manufacturers. As a result of these initiatives, a test for Bacterial endotoxins would be included in a number of monographs in the BP 2000 or in the following publication.

**Glucagon Injection; Gonadorelin Hydrochloride & Injection** Members noted that it had not been possible to harmonise these monographs with the corresponding Ph Eur monographs due to a lack of information from manufacturers.

704 **Committee B: Medicinal Chemicals** COM(2K)12

The report of the Committee B meeting (17:11:99) was approved and the following points raised.

**Betaxolol Eye Drops** The Committee's concerns over the inclusion of manufacturers' methods rather than Ph Eur methods were acknowledged. Commission confirmed that where validated methods existed they should be published but that, in line with current policy, such methods should be reviewed and harmonised with the Ph Eur methods at a later date if possible. The Committee's proposals to seek justification for apparently wide limits and to ask manufacturers routinely for alternative solvents to chloroform were endorsed.

**Fluoxetine Oral Solution; Related substances** The Commission agreed in principle that, where feasible, an analyst should be instructed to disregard any peak/spot due to a known flavouring if it was known to interfere with the related substances test. This matter would be given further consideration at a future meeting.

**Selegiline Tablets** In view of the widely different limits proposed for related substances, Commission endorsed the Committee's proposal that two sets of limits should be included in order to accommodate all available formulations but also to avoid the inclusion of unnecessarily wide limits.

705 **Committee C: General Chemicals**

COM(2K)13

The report of the Committee C meeting (29:11:99) was approved and the following points raised.

**BPCRS Assay Standards: Declared content** There had been a divergence of opinion over whether a substance should be assigned a single figure representing the actual purity or whether different figures should be assigned appropriate to the method of assay. The Committee had recognised that there would be practical difficulties in having more than one figure and agreed that the preferred approach was to avoid the need to use more than one figure by harmonisation of methods used. It was recognised, however, that separate values would be required if different methods had to be maintained. It was noted that Committee A: Medicinal Chemicals had also discussed this matter and had reached a similar view. This matter would be given further consideration at a future meeting.

**Glyceryl Trinitrate Preparations** The Commission noted the difficulties the Laboratory had experienced in trying to obtain a suitable assay standard for Glyceryl Trinitrate. While recognising the problems due to the explosive nature of the material and its associated transportation problems, it was agreed that the Laboratory should take all possible steps to obtain a suitable standard. A number of members offered to look into the possibility of supplying the material.

706 **Committee N: Nomenclature**

COM(2K)14

The report of the Committee N meeting (1:12:99) was approved and the following points raised.

**Eufausease** The Commission strongly supported the Committee in its view that the name for this enzymatic extract of krill should be closely related to the name of the natural source genus.

**Dual-labelling** The Committee had been concerned that no Statutory Instrument had yet been issued regarding those names for which it had been agreed that the former British Approved Name should be included on the label in addition to the recommended International Nonproprietary Name (rINN).

Statements on dual-labelling had been included in the BP 1998 and BP 1999 and in several editions of the BNF on the understanding that the position would be formalised by means of a Statutory Instrument. In the absence of any legal basis for dual-labelling, however, it was possible that certain products were now required to use the rINN only but that others still used the former BAN. Members were reminded that the MCA/DH intention had been that, once a Statutory Instrument had been issued, there would be a continuing education programme until such time as it was considered safe to effect the change to sole use of the rINN (at least five years). It was suggested

that, in the absence of a Statutory Instrument, the Commission would need to reconsider the approach taken in the BP. While dual-labelling would be maintained in the BP 2000, text for which was nearing completion, it might need to be abandoned in the 2001 edition. It was agreed that the Secretary and Scientific Director should draw the Commission's concerns to the attention of those responsible for UK product labelling.

707 **Committee A: Medicinal Chemicals** COM(2K)15

The report of the Committee A meeting (10:12:99) was approved and the following points raised.

**BPCRS Assay Standards: Declared Content** A member of the Committee had expressed concern at inconsistencies in the depth of instructions given in BP monographs for the preparation of test solutions. In some cases a quantity of substance was specified. In other cases a concentration of solution was given, thereby giving the analyst more freedom to decide on the amount of substance to be used and the dilution sequence. Commission agreed that the feasibility of adopting a more standard approach for the future should be examined but that retrospective changes to monographs should not be considered. This matter would be given further consideration at a future meeting.

**Meloxicam: Suitability of gradient elution LC programmes in the Pharmacopoeia** Attention was drawn to the Committee's concerns over the problems with gradient elution HPLC methods, particularly the variation in retention times depending on the characteristics and condition of the column used. A number of options were available to ensure that all potential impurities had eluted such as extending the linear gradient elution programme at the start of the run or by including an isocratic requirement at the end of the run. While acknowledging the problems associated with gradient elution methods, it was recognised that they were essential for certain separations. Problems were also experienced with gradient methods at Ph Eur level where there was an increasing tendency to publish reference chromatograms. This matter would be given further consideration at a future meeting.

**VI EUROPEAN PHARMACOPOEIA**

708 **105<sup>th</sup> Session of the EP Commission**

Members were informed of issues discussed at the 105<sup>th</sup> Session of the EP Commission (November 1999).

709 **Appointment of Specialists** COM(2K)16

The list of UK specialists who had been appointed by the EP Commission at the November 1999 Session was received for information. It was noted that most of the work to be undertaken by the specialists would be carried out by correspondence. Members were invited to consider areas of work in which a UK specialist had not been appointed and to make suitable proposals.

**VII REPORTS OF THE SECRETARY AND SCIENTIFIC DIRECTOR**

710 **Secretariat** The Secretariat had recently moved offices within Market Towers and this had caused severe disruption, including cancellation of the December 1999 Commission meeting.

711 **ABPI** The Chairman, Vice-Chairman and Secretary & Scientific Director had had a successful meeting with the ABPI Technical Committee in which matters such as Certification had been discussed. ABPI had indicated that they would continue to support the BP and had agreed to consider suitable additional candidates to act as UK specialists (minute 709 refers).

712 **Assay** The Vice-Chairman, Secretary & Scientific Director and Professor Fell had presented papers at a recent conference on the Global Approach towards Setting Specifications. Members

were reminded that, whereas in the past the Commission's policy had been to include different methods for identification, related substances and assay, in response to criticism of this policy a more flexible approach was now used in monograph development, particularly the move away from precise, non-specific methods of assay.

- 713 **Certification** Members were informed that an assessor had been proposed by the Veterinary Medicines Directorate to participate in the established scheme. The MCA had agreed that two assessors should be involved in the Certification scheme for products with a risk of transmitting agents of animal spongiform encephalopathies.

**VIII ANY OTHER BUSINESS**

- 714 **Date of next meeting** Monday 10 April 2000.