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 13th October 2021.

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 and Dr M Westwood.

In attendance: Dr F J Swanson, Mr A Evans and Mr C Thompson.

Apologies for absence were received from Mr A Sully and Mr P Weir. Ms M Godber did not attend the meeting.

620 **Introductory Remarks**

Welcome The Chair welcomed members to the meeting. He also welcomed Mr Thompson from the BP Laboratory.

Confidentiality Members were reminded of the confidential nature of the meeting and that the 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.

Co-operation Agreement with Croatia A Co-operation Agreement between the BP/MHRA and the Croatian Agency for Medicinal Products and Medical Devices had been in place since 2015. This agreement had recently been renewed for a second time and would be in place until March 2026. The terms of the agreement permitted the Croatian Pharmacopoeia to reproduce the BP general text relating to unlicensed medicines in their publication.

Appointments The Secretariat were currently working with the Department of Health and Social Care to appoint new members to the British Pharmacopoeia Commission. The term of office for all members of BP Expert Advisory Groups would end on 31st December 2022 and a comprehensive review of EAG membership would be undertaken during 2022.

Dr Barnes, Mr Bosley, Ms Hartley, Dr Kirby and Dr Smith declared interests in one or more agenda items and appropriate action was taken.

I MINUTES

621 The minutes of the meeting held on 14th October 2020 were confirmed.

II MATTERS ARISING FROM THE MINUTES

622 The following matters arising from the meeting held on 14th October 2020 were noted.

Minute 595 – Lorazepam Oral Suspension The report on Related substances was still awaited.

Minute 595 – Paediatric Formulary Working Party The work programme of the Paediatric Formulary Working Party was increasing. The monographs published by this group remained non-mandatory.

Minute 612 – Ascorbic Acid Injection The discussions at the last meeting had been drawn to the attention of EAG MC3: Medicinal Chemicals and no action was required at this time.

Minute 613 – Methadone Hydrochloride Oral Concentrate A new monograph for Methadone Concentrate for Oral Solution (licensed product that is diluted before administration) had been published in the British Pharmacopoeia 2022. No information had been received relating to the use of the undiluted form directly and so this item would not be added to the work programme.

III REPORTS AND CORRESPONDENCE

623 Secretariat Updates

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

624 British Pharmacopoeia 2022 ULM(21)1

BP 2022 The British Pharmacopoeia 2022 had been published in August and would come into effect on 1st January 2022. It contained all of the text from the 10th edition of the European Pharmacopoeia, together with that from Supplements 10.1 to 10.5. Updates to the online version of the BP 2022 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 2022 was provided for information. The Chair was pleased to note the progress the group had made despite the difficulties over the past 18 months.

EU Exit Following the exit of the UK from the European Union and the end of the Transition Period, the UK remained a member of the European Pharmacopoeia and the text of the Ph Eur would continue to be included in the British Pharmacopoeia. Several BP texts had been amended in the BP 2022 to remove references to EU Directives, including Supplementary Chapter V: Unlicensed Medicines.

BP Website Improvements Members noted the “Revision History” feature that had been introduced in the BP 2022. This feature enabled users to view the reason(s) behind the changes to monographs and had been added in response to feedback from users.

625 Issues Arising through the BP Commission ULM(21)2

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

Monograph Titles Members were informed of the European Pharmacopoeia Commission decision that the title of Ph Eur finished product monographs should include the full name of the active ingredient, whether this was the base, acid or salt form. This contrasted with the established BP policy which was to use the shortest title possible combining the name of the active ingredient and the appropriate standard term. Where the active ingredient was in the form of a salt, this was usually omitted from the BP monograph title unless the same dosage form was available containing more than one form of the same active substance.

Product-specific Tests The suitability of including tests for Water/Loss on Drying or pH in formulated preparation monographs had been questioned. It had been agreed that there would be some instances where a monograph limit was justified, and the Secretariat would be developing policy guidelines regarding the inclusion of product-specific tests.

Related substances; Numerical limits A copy of the response to the BP consultation on the proposed change from the established practice of calculating limits based on the comparison of peak areas to the use of numerical limits was provided. There would be a gradual introduction of numerical limits from the BP 2023 onwards, accompanied by the publication of relevant guidance.

626 **Identification Tests Using LC/UV-DAD** ULM(21)3

A copy of the response to the BP consultation relating to the introduction of LC/UV methods using Diode Array Detection as a test for identification in BP monographs was provided. Infrared would remain as the preferred method for identification purposes, but the use of LC/UV-DAD methods would provide a suitable test for formulations for which infrared was less suitable, eg. for Oral Liquids and for low-strength or multi-component formulations. It was noted that several monographs had been updated in the BP 2022 to include LC/UV-DAD methods. This approach was not expected to cause any problems for Specials manufacturers and members welcomed the move to include these methods in the BP.

627 **British Pharmacopoeia Chemical Reference Substances** ULM(21)4

Further to the work on the BP Portfolio Review noted at previous meetings the Secretariat and Laboratory had worked hard to ensure that (i) new BPCRS were available in advance of publication of new editions of the BP and (ii) the number of out-of-stock BPCRS was kept to a minimum.

Members were provided with the BPCRS principles which had recently been agreed by the BP Commission.

628 **Declaration of Interests** ULM(21)5

A copy of the updated guidance note provided with the Code of Practice on Declaring Interests in the Pharmaceutical Industry for Chairs and members of the BP Commission and the Expert Advisory Groups, Panels of Experts and Working Parties was provided for information.

629 **Parenteral Nutrition Solutions** ULM(21)6

Aluminium The current limit of 25 µg per litre was based on the USP limit for large volume parenteral preparations, although it had been acknowledged that it might not be suitable across the range of Parenteral Nutrition Solutions available.

Data provided had shown levels above 25 µg per litre in most of the adult formulations tested. The current limit was suitable for some formulations, but in paediatric and neonatal solutions higher levels were observed due to the use of more concentrated solutions.

As the monographs for many of the component ingredients did not contain a limit for aluminium it was difficult for suppliers of Parenteral Nutrition Solutions to reach consensus on an appropriate limit for the final solution.

Members discussed whether the current limit should be retained or increased, whether separate limits for adult and paediatric formulations should be included or whether the requirement for aluminium should be removed from the monograph until more comprehensive data was provided.

Members affirmed that the current limit should be retained. It was recognised that there could be non-compliance issues, but the chances of this occurring could be minimised by storing the ingredients in plastic containers and encouraging the aluminium content to be included on the ingredient labels. If suppliers requested an increase in the limit, they would be asked to provide supporting data.

Bacterial endotoxins Data showing that the monograph limit was not suitable had been received. The limit had been based on that for Peritoneal Dialysis Solutions which were administered in larger volumes than Parenteral Nutrition Solutions. It was agreed that the current limit was not justified and that the limit should be increased in line with that for the component ingredients. Members preferred retaining the test in the monograph for transparency and it was agreed that the limit should be increased to 0.25 IU per mL.

630 **Labelling of Specials** ULM(21)7

Following two adverse incidents a short-term NHS Working Group, including two representatives from the MHRA, had met over the last few months to develop best practice guidance for the labelling and packaging of Specials.

A number of recommendations had been made regarding the labelling of packaging and containers with the aim of minimising the chance of further medication errors due to similarities in the drug name and/or packaging, including incorporating an additional requirement in the list of critical items included under Labelling in the BP General Monograph on Unlicensed Medicines.

As the proposed change to the General Monograph reflected the MHRA guidance it was agreed that a draft amendment should be prepared and included on the BP website for public comment. Members were also asked to raise awareness of the proposed change within their networks.

631 **Compliance Issues** ULM(21)8

Introduction Preliminary discussions had been held at the last meeting regarding how to address 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.

Compliance It was noted that although a producer of an unlicensed medicine did not have to carry out the pharmacopoeial methods routinely, they must be able to demonstrate compliance if tested. The Secretariat pointed out that, subject to the receipt of supporting data, monographs could be revised to accommodate different formulations. Attention had also been drawn to Supplementary Chapter V A: Monograph Selection – Unlicensed Medicines which included a list of criteria that were used when deciding whether to add a new monograph to the BP work programme.

Reconstituted Licensed Products vs Unlicensed Ready-to-Administer Injections Members confirmed that there was a clinical need for the unlicensed formulations and that the inclusion of BP monographs would be beneficial. Members were reminded that the BP Commission had supported the development of separate monographs for unlicensed

buffered antibiotics that were not covered by existing monographs, where this was justified by supporting data. The EAG would continue to develop monographs, where appropriate.

632 **New Supplementary Chapter** ULM(21)9

A template had been prepared in 2016 which provided guidance on the type of information required to support the development of monographs for unlicensed medicines.

Members agreed that it would be helpful to incorporate the guidance within the BP Supplementary Chapters. The Secretariat undertook to review the current guidance and consider if this should be added to Supplementary Chapter V A: Monograph Selection – Unlicensed Medicines or included as a new Chapter.

IV MONOGRAPHS IN PROGRESS

633 **Glycopyrronium Bromide Solution (Topical)** ULM(21)10

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

634 **Glycopyrronium Bromide Cream** ULM(21)11

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

635 **Flecainide Oral Solution** ULM(21)12

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

636 **Quinine Sulfate Oral Suspension** ULM(21)13

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

637 **Work Programme** ULM(21)14

The work programme had been updated to reflect the decisions taken at the last meeting and to reflect changes included in the BP 2022. The following points were agreed, taking note of the items previously identified from the Top 100 Special Order Products list for which it had been agreed that monographs should be prioritised.

Acetylcysteine Effervescent Tablets A licensed product was available and the item would be removed from the work programme.

Adrenaline Eye Drops; Adrenaline Solution; Vancomycin Eye Drops It was agreed that the proposed revisions should be removed from the work programme at this time.

Carvedilol Oral Suspension In view of the high use of this item, it was agreed that it should be retained on the work programme.

Clomipramine Oral Suspension Due to low usage figures and previous difficulties in trying to develop monograph tests, it was agreed that this item should be removed from the work programme.

Lansoprazole Oral Suspension It was agreed that a monograph should be prepared based on the current monographs for Lansoprazole Gastro-resistant Capsules and Tablets and that the proposed methods should be examined by the Laboratory.

Naltrexone formulations Although the Oral Liquid formulations did not appear to be widely used there was significant usage of the Capsules formulation. It was agreed that all three monographs should be kept on the work programme for the time being.

V READY-TO-ADMINISTER INJECTIONS

638 Ready-to-Administer Injections ULM(21)15

The text on Ready-to-Administer Injections had been added to the Supplementary Chapter on Aseptic Preparation of Unlicensed Medicines in the BP 2022.

Starting Materials In was agreed that the first sentence should be amended to "*All materials used for the preparation of the injections must be manufactured or prepared in licensed facilities*.". This would also cover the diluents used to prepare the ready-to-administer preparations.

Opening paragraph The Chapter was applicable to aseptic preparations which were "prepared in anticipation of demand and stored in a ready-to-administer form until administered to the patient" and **not** to stock solutions. In order to clarify this distinction, it was agreed that the final sentence in the opening paragraph should be moved to the start of the document.

Stability It was agreed that reference to the guidance document prepared by the European Society of Hospital Pharmaceutical Technologies (Gerpac) relating to the assignment of shelf-life for parenteral preparations prepared in hospital aseptic units should be included in this section.

639 Pemetrexed Infusion (Injection) ULM(21)16

Monograph Priority In view of the existence of licensed products with extended shelf-lives, it was agreed that a monograph for the unlicensed products should not be prepared but that a monograph for the licensed products should be added to the BP work programme as a high priority item. In view of the benefit to the NHS of having a monograph available in a timely manner it was agreed that this matter should be drawn to the attention of the British Pharmacopoeia Commission.

640 Piperacillin and Tazobactam Infusion ULM(21)17

It had been agreed that a monograph for Piperacillin and Tazobactam Infusion should be developed. Several members undertook to provide data. The Secretariat would prepare a first draft based on the current monograph for Piperacillin Infusion and the data received from members and the text would be progressed at the next meeting.

VI NEW MONOGRAPHS

641 Diltiazem Cream ULM(21)18

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

642 **Melatonin Oral Suspension** ULM(21)19

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

VII REVISION OF MONOGRAPHS

643 **Glycopyrronium Bromide Oral Solution** ULM(21)20

Identification; Assay In light of the discussions relating to the new monographs for Glycopyrronium Bromide Solution and Glycopyrronium Bromide Cream it was agreed that the Oral Solution monograph should be updated in line with the draft new monographs.

VIII ANY OTHER BUSINESS

644 **Date of next meeting**

To be confirmed.