BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group: Antibiotics

SUMMARY MINUTES

A meeting of Expert Advisory Group: Antibiotics was held via videoconference on Thursday 04th March 2021.

Present: Dr R Horder *(Chair),* Dr G Cook (*Vice-chair*), Mr G Blake, Dr G Clarke, Mr E Flahive, Mr V Jaitely, Dr W Mann, Prof J Miller, Dr M Pires, Mr J Sumal, and Mr I Williams.

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

In attendance: Mr S Maddocks, Mr P Crowley, Ms A Thomson, Ms K Busuttil and Ms M Nanasi.

502 Introductory remarks

Welcome The Chair welcomed Ms Busuttil and Ms Nanasi from the BP Laboratory.

Membership Members were asked to let the Secretariat know if any of their details had changed.

503 General Matters **ABS(21)01**

Declaration of Interests Members were reminded to declare specific interests as they arose during the meeting and to inform the Secretariat of any changes to their interests throughout the year.

Freedom of Information Members were reminded that any FOI queries that they receive from the media were to be referred to the Secretariat.

I MINUTES **ABS(21)02**

504 The minutes and summary minutes for the meeting held on 23rd September 2020 were confirmed without comment.

II MATTERS ARISING FROM THE MINUTES **ABS(21)03**

504 The following matters arising from the meeting held on 23rd September 2020 were noted.

Amoxicillin Injection, Co-Amoxiclav injection (minute 488) The Secretariat were awaiting publication of the Amoxicillin API monographs before progressing these monographs.

Vancomycin Preparations (minute 488) The Secretariat were awaiting data from manufacturers with regard to a suitable dissolution method for all preparations before progressing the Tablets and Capsules monographs. A laboratory report was pending for the Related substances method of the Oral Solution monograph.

Tacrolimus Ointment (minute 490) The monograph had been amended as agreed and the remaining monographs for the Tacrolimus family would be presented at a future meeting.

Ofloxacin Preparations (minute 491) The monographs had been amended as agreed and placed on the website for public consultation in October 2020. Comments from manufacturers had been received and the monographs would be presented at a future meeting.

Levofloxacin Preparations (minute 492) The monographs had been amended as agreed and placed on the website for public consultation in January 2021. Comments from manufacturers had been received and the monographs would be presented at a future meeting.

Clarithromycin Preparations (minute 493) The monographs had been amended as agreed and the infusion, Prolonged-release tablets and the Tablets monographs placed on the website for public consultation in October 2020. No comments had been received, and the monographs were expected to be published in the BP 2022.

III MONOGRAPHS FOR THE BP 2022

506 Cefalexin Preparations **ABS(21)04**
Cefalexin Capsules (Revised)
Cefalexin Oral Suspension (Revised)
Cefalexin Tablets (Revised)

Following the March 2020 meeting of this EAG, the Secretariat had amended monographs for Cefalexin Capsules and Cefalexin Tablets and dissolution tests and limits had been developed. The monographs had been made available on the BP website for consultation between October and December 2020 and manufacturers contacted to provide comment.

The monographs for Cefalexin Tablets and Cefalexin Capsules had been finalised with a view to publication in the BP 2022 pending comments from the EAG and the British Pharmacopoeia Commission.

Content It was noted that the upper content limit of 110% was generous based on current expectations and should be tightened. Members agreed that in the interests of time, the monograph should be published with its historic limit, but that manufacturers be consulted on tightening the limit for a future revision.

Dissolution A dissolution test had been drafted using BP dissolution apparatus 1, rotating the basket at 100RPM with Water as the dissolution medium.

Acceptance criterion had been set at 80% (Q) in 30 minutes which was in-line with licensed specification for the Capsules.

Cefalexin Oral Suspension The monograph for Cefalexin Oral Suspension had been prepared for Laboratory evaluation and was awaiting scheduling for lab work.

507 Oxytetracycline Preparations **ABS(21)05**

Oxytetracycline Calcium (Revised)
Oxytetracycline Capsules (Revised)
Oxytetracycline Tablets (Revised)
Oxytetracycline Veterinary Oral Powder (Revised)
Oxytetracycline Veterinary Cutaneous Spray (New)

The BP Laboratory had evaluated the Ph Eur Related substances and Assay procedures for Oxytetracycline Tablets. The outcomes of this laboratory work had informed the revision of the other Oxytetracycline monographs.

The draft monograph for Oxytetracycline Veterinary Cutaneous Spray would be included in a future publication, subject to resolution of any outstanding points.

All other draft monographs had been posted to the BP website as part of the Q1 2021 public consultation and no comments had been received prior to the meeting.

Definition (Oral Powder) It was noted that reference to the product containing Lactose was included in the definition for the Oral Powder and agreed that as this may be product specific, it should be replaced with “a suitable vehicle”.

Content (Calcium) Members noted that the content limit for the Calcium should be refined to 94.5% to 102.0% based on current expectations.

Dissolution (Capsules and Tablets) The dissolution test for the capsules and the tablets monographs had been updated in-line with the BP policy for solid oral dosage forms and the Secretariat would confirm the limits.

Light-absorbing Impurities Members queried the relevance of the light-absorbing impurities test given the updated related substances procedure. IT was noted that this had been retained in the Ph Eur drug substance monographs and the secretariat agreed to investigate why EDQM had taken this approach to inform a future revision.

It was agreed that that use of chloroform as a solvent in this test should be replaced with dichloromethane in the Tablets monograph.

Related substances The related substances procedure adopted by the Ph Eur for Oxytetracycline and Oxytetracycline hydrochloride had been assessed by the laboratory. This laboratory work included an assessment of the performance of the method, the system suitability requirements, and its application to Oxytetracycline Tablets.

The methodology was found to be suitable for the products on the market and had been applied across the monographs. The laboratory noted that degradation of impurity F in the system suitability solution had been observed across 24 hours and had therefore used an autosampler temperature of 5 °C during the analysis which had increased the stability of the solutions. The Secretariat had included these aspects in the draft monographs. Members noted that the laboratory had also recommended the amount of taken to prepare the sample solutions for related substances and Assay should have been increased from 80mg to 160mg, which the Secretariat agreed to update.

Impurity limits As there were no licensed impurity specifications, the drafted limits had remained harmonised with the API monograph with exception for the sum of all secondary peaks, which had been increased from 3.5 to 4.0% based on levels observed

by the BP laboratory. Members noted that VICH limits were different from ICH and so the veterinary monographs should be updated inline with this guidance.

Assay (all) The Assay had been largely harmonised with the related substances procedure and represented an improvement in column technology and efficiency from the previous methodology. The mobile phase and separation mechanisms were not entirely different from the existing method and the conditions had been assessed by the BP laboratory.

The method utilised reversed phase chromatography and a simple mobile phase with Trifluoroacetic acid, methanol and acetonitrile. An end-capped C18 column was used to provide separation and the API quantified at 254nm.

Impurities An impurities section had been added to the monographs following the addition of the related substances procedure.

508 **Ciprofloxacin Preparations** **ABS(21)06**
Ciprofloxacin Ear Drops (New)
Ciprofloxacin Hydrochloride Eye Drops (New)
Ciprofloxacin Infusion (Revised)
Ciprofloxacin Oral Suspension (New)
Ciprofloxacin Tablets (Revised)

Draft monographs for Ciprofloxacin Ear Drops, Ciprofloxacin Hydrochloride Eye Drops and Ciprofloxacin Oral Suspension would be included in a future publication, subject to resolution of any outstanding points.

Dissolution (Capsules and Tablets) The dissolution test for the Tablets had been updated in line with BP Policy. The existing limits of 80% (Q) in 30 minutes had not been revised. The Secretariat internal procedures stated that all solid-oral dose monographs should be revised to contain a suitable dissolution test with (Q) acceptance criteria, but such a revision should not hold up the publication of a monograph.

509 **Tylosin Preparations** **ABS(21)07**
Tylosin Injection (Revised)
Tylosin Premix (New)
Tylosin Oral Solution (New)

Following the March 2020 meeting, the Secretariat had placed the Tylosin monographs for public consultation on the BP website. A manufacturer had performed extensive investigations on the monographs and provided the Secretariat with comments on the related substances and assay procedures.

Draft monographs for Tylosin Premix and Tylosin Oral Solution would be included in a future publication, subject to resolution of any outstanding points.

Related substances and Composition (Injection) The manufacturer had noted that the methodology adopted by the BP contained a gradient of 90 minutes which was required to separate the impurities. The current BP monograph for Tylosin injection contained a 30-minute isocratic, Composition only method. The Secretariat believed that the extra control of impurities lead to a preference for the Ph Eur procedure in the

short term and agreed to work with the MAH to gather all data required to justify a change to a separate procedure, while maintaining the specificity that the existing procedure provided.

The Secretariat noted that the impurity profile of Tylosin in the Injection products was complex and so would work with the MAH to determine the structure of the "Tylosin Degradation Product" and agree appropriate impurity limits.

Microbiological Assay (Injection) The Secretariat noted that the Tylosin API content was controlled by Activity rather than a conventional external standard content Assay. The MAH had proposed that the fiducial limits of error in the proposed monographs were too tight, especially considering the levels of impurities present. The Secretariat had re-drafted limits to align with the MAH licensed specifications.

The Secretariat had aligned the fiducial limits of error as suggested by the MAH: *'The upper fiducial limit of error is not less than 90.0% and the lower fiducial limit of error is not more than 112.5% of the stated number of IU.'*

510 Clindamycin Injection (Revised) ABS(21)08

Members had previously approved tighter impurity limits for the Clindamycin family of monographs, that were deemed suitable based on the sample tested and were shown to reflect the analytical capability of the improved LC method.

Related Substances The Secretariat had received stability data from a manufacturer of the Clindamycin Injection product indicating that the current limit for Impurity F (NMT 4%) was too tight for the product over its shelf-life. Impurity F was understood by the MAH to be a potential degradant arising from hydrolysis of Clindamycin Phosphate, and prone to increase over time. Furthermore, the MAH's registered specification included a limit of NMT 8% for total impurities (all known and unknown peaks), compared to the current BP limit of NMT 5% (all secondary peaks).

Members approved a revision of the Clindamycin Injection monograph impurity limits to align with the registered specification and data provided to the BP.

The Secretariat had not received complaints from manufacturers of the other Clindamycin Phosphate medicinal products. As this was the only entirely aqueous based formulation, it was not considered necessary to revise the other product monographs.

IV MONOGRAPHS FOR THE BP 2023+

511 Erythromycin Stearate Tablets (Revised) ABS(21)09

Members had previously agreed to the revision of the Erythromycin family of monographs for the BP 2021 following extensive laboratory investigations. Following these revisions, an MAH had approached the Secretariat claiming that the levels identified for impurity S in the Erythromycin Stearate Tablets monograph were too restrictive for their products as well as claiming stearic acid to be impurity S.

Related Substances The Secretariat received correspondence from a manufacturer of Erythromycin Stearate Tablets (250 mg and 500 mg), who reported significantly higher levels of impurity S, compared to the newly revised specification limit of 1%, which had been based on the Ph Eur API. The MAH had requested for the limit to be reconsidered based on the evidence given.

The structure of impurity S was listed as an unknown structure in the EP/BP. The MAH had suggested that impurity S was stearic acid and had supplied LC-DAD chromatograms to support their claim, which demonstrated similar UV spectra for Impurity S and stearic acid. The MAH had also supplied data showing the observed levels of impurity S in stability batches just before and just after shelf life (5 years). This data suggests the levels of impurity S observed from preparation to preparation varies greatly, even within the same batch. The data also shows that the level of impurity S effectively doubles between the 250 mg and 500 mg tablets.

Members reviewed the MAH data along with data available for the Erythromycin fir impurity S identification EPCRS and noted a number of discrepancies. It was agreed that that the peak identified as impurity S in the MAH data was not due to likely to be due stearic acid but could potentially be an adjuvant of the stearate salt form with Erythromycin. It was agreed that the MAH would need to develop further characterisation to confirm the structure of the impurity associated with the peak in question before its identity could be confirmed. As impurity S was defined as an unknown structure in the Ph Eur drug substance monograph, a request for revision would need to be submitted to the EDQM.

V FOR INFORMATION

512 Out of Stock BPCRS report ABS(21)10

The out of stock BPCRS for monographs under the remit of EAG ABS were presented to the group. The Secretariat reported no out of stock items that the laboratory team could not confirm re-establishment dates for.

513 Work Programme ABS(21)11

The EAG ABS work programme was presented to the members for discussion.

514 British Pharmacopoeia Matters ABS(21)12

The Secretariat highlighted the recent work of the British Pharmacopoeia.

Innovation Board – Online developments of the BP A round of user research had been initiated to develop operational and strategic level insight to direct future developments and direction for BP innovations.

A project to introduce Annotations, providing narrative to the Tracked Changes added in the BP 2021, was in its closing stages of development and expected to be available for the BP 2022.

Advanced Therapy Medicinal Product The British Pharmacopoeia formed a working party for Advanced Therapy Medicinal Products which have produced guidance on the use of Analytics supporting the manufacture of these type of products.

Guidance was being developed through extensive collaborations with experts and the bio industry and would cover Flow Cytometry and Vector Copy Number. The guidance was expected to be accompanied by a short consultation.

British Pharmacopoeia Secretariat appointments Members were introduced to changes within the Secretariat and were made aware of specific points of contact for the EAG.

515 European Pharmacopoeia Matters ABS(21)13

An informal report from the 168th meeting of experts Group 7 was presented to the EAG.

VI ANY OTHER BUSINESS

None

VII DATE OF NEXT MEETING

Wednesday 15th September 2021