BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group ULM: Unlicensed Medicines

SUMMARY MINUTES

A meeting of the Expert Advisory Group on Unlicensed Medicines was held at 10 South Colonnade, Canary Wharf, London E14 4PU on Wednesday 16th October 2019.

Present: Dr M G Lee (*Chair*), Mr V Fenton-May (*Vice-Chair*), Mr A Bosley, Ms M Godber, Mr W Goddard, Dr D Kirby, Mr J Ramada-Magalhaes, Mr M Santillo, Dr J Smith, Mr P Weir and Dr M Westwood.

In attendance: Dr F J Swanson, Mr A Evans, Ms K Busuttil, Ms M Nanasi and Ms Y El Dabh.

Apologies for absence were received from Ms S Hartley and Mr A Sully.

560 **Introductory Remarks**

Welcome The Chair welcomed members to the meeting. A special welcome was extended to the four new members of the EAG (Mr Bosley, Ms Godber, Dr Kirby and Mr Ramada-Magalhaes), who were attending their first meeting, and also to Mr Evans from the BP Secretariat and to Ms Busuttil, Ms Nanasi and Ms El Dabh from the BP Laboratory. Members introduced themselves to the group.

MHRA Dr Ian Hudson had retired from his position as Chief Executive Officer of the MHRA in September. Dr June Raine, the former Director of the Vigilance and Risk Management of Medicines Division, had been appointed as the interim CEO until a permanent replacement for Dr Hudson had been appointed.

Declaration of Interests Members were reminded of the need to declare any specific interests as they arose during the meeting for the purposes of transparency.

Mr Bosley and Ms Hartley (by correspondence) declared interests in one or more agenda items and appropriate action was taken.

I MINUTES

561 The minutes of the meeting held on 15th October 2018 were confirmed, subject to correcting the opening statement to reflect the Canary Wharf location.

II MATTERS ARISING FROM THE MINUTES

562 The following matters arising from the meeting held on 15th October 2018 were noted.

Minute 536 – Lorazepam Oral Suspension Mr Sully had provided a preliminary report of the work carried out by St. Mary's Pharmaceutical Unit on Related substances. It was hoped that further information would be available for the next meeting.

Minute 543 – Adrenaline Preparations The addition of Related substances tests to the monographs for Adrenaline Eye Drops and Adrenaline Solution had been deferred pending the outcome of laboratory evaluation of the licensed Adrenaline-containing formulations.

III REPORTS AND CORRESPONDENCE

563 **Membership** ULM(19)1

Following the review of membership undertaken in 2018, four new members had been appointed to EAG ULM: Mr Alex Bosley, Ms Mandy Godber, Dr Daniel Kirby and Mr Joaquim Ramada-Magalhaes. Dr Branch, Mr Caulfield and Mr Rickard had retired from the group at the end of 2018 and all other members had been re-appointed for a further four-year term.

564 **British Pharmacopoeia 2020** ULM(19)2

The British Pharmacopoeia 2020 had been published in August and would come into effect on 1st January 2020. It contained all the text from the 9th edition of the European Pharmacopoeia, together with that from Supplements 9.1 to 9.8. The 10th edition had been published in July and the content of the new edition would be incorporated into the online BP in December and in the BP 2021. Updates to the online version of the BP 2020 would be made during the year, adding the text of further Ph Eur Supplements.

A list of the new and revised texts that were the responsibility of this EAG that had been published in the BP 2020 was provided for information. The previously agreed changes to the opening statement and cross-reference to General Monographs had also been made to 70 monographs for unlicensed formulations in the 2020 edition.

565 **Issues Arising Through the BP Commission** ULM(19)3

Members noted the following issues, which had recently been discussed by the British Pharmacopoeia Commission.

BP User Guide; BP Website A BP user guide had been developed and was available on the website (https://www.pharmacopoeia.com/how-to-use-the-bp). A number of improvements had recently been made to the BP website, including the introduction of a "timeline feature" which highlighted the editions in which changes to individual monographs had been made. Further improvements would be added in the future.

Assay for Liquid Formulations; Weight per mL Following confusion over which monographs should include a weight per mL requirement, the BP Commission had confirmed the general approach to follow. Formulations that can easily be withdrawn by pipette should be sampled by volume and there was no need for a weight per mL determination to be carried out. Viscous formulations that cannot be accurately withdrawn by pipette should be sampled by weight and a weight per mL requirement included in the monograph. This would mainly affect monographs for Oral Suspensions, but also applied to other liquid formulations.

Related substances: Use of correction factors The Commission had discussed whether the current policy relating to the use of correction factors only when the response of an impurity compared to that of the active substance was outside the range "0.8 to 1.2" should be extended to all impurities in order to avoid the possibility of under- or over-estimating impurities and affecting pass or fail results. It had been agreed that a pragmatic approach should be followed and that no retrospective changes were required.

Assay for Capsules It had been agreed that in line with the method of sample preparation for Tablets, an explicit weighing step should be included for Capsules. Draft wording had been accepted and would be included in new and revised monographs going forward.

566 **Supplementary Chapter V F** ULM(19)29

Background At the meeting in April 2018 proposals for a "Compendium of Usage Monographs for Reconstituted Intravenous Medicines" had been presented. The intention had been to provide guidance and information on the stability of reconstituted injections. Members had agreed that provision of this type of information would be useful but noted that it would involve significant resources to obtain current, relevant information and to keep it up to date. It had also been questioned whether it was appropriate to include such information in the BP and the consensus had been that it was more suited to a separate publication. It had been agreed, however, that it would be helpful to include general information in a Supplementary Chapter.

Ready to Administer Injections Draft text on **Ready to Administer Injections** had been prepared for inclusion in the section on ***Types of Formulation*** included in Supplementary Chapter V F (Aseptic Preparation of Unlicensed Medicines).

A number of issues were raised at the meeting. Members were asked to send further comments to the Secretariat **by 30th November** and were encouraged to circulate the draft document within their networks. It was hoped that the text could be finalised for inclusion in the BP 2021.

567 **Buffered Antibiotics** ULM(19)4

At the last meeting it had been noted that some parenteral antibiotics were prepared in citrate buffers rather than in Water for Injections and it had been questioned whether such formulations would meet the requirements of published monographs and whether consideration should be given to preparing separate monographs for buffered and non-buffered products.

Information had been provided on several ready-to-use infusions. While acknowledging the need to avoid the proliferation of similar monographs, the preparation of stand-alone monographs for ready-to-use and dry powder injections/infusions was in accordance with BP Commission policy.

Flucloxacillin Infusion; Benzylpenicillin Infusion Draft monographs would be prepared for inclusion in a future publication.

568 **Dissolution of Unlicensed Oral Suspensions** ULM(19)5

BP Consultation The response to the consultation on "Dissolution Testing in BP Finished Product Monographs for Solid Oral Dosage Forms" had been published on the BP website and the Expert Advisory Group on Pharmacy were developing an updated policy on dissolution testing.

General Monograph As the dissolution profile of Oral Suspensions could be affected by the way the sample was collected and introduced into the dissolution vessel, it had been agreed that a standardised approach should be included in the General Monograph for Unlicensed Medicines. Members had been asked to provide details of the approach used in their organisations and a draft amendment had been prepared based on information provided. It was suggested that it might be helpful to expand the current text and the Secretariat agreed to review the text and circulate revised proposals for confirmation.

569 **Ketamine Nasal Spray** ULM(19)6

A communication had been received regarding the potential for misuse of Esketamine Nasal Spray and Ketamine Nasal Spray.

Identification A company had requested that an optical rotation test should be included as an additional identification test in order to provide assurance that Ketamine Hydrochloride (racemate) was present rather than Esketamine Hydrochloride (single enantiomer). A draft amendment, based on the test in the monograph for Ketamine Hydrochloride, had been prepared and was accepted.

Action and use It was agreed that no change to the current action and use statement (Anaesthetic) should be made.

570 **BP Portfolio Review** ULM(19)7

Background A comprehensive review of the BP portfolio of standards (both monographs and British Pharmacopoeia Chemical Reference Substances) was being undertaken in order to ensure that the BP directed its limited resources to those standards that were of the greatest value to public health.

The matter had been discussed by the BP Commission at their meeting in March 2019 and a set of general principles and measures were agreed to support a comprehensive review of the BP portfolio. Although the general principles were intended to apply across the EAGs, different factors would need to be taken into consideration for some of the groups.

EAG ULM Monographs Monographs containing low-selling BPCRS had been identified and appropriate courses of action were agreed.

571 **British Pharmacopoeia Chemical Reference Substances** ULM(19)8

The current BPCRS catalogue was increasing in size each year and was becoming difficult to maintain. A status report was published on the BP website every month listing newly established materials and those which were out of stock, together with tentative dates when these were expected to be available. In cases where materials could not be obtained it would be necessary to amend monographs to remove the need for the specific BPCRS.

IV MONOGRAPHS IN PROGRESS

572 **Carvedilol Oral Suspension;** ULM(19)9
Clomipramine Oral Suspension

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

573 **Nadolol Oral Suspension** ULM(19)10

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

574 **Nifedipine Oral Suspension** ULM(19)11

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

575 **Parenteral Nutrition Solutions** ULM(19)12

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

V NEW MONOGRAPHS

576 **Work Programme** ULM(19)13

Progress The work programme had been updated to reflect the decisions taken at the last meeting and to reflect changes included in the British Pharmacopoeia 2020. There were several items on the list for which members had previously agreed to provide information which had not been forthcoming. Members were asked to advise the Secretariat if/when they would be able to provide the necessary information.

The Secretariat had prepared draft monographs for several outstanding items on the list; these had been chosen on the basis of (i) discussions at the last meeting, (ii) the ability to arm-chair methods from existing monographs and (iii) the usage figures. It was hoped that several of these items would be suitable for publication in the next edition of the BP.

University collaboration The BP was still keen to work with universities on suitable projects but it had been clear from the studies undertaken to date that a full monograph evaluation would not be feasible in the time available to students.

577 **Atropine Oral Solution** ULM(19)14

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

578 **Benzylpenicillin Eye Drops** ULM(19)15

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

579 **Etoposide Oral Solution** ULM(19)16

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

580 **Flecainide Oral Liquid Preparations** ULM(19)17

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

581 **Glycopyrronium Bromide Topical Preparations** ULM(19)18

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

582 **Ketamine Preparations** ULM(19)19

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

583 **Potassium, Magnesium and Sodium Chloride Infusion** ULM(19)20

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

584 **Quinine Preparations** ULM(19)21

The draft monograph for Quinine Sulfate Oral Suspension would be included in a future publication, subject to resolution of any outstanding points.

585 **Sodium Benzoate Oral Solution** ULM(19)22

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

586 **Tranexamic Acid Oral Solution** ULM(19)23

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

VI REVISION OF MONOGRAPHS

587 **Review of Extemporaneous Preparations: Update** ULM(19)24

Members were reminded that the final outcomes of the review of monographs containing extemporaneous preparation information by the Expert Advisory Group on Pharmacy and EAG ULM had been endorsed by the BP Commission.

In addition to the changes to the individual monographs, several areas of the BP would also need to be amended and it was highlighted that these changes would need to be made concurrently.

General Notices The General Notice on Manufacture of Formulated Preparations would need to be amended to reflect that extemporaneous preparation information could be included both in individual monographs and in the Supplementary Chapter.

Supplementary Chapter The current Supplementary Chapter on Extemporaneous Preparations would need to be expanded and moved from the section on Unlicensed Medicines. A preliminary draft of the new Chapter had been prepared and was confirmed by members. It was noted that the format would permit the inclusion of additional formulation details where appropriate.

588 **Dithranol and Salicylic Acid Ointment** ULM(19)25

Assay for salicylic acid The current HPLC Assay method had been developed by the BP Laboratory. During development of the method the Laboratory had observed a shift in retention times and a change of the peak shape. It had been recognised that the method was not ideal, but both UV and titrimetric methods had been found unsuitable due to interference from the Dithranol component and a more robust method had not been identified.

Members were asked if they had any experience with the current method and if they had any suggestions as to how it could be made more robust. The BPCRS report had indicated that there was a slight improvement in the peak symmetry if a Lichrosorb column rather than a Spherisorb column was used. It was noted that several formulations appeared to be available and that reference was made to the product within the list of Specials recommended by the British Association of Dermatologists. It was agreed that the current method should be retained and that reference to a Lichrosorb column should be included.

589 **Melatonin Capsules** ULM(19)26

Identification The Secretariat had received reports from two suppliers of Melatonin Capsules failing to comply with the UV identification test. It was agreed that the Laboratory should check their records to ascertain if there was any additional information available on the development of the method and to re-examine the method subject to the receipt of samples.

590 **Mexiletine Capsules** ULM(19)27

The monograph for Mexiletine Capsules, which was currently written in terms of Mexiletine Hydrochloride, would be re-drafted in terms of mexiletine for the BP 2021. The monograph was the responsibility of EAG MC2: Medicinal Chemicals but EAG ULM had been asked whether the change would have any implications for unlicensed formulations.

The Secretariat would inform EAG MC2 that there were no apparent issues relating to unlicensed formulations and that the proposed changes should go ahead.

VII INTERNATIONAL

591 **Paediatric Formulary Working Party** ULM(19)28

The reports of the 12th and 13th meetings of the Paediatric Formulary Working Party were provided for information, together with a report of a recent teleconference. The European Directorate for the Quality of Medicines and HealthCare had launched the first texts for public consultation in October 2018. Registered users could access draft documents through Pharmeuropa Paedform (https://paedform.edqm.eu/home) which was a free access platform through which users could review and comment on draft text. Members were reminded that the monographs produced by this route would not be included in the European Pharmacopoeia and would not be legally binding.

VIII ANY OTHER BUSINESS

592 **Date of next meeting**

To be confirmed.