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 19th October 2022.

Present: Dr M G Lee (*Chair*), Mr V Fenton-May (*Vice-Chair*), Dr A Barnes, Mr A Bosley, Ms S Hartley, Dr D Kirby, Mr J Ramada-Magalhaes, Dr J Smith and Dr M Westwood.

In attendance: Dr F J Swanson, Ms H Corns and Mr C Thompson.

Apologies for absence were received from Ms M Godber, Mr W Goddard, Mr M Santillo, Mr A Sully and Mr P Weir.

645 **Introductory Remarks**

Welcome The Chair welcomed members to the meeting. He also welcomed Ms Corns from the Secretariat and 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.

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

I MINUTES

646 The minutes of the meeting held on 13th October 2021 were confirmed.

II MATTERS ARISING FROM THE MINUTES

647 The following matters arising from the meeting held on 13th October 2021 were noted.

Minute 622 – Lorazepam Oral Suspension The report on Related substances was still awaited.

Minute 625 – Product-specific Tests The Secretariat was in the process of developing policy guidelines relating to the inclusion of product-specific tests in individual monographs and proposals would be presented to the British Pharmacopoeia Commission in due course.

Minute 625 – Related substances; Numerical limits Several new and revised monographs published in the British Pharmacopoeia 2023 included numerical limits. It had been agreed that this approach would only be taken when appropriate data had been provided.

III REPORTS AND CORRESPONDENCE

648 Secretariat Updates

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

British Pharmacopoeia Commission Dr Anna-Maria Brady had been appointed as the new Chair of the BP Commission with effect from 1st October 2022, taking over from Professor Kevin Taylor who had served for nine years as Chair. Five long-standing members had retired at the end of 2021 and four new members had been appointed on 1st May 2022.

Hybrid Working There had been a gradual increase in the number of MHRA staff working in the office as the MHRA moved towards a flexible, hybrid way of working for office-based staff in line with other government departments.

MHRA Transformation Members were informed that following the extensive transformation of the MHRA noted at the last meeting, the agency now incorporated three frontline groups – Healthcare Quality & Access (HQA), Scientific Research & Innovation, Safety & Surveillance; four supportive sectors – Governance, Communications, Transformation and Partnerships; together with groups providing Corporate Services and Technology. The BP operation was situated within the Standards and Compliance group, which was part of HQA.

649 British Pharmacopoeia 2023 ULM(22)1

BP 2023 The British Pharmacopoeia 2023 had been published in August and would come into effect on 1st January 2023. It contained all the text from the 10th edition of the European Pharmacopoeia, together with that from Supplements 10.1 to 10.8. Updates to the online version of the BP 2023 would be made during the year, adding the text of the 11th edition of the European Pharmacopoeia and 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 2023 was provided for information.

Glycopyrronium Bromide Oral Solution The responsibility for Glycopyrronium Bromide Oral Solution had reverted back to EAG ULM by means of the BP 2023.

Captopril Oral Solution The monograph for Captopril Oral Solution had been amended to replace the use of captopril disulfide BPCRS by *in-situ* generation of the impurity.

650 BP Website: Changes and Improvements ULM(22)2

Revision History The Secretariat were continuing to develop the Revision History feature, first introduced in the online version of the BP 2022, to ensure that a clear and consistent approach was adopted. For monographs amended over several publications, the full history would be retained in the entries.

Monograph consultations In order to increase the awareness of the regular consultation windows for new and revised monographs, these postings were now accompanied by a news item alerting users that text was available for comment. Members were encouraged to raise awareness within their networks when monographs for unlicensed medicines were available for public comment.

Website improvements; How to use the BP Guide As part of the continuous improvement of the BP, members were invited to suggest ways to improve the website. The “How to use the BP” guide had been added to the website in 2019 and would be updated to

reflect recent changes as part of the overall improvements. Members were asked if they had any suggestions that could help increase the usefulness of the current guidance.

Advanced Therapy Medicinal Products Attention was drawn to the non-mandatory guidance on Advanced Therapy Medicinal Products that had been included on the website for use by interested parties, but which did not form part of the official requirements of the British Pharmacopoeia.

651 **Issues Arising through the BP Commission** ULM(22)3

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

Review of Membership The term of office for all members of the BP Expert Advisory Groups, Panels of Experts and Working Parties had been extended for one year until 31st December 2023.

Members had a wide-ranging discussion on the future membership of the group and how to attract suitable candidates who would be able to actively contribute to the work and be able to provide methods and samples for testing.

Alkylsulfonate Ester Impurities Current BP and Ph Eur monographs for mesilate-containing substances and products included a Production statement which required that a risk assessment should be carried out to evaluate the potential for the formation of genotoxic methanesulfonate ester impurities. The current UK position was that these statements provided a proportionate means of controlling these genotoxic impurities. A short "call for feedback" document had been posted on the BP website between July and September seeking a view from users and the feedback would be reviewed by the BP Commission in due course.

Nitrosamines The inclusion of Production statements in BP monographs for drug substances and products which had a high risk of nitrosamine contamination had been deferred pending the outcome of further discussions by the European Pharmacopoeia Commission.

Bacterial endotoxins The current policy relating to the inclusion of tests for Bacterial endotoxins in BP monographs was under review by the Expert Advisory Group on Biological and Biotechnological Products.

BP Portfolio Review As part of the ongoing review of the BP portfolio, a number of steps to rationalise the BP work programme had been agreed by the BP Commission. The main area of interest for EAG ULM concerned the expansion of Laboratory work to routinely include unlicensed formulations when examining a family of monographs (see minute 658).

652 **Code of Practice on Interests; Governance Activities** ULM(22)4

Code of Practice A new MHRA-wide Code of Practice on Identifying, Declaring and Managing Interests had been launched on 8th September, following a public consultation. This replaced all existing Codes of Practice, including the BPC Code of Practice on declaring interests in the pharmaceutical industry.

Governance Activities Members were informed that some governance activities relating to the work of the BP Commission and the Expert Advisory Groups, Panels of Experts and Working Parties were being/had been transferred from the BP to the Committee Services team, which was part of the MHRA Governance group.

653 **Methadone Concentrate for Oral Solution** ULM(22)5

Although the undiluted Concentrate was outside the scope of the current monograph, members strongly agreed that a separate monograph was not required and that reference to such usage should not be highlighted in the existing text as this was adequately covered under Labelling.

IV READY-TO-ADMINISTER INJECTIONS

654 **Ready-to-Administer Injections: Criteria for Monograph Development** ULM(22)6

Number of monographs The ready-to-administer products were not equivalent to licensed products for the corresponding dry powder formulations, since they might contain buffers and they were not used immediately after preparation or within the terms of the SmPC but were prepared in advance and stored in a ready-to-use form until administered to the patient. Monographs would only be developed when supporting information was provided and it was unlikely that a large number of monographs would be developed by this route.

Justification for the use of Unlicensed Medicines The inclusion of a monograph did not promote the use of unlicensed medicines, but provided a publicly available quality standard for such medicines. It was stressed that unlicensed medicines should only be prescribed where there was a clinical need to address the requirements of an individual patient that could not be met by current licensed medicines and that they should not be provided for convenience.

Impurity Limits It was agreed that impurity limits should be based on those for the corresponding licensed product (dry powder formulation), unless otherwise justified. A member highlighted ongoing stability studies being carried out within NHS Aseptic Units and it was noted that it would be helpful if relevant data could be made available to the Secretariat to assist in monograph development.

After a wide-ranging discussion members confirmed that the EAG should continue to develop monographs for these products, where appropriate.

Monograph Criteria It was agreed that a set of specific criteria/conditions should be developed, in addition to those listed in Supplementary Chapter V A1: Monograph Selection – Unlicensed Medicines, that would help determine whether a monograph for an unlicensed ready-to-administer injection should be added to the BP work programme. Draft criteria had been prepared by the Secretariat and were agreed. The Secretariat would consider the best way to incorporate the criteria within the existing guidance documents.

655 **Ready-to-Administer Injections: Final Product Testing** ULM(22)7

Supplementary Chapter V F It had previously been agreed that text encompassing risk-based analysis of final products should be added to the section on Ready-to-Administer Injections included in Supplementary Chapter V F: Aseptic Preparation of Unlicensed Medicines.

It was agreed that the draft text was suitable for publication subject to the removal of specific references to content and impurity limits and the inclusion of a statement that products must comply with BP monographs, where available, throughout shelf-life. The Secretariat would update the text and circulate for confirmation.

656 **Piperacillin and Tazobactam Infusion** ULM(22)8

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

V WORK PROGRAMME

657 **Work Programme** ULM(22)9

The work programme had been updated in accordance with the decisions taken at the last meeting and to reflect changes made in the British Pharmacopoeia 2023. The following points were noted.

Copper Sulfate Injection It was agreed that a monograph for Copper Sulfate Injection should be added to the work programme.

Pemetrexed Injection The monograph had been transferred to EAG MC1: Medicinal Chemicals since licensed products with extended shelf-lives were available.

Gliclazide Oral Suspension; Clopidogrel Oral Suspension These monographs had been identified as ones that could be developed as part of a series of family monographs.

Topiramate Oral Suspension A licensed product was available and so the monograph would be transferred to the appropriate Medicinal Chemicals Expert Advisory Group.

Items from the Top 100 Special Order Products List The list of high priority items had been updated to reflect the information in the June 2022 top 100 list.

658 **BP Portfolio Review** ULM(22)10

Members had been made aware of the comprehensive review of the BP portfolio in 2019 and 2020. The first stage of the review had focussed on identifying monographs and reference substances that were no longer used or had low usage figures. This had resulted in the omission of over 90 monographs from the BP and the removal of over 60 BPCRS from the catalogue. An update was provided on the next phases of the review

Bringing monographs up to date A list of monographs that required updating had been identified across the whole BP work programme, including those without Related substances tests and those specifying the use of obsolete technologies. The list of affected EAG ULM monographs was provided for information.

Rolling review and work programme refresh The BP Commission had recently agreed a list of high priority new and revised monographs relating to the work of the Medicinal Chemicals and Antibiotics Expert Advisory Groups, taking into consideration primary and secondary care usage data and monographs on the European Pharmacopoeia Commission work programme. The aim was to identify and prioritise those monographs that would provide most benefit to patients. Data on the use of Special Order Products had also been examined and this had been used to identify monographs for unlicensed formulations that could be developed alongside related family monographs for licensed products.

Data and samples There was limited information available relating to unlicensed medicines that could help to inform and prioritise the ULM work programme. Members were asked to help identify additional sources of information with the aim of providing a refreshed and realistic work programme. In addition, members were asked to share information on

commonly used suspending agents and excipients that would help in those instances where samples could not be sourced and the Laboratory had to prepare a formulation for testing.

659 **Ciclosporin Eye Ointment** ULM(22)11

The Expert Advisory Group on Antibiotics had recently developed a monograph for a licensed veterinary product which was also used as an unlicensed formulation in human medicine for patients that were unable to tolerate Ciclosporin Eye Drops.

Members were reminded that monographs for items that are used solely in human medicine or in both human and veterinary medicine are included in the BP, whereas monographs for items that are used solely in veterinary medicine are included in the BP (Vet). The Secretariat informed members that in the past there had been instances where monographs for the same formulation had been included in both the BP and the BP (Vet).

It was agreed that further information was required before a decision could be taken on whether the monograph should be published in the BP and/or the BP (Vet).

It was also agreed that steps should be taken to try and ascertain the extent of use of the eye ointment in humans. The matter would also be drawn to the attention of the BP Commission.

VI MONOGRAPHS IN PROGRESS

660 **Flecainide Oral Solution** ULM(22)12

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

661 **Quinine Sulfate Oral Suspension** ULM(22)13

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

662 **Carvedilol Oral Suspension** ULM(22)14

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

663 **Diltiazem Cream** ULM(22)15

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

664 **Melatonin Oral Suspension** ULM(22)16

As there was a licensed Oral Solution members agreed that the draft monograph for Melatonin Oral Suspension should not be published at this time.

VII NEW MONOGRAPHS

665 **Lansoprazole Oral Suspension** ULM(22)17

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

VIII REVISION OF MONOGRAPHS

666 **Parenteral Nutrition Solutions** ULM(22)18

Aluminium Further data had been received on a wide range of formulations indicating that many products failed to comply with the monograph limit of 25 µg per litre.

Members agreed that it was difficult to meet the current monograph limit for the final solution, particularly when there were no limits for aluminium in many of the monographs for the component ingredients. Increasing the monograph limit would help to ensure that more products complied, if tested, but it was also important to control aluminium levels in the ingredients.

Members reluctantly agreed that the limit should be raised to 50 µg per litre, as the current limit could not be met routinely, but that the monograph should be kept under review with the intention of reducing the limit when it was feasible to do so.

Preparation; Lipid emulsion It had been proposed that the statement regarding the need to demonstrate the stability of the lipid emulsion should be replaced by a suitable test method. Members were reminded that the general statement had been added by means of the BP 2022, following a request to include information on this aspect in the monograph. In the absence of a suitable method and limit, however, the general statement had been agreed for inclusion. Although several methods might be suitable, for example particle size distribution, laser diffraction, microscopy, physical appearance, etc., it was recognised that in view of the range of formulations available it would be difficult to develop a suitable pharmacopoeial method. It was agreed that unless information was provided to support inclusion of a specific method, no changes should be made.

667 **General Monograph: Labelling** ULM(22)19

At the last meeting members had discussed the recommendation to include a requirement in the Unlicensed Medicines General Monograph Labelling statement that the “full name of the medicine should appear on at least three non-opposing faces of the pack”. Although this was in line with the MHRA Best Practice Guidance on the Labelling and Packaging of Medicines, some concerns at how this requirement could be implemented had been expressed. Further comments had been received after the meeting and a modified statement had been included in the British Pharmacopoeia 2023 highlighting that the requirement should be fulfilled “unless otherwise justified”. It was agreed that no further action was required.

IX ANY OTHER BUSINESS

668 **Date of next meeting** To be confirmed.

FOR INFORMATION:

669 **Pan-European Formulary**

Members were informed that the European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH) were considering developing a pan-European formulary aimed at tackling medicines shortages, particularly during public health emergencies. The initiative was targeted at addressing shortages in general and did not encompass unlicensed medicines and Specials.