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 Monday 4th July 2016.

Present: Professor K Taylor (*Chair*), Professor A G Davidson (*Vice-Chair*), Professor M Almond, Dr J Beaman, Dr A M Brady, Dr G Cook, Mr A Coulson, Dr A Gleadle (*lay member*), Dr R L Horder, Dr M G Lee, Mr R A Lowe, Dr B Matthews, Professor J Miller, Ms S Palser (*lay member*), Professor M Simmonds, Dr R Torano, Dr P Varley.

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

An apology for absence was received from Mr J Pound.

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

62 **Introductory Remarks**

Welcome The Chair welcomed Ms Christina Gkouva from the BP-NIBSC Herbals Laboratory, who was attending the meeting for training purposes, and Ms Charlotte Hill from the Department of Health.

Award Members were pleased to note that Professor Derek Calam, former Chair of the British Pharmacopoeia Commission, had been awarded a CBE in the Queen's Birthday Honours List in recognition of his services to public health and the regulation of medicines.

EU Referendum In line with the rest of the MHRA, the BP was continuing with business as usual following the result of the recent EU referendum.

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.

Professor Davidson, Dr Matthews and Dr Torano declared interests in one or more agenda items and appropriate action was taken.

I MINUTES

63 The minutes of the meeting held on 7th March 2016 were confirmed.

II MATTERS ARISING FROM THE MINUTES

64 The following matters arising from the meeting held on 7th March 2016 were noted.

Minute 32 – EAG MC2 Minutes; Itraconazole Capsules The item on the proposed use of HPLC with diode array detection as a means of Identification had been deferred to a future meeting.

Minute 35 – British Pharmacopoeia Commission: Membership The BP website had been updated to include the list of current members.

Minute 38 – British Pharmacopoeia 2017 Publications; Minute 42 – British Approved Names
The Secretariat was in the final checking stages for the BP 2017, the BP (Vet) 2017 and the BAN 2017 publications, which will be published in August. The Chair thanked members for reviewing the new and revised text via the Document Review Tool.

III REPORTS AND CORRESPONDENCE

GOVERNANCE

65 **Triennial Review** COM(16)25

A summary report indicating the status of the 11 recommendations arising from the Triennial Review of the BP Commission was provided for information.

66 **British Pharmacopoeia: Business Review** COM(16)26

Members were provided with a copy of the finalised Business Review. The document had been prepared taking into account the recommendations of the Triennial Review, the feedback received in response to the Customer Insight Research Project and the current 5 Year Strategy for the BP operation. The Business Review had been endorsed by the MHRA Corporate Executive Team.

Digital Element One of the recommendations from the Triennial Review had been to "explore the feasibility of bringing the digital element of the BP in-house". Funding had been approved for the feasibility study and Ms Charlotte Hill, Department of Health, was spending six months at the Secretariat on this project.

67 **Biologicals and the Pharmacopoeia** COM(16)27

Members were provided with background information relating to the control of biological medicines. The presentation highlighted differences between biological and chemical drugs in terms of their size, complexity, method of synthesis and structure. It also highlighted differences in the analysis and clinical studies required to control small molecules, biological drugs and biosimilars. It was pointed out that 6 of the 10 best selling products today were of biological origin and that about half of the new biological products in development were for monoclonal antibodies.

68 **BP Biologicals Vision and Strategy** COM(16)28

A draft of "The BP Biological Vision and Strategy" document was provided for information.

The document was intended to provide guidance that would be used to direct the generation of a programme of supporting work, it was not intended to act as a work programme.

OPERATIONAL

69 **Monograph Lifecycle Review: Development; Publication; Revision** COM(16)29

Prioritisation Review The Secretariat had been reviewing the processes and prioritisation for monograph development and revision in order to ensure a consistent approach across the Expert Advisory Groups and to provide a more realistic work programme for the Secretariat and Laboratory. The following aspects had been identified to help prioritise those monographs that should be developed/revised and to identify whether practical work should be carried out:

- Known product risks / request received from Licensing or the NHS / patient need;

- Number of prescriptions / usage from the NHS or stakeholders;
- Known problem with the monograph (revision);
- Number of Marketing Authorisation Holders or stakeholders;
- Multiple pharmaceutical forms (monograph family) for an active pharmaceutical ingredient.

The work programme of EAG MC3 (Medicinal Chemicals) had been updated to incorporate the above aspects and this was provided for information. Members were informed that the proposed prioritisation exercise did not alter the ways of working. It was intended to provide a more formalised approach and ensure that in each new edition of the BP there was a good mix of new and revised monographs across the EAGs.

Discussion Members supported the proposals outlined by the Secretariat and it was agreed that the proposed approach should be applied in future prioritisation exercises.

70 **Monographs for Products which are no longer Licensed** COM(16)30

Expert Advisory Group ULM: Unlicensed Medicines Members were reminded that EAG ULM had been established to develop publicly available standards for medicines that were prepared in order to address patient requirements that were not met by current UK licensed medicines. Such monographs included a cross-reference to the General Monograph for Unlicensed Medicines and the following statement: "NOTE: *[Monograph Title] is not currently licensed in the United Kingdom*". The monographs were included in the main body of the BP since this facilitated changing the status of a monograph if (a) licensed products become available for previously unlicensed formulations or (b) if there was a need to retain a monograph for a product which was no longer licensed but for which there was still a patient need for unlicensed formulations.

Omitted or Transferred Monographs EAG ULM were increasingly being asked to consider whether monographs for which licensed products were no longer available should be transferred to EAG ULM. It had been agreed that the EAG should develop clear policy guidelines to ensure that a consistent approach was applied when deciding if monographs should be transferred or omitted. Proposals had been presented at the recent meeting of EAG ULM and these had been accepted by the group.

Members endorsed the recommendations of EAG ULM.

71 **Extemporaneous Preparations** COM(16)31

Background There were currently about 116 monographs and other text within the British Pharmacopoeia that referred to extemporaneous preparation. Although the current policy was to move away from including formulae and extemporaneous preparation details in individual monographs, the information was still considered valuable to some users, particularly those in the NHS.

Review A number of discussions had been held at EAGs PCY (Pharmacy) and ULM (Unlicensed Medicines) regarding the continued inclusion of this information within the BP and the need for a consistent policy had been highlighted. The views of users had been sought through a stakeholder consultation process.

Members were invited to discuss the options proposed by the Secretariat.

Option 1 This involved moving the extemporaneous preparation details to a Supplementary Chapter and including a reference to this Chapter within the relevant monographs.

Option 2 This involved retaining the formulation details within the monograph.

Option 3 This involved carrying out a review of each affected monograph, in consultation with stakeholders, to ascertain if any of the extemporaneous information could be moved to a new Production statement (mandatory) and moving the formula to a Supplementary Chapter (non-mandatory).

Discussion The consensus was that option 1 offered the best way forward. This allowed for the retention of valuable formulation information within the BP, while ensuring that the majority of monographs were presented in open-strength format. It was agreed that there may be justification to retain the current information in certain monographs, due to safety concerns, and that each monograph should be considered case-by-case rather than imposing a global change. Members confirmed that the Production statement approach was not appropriate. The views of Commission would be drawn to the attention of EAGs PCY and ULM before any action was taken.

72 **Soft Gel Paracetamol Capsules** COM(16)32

A monograph for Paracetamol Capsules had first been published in the BP 2008. Laboratory work had been carried out on hard capsules and a dissolution test using a pH 5.8 buffer had been included. EAG MC1 (Medicinal Chemicals) had been made aware that a soft gel capsule formulation was available which was unable to comply with the published BP dissolution test. EAG MC1 had been asked whether the current monograph could be updated to accommodate the soft gel product and had sought advice from the Pharmacy EAG before their December 2015 meeting. EAG PCY had been unable to reach a consensus and EAG MC1 had been uneasy at updating a monograph to accommodate a product that was not licensed in the UK.

The matter had been discussed further at the meeting of EAG MC1 held in June 2016 when the group had decided against amending the current method. Concerns had been raised at possible additional requests for change once other soft gel products became available and at the implications for existing manufacturers of licensed hard capsules. EAG MC1 had requested guidance from the Commission should similar requests arise in the future.

Suggestions included: specifying different tests for hard or soft capsules; removing the test from the monograph and relying on a Production statement as for prolonged-release preparations; asking manufacturers if 0.1M HCl was a suitable medium for their product; examining if the USP dissolution medium (water) was suitable. After further discussion, there appeared to be a preference for the inclusion of separate tests for hard and soft capsules. It was agreed that wide consultation should be undertaken before any changes were introduced.

73 **Alkylsulfonate Esters: Production Statements in BP Monographs** COM(16)33

Background European Pharmacopoeia monographs for alkanesulfonate salts included a Production statement which (a) alerted users to the potential presence of genotoxic alkylsulfonate esters and the need to take into account the quality of starting materials and other factors during manufacture and (b) included reference to the general methods for the control of alkylsulfonate esters.

At the recent meeting of EAG MC1 (Medicinal Chemicals), members had agreed that Commission should be asked whether a similar Production statement should also be included in BP product monographs for alkanesulfonate salts to alert users to the potential for ester formation. The view of EAG MC1 had been that statements should be added to the individual monographs.

Members were invited to discuss whether (i) a Production statement should be added to relevant BP monographs and (ii) whether a general method for the detection of alkylsulfonate esters in formulated preparations should be developed. In addition to the product monographs listed in the paper, there were three BP monographs for active substances that did not contain a Production statement: Benzatropine Mesilate, Loprazolam Mesilate, Prochlorperazine Mesilate.

BP Product Monographs After discussion, a divergence of views remained. The Chair asked that EAG MC1 seek further information regarding the likelihood of ester formation during product manufacture and for the discussions to be continued at a future meeting.

BP Active Substance Monographs Members agreed that, for consistency, a Production statement, based on that included in the Ph Eur, should be added to the three BP substance monographs for Mesilates.

Professor Simmonds left the meeting at this point.

74 **British Pharmacopoeia Laboratory** COM(16)34

British Pharmacopoeia Laboratory Reports The list of reports concerning new and revised monographs that had been prepared by the Laboratory since the March 2016 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 March 2016 meeting was provided for information.

Laboratory Management Review A copy of the BPC and MHRA Laboratory Annual Management Review was provided for information.

IV FUTURE PUBLICATIONS

75 **Monograph Initiation: Candidate Monographs** COM(16)35

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 items had been identified as potential candidate monographs: Marbofloxacin [Powder] for Injection, Tobramycin and Dexamethasone Eye Drops, Prolonged-release Doxycycline Capsules, Baclofen Injection/Infusion, Prolonged-release Diltiazem Capsules. Commission endorsed the recommendation to add the items to the work programme.

Monographs Arising from EAG Advice A number of potential new monographs had been identified during routine EAG work: Rifampicin, Isoniazid and Pyrazinamide Tablets; Meropenem Injection/Infusion; Capsicum Oleoresin; Capsicum Tincture. Commission endorsed the recommendation to add the items to the work programme.

Veterinary Autogenous Vaccines In view of the fact that the Veterinary Medicines Directorate had received requests to authorise a number of these vaccines, Commission endorsed the recommendation to add the item to the work programme.

Bovine Heparin; Bovine Heparin Injection The EAG had considered that the publication of suitable standards would support the provision of heparin if there were shortages of the porcine-derived products in the future and Commission endorsed the recommendation to add these items to the work programme.

Informal Harmonisation The following items were licensed in the UK and were also on the work programme of the International Pharmacopoeia: Rifabutin Capsules, Oseltamivir [Powder] for Oral Suspension, Sulfadiazine Tablets. It had been proposed that the monographs should be developed jointly by the BP and WHO. Commission endorsed the recommendation to add the items to the work programme.

V ANALYTICAL ISSUES

NONE.

VI EXPERT ADVISORY GROUPS / PANELS OF EXPERTS

76 **Expert Advisory Groups, Panels of Experts and Working Parties** COM(16)36

Changes to Chairs/Vice-Chairs Following the retirement of eight members at the end of 2015, and the appointment of new members with effect from 1st January 2016, a number of changes to the Expert Advisory Groups and Panels of Experts had recently been made. These changes had been made following discussions with the current EAG Chairs/Vice-Chairs and with the individuals concerned and were endorsed by members.

Expert Advisory Group BIO: Biological and Biotechnological Products Dr Varley had agreed to take on the role of Chair and Dr Brady had agreed to become a member of EAG BIO.

Expert Advisory Group HCM: Herbal and Complementary Medicines Professor Simmonds had agreed to take on the role of second Vice-Chair of EAG HCM.

Panel DNA: Identification Techniques Professor Adrian Slater (current Vice-Chair, De Montfort University) had agreed to take on the role of Chair of Panel DNA.

New/Retired Members Dr Edward Bush, Mr James Rickard and Ms Marion Chatfield had accepted the invitations to join EAGs MC1 and ULM and the AQbD Working Party respectively.

Expert Advisory Group ABS: Antibiotics Members endorsed the recommendation to appoint Mr Greg Blake (QA Operations Manager, GlaxoSmithKline) to EAG ABS. Mr Andrew Gibson had resigned from EAGs ABS and MC2 and as the UK member of Ph Eur Group 7 (Antibiotics) and a replacement Group 7 member would be identified in due course.

Expert Advisory Group ULM: Unlicensed Medicines Mr Gary Bennett had resigned from EAG ULM following his retirement from the NHS and a letter of thanks for his past service had been sent.

Expert Advisory Group HCM: Herbal and Complementary Medicines Members endorsed the recommendation to appoint Dr Erik Reich (Head of CAMAG, Switzerland; adviser to the Ph Eur, USP and American Herbal Pharmacopoeia on the use of HPTLC in monographs for herbal drugs) to EAG HCM.

Working Party AQbD: Analytical Quality by Design Members endorsed the recommendation to appoint Dr William Sherwin (Director of Chemistry Section, TGA, Australia) as a corresponding member of the Working Party.

Expert Advisory Groups NOM: Nomenclature and PCY: Pharmacy Ms Belen Granell-Villen (BNF) had resigned from EAGs NOM and PCY and a letter of thanks for her past service had been sent. A replacement representative from the BNF would be identified in due course.

77 **Expert Advisory Group PCY: Pharmacy** COM(16)37

The report of the EAG PCY meeting (5:2:16) was approved.

78 **Expert Advisory Group ABS: Antibiotics** COM(16)38

The report of the EAG ABS meeting (8:2:16) was approved and the following point raised.

Moxifloxacin Tablets; Analytical Methods Evaluation Assessment EAG ABS had trialled the evaluation assessment procedure for this monograph. The group had stressed the importance of the formulation review stage.

79 **Expert Advisory Group MC3: Medicinal Chemicals** COM(16)39

The report of the EAG MC3 meeting (25:2:16) was approved and the following point was raised.

Nitrazepam Oral Solution; Assay The Laboratory had been unsuccessful in developing an alternative Assay procedure and the EAG had recommended that the current method should be retained, even though it specified the use of chloroform.

80 **Expert Advisory Group MC2: Medicinal Chemicals** COM(16)40

The report of the EAG MC2 meeting (2:3:16) was approved and the following point was raised.

Prolonged-release Indapamide Tablets It was noted that a decision on whether an increase in the level of impurity C was justified had been deferred, pending receipt of a toxicological assessment.

VII EUROPEAN PHARMACOPOEIA

81 **European Pharmacopoeia Update** COM(16)41

9th Edition The 9th Edition of the European Pharmacopoeia would come into force on 1st January 2017 and would be incorporated as part of the on-line update to the BP 2017.

European Pharmacopoeia Commission The draft report of the 154th Session of the EP Commission (March 2016) had been posted on the BP website.

A copy of the agenda of the 155th Session (June 2016) was provided for information.

Questionnaires sent to the UK National Authority Members were informed that national pharmacopoeial authorities regularly received questionnaires from the EDQM seeking information on whether or not products were licensed and/or on the market with a view to recommending whether items should be added to or removed from the Ph Eur work programme or whether monographs should be suppressed in future publications. The Secretariat made enquiries and sought advice, as appropriate, before sending a response on behalf of the UK delegation.

VIII INTERNATIONAL COLLABORATION

82 **International Collaboration** COM(16)42

Members were provided with an update on international activities.

Brazil A teleconference had been held with the Head of the Brazilian Pharmacopoeia Coordination, ANVISA, to discuss possible collaboration between the British and Brazilian Pharmacopoeias. A draft Memorandum of Understanding was in preparation.

China Dr Atkinson and Mr Evans had attended the 8th Annual DIA (Develop Innovate Advance) Conference in Beijing, China. Participants at the conference had benefitted from making useful contacts and gaining an understanding of current and future pharmaceutical activities in China. During their visit Dr Atkinson and Mr Evans attended a number of useful and informative meetings with other organisations.

Chinese Pharmacopoeia A Memorandum of Understanding between the British and Chinese Pharmacopoeias was signed which will permit the establishment of three working groups to jointly develop monographs in the areas of biologicals, traditional herbal medicines (THM) and medicinal substances and products.

India A teleconference had recently been held with the Indian Pharmacopoeia to discuss potential future collaborations following the signing of the Memorandum of Understanding between the MHRA and the Indian Regulatory Authority.

Australia A teleconference had been held with the Therapeutic Goods Administration Office of Laboratories and Scientific Services to discuss knowledge sharing and organisational updates. It had been agreed that the TGA would participate in the BP/MHRA Analytical Quality by Design feasibility study and in a number of inter laboratory studies on new monographs.

World Health Organization Dr Holland and Mr Evans had attended the April consultation on International Non-proprietary Names. This had been the first meeting chaired by Dr Holland and had been very successful. A significant number of applications were for names for new types of biological substances which posed challenges for the experts. Mr Evans had presented a paper on the difficulties of protecting two-letter INN stems when assessing invented names.

Ms Corns had attended the Consultation on "Quality Control Laboratory Tools and Specifications for Medicines" at which draft documents relating to the International Pharmacopoeia (Ph. Int.) were discussed, including a monograph for Moxifloxacin Tablets which was being jointly prepared by the BP and Ph. Int. by informal harmonisation.

National Pharmacopoeial Authority Secretaries Meeting Dr Atkinson had attended the meeting of NPA Secretaries in Prague at which discussions had been held on the appointment and re-appointment of Ph Eur Expert Group and Working Party members, the Code of Practice and Declaration of Interests.

IX REPORTS OF THE SECRETARY AND SCIENTIFIC DIRECTOR

83 **Laboratory**

It was intended to review ways of working to ensure that future contracts offered the best possible level of laboratory services and adequately met the needs of the BP.

X ANY OTHER BUSINESS

84 **Panel CX: Excipients** It was agreed that, where appropriate, comments on draft documents should be sought from all Panel CX members.

85 **Date of next meeting** Monday 14th November 2016.