BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group ULM: Unlicensed Medicines

SUMMARY MINUTES

A meeting of the Expert Advisory Group on Unlicensed Medicines was held at 151 Buckingham Palace Road, London, SW1W 9SZ on Thursday 8 October 2015.

Present: Dr M G Lee (*Chair*), Mr V Fenton-May (*Vice-Chair*), Mr G Bennett, Mr D Caulfield, Mr S Jones, Dr J Smith, Mr A Sully and Mr P Weir.

Dr N Hussain attended the meeting for items ULM(15)1 to ULM(15)13 and ULM(15)28.

In attendance: Dr F J Swanson, Mr S Young, Mr S Wilson, Mr A Murphy and Miss C Pitt.

Apologies for absence were received from Dr S Branch, Mr W Goddard and Mr M Santillo.

Absent: Mr J Rothwell.

Mr Bennett, Mr Caulfield and Mr Sully declared interests in one or more agenda items and appropriate action was taken.

365 **Introductory Remarks**

Welcome The Chairman welcomed members to the meeting. A special welcome was extended to the four new members of the EAG: Mr G Bennett, Mr D Caulfield, Dr N Hussain and Mr A Sully, and also to Mr Wilson and Mr Murphy who were attending on behalf of the Laboratory. Each member introduced themselves and provided a brief overview of their background relevant to the work of the EAG.

Declaration of Interests Members were reminded to declare specific interests as they arose during the meeting and to inform the Secretariat of any changes to their interests throughout the year.

Correspondence with the Secretariat The Chairman highlighted the importance of communication between members and the Secretariat and indicated that a "nil response" was better than no response to requests for information/comments. Members were specifically chosen for their expertise and experience in order to enable the role of the EAG to be fulfilled.

I MINUTES

366 The minutes of the meeting held on 4 November 2014 were confirmed.

II MATTERS ARISING FROM THE MINUTES

367 The following matters arising from the meeting held on 4 November 2014 were noted.

Minute 333 – Moxifloxacin Intracameral Injection The Laboratory had not yet carried out the work to develop an infrared identification test.

Minute 333 – Phenylephrine Intracameral Injection The Laboratory had not yet carried out the work to develop a related substances test.

Minute 336 – BP 2015: Intraocular/Intracameral Injections The Secretariat had not yet received any further information regarding the proposed guidance on standards for intraocular injections. As

there was still a demand for these products, it was agreed that BP monographs should continue to be prepared where possible.

Minute 347 – Bendroflumethiazide Oral Suspension The monograph had been included in the British Pharmacopoeia 2016 as agreed. The Laboratory work had not yet been carried out and a report would be presented at a future meeting.

Minute 357 – Paediatric Oseltamivir Oral Solution No further information had been received regarding Related substances and no changes to the monograph were proposed at this time.

Minute 360 – Co-operation Agreement with Croatia A co-operation agreement, permitting the inclusion of BP texts relating to unlicensed medicines in the Croatian Pharmacopoeia had been signed by the Chief Executive of the MHRA and the Head of the Croatian Agency for Medicinal Products and Medical Devices in February 2015.

III REPORTS AND CORRESPONDENCE

368 **Introduction to the BP** ULM(15)1

Members had been provided with a written presentation intended to give a brief overview of the work of the British Pharmacopoeia and its position within the Medicines and Healthcare products Regulatory Agency. The Secretariat would be available to answer any questions at any time.

369 **Membership** ULM(15)2

Following the review of membership undertaken in 2014, four new members had been appointed to the Expert Advisory Group on Unlicensed Medicines: Mr Gary Bennett; Mr David Caulfied; Dr Nasir Hussain; Mr Andrew Sully. Mr Charvill and Mr Oldcorne had retired from EAG ULM at the end of 2014.

Members were invited to alert the Secretariat to any potential additional candidates for the group. The Chair stressed that the Secretariat relied heavily on members to provide suitable methods for the elaboration of BP monographs for unlicensed medicines. He also highlighted that access to laboratory facilities to enable testing of proposed methods was important.

Criteria for Appointment and Re-appointment of Members Following the 2014 membership review, a set of criteria had been approved by the BP Commission that would be used as part of the process to consider whether proposed new members were suitable for appointment and whether existing members should be re-appointed. These were provided for information.

370 **Data Integrity** ULM(15)3

A presentation and guidance document on data handling for external experts had been provided following a recent review of data integrity procedures.

Confidentiality Members were reminded that the proceedings of the Expert Advisory Group were confidential and that all material required for meetings should be retained or disposed of in a secure and confidential manner.

Electronic Working In line with the increased use of electronic working within the MHRA, the Secretariat had proposed to trial electronic working within the BPC and EAGs/Panels for a period of one year. Members were asked to provide any feedback on the data integrity procedures to input into the review.

371 **Triennial Review of the BP Commission** ULM(15)4

The British Pharmacopoeia Commission had been the subject of a Triennial Review during 2014-2015. The review had been published at the end of March and had confirmed that the functions of the BPC were still required and that the Commission should be retained as an Advisory Non-Departmental Public Body. A number of recommendations had been made and the Secretariat would be addressing these in the coming months.

Recommendation 8: the BPC and Secretariat should consider draft monograph publication to a specific predictable time-table, including a deadline for comment The review had recommended publication of draft monographs at agreed times and with a set date for comments. It had been agreed that draft new and revised monographs should be posted on the BP website, but the dates and commenting periods were still under discussion. It was noted that a degree of flexibility would be permitted in order to allow publication of text that had not been posted on the website if the need arose.

372 **British Pharmacopoeia 2016** ULM(15)5

The British Pharmacopoeia 2016 had been published at the end of August and would come into effect on 1st January 2016. It contained all of the text from the eighth edition of the European Pharmacopoeia, together with that from Supplements 8.1 to 8.5. Updates to the online version of the BP 2016 would be made during the year, adding the text of Supplements 8.6, 8.7 and 8.8. A list of the 5 new monographs and 11 revised texts published in the BP 2016 that were the responsibility of this EAG had been provided for information. Complimentary copies of the new edition (either hard copy or online access) would be provided to members shortly.

Chloral Hydrate Oral Solution The statement on diluting the solution before use had been deleted from the monograph in the BP 2016.

Lorazepam Oral Solution The content limits had been widened to "92.5 to 105.0%" prior to publication, in view of the limit for total impurities.

373 **Issues arising through the BP Commission** ULM(15)6

Assay Limits The standard assay limits for BP formulated preparation monographs were "95.0 to 105.0% of the stated amount", unless wider limits were justified. Members noted that there were a number of reasons why wider limits might be justified, for example if the sum of total impurities was 5% or greater or to account for degradation during shelf-life, and that these had been accepted by the BP Commission.

Application of ICH Disregard Limits The BP Commission had discussed the approach that should be adopted if a manufacturer applied a lower disregard limit than that required by the ICH Guidelines on Impurities. The Commission had agreed that the preferred BP policy should be to follow ICH guidelines, but that a flexible approach could be adopted, where justified.

Monograph lifecycle review The Secretariat was currently reviewing the processes and prioritisation involved in the initiation, development, publication and revision of monographs.

A member stressed that consideration of inclusion/retention of monographs for unlicensed medicines should be based on patient need and not just if a product was widely used.

374 **Evaluation of Methods** ULM(15)7

Background The BP Commission had endorsed a proposal to carry out a formal documented assessment when methods were adopted without laboratory evaluation in order to ensure a consistent approach across the EAGs.

Discussion The intention was to apply this approach to monographs for Medicinal Chemicals and Antibiotics; it would not be applied to monographs for Unlicensed Medicines at this time.

Provision of information and feedback The level of data provided on unlicensed medicines varied considerably. Members agreed that it would be helpful if they could be provided with guidance, in the form of a template, of the type and level of information that should be provided and the Secretariat agreed to provide this.

It was noted that stakeholder feedback was critically important for the development of robust methods and the earlier this was available the better. The need to raise awareness of published and draft BP monographs was recognised. Members agreed to provide the Secretariat with named contact points to ensure that monographs were seen by the most appropriate personnel. It was agreed that publication of monographs on the website should encourage more feedback.

375 **Inhaled Products** ULM(15)8

British Pharmacopoeia Monographs for Inhaled Products; Supplementary Chapter I O - Inhaled Products The revised policy document concerning the content and format of monographs for Inhaled Products had been approved by the BP Commission at its March 2015 meeting. The revised Supplementary Chapter on Inhaled Products (I O) had been published in the BP 2016. The recommendations were being referred to the EAGs responsible for the monographs and would be reviewed in spring 2016, following feedback from the individual EAGs. Members were asked to contact the Secretariat if they had any comments.

Sodium Chloride Nebuliser Solution (ULM)

Definition The Definition had been amended to reflect the revised templates for inhaled product monographs and was accepted.

Production The proposal to remove the Production statement, to reflect the revised policy of not including the Aerodynamic Assessment of Nebulised Aerosols and Preparations for Nebulisation, Characterisation test in individual monographs (because of the device-specific nature of the requirement), was accepted.

376 **Extemporaneous Preparations** ULM(15)9

Members noted a progress report which had been presented to EAG PCY (Pharmacy) and which was provided for information. It was intended that the Secretariat should consult with stakeholders about whether the extemporaneous formulae in the BP should be retained, deleted or moved to a Supplementary Chapter. A full paper on this would be presented at the next meeting and would include the results of the stakeholder consultation.

It was suggested that Chief Pharmacists and the Paediatric Formulary Working Party should be contacted as part of the stakeholder consultation exercise.

IV NEW MONOGRAPHS AND OTHER TEXTS

377 **Sodium Benzoate Injection** ULM(15)10

The draft monograph would be included in a future publication, subject to resolution of any outstanding points.

378 **Tretinoin Cream** ULM(15)11

It was agreed that a monograph for the formulation should be added to the work programme as the product was widely-used for the treatment of skin discolourations.

379 **Supplementary Chapter - Aseptic Preparations** ULM(15)12

The draft Supplementary Chapter would be included in a future publication, subject to resolution of any outstanding points.

380 **Parenteral Nutrition Solutions** ULM(15)13

The draft text for addition to the General Monograph on Unlicensed Medicines would be included in a future publication, subject to resolution of any outstanding points.

V MONOGRAPHS IN PROGRESS

381 **Betamethasone Valerate and Coal Tar Paste** ULM(15)14

The draft monograph would be included in a future publication, subject to resolution of any outstanding points.

382 **Lorazepam Oral Suspension** ULM(15)15

The draft monograph would be included in a future publication, subject to resolution of any outstanding points.

383 **Tobramycin Oral Solution** ULM(15)16

The draft monograph would be included in a future publication, subject to resolution of any outstanding points.

VI REVISION OF MONOGRAPHS

384 **Monographs For Anti-Epileptic Drugs** ULM(15)17

The comments from EAG ULM on the inclusion of non-interchangeability statements in monographs for unlicensed oral liquid formulations for antiepileptics had been brought to the attention of the BP Commission. The wording had subsequently been revised by the Secretariat and approved by the Chair and Vice-Chair of EAG ULM and the BP Commission.

Paediatric Phenobarbital Oral Solution The monograph had been revised in the BP 2016 to include the following statement: *"Different formulations of Paediatric Phenobarbital Oral Solution may vary in bioavailability. Patients should be monitored to ensure blood levels remain within the required therapeutic range."* It was agreed that the statement should be retained in view of the need for therapeutic drug monitoring for phenobarbital.

Clonazepam Oral Suspension As the BNF did not recommend therapeutic drug monitoring for this preparation, it was agreed that the following statement should be included in the monograph: *"Different formulations of Clonazepam Oral Suspension may vary in bioavailability. Patients should be monitored in accordance with appropriate clinical guidelines."*

Supplementary Chapter V C: Bioequivalence of Oral Liquids It was agreed that the patient monitoring statement should be revised to: "*Patients should be monitored in accordance with appropriate clinical guidelines"*.

Azathioprine Oral Suspension Although the preparation was not used as an antiepileptic, the monograph contained a patient monitoring statement in view of the narrow therapeutic range of the product. It was agreed that the statement should be revised to: *"Different formulations of Azathioprine Oral Suspension may vary in bioavailability. Patients should be monitored in accordance with appropriate clinical guidelines."*

385 **Ph Eur Monograph Titles – Degree Of Hydration** ULM(15)18

Ph Eur proposal Members noted the Ph Eur proposal to revise monograph titles for pharmaceutical and medicinal substances to:

(1) Include the degree of hydration for substances that are hydrates;

(2) Remove the term anhydrous from anhydrous substances.

Impact of the changes on BP texts If the changes were agreed at the Ph Eur Commission, the consequential revisions required to BP texts to reflect the proposed revised Ph Eur monograph titles would be carried out in accordance with a revision programme, which was being developed by the Secretariat.

386 **Chlorhexidine Gluconate Eye Drops** ULM(15)19

Related substances A request had been received to relax the total impurity limits in the monograph for Chlorhexidine Gluconate Eye Drops. A member agreed to provide supporting data, if available, to enable a realistic limit to be set.

387 **Dithranol and Salicylic Acid Ointment** ULM(15)20

Assay for salicylic acid The Laboratory had been asked to develop a suitable assay method, using either titration or HPLC, following reports of extraction problems using the published method.

The titration method from the monograph for Salicylic Acid Ointment had been found unsuitable due to interference from the dithranol component. Potentiometric titration had also been found unsuitable as a 20% reduction in the Assay for Salicylic Acid was observed in the presence of Dithranol.

The Laboratory had found that the existing dithranol extraction procedure and a modification of the chromatographic conditions from the Related substances test for Dithranol was suitable. A draft amendment had been prepared and was accepted.

The amount of Salicylic Acid was dependent on the Dithranol concentration. This had been reflected in the proposed method and in the Content of salicylic acid.

Content limits It was agreed that the current 90.0 to 110.0% limits were acceptable for this type of formulation.

Assay for dithranol The HPLC method had also been found suitable for determination of the Dithranol component. However it was not intended to change the Assay for dithranol at this time.

388 **Omeprazole Oral Suspension** ULM(15)21

Buffer Capacity Following deletion of the Dissolution and Alkalinity requirements, a Buffer Capacity test (a measure of the efficiency of a buffer in resisting changes in pH) had been drafted, based on work carried out by the MHRA Laboratory.

The proposed test has been circulated to suppliers for comment and the responses received supported inclusion of the test and limits. It was noted that the test was independent of the buffer used and it was agreed that the revised monograph should be published in the BP 2017.

389 **Sodium Bicarbonate Oral Solution** ULM(15)22

The agreed changes to the monograph for Sodium Bicarbonate Oral Solution had been included in the BP 2016 (Action and Use, Labelling, Dispensing and Supply statement).

Scope of monograph A number of options were proposed to reflect the existence of unlicensed and licensed products for both the oral solution and the powder for reconstitution. The licensed product was used for the treatment of dyspepsia but the unlicensed product was used for the treatment of uraemic acidosis and renal tubular acidosis.

After discussion it was agreed that the current sub-monograph for the powder for reconstitution should be retained. A revised monograph had been prepared and was accepted.

VII WORK PROGRAMME

390 **Work Programme** ULM(15)23

The work programme had been updated to reflect changes since the last meeting and to remove any items that had been published in the British Pharmacopoeia 2016. Items for which licensed products were now available had also been removed and the Secretariat would inform the relevant Medicinal Chemicals Expert Advisory Groups that these monographs had previously been included on the EAG ULM work programme. The work programme had been sent to the new members for information and a number of comments and proposals for new monographs had been received.

Proposed New Monographs to add to the work programme It was agreed that the following items should be added to the work programme: Glycopyrronium Bromide Topical Gel; Magnesium Glycerophosphate Oral Suspension; Ethambutol Oral Solution (*see item on anti-tuberculosis medicines*); Calcium Carbonate Oral Suspension.

Adenosine Injection Licensed products were available. It was agreed that the relevant EAG should be informed that this widely-used product was a high priority.

Sildenafil Oral Solution It was agreed that the Secretariat should check if licenced products were available before adding the item to the work programme.

Advanced Therapy Products These preparations fell under the remit of the EAG on Biological and Biotechnological Products (BIO), but products were available as unlicensed medicines. A member agreed to send information to the Secretariat. It was suggested that EAG ULM could collaborate with EAG BIO, as necessary, in the development of future monographs for such products.

Ceftazidime Injection A member had requested that a monograph should be prepared to cover unlicensed formulations of Ceftazidime Injection (ready-to-use solution). There was already a monograph for the licensed formulation (powder for re-constitution). It was agreed that a monograph

should be added to the work programme and developed on receipt of suitable information. Two members agreed to work together in order to provide suitable information to the Secretariat.

Eye Preparations Members were encouraged to provide supporting information on specific requirements for unlicensed Eye Drops.

391 **Unlicensed Oral Medicines for the Treatment of Tuberculosis** ULM(15)24

A member had provided two papers on the need for fixed formulation monographs for a number of paediatric preparations used in the treatment of tuberculosis. The papers had recommended that fixed formulation monographs for the three main liquid formulations (see below) should be added to the British Pharmacopoeia.

Ethambutol Oral Liquid (400 mg / 5 ml) The item was included on the secondary work programme. Two members agreed to provide information to enable development of a monograph.

Isoniazid Oral Liquid (100 mg / 5 ml); Pyrazinamide Oral Liquid (500 mg / 5 ml) Open strength monographs had already been published for these formulations. Members noted that TB was a growing problem in the UK and that there were a number of different strength products available. It was agreed that further information should be requested before any changes were considered. Any proposals would need to take account of the on-going discussions within the wider Secretariat and EAGs regarding monographs for extemporaneous preparations and the BPC policy of developing open-strength monographs, where possible.

392 **USP Monographs for Compounded Preparations** ULM(15)25

The Secretariat had examined the list of monographs for compounded preparations published in the United States Pharmacopeia (USP) to identify monographs that were on the EAG ULM work programme for which it might be possible to prepare a monograph.

Diltiazem Hydrochloride Oral Suspension; Metoprolol Tartrate Oral Suspension It was agreed that BP monographs should be developed and circulated for comment to the suppliers listed in Pro-file. Where appropriate, existing BP methods would also be considered.

393 **Monographs Proposed for Omission** ULM(15)26

It was agreed that a number of monographs should be omitted from a future edition of the BP, subject to approval by the BP Commission and overseas authorities. There were no current UK licences for the preparations.

394 **Monographs Proposed for Referral to EAG ULM** ULM(15)27

There were no current UK licenses for the following products and it had been proposed that the responsibility for the monographs should be transferred to EAG ULM.

Paediatric Digoxin Injection It agreed that the responsibility for the monograph should be transferred to EAG ULM as it was a widely-used unlicensed medicine.

Definition; Extemporaneous formula It was suggested that advice should be sought regarding whether the extemporaneous formula should be retained, removed from the monograph or added to the Supplementary Chapter on Extemporaneous Preparations.

Members were informed that the Secretariat would be undertaking a consultation exercise regarding whether all the extemporaneous formulae in the BP should be moved to a Supplementary Chapter and a report and proposals would be presented at a future meeting.

Adrenaline Eye Drops It was agreed that the monograph should be omitted from a future edition of the BP, unless advice was received that the preparation was made in unlicensed facilities.

Adrenaline Solution; Benzatropine Tablets; Dithranol Ointment; Naproxen Oral Suspension It was agreed that the responsibility for these monographs should be transferred to EAG ULM.

Tetracaine Eye Drops The product was not used as an unlicensed medicine because a licensed preparation was available. The monograph would not be transferred to EAG ULM.

Policy The need for a consistent policy regarding transfer of monographs to EAG ULM was highlighted and the Secretariat undertook to draft proposals for consideration at the next meeting. It was agreed that monographs should only be transferred if products (a) did not have UK licenses and (b) were known to be used as unlicensed medicines.

VIII INTERNATIONAL

395 **Pan-European Paediatric Formulary Project** ULM(15)28

An update was provided on the project for the elaboration of a pan-European formulary for unlicensed paediatric medicines.

The Working Party had established a set of criteria upon which to develop a paediatric formulary based on clinical and quality issues. The final meeting of the Working Party would take place in the week beginning 12th October and further work would then be undertaken by a new group that would source monographs for inclusion in the formulary and establish how the criteria could be applied to available preparations.

It was noted that there might be a move towards specifying fixed formulae in the monographs, but that the monographs would not be legally binding and would not be published in the European Pharmacopoeia.

IX ANY OTHER BUSINESS

396 **Date of next meeting** To be arranged.