BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group ULM: Unlicensed Medicines

SUMMARY MINUTES

A meeting of the Expert Advisory Group on Unlicensed Medicines was held via videoconference on Wednesday 14th October 2020.

Present: Dr M G Lee (*Chair*), Mr V Fenton-May (*Vice-Chair*), Dr A Barnes, Mr A Bosley, Mr W Goddard, Ms S Hartley, 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 and Mr A Evans.

Apologies for absence were received from Ms M Godber and Mr A Sully.

593 **Introductory Remarks**

Welcome The Chair welcomed members to the meeting. A special welcome was extended to Dr Barnes, who was attending his first meeting of EAG ULM.

Confidentiality Members were reminded of the confidential nature of the meeting and that papers and minutes should not be disclosed.

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.

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

I MINUTES

594 The minutes of the meeting held on 16th October 2019 were confirmed.

II MATTERS ARISING FROM THE MINUTES

595 The following matters arising from the meeting held on 16th October 2019 were noted.

Minute 562 – Lorazepam Oral Suspension Work on Related substances had been carried out but completion of the report had been delayed.

Minute 562 – Adrenaline Preparations The monographs for Adrenaline Eye Drops and Adrenaline Solution (licensed formulations) had been amended in the BP 2021 to include Related substances tests. Consideration would be given to including the methods in the monographs for the unlicensed Adrenaline formulations at a future meeting.

Minute 587 – Review of Extemporaneous Preparations Implementation of the agreed changes to monographs containing extemporaneous preparation information had been postponed due to current priorities.

Minute 590 – Mexiletine Capsules The proposed changes to the monograph relating to the licensed product had been deferred for publication in the BP 2022.

Minute 591 – Paediatric Formulary Working Party The first two non-mandatory monographs developed by the Working Party had been published (Hydrochlorothiazide Oral Solution and Sotalol Hydrochloride Oral Solution).

III REPORTS AND CORRESPONDENCE

596 Secretariat Updates: Covid-19; MHRA

An update on recent activities within the BP and wider MHRA was provided.

597 Issues Arising through the BP Commission ULM(20)1

Members noted the following issues, which had recently been discussed by the British Pharmacopoeia Commission and the Expert Advisory Group on Pharmacy.

Buffered Antibiotics The Commission had endorsed the recommendation that separate monographs for unlicensed ready-to-use infusions should be prepared, where appropriate, providing there was stability data available to support their inclusion. The need to ensure that the titles of any such monographs were clearly distinguishable from those for any corresponding monographs for licensed preparations had been highlighted.

Monograph Titles for Unlicensed Oral Liquids In light of previous discussions regarding suitable monograph titles for Oral Liquid preparations, the Pharmacy EAG had confirmed that separate monographs for Oral Solutions and Oral Suspensions should be developed in line with the BP policy of developing separate monographs for similar pharmaceutical forms containing the same active ingredient.

Rapid Revision of BP Monographs A procedure had recently been agreed to allow for the revision of a BP monograph outside the usual publication process, should the need arise.

Action and Use Statements It had been agreed that the suitability of action and use statements for all new and revised monographs, including those for unlicensed formulations, would be reviewed by the Commission's Nomenclature and Pharmacy experts for each new edition of the BP.

598 BP Website: Consultations and Improvements ULM(20)2

Recent Consultations The recent consultations relating to the proposed introduction of HPLC/UV Diode Array Detection as a routine test for Identification purposes, the proposed move to numerical limits (rather than limits based on peak area comparison) and the proposed introduction of HPLC methods using Pulsed Amperometric Detection had now closed.

BP Website Improvements Members noted recent improvements to the website, including the timeline feature and the ability to view revised monographs in different ways (as clean text or with the changes from the previous version of the monograph highlighted).

Draft Monographs New and revised monographs were posted for comment on the BP website at regular intervals during the year. Members were encouraged to raise awareness of texts relating to unlicensed medicines throughout their networks.

599 Ceftazidime Preparations ULM(20)3

Stability information had been received relating to unlicensed Ceftazidime formulations. Several changes to the monographs for Ceftazidime Eye Drops and Ceftazidime Injection

had been proposed to enable compliance over shelf-life for products that were used in the home environment.

Definition (Eye Drops) The current definition specified “a sterile solution in Purified Water”. It was agreed that the statement should be amended to refer to “a sterile solution in a suitable vehicle” to encompass all relevant formulations.

Acidity or alkalinity (Eye Drops) It was agreed that the pH limits should be amended to “6.0 to 8.0” to reflect available data.

Related substances The current impurity limits for the Eye Drops and the Injection were different and reflected the information available at the time of monograph development. Increased levels of impurity G in the Eye Drops and levels of secondary peaks above the monograph limits for unspecified impurities in both the Eye Drops and the Injection formulations had been observed. Based on the data provided, and the different routes of administration, the following changes were agreed:

Ceftazidime Eye Drops The limit for impurity G to be increased to 1%; the limit for unspecified impurities to be increased to 0.2%;

Ceftazidime Injection The limit for unspecified impurities to be increased to 0.2%.

Pyridine The current limit for pyridine was acceptable and was in line with the limit in other Ceftazidime monographs.

Assay for sodium carbonate (Eye Drops) The current monograph included an Assay for Sodium Carbonate. It was agreed that this should be deleted as the method was only relevant for the dry ingredients.

600 **Parenteral Nutrition Solutions** ULM(20)4

The monograph for Parenteral Nutrition Solutions had been published in the BP 2021.

Aluminium In the absence of any sample data it had been agreed to retain the proposed 25 µg per litre limit, in line with the USP limit for Large Volume Parenteral preparations.

It was agreed that the limit should be as low as practicable. The Chair noted that limits of 10 µg per litre were included for Peritoneal Dialysis Solutions and for Haemodialysis Solutions, but that much higher volumes of these formulations were given to the patient than of Parenteral Nutrition Solutions and the component ingredients were not stored in glass containers. It was noted that the presence of different glycerophosphates might affect the amount of aluminium present. As glycerophosphates could be stored in glass containers, members agreed that the current note stating that “*Calcium Gluconate Injection stored in glass containers should not be used in the preparation of Parenteral Nutrition Solutions*” should be expanded to include reference to glycerophosphates.

Lipid Emulsion Stability Members agreed that there was a need to ensure that the solutions did not contain large droplets, but were uneasy about including a test in the monograph without supporting data. It was suggested that a suitable statement could be included under the Preparation section to highlight this aspect for lipid-containing formulations and the Secretariat agreed to circulate a draft form of words for consideration.

Labelling Members discussed whether there was a need to amend the Labelling statement to include reference to the amount of added antioxidants. The Secretariat would consider this aspect further and circulate proposed wording for comment.

601 **Compliance with BP Impurity Limits** ULM(20)5

Members were invited to discuss general issues relating to situations where (i) unlicensed formulations were unable to comply with BP impurity limits and (ii) there was no BP monograph for a particular formulation but there was a corresponding monograph in a different pharmacopoeia.

General considerations It was recognised that in the absence of a monograph for an individual dosage form, a product was still required to meet the requirements of the Ph Eur monograph for Pharmaceutical Preparations and the relevant General Monograph.

Attention had been drawn to cases where there was either no BP monograph for the ready-to-use injection or for the corresponding dry powder formulation. In such cases, the impurity limits from the parent monograph were used as the starting point, but these might not be suitable for ready-to-use formulations, especially if they related to synthetic impurities rather than degradation products. The ideal situation would be to include monographs for both the dry powder and the ready-to-use solution, where both existed, with appropriate limits supported by stability data.

It was suggested that general guidance could be included in the BP, especially if more monographs for unlicensed ready-to-use injections were developed in the future.

Pemetrexed Injection It was agreed that Pemetrexed Injection should be added to the EAG ULM work programme.

602 **British Pharmacopoeia 2021** ULM(20)6

The British Pharmacopoeia 2021 had been published in August and would come into effect on 1st January 2021. It contained all of the text from the 10th edition of the European Pharmacopoeia, together with that from Supplements 10.1 and 10.2. Updates to the online version of the BP 2021 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 2021 was provided for information.

603 **BP Portfolio Review; BPCRS Update** ULM(20)7

Portfolio Review The first phase of the BP portfolio review had resulted in the omission of several monographs from the BP 2020 and the BP 2021, the revision of several monographs to remove the need to maintain low-selling BPCRS and the removal of a number of BPCRS from the catalogue. The next phase of the review would be to review outdated methods and would focus on updating monographs to contain improved methods, where appropriate. Monographs for unlicensed medicines would be included as part of the review of relevant "family" monographs and Laboratory evaluations would be undertaken as required.

British Pharmacopoeia Chemical Reference Substances Updates relating to out of stock BPCRS were published every month on the BP website. There were currently no items of concern relating to monographs that were the responsibility of EAG ULM.

IV NEW MONOGRAPHS AND OTHER TEXT

604 **Benzylpenicillin Infusion** ULM(20)8

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

605 **Flucloxacillin Infusion** ULM(20)9

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

606 **Ready to Administer Injections** ULM(20)10

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

V MONOGRAPHS IN PROGRESS

607 **Glycopyrronium Bromide Preparations** ULM(20)11

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

608 **Magnesium Sulfate and Potassium Chloride Infusion** ULM(20)12

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

609 **Tranexamic Acid Oral Solution** ULM(20)13

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

610 **Progress Report** ULM(20)14

Carvedilol Oral Suspension; Clomipramine Oral Suspension The intention was still to progress these monographs as student projects, if possible. The Secretariat had not been able to identify suppliers and it was noted that the formulations might be prepared extemporaneously. It was suggested that samples could be prepared using the active ingredient and commercial suspending agents.

Flecainide Oral Suspension; Quinine Sulfate Oral Suspension This work had not yet been scheduled into the work programme of the Laboratory and it would be necessary to ensure that samples were available prior to the start of the practical evaluations.

VI WORK PROGRAMME

611 **Work Programme** ULM(20)15

Update The work programme had been updated to reflect the decisions taken at the last meeting and to reflect changes included in the BP 2021. Members were asked to inform the Secretariat if/when they would be able to provide the information they had previously offered to supply to support monograph development.

Future Monograph Development In light of the on-going BP portfolio review, which was focused on directing resources to monographs that would provide the greatest value to public health, members were asked to consider how best to prioritise the current work programme taking note of the criteria listed in Supplementary Chapter V A: Monograph Selection – Unlicensed Medicines. The Secretariat had examined the top 100 products taken from the most recent "Top 500 Special Order Products List (March 2020)" and it was noted that many of these items were already the subject of a published monograph or were on the work programme. A list of about 10 items had been prepared where it might be possible to develop monographs based on existing texts and members agreed that efforts should be directed on these items. Some of the top 100 items were tablets and it was agreed that this EAG should prioritise monographs for oral liquid formulations, many of which were prepared extemporaneously and for which a standard would be beneficial.

BP Laboratory There was a need to identify further items for Laboratory evaluation.The difficulties associated with identifying potential suppliers and ensuring samples were received on time was again highlighted.

612 **Ascorbic Acid Injection** ULM(20)16

Information had been provided relating to Ascorbic Acid Injection used in pharmacy compounding units.

Characteristics Whereas the monograph described the injection as a "colourless liquid", the product was described as "slightly yellow". Although statements under the heading Characteristics were non-mandatory, questions were often raised regarding interpretation of this section of a monograph. It was noted that designation of colour was subjective and that the appearance could vary depending upon the volume of the container.

Assay limits; Storage The content limits for the Injection were 95.0 to 105.0% for a preparation that was stored in the fridge. The product had a shelf-life of 12 months when stored at room temperature with release limits of ± 5% and shelf-life limits of ± 10%. It was noted that the product should comply with the BP monograph requirements.

It was agreed that no action for this EAG was required but that the matters should be raised with the Expert Advisory Group responsible for the licensed product.

613 **Methadone Hydrochloride Oral Concentrate** ULM(20)17

Expert Advisory Group MC3: Medicinal Chemicals were in the process of revising the licensed Methadone formulation monographs. There was currently a monograph for Methadone Oral Solution which was available either as a ready-to-use solution or prepared by diluting Methadone Hydrochloride Oral Concentrate.

It was understood that, historically, use of the undiluted Oral Concentrate had been permitted on a named patient basis. Members agreed to make enquiries to ascertain if there was any evidence that the undiluted Oral Concentrate was used. The item would not be added to the work programme at this time.

614 **Piperacillin and Tazobactam Infusion** ULM(20)18

New Monograph It was noted at the last meeting that ready-to-use solutions of Piperacillin and Tazobactam Infusion were undergoing stability studies. Licensed products containing Piperacillin Sodium and Tazobactam in dry powder form for re-constitution were available. It was noted that the buffered formulation was widely used within the NHS and members agreed that it should be added to the work programme.

VII REVISION OF MONOGRAPHS

615 **Lidocaine Intraocular Injection** ULM(20)19

Related substances During work to replace lidocaine hydrochloride BPCRS the Laboratory had highlighted several possible errors in the published method relating to the buffer used in the mobile phase and the system suitability test and these would be corrected at the earliest opportunity.

616 **Melatonin Capsules** ULM(20)20

Identification Following the reports of non-compliance with the UV identification test (test A), the Laboratory had examined the test on melatonin BPCRS and confirmed that there were differences between the observed and published absorbance maxima. Members agreed that test A should be deleted from the monograph by means of the BP 2022.

617 **Trichloroacetic Acid Solution** ULM(20)21

Assay The current Assay for Trichloroacetic Acid Solution was based on an HPLC method supplied at the time of monograph development.

The Secretariat had proposed that to avoid the need to establish a new BPCRS the suitability of the titrimetric Assay included in the Ph Eur monograph could be examined and this approach had been endorsed by the Chair and Vice-Chair of EAG ULM.

In the absence of a commercial sample, the Laboratory had prepared a solution in water and carried out the titrimetric method using the solution concentration specified in the current Assay. The method was found to be satisfactory, with results of about 99%, and members agreed that the monograph should be updated to include the titrimetric method in the BP 2022. A draft amendment had been prepared and was accepted.

Identification The current test B referred to the HPLC retention time from the Assay. It was agreed that this test should be replaced by Identification test C from the parent monograph which specified that a 10% aqueous solution was “strongly acidic”.

VIII ANY OTHER BUSINESS

618 **Date of next meeting**

To be confirmed.

FOR INFORMATION:

619 **Analytical Quality by Design and the BP**

The outcome of the consultation relating to the application of Analytical Quality by Design (AQbD) concepts to pharmacopoeial standards for medicines had been published on the GOV.UK website in August. Members were informed that work was on-going to explore how AQbD concepts could be incorporated within the BP. It was not expected that there would be an impact on the work of EAG ULM at this time.