

SUMMARY MINUTES
of the
BRITISH PHARMACOPOEIA COMMISSION

A meeting of the British Pharmacopoeia Commission was held at 151, Buckingham Palace Road, London SW1W 9SZ on Wednesday 4th November 2015.

Present: Professor K Taylor (*Chair*), Professor A G Davidson (*Vice-Chair*), Mr B J Capon (*Lay Member*), Professor D Cairns, Dr G Cook, Mr C T Goddard, Dr K Helliwell, Dr R L Horder, Dr M G Lee, Dr B Matthews, Professor J Miller, Dr R Torano, Dr L Tsang, Dr P Varley, Professor E Williamson.

Sir Michael Rawlins, Chair of the MHRA, attended the meeting for the item recorded under minute 28.

In attendance: Dr S Atkinson (*Secretary & Scientific Director*), Dr F J Swanson, Mr P Crowley.

Apologies for absence were received from Mr A Coulson and Mrs J M Turnbull (*Lay Member*).

Also present: Mrs M Barrett, Ms H Corns, Mr A Evans, Ms J Francomb, Miss A Gardiner, Mr A Gibb, Dr P Holland, Dr C Howard, Dr R A Pask-Hughes, Ms C Pitt, Mr J Pound, Mr M Whaley and Mr S Young.

1 Introductory Remarks

Staff The Chair welcomed members to the last meeting of the current British Pharmacopoeia Commission. He welcomed Alice Gardiner, who had joined the Secretariat in August, who would be assisting in the work of the Antibiotics (ABS) and Medicinal Chemicals (MC3) Expert Advisory Groups and with the BP website.

British Pharmacopoeia 2016; BP Website The BP 2016, BP (Vet) 2016 and Supplement No. 4 to British Approved Names 2012 had been published at the end of August and would come into effect on 1st January 2016. The new BP website had been launched successfully on 10th August and a short demonstration of the new site was provided during the meeting.

Declaration of Interests; Confidentiality of Proceedings Members were reminded of the need to inform the Secretariat of any changes to their interests throughout the year and of the need to declare any specific interests at the start of relevant discussions during the meeting. The Chair reminded members of the confidential nature of the meeting and that the papers should not be disclosed.

Dr Helliwell and Dr Horder declared interests in one or more agenda items and appropriate action was taken.

I MINUTES

2 The minutes of the meeting held on 6th July 2015 were confirmed.

II MATTERS ARISING FROM THE MINUTES

3 The following matters arising from the meeting held on 6th July 2015 were noted.

Minute 972 – Analytical Methods – Evaluation Assessment The proposed approach for documenting decisions on whether or not laboratory work should be undertaken had been trialled at a number of recent EAG meetings. It was intended that the test cases, together with feedback from experts, would be presented at the next meeting.

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Minute 979 – Assay Limits The Secretariat would amend the Aide Memoire to include the additional reasons for deviating from the usual $\pm 5\%$ assay limits in the next revision of the document, which would be presented at a future meeting.

Minute 980 – Expert Advisory Groups, Panels of Experts and Working Parties Dr Cooney has accepted the invitation to join the Panel of Experts on Veterinary Immunological Products.

III REPORTS AND CORRESPONDENCE

GOVERNANCE

4 **Triennial Review** COM(15)38

The Triennial Review of the British Pharmacopoeia Commission had been published at the end of March and a copy had been provided at the July meeting. A report indicating the status of the 11 recommendations arising from the review was provided for information. Members were informed that a formal update would be provided to the Cabinet Office in January 2016 and Commission would be kept informed of developments at future meetings.

5 **BP Team Structure** COM(15)39

An organogram highlighting where the British Pharmacopoeia and Laboratory Services group sat within the MHRA Inspection, Enforcement and Standards Division was provided for information. A revised version of Supplementary Chapters III A1: Contact Points and III A2: Expert Advisory Groups was also provided for information.

OPERATIONAL

6 **Customer Insight Research** COM(15)40

The British Pharmacopoeia had been the subject of a detailed Customer Insight Research project in the early part of 2015. A number of Commission and EAG members had taken part in the interviews and survey. Overall, a very positive perception of the BP publication and activities had been received. A number of areas for improvement had been identified. The intention was to undergo further research in due course to assess the effectiveness of any changes introduced.

7 **Analytical Quality by Design** COM(15)41

An update of the work being undertaken by the Working Party on Analytical Quality by Design, and on wider issues relating to this area of work, was provided for information.

Global Perspective An ICH Expert Working Group was to be established to consider “Enhanced Approaches for the Development and Utilisation of Analytical Procedures”. It was expected that pharmacopoeias would be invited to participate in the work of this group. The US FDA had published an updated guideline for “Analytical Procedures and Methods Validation for Drugs and Biologics”.

Feasibility Study; Next Steps A feasibility study was being undertaken to investigate the extraction, chromatography and solution stability parameters for an Assay procedure.

8 **General Comments on the British Pharmacopoeia**

COM(15)42

HPLC Related Substances – Disregard Limits Attention had been drawn to an apparent discrepancy between the way disregard limits were reported in the BP and in the ICH Guideline on Impurities in New Drug Products (Q3B).

The general consensus was that although it would be preferable for the BP and ICH approaches to be aligned, there were justifications to adopt different approaches in view of the fact that the BP and ICH served different functions. It was suggested that a dual approach of including both the BP and the ICH approach to disregard limits should be trialled in draft new monographs for a short time. The views of the EAGs could then be discussed by Commission before any changes in policy were considered.

Expression of Related Substances Test Specifications It had been requested that consideration should be given to changing the current wording of BP monographs in line with the new style being introduced into new and significantly revised Ph Eur monographs. The current approach included limits based on comparison of peak areas (eg. not more than x times the area of the principal peak in the chromatogram obtained with (y%)”, whereas the new Ph Eur approach stated limits in terms of numerical values only.

It was agreed that the Secretariat should trial a dual approach for a short time, as agreed for the disregard limits, and report back to Commission at a future meeting.

Weighing Attention had been drawn to the fact that there was no information on the use of balances in the BP/Ph Eur. It had been proposed that some guidance should be prepared for inclusion in the BP and that this could be based on that included in the USP. Members agreed that it would be useful to include guidance as suggested and it was agreed that the Secretariat should draft text for consideration at a future meeting.

Dissolution Specifications It was accepted that the different approach for specifying the dissolution acceptance criteria in monographs published before and after the BP 2008 was confusing. It was agreed that the resource implications of any changes would need to be assessed and a revision programme and timetable developed.

9 **Designing and Developing the *trnH-psbA* BPNARM:
Overcoming Challenges Encountered**

COM(15)43

The new Appendix for DNA-Based Identification Techniques for Herbal Drugs had been published in the British Pharmacopoeia 2016. A novel reference material, *trnH-psbA* BPNARM, had been established to support the Appendix, the purpose of which was to (i) confirm the suitability of the DNA extraction technique used and (ii) to confirm the suitability of the polymerase chain reaction chemistry and system used.

10 **British Pharmacopoeia Laboratory**

COM(15)44

British Pharmacopoeia Laboratory Reports The list of reports concerning new and revised monographs that had been prepared by the Laboratory since the July 2015 meeting was provided for information.

British Pharmacopoeia Chemical Reference Substances The list of reports concerning British Pharmacopoeia Chemical Reference Substances (BPCRS) that had been tested since the July 2015 meeting was provided for information.

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A list showing BPCRS stock levels between October 2014 and September 2015 was also provided. Members were pleased to note that the levels of in-stock material had been maintained at a high level for several months, which should allow the Laboratory staff to spend more time undertaking monograph work.

IV FUTURE PUBLICATIONS

11 Monograph Initiation: Candidate Monographs COM(15)45

Monographs arising from the current Work Programme In accordance with the decision to elaborate monographs for all known formulations of a particular active ingredient, the following item had been identified as a potential candidate monograph: Ferrous Fumarate and Folic Acid Capsules. Commission endorsed the recommendation to add the item to the work programme.

Informal Harmonisation A company had requested that the following monographs be developed by informal collaboration with the United States Pharmacopoeia: Metformin and Sitagliptin Tablets; Sitagliptin and Prolonged-release Metformin Tablets. Members endorsed the recommendation to add these items to the work programme.

2014 PCA Prescribing Data and CMU Hospital Pharmacy Data The Secretariat had examined the most recent lists of prescribed products provided by the NHS Information Centre and the Department of Health Commercial Medicines Unit. A number of items had been identified as potential candidate monographs from the top 500 most widely prescribed items and the top 200 items used in hospitals during 2014 and it was agreed that these should all be added to the work programme.

12 Approved Synonyms COM(15)46

New Monographs Members confirmed that there was no need to create any approved synonyms as a consequence of new monographs added to the European Pharmacopoeia by means of Supplements 8.6 and 8.7 and recommended that the Ph Eur titles should be used when the monographs were reproduced in the BP 2017 and BP (Vet) 2017.

British Approved Names As a consequence of additions to the Ph Eur, the following names would be added as new British Approved Names in a future BAN publication: Entecavir (antiviral); Gadobutrol (MRI contrast agent); Thiocolchicoside (muscle relaxant/anti-inflammatory/analgesic).

Title Changes The title of the monograph for Amiloride Hydrochloride had been changed to Amiloride Hydrochloride Dihydrate by means of Supplement 8.6. This change would be reflected in the BP 2016 online update and in the BP 2017. A consequential amendment to the BP monograph for Amiloride Tablets would also be required.

13 Supplementary Chapter: Aseptic Preparations COM(15)47

Supplementary Chapter The draft Supplementary Chapter on Aseptic Preparation of Unlicensed Medicines had been developed by the Expert Advisory Group on Unlicensed Medicines in response to a request to consider the publication of standards for Aseptic Preparations within the British Pharmacopoeia. This had followed discussions within EAG ULM regarding publication of a Supplementary Chapter and General Monograph on Parenteral Nutrition Solutions.

The draft text had been discussed at the recent meeting of EAG ULM. It was intended to circulate the text to interested organisations before it was finalised, with a view to inclusion in the British Pharmacopoeia 2017. Members confirmed that the draft text was acceptable and agreed to send any specific comments to the Secretariat by 30th November.

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- 14 **British Pharmacopoeia 2017: Text Review Dates** COM(15)48

Text Review (DRT) and Feedback stage Dates for reviewing text using the document review tool (DRT) had been agreed within the Secretariat and the dates relating to the review by Commission were provided for information.

Public Consultation on Draft Monographs (*Recommendation 8 of the Triennial Review*)

Following the discussion at the last meeting, revised dates for the public consultation of new and revised monographs had been agreed. Four separate consultations (each of three months) would be undertaken during 2016 and the process would be reviewed after one year.

- 15 **BP Revisions to Reflect Changes in Ph. Eur. Policy** COM(15)49

Members were informed of a number of changes to BP monographs that would be required to reflect recent changes in European Pharmacopoeia policies.

Elemental Impurities In line with the implementation of the ICH guideline on Elemental Impurities (Q3D), the European Pharmacopoeia was intending to remove tests for Heavy Metals from individual monographs for medicinal substances and excipients and to replace these with reference to the test for Elemental Impurities in the General Monograph for Pharmaceutical Preparations by means of the 9th Edition. In order to harmonise with the Ph Eur, it was intended to remove the heavy metals test from about 50 relevant BP monographs and other text. These changes would be made in the BP 2017.

Ph Eur Monograph Titles – Degree of Hydration In line with the policy agreed in 2014 the European Pharmacopoeia was intending to change monograph titles for pharmaceutical and medicinal substances by means of the 9th Edition to (1) include the degree of hydration for hydrated substances and (2) remove the term anhydrous from anhydrous substances. These changes would need to be reflected in a significant number of BP formulation monographs and the Secretariat had prepared a detailed revision programme to ensure that all the necessary changes would be made. The Secretariat was currently seeking confirmation that these changes would go ahead and, if it was confirmed, the relevant BP monographs would be amended appropriately in the BP 2017.

V ANALYTICAL ISSUES

- 16 **Prolonged-release Dissolution** COM(15)50

A project had been undertaken to investigate the inclusion of specific dissolution tests in monographs for prolonged-release formulations. Members were reminded that the current policy relating to monographs for prolonged-release formulations was to include a general requirement for dissolution under Production rather than to include a specific test in a monograph.

Work had been undertaken on a range of products with different release profiles and formulations and the results had indicated that it was possible to develop a generic method to control dissolution in prolonged-release formulations, although a number of challenges had been identified.

Information relating to one product had been provided to EAG MC1: Medicinal Chemicals. The EAG had agreed that the proposed method was a useful starting point and would be considered further at a future meeting.

Members agreed that including a specific dissolution test in a monograph was preferable to the current Production statement approach. However, it was recognised that this would be a complete

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change in approach for BP monographs and it was agreed that wide consultation should be undertaken before any changes to the current policy were considered.

VI EXPERT ADVISORY GROUPS / PANELS OF EXPERTS

17 Expert Advisory Group MC2: Medicinal Chemicals COM(15)51

The report of the EAG MC2 meeting (21:5:15) was approved and the following points were raised.

Fosaprepitant for Injection Members were informed that responsibility for development of this monograph has been transferred to the EP Commission.

Verapamil Oral Solution; Related substances The EAG had accepted impurity limits that were tighter than the ICH limits, but were in line with the UK registered limits.

18 Expert Advisory Group MC1: Medicinal Chemicals COM(15)52

The report of the EAG MC1 meeting (8:6:15) was approved and the following points were raised.

Prolonged-release Carbamazepine Tablets The Expert Advisory Group on Pharmacy had confirmed that a monograph for the Prolonged-release Tablets formulation should be developed in addition to the new monograph for Chewable Carbamazepine Tablets.

Itraconazole Capsules A manufacturer had proposed the use of HPLC with diode array detection as an Identification test. As diode array detection was not currently specified in any BP monograph, it had been agreed that the views of the BP Commission should be sought and a paper would be presented at a future meeting.

Digoxin Injection Members noted the proposed removal of the extemporaneous formula and retention of the fixed strength of Digoxin. In view of the established use of the fixed strength product, EAG PCY had recommended that rather than changing to open format, the strength should be specified in the monograph.

19 Expert Advisory Group HCM: Herbal and Complementary Medicines COM(15)53

The report of the EAG HCM meeting (25:6:15) was approved and the following point was raised.

Liquorice Liquid Extract Although the product was widely used in the UK it had been recognised that the method of preparation detailed under Definition was no longer appropriate. Commission endorsed the EAG HCM recommendation to omit the monograph from the next edition of the BP, prior to revision and re-instatement in a future publication.

20 Working Party DNA: Identification Techniques COM(15)54

The report of the WP DNA meeting (10:7:15) was approved and the following point raised.

Next Generation Sequencing (NGS) The initial work had been carried out using Sanger sequencing methods. Members were informed that some work on NGS techniques had been carried out and that this might offer an alternative method, thereby providing greater flexibility for users in the future.

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VII EUROPEAN PHARMACOPOEIA

- 21 **European Pharmacopoeia Update** COM(15)55

European Pharmacopoeia Commission A copy of the agenda for the 153rd Session of the EP Commission (November 2015) was provided for information. A number of nominations for new UK experts to the Ph Eur Groups of Experts and Working Parties would be presented at the Session.

Directive 98/34/EC; British Pharmacopoeia 2016 Members were informed that it was a legal requirement for member states to inform the EP Commission and other member states about their technical regulations at a draft stage. In order to comply, the BP Secretariat provided the Department of Business Innovation and Skills with the new and technically revised monographs for each publication, who then submitted these texts to Brussels. This was followed by a three month period during which objections could be raised. The BP also provided the EPC with a list of new and revised BP text each year.

- 22 **European Pharmacopoeia Technical Guide** COM(15)56

Clarification of text A number of concerns had been raised regarding the recently revised Ph Eur Technical Guide, which was available on the BP website. A number of minor amendments had been proposed for clarity and it was agreed that these should be drawn to the attention of the European Pharmacopoeia Commission.

VIII INTERNATIONAL COLLABORATION

- 23 **International Collaboration** COM(15)57

Members were provided with an update on international activities.

WHO 6th International Meeting of World Pharmacopoeias Dr Atkinson and Mr Evans had attended this meeting, which had been hosted by the Chinese Pharmacopoeia in Suzhou. The meeting had focussed on the continued development of the guidance on Good Pharmacopoeial Practices; the latest draft had been discussed, together with comments received from pharmaceutical companies and industry groups.

WHO Activities Dr Atkinson and Ms Corns had visited the WHO offices in July to review the current Memorandum of Understanding and collaborative projects between the two organisations. Ms Corns had attended the Expert Committee on Specifications for Pharmaceutical Preparations in October. A wide range of activities had been covered, including the adoption of new monographs for inclusion in the International Pharmacopoeia, together with adoption of the latest version of the Good Pharmacopoeial Practices document.

Dr Holland and Mr Evans had attended the 61st INN Consultations. The meeting was the first at which the number of applications for names for biological substances exceeded those for chemical substances. Members were pleased to note that Dr Holland had been appointed as Chair of the INN Committee, a post previously held by Professor Derek Calam, former Chair of the BP Commission.

Indian Pharmacopoeia The MHRA had signed a Memorandum of Understanding with the Indian regulatory authorities and it was hoped that this would facilitate future liaison between the BP and the Indian Pharmacopoeia.

Indian Ministry of Ayush Dr Atkinson and Mr Whaley had met with a delegation from the Ministry of Ayurveda, Yoga, Unani, Sihda and Homoeopathy (Ayush) at the MHRA. The discussions had led to a greater understanding of shared areas of interest and identification of opportunities for future collaboration between the BP and the Indian Ayurvedic Pharmacopoeia.

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Indonesian Pharmacopoeia; State Pharmacopoeia of Ukraine (SPU) Meetings had been held with representatives of these pharmacopoeias during the WHO 6th International meeting. Current activities and future collaboration opportunities had been discussed.

IX REPORTS OF THE SECRETARY AND SCIENTIFIC DIRECTOR

24 Appointments to the BP Commission

Following a successful recruitment campaign, interviews for new appointees had been held and eight new members (six professional and two lay) had been identified. A submission would shortly be sent to Ministers for approval before announcement of the new members could be made.

25 NIBSC

Dr Stephen Inglis, Director of NIBSC, would be retiring at the end of March 2016. Dr Christian Schneider (Danish Health and Medicines Authority) had been announced as his replacement.

X ANY OTHER BUSINESS

26 Allergens

A member had raised concerns regarding a recent internal policy change at the EDQM whereby applicants for Certificates of Suitability (CEP) were now required to provide a significant amount of information relating to the allergenicity of any antioxidants added to Ph Eur grade oils. It was agreed that the UK delegation should draw attention to this matter during the next session of the EP Commission.

27 Working Party: General Methods

Professor Davidson informed members that a new Ph Eur Working Party on General Methods had been established and that he was the Chair of the group. The remit of the Working Party was to develop a strategy to update current pharmacopoeial methods of analysis.

28 Retiring Members of the Commission

This was the last meeting for Professor Cairns, Mr Capon, Mr Goddard, Dr Helliwell, Dr Tsang, Mrs Turnbull and Professor Williamson. The Chair paid tribute to the outgoing members, all of whom had served on the British Pharmacopoeia Commission for many years. He thanked them for their dedication and commitment to the work of the Commission over the years and for their continuing involvement in the work of the Expert Advisory Groups, Panels of Experts and Working Parties. He noted that Mr Capon and Mrs Turnbull had been the first lay members to be appointed to the BPC and had attended meetings of the Lay Members Forum.

Sir Michael Rawlins, Chair of the MHRA, presented the retiring members with a thank you gift. He acknowledged the contribution of all members of the Commission to the safeguarding of public health and, on behalf of the MHRA, thanked the retiring members for their long service.

29 Date of next meeting

Monday 7th March 2016.