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 20th October 2016.

Present: Dr M G Lee (*Chair*), Mr V Fenton-May (*Vice-Chair*), Mr D Caulfield, Mr W Goddard, Mr J Rickard, Mr M Santillo, Dr J Smith, Mr A Sully and Mr P Weir.

In attendance: Dr F J Swanson, Mr P Crowley, Mr S Young, Ms F Lee and Ms C Galdino. Dr M Westwood also attended the meeting.

An apology for absence was received from Dr N Hussain. Dr S Branch did not attend the meeting.

426 **Introductory Remarks**

Welcome The Chair welcomed members to the meeting. A special welcome was extended to Ms Lee and Ms Galdino, who were attending on behalf of the Laboratory, and to Dr Marion Westwood (MHRA).

Secretariat A number of changes had recently taken place within the Secretariat. Miss Pitt was no longer working on EAG ULM. The Secretariat members responsible for the group were now Dr Fiona Swanson and Mr Peter Crowley.

Membership Mr Sean Jones had resigned from EAG ULM due to conflicting work commitments. Mr Jones had been associated with the work of the group since it had been established and had provided valuable input over the years. Dr Westwood was the new representative from the Licensing Division.

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.

Mr Caulfield declared an interest in one or more agenda items and appropriate action was taken.

I MINUTES

427 The minutes of the meeting held on 21st April 2016 were confirmed.

II MATTERS ARISING FROM THE MINUTES

428 The following matters arising from the meeting held on 21st April 2016 were noted.

Minute 403 – Triennial Review Update: Public Consultation on Draft Monographs
A number of new and revised monographs that were the responsibility of EAG ULM had been posted on the BP website for public comment. The deadline was 31st December and members were encouraged to alert anyone who might have an interest to the draft text.

Minute 411 – Parenteral Nutrition Solutions It had not been possible to progress this item since the last meeting.

Minute 416 – Paediatric Digoxin Injection Further revision of the monograph had been deferred pending the wider review of monographs containing extemporaneous preparations.

Minute 420 – Standards for Intraocular Injections It had not been possible to progress this item since the last meeting.

Minute 420 – Moxifloxacin Intracameral Injection A supplier was now listed in Pro-file. The Secretariat would try and obtain samples in order to enable the outstanding Laboratory work to be carried out.

Minute 424 – BP Laboratory Further to the discussion regarding preparing preparations extemporaneously if products could not be obtained, a member had kindly advised that his laboratory might be able to provide guidance to the BP Laboratory. It had been agreed that the best time to seek the advice was close to the start of any practical evaluation.

III REPORTS AND CORRESPONDENCE

429 Issues Arising through the BP Commission ULM(16)25

Monograph Lifecycle Review The Secretariat had undertaken a review of the processes and prioritisation involved in the initiation, development, publication and revision of monographs. The proposals arising from the review had been endorsed by the British Pharmacopoeia Commission at their meeting in July 2016 and a copy was provided for information. It was stressed that the proposals were intended to ensure a consistent and formalised approach across the Expert Advisory Groups and to provide more realistic work programmes for the Secretariat and the Laboratory. A set of criteria had been agreed which were intended to assist in prioritising those monographs that should be developed or revised and to identify whether practical work should be undertaken by the Laboratory.

While members agreed that the criteria would help prioritise work generally, it was pointed out that the nature of the work of EAG ULM could mean that different criteria were awarded higher priority than those for licensed medicines.

430 Policy For Transferring Monographs to EAG ULM ULM(16)26

The approach agreed at the last meeting regarding the proposed transfer of monographs to EAG ULM when licensed products were no longer available had been endorsed by the British Pharmacopoeia Commission at their meeting in July 2016. It had been confirmed that if a monograph was to be retained in the BP the relevant EAG should make any changes to the text as required **before** the responsibility for the text was transferred to EAG ULM. Members confirmed that the opening statement highlighting the purpose of an unlicensed medicine was acceptable.

431 EAG ULM Data Template ULM(16)27

The template designed to provide guidance to members on the type of information required to enable monograph development had been amended as agreed to include reference to the form of active ingredient, the maximum daily dose and the therapeutic indications. The revised template was accepted.

432 **Cefuroxime Intracameral Injection** ULM(16)28

Content of cefuroxime The current 95.0 to 105.0% content limits were based on data provided during development of the monograph. The Secretariat had been alerted to correspondence regarding the shelf-life of a product based on a 90.0% lower content limit.

Members were reminded that a product must comply with BP limits throughout shelf-life. Although the usual BP content limits were 95.0 to 105.0%, more relaxed limits could be published if the product degraded over time and supporting data was provided. It was noted that the monograph for the licensed Cefuroxime Injection (dry powder for reconstitution) included limits of 90.0 to 105.0%, indicating degradation during the recommended period of use for the reconstituted product.

A number of issues were highlighted during the discussion: (i) the specific issue relating to Cefuroxime Intracameral Injection; (ii) the need to comply with a published monograph; (iii) the fact that the ± 5% content limits might not be appropriate for re-constituted products; (iv) the possible need to allow wider limits in general for unlicensed medicines; (v) the need to consider the content of the active ingredient since the amount in the product would be dependant on the level in the starting material; (vi) the need to base limits on stability data rather than shelf-life.

It was agreed that the EAG should develop some policy guidelines regarding limits for unlicensed medicines, paying particular reference to reconstituted preparations. It was agreed that the limits for Cefuroxime Intracameral Injection should be widened to 90.0 to 105.0% in line with the licensed injection formulation. It was noted that the published limits for Cefuroxime Eye Drops were 95.0 to 105.0%.

433 **Extemporaneous Preparations** ULM(16)29

Background The discussions at the last meeting had been brought to the attention of the British Pharmacopoeia Commission in July. The BP Commission had strongly supported the approach preferred by EAG ULM to move extemporaneous preparation details to a Supplementary Chapter and include a reference to the Chapter within relevant monographs. The Commission had also accepted that there might be justification to retain the extemporaneous preparation information within certain monographs for safety reasons and that a review of each monograph should be undertaken before any changes were made.

This matter had been further discussed at the September meeting of the Expert Advisory Group on Pharmacy and further discussions would be held before the review was completed.

434 **Supplementary Chapter V: Unlicensed Medicines** ULM(16)30

The Supplementary Chapter on Unlicensed Medicines had been updated in the BP 2014 to reflect changes arising as a consequence of the introduction of The Human Medicines Regulations 2012. The Secretariat had received comments on the current text and a number of changes would be made in a future publication.

435 **Supplementary Chapter V F: Aseptic Preparation of Unlicensed Medicines** ULM(16)31

Supplementary Chapter V F The Supplementary Chapter on Aseptic Preparation of Unlicensed Medicines had been published in the British Pharmacopoeia 2017. The fifth edition of the guidance on "*Quality Assurance of Aseptic Preparation Services: Standards*

Handbook" was now available and was a joint initiative between the Royal Pharmaceutical Society and the NHS Pharmaceutical Quality Assurance Committee.

It was agreed that the text should be amended to remove reference to the various editions of the NHS/RPS guidance, and to note that the guidance was regularly updated, but that no other changes were required.

IV NEW MONOGRAPHS

436 **Work Programme** ULM(16)32

The work programme had been updated to reflect changes since the last meeting and to remove items included in the BP 2017. A copy was provided for information. Members were encouraged to provide information to assist in the development of suitable monographs and, where possible, to test the suitability of draft methods.

Carvedilol Oral Suspension; Clomipramine Hydrochloride Oral Suspension; Naltrexone Oral Suspension These items had been added to the secondary work programme. Members were asked to inform the Secretariat if they were aware of any suppliers of these products.

Midazolam Oral Liquid In light of the published monographs for Midazolam Oral Solution and Midazolam Oromucosal Solution, members agreed that a monograph for Midazolam Oral Suspension was not required.

Hydrochlorothiazide Oral Liquid; Pentoxifylline Oral Liquid These items did not appear to be widely used and it was agreed that, unless suppliers could be identified, the monographs should not be added to the work programme at this time.

It was agreed that the Secretariat should circulate the work programme to Special Order manufacturers and suppliers listed in Pro-file to try and identify potential monographs for which information might be forthcoming.

437 **Ethambutol Oral Solution/Suspension** ULM(16)33

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

438 **Loperamide Oral Suspension** ULM(16)34

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

439 **Nadolol Oral Suspension** ULM(16)35

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

440 **Nifedipine Oral Suspension** ULM(16)36

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

V MONOGRAPHS IN PROGRESS

441 **Ceftazidime Injection [Infusion]** ULM(16)37

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

442 **Diltiazem Oral Suspension; Diltiazem Oral Solution** ULM(16)38

It was agreed that a monograph for Diltiazem Oral Suspension should only be prepared at this time. The draft monograph would be included in a future publication, subject to resolution of any outstanding points.

443 **Lorazepam Oral Suspension** ULM(16)39

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

444 **Metoprolol Oral Suspension; Metoprolol Oral Solution** ULM(16)40

It was agreed that a monograph for Metoprolol Oral Suspension should only be prepared at this time. The draft monograph would be included in a future publication, subject to resolution of any outstanding points.

445 **Tobramycin Oral Solution; Tobramycin Sulfate** ULM(16)41

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

446 **Tretinoin, Hydrocortisone and Hydroquinone Cream; Hydroquinone** ULM(16)42

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

VI REVISION OF MONOGRAPHS

447 **Bendroflumethiazide Oral Suspension** ULM(16)43

Identification The Laboratory had confirmed that the TLC method for Bendroflumethiazide Tablets was suitable for application to the Oral Suspension and members agreed that the test should be added to the monograph in the BP 2018.

Related substances; Assay When testing the published methods, the Laboratory had observed a decrease in the content of the active substance of about 3% in solutions left overnight and had recommended that the injection vials should be stored at 4° before use.

Content of bendroflumethiazide The current content limits (92.5 to 105.0%) reflected the shelf-life limits and would remain unchanged.

448 **Chlorhexidine Gluconate Eye Drops** ULM(16)44

Related substances; 4-Chloroaniline Further information on impurity limits had been provided. It was agreed that the test should be amended to include a limit of not more than 1% for 4-chloroaniline and not more than 3.5% for the sum of total impurities.

Column The Secretariat had received a report of difficulties with the method when using the column specified in the monograph (Spherisorb ODS, 20 cm × 4 mm). It had been noted that a different column had been used during testing (Phenomenex Luna C18, 25 cm × 4.6 mm) and it was agreed that the method should be updated accordingly.

Assay It was agreed that no change to the Assay, which used different chromatographic conditions from the related substances test, should be made at this time.

449 **Folic Acid Injection** ULM(16)45

Acidity or alkalinity Further information and batch data had been received to support the proposed change in pH limits from "8.0 to 11.0" to "7.0 to 9.0", in line with Guidelines from the Royal College of Nursing and the specifications of some preparations. It was agreed that the pH limits should be amended in the BP 2018.

450 **Paediatric Phenobarbital Oral Solution** ULM(16)46

Related substances; Assay The proposed related substances test had been sent to interested parties for comment. In the absence of any adverse comments it was agreed that the monograph should be updated to use the same method for Assay and Related substances in the next edition of the BP.

451 **Phenylephrine Intracameral Injection** ULM(16)47

Related substances The Laboratory had been asked to confirm the suitability of the HPLC method included in the monograph for Phenylephrine Hydrochloride to the Intracameral Injection formulation. In the absence of any commercial samples, the method has been examined on a formulation prepared by the Laboratory from Phenylephrine Hydrochloride and a range of typical excipients. The method had been found suitable, subject to using a different column from that specified in the European Pharmacopoeia in order to meet the system suitability requirements. No impurities had been detected and a method incorporating the limits from the Ph Eur monograph had been drafted for consideration.

It was agreed that the draft amendment should be published in the BP 2018, subject to any comments from interested parties.

VII INTERNATIONAL

452 **Paediatric Formulary Working Party** ULM(16)48

The report of the first meeting of the Paediatric Formulary Working Party was provided for information. Members were reminded that monographs produced by the Working Party would not be included in the European Pharmacopoeia and would not be legally binding.

453 **Council of Europe Resolutions** ULM(16)49

Copies of the following two Council of Europe Resolutions, which had been adopted by the European Committee of Ministers of the Council of Europe in June 2016, were provided for information. Members were informed that the Resolutions were not mandatory, but that EU Member States were encouraged to comply.

CM/Res(2016)1: Quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients This resolution superseded CM/ResAP(2011)1. The Chair had provided comments prior to the adoption of the original

version. It was understood that the updated text reflected UK practices and was not expected to cause any issues.

CM/Res(2016)2: Good reconstitution practices in health care establishments for medicinal products for parenteral use Members confirmed that the new Resolution reflected UK practices and should not cause any issues.

VIII ANY OTHER BUSINESS

454 **Magnesium Glycerophosphate Oral Solution** The MHRA Laboratory had recently carried out some testing of Magnesium Glycerophosphate Oral Solution using the methods in the BP monograph following receipt of a report from the MHRA Defective Medicines Reporting Centre. The testing had highlighted that an insufficient amount of magnesium was present in the suspect product and an MHRA inspection had subsequently identified a manufacturing issue. This work highlighted the value of publishing monographs for unlicensed medicines.

455 **Glycopyrronium Bromide Oral Solution; Methotrexate Oral Solution** Licensed products were now available and so the monographs would be transferred to the relevant Expert Advisory Groups.

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