BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group: Antibiotics

SUMMARY MINUTES

A meeting of Expert Advisory Group: Antibiotics was held via videoconference on Tuesday 22nd February 2022.

Present: Dr R Horder (*Chair*), Dr G Cook (*Vice-chair*), Mr G Blake, Dr G Clarke, Dr W Mann, Dr M Pires, and Mr I Williams.

Apologies: Mr E Flahive, Mr V Jaitely, Prof J Miller, and Mr J Sumal.

In attendance: Mr P Crowley, Ms A Thomson, and Ms K Busuttil.

532 Introductory remarks

Welcome The Chair welcomed members to the meeting and Ms K Busuttil from the BP Laboratory.

533 General Matters **ABS(22)01**

Declaration of Interests Members were reminded about the introduction of Microsoft Forms to declare specific interests, and to inform the Secretariat of any changes to their interests throughout the year.

Dr G Cook declared interests in one or more agenda items and appropriate action was taken.

Confidentiality The confidential nature of the papers, discussions, and minutes of the meeting was highlighted. In view of this aspect of the work all papers were marked OFFICIAL-SENSITIVE and papers were made available by posting on the website.

Freedom of Information Members were asked to refer any FOI queries that they receive from the media to the Secretariat.

Membership Members were asked to inform the Secretariat if amendments were required to their contact details. It was noted that a review of BP advisory group memberships was scheduled to take place in 2022.

I MINUTES **ABS(22)02**

534 The minutes of the meeting held on 12th October 2021 were confirmed.

II MATTERS ARISING FROM THE MINUTES **ABS(22)03**

535 The following matters arising from the meeting held on 12th October 2021 were noted.

Pivmecillinam Tablets (minute 520) The draft monograph would be included in a future publication subject to resolution of any outstanding points.

Teicoplanin for Injection (minute 521) The draft monograph would be included in a future publication subject to resolution of any outstanding points.

Cefalexin Preparations (minute 523) The monograph had been amended as agreed and were intended to be posted on the website for the Q2 2022 public consultation with a view to being published in the BP 2024.

Clarithromycin Preparations (minute 524) The Secretariat would amend the draft monographs as agreed and circulate to manufacturers for comment once it had been confirmed why there was a difference in correction factors in the related substances.

Tetracycline Preparations (minute 525) The Secretariat would amend the draft monographs as agreed and circulate to manufacturers for comments specifically on the impurity limits.

III MONOGRAPHS FOR THE BP 2023

536 CILASTATIN AND IMIPENEM FOR INFUSION (Revised) ABS(22)04

Following publication in the BP 2020, a number of queries had been received regarding the retention times of the imipenem and cilastatin epimers as well as cilastatin impurity E. Queries had also been received regarding the wording of the system suitability.

Although corrections had been published in the BP 2022, a thorough review of the monograph against the donor method revealed a need for further attention. A draft monograph with corrections had been published for public consultation to which one manufacturer had responded.

Acidity or Alkalinity; Colour and clarity of solution Based on a review of the manufacturers' data package, members agreed that the monograph should be updated to reflect the correct reconstitution concentration (0.5% w/v cilastatin) and diluent (0.9% w/v sodium chloride).

Related Substances Corrections had been made, affecting the solution preparations, system suitability criteria, gradient table and identification of cilastatin impurities. Through the subsequent public consultation, one manufacturer had reported difficulty in identifying the cilastatin impurity G epimers and provided a sample chromatogram.

Members confirmed all proposed revisions, and supported inclusion of sample chromatography to aid the analyst.

Assay Members agreed to revision of the sample and standard solution preparations in line with the donor method.

537 VANCOMYCIN PREPARATIONS (Revised) ABS(22)05
Vancomycin Capsules
Vancomycin for Infusion

Members had previously endorsed the omission of the Oral Solution monograph from the BP 2023 publication and that reference to the oral solution preparation be made in the 'for Infusion' monograph, on the basis that it was the infusion product that was licensed and this was occasionally prepared as an oral solution as a secondary route of administration. Members had also agreed to the inclusion of the Ph. Eur. drug

substance limits in the monographs with a view to reviewing any proposals for wider limits from manufacturers prior to publishing.

Manufacturers had responded to the draft monographs posted for public consultation and provided batch data supporting wider limits which were the subject of this item with a view to confirming the monographs for publication in the BP2023.

Letters of intent for the 'for Infusion' and 'for Oral Solution' monographs had been posted to the website in January 2022 detailing corrections to the BP 2022 monographs which had been published in error.

Definition (for Infusion only) As agreed with EAG PCN, the definition statement had been modified to draw attention to the preparation of the infusion as an oral solution and it was noted that this had been included in the letters of intent.

Vancomycin B and Related Substances Revised monographs for Vancomycin for Infusion and Vancomycin Capsules had been posted for public consultation in the Q4 2021 window. Comments on the Vancomycin B and Related Substances procedure had been received from several manufacturers and were discussed by members who agreed to make a number of changes to the impurity specification based on licensed specifications and a review of batch data.

Labelling (for Infusion only) Members confirmed the labelling statement, modified in agreement with PCN, highlighting that infusion products that could be administered as oral solutions should be labelled appropriately, which had been included in the letters of intent.

IV MONOGRAPHS FOR THE BP 2024

538 TACROLIMUS PREPARATIONS (New) ABS(22)06

Tacrolimus Capsules
Tacrolimus Granules for Oral Suspension
Tacrolimus Prolonged release Capsules
Tacrolimus Prolonged release Tablets
Tacrolimus Sterile Concentrate

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

539 CHLORAMPHENICOL PREPARATIONS (Revised) ABS(22)07

Chloramphenicol Capsules
Chloramphenicol Ear Drops
Chloramphenicol Eye Drops
Chloramphenicol Eye Ointment

The BP Laboratory had completed evaluation of the revised drug substance methodology for suitability across four Chloramphenicol preparations.

Identification Members endorsed the laboratory approved infrared procedures utilising extraction in petroleum ether (40 – 60 °C) for the ointment, and ethyl acetate and water for the other three preparations. Members proposed removal of the secondary identification requirement by colour reaction given the sufficient discriminatory nature of the infrared test.

Dissolution (Capsules only) Members had previously approved the USP compendial dissolution procedure for adoption. Licensing colleagues recommended setting a limit of Q=80% in 30 minutes. Manufacturers would be invited to comment during the public consultation window to confirm suitability.

Related Substances Laboratory evaluation of the improved Ph. Eur. related substances methodology, utilising gradient elution and detection at 277 nm, had been completed, providing greater control of impurities with a detection limit in line with current ICH requirements for small chemicals. Members endorsed the approach with modifications as per laboratory recommendation.

Eye drop samples from one manufacturer were found to contain impurity A at a quantity greater than 2.0%. Licensing colleagues proposed a revised limit of 6.0%, which was approved by members, with a view that the limit could be tightened in the future.

Assay The Assay methodology, utilising the same chromatographic system as the related substances test, was found to be suitable for all capsules, ear drops and eye drops tested. All samples were able to meet the various content requirements, which had been unchanged since the previous published versions. Members approved the Assay methodology for these three monographs without amendment.

However for the ointment, despite the average Assay results passing the monograph limits, results from a few individual injections were found outside this range. It was noted that, in the corresponding USP compendial text, sample size was scaled up to 25 mg to reduce variability. Members recommended investigating alternative extractions by enquiring with manufacturers, however licensing colleagues felt that the USP compendial approach was likely to be suitable given the similarity in formulation of the various licensed products.

540 CICLOSPORIN PREPARATIONS ABS(22)08
Ciclosporin Eye Drops (Revised)
Ciclosporin Eye Ointment, Veterinary (New)

Laboratory assessment of the revised Ph. Eur. related substances and Assay LC methodologies was reported to be underway, with difficulties experienced by the analyst.

It was noted that the key issue remaining was significant chromatographic interference when injecting the disregard solution leading to a low signal to noise. Also, given the eye drops were a low dose emulsion, it was considered necessary to dilute out the excipients which could be contributing to the issue.

Members noted that the column was large (250 x 4.6mm) and the flow rate was high, which would lend itself to an increased injection volume, without overloading the column, which would counter act a reduced sample concentration.

541 LEVOFLOXACIN PREPARATIONS (New) ABS(22)09
Levofloxacin Tablets
Levofloxacin Infusion
Levofloxacin Eye Drops

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

V **FOR INFORMATION**

542 OUT OF STOCK BPCRS REVIEW ABS(22)10

It was noted that only the Cefradine BPCRS was currently out of stock. The laboratory team had been experiencing continued difficulty in procuring material of suitable quality but had identified a suitable source.

543 WORK PROGRAMME ABS(22)11

The EAG ABS work programme had been expanded to cover all anti-infectives, leading to the transfer of approximately 60 monographs. It had also been agreed to exploit economies of scale through inclusion of ULM product monographs in the development of family monographs where possible.

Members noted that VMD would have access to some usage data which could be provided with a view to prioritising veterinary monographs.

544 BRITISH PHARMACOPOEIA MATTERS ABS(22)12

BPC and EAG membership Interviews of potential new BPC members had taken place in the week commencing 25 October. The 4 yearly EAG membership cycle would finish at the end of 2022, so all members would be contacted later this year to ask whether they wished to be re-appointed and a review undertaken into any gaps in skills/capabilities within the groups.

Innovative standards Two new biological sub-groups were being established to focus on topics related to empty capsids for adeno-associated virus products and T cell potency assay. A profile for experts was in development and members were asked to provide the secretariat of any colleagues who may be interested in getting involved in either group.

A scoping project into digital therapeutics was being undertaken by a fast-streamer who had joined us from the Government Science and Engineering scheme to understand if the BP can support this area. This work had been developed closely with Agency Devices colleagues as well as with USP to understand their activities in this area.

BP product improvements It was noted that 'Revision History' functionality had been launched in the online BP 2022 and allowed users to see monograph revision history.

MHRA leadership update Dr Laura Squire OBE had joined the MHRA as Chief Healthcare Quality and Access Officer.

BP and Lab Services team Stephen Maddocks had accepted a 2-year loan position to DHSC as the Medicines Supply Resilience Lead and Becky Hunter had joined the BP team on a 6-month Government Science & Engineering fast stream placement.

VI EUROPEAN PHARMACOPOEIA ABS(22)13

545 **Group of Experts 7 – Antibiotics** An informal report from the 170th meeting (17th – 18th November 2021) of Group of Experts 7 was presented to the EAG.

Pharmeuropa A draft monograph for Caspofungin acetate (3029) had been made available for comment in PharmEuropa 34.1 with a public deadline for comments of 31st March 2022.

Members were thanked for their continued support to the work of the UK Delegation to the European Pharmacopoeia.

European Commission The 172nd Session was scheduled to take place on 22nd and 23rd March 2022.

VII ANY OTHER BUSINESS

546 None.

VIII NEXT MEETING

547 Tuesday 13th September 2022.