**BRITISH PHARMACOPOEIA COMMISSION**

**Expert Advisory Group: Antibiotics**

**SUMMARY MINUTES**

A meeting of Expert Advisory Group: Antibiotics was held at 10 South Colonnade, Canary Wharf, London E14 4PU on Thursday 7th February 2019.

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

**Apologies:** Dr M Pires

**In attendance**: Mr P Crowley, Mr S Maddocks, Ms K Busuttil, Ms M Nanasi and Mr C Thompson.

Dr G Clarke from the VMD attended the meeting as an invited expert and Mr A Evans attended the meeting for the item discussed under minute 451.

**438 Introductory remarks**

**Welcome**
The Chair welcomed Dr Clarke to the meeting, who was attending as an invited expert, and also to Ms Busuttil, Ms Nanasi and Mr Thompson from the BP Laboratory.

**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.

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

**439 General Matters** **ABS(19)01**

**Fire evacuation procedure**
Members were introduced to the new evacuation procedure in the event of a fire alarm.

**I MINUTES** **ABS(19)02**

440 The minutes and summary minutes of the meeting held on 27th September 2018 were confirmed.

**II MATTERS ARISING FROM THE MINUTES** **ABS(19)03**

441 The following matters arising from the meeting held on 27th September 2018 were noted.

**Marbofloxacin Preparations (minute 365 refers)** The monograph would be included in a future publication.

**Ceftiofur Hydrochloride Suspension for Injection (minute 365 refers)** The monograph would be included in a future publication.

**Fusidic Acid and Sodium Fusidate Preparations (minute 365 refers)** A laboratory report was pending for the assessment of the Identification, Related substance and Assay procedures.

**Oxytetracycline Preparations (minute 372 refers)** A laboratory report was pending for the assessment of the Related substance and Assay procedures.

**Ciprofloxacin Preparations (minute 399 refers)** A laboratory report was pending for the development of an Identification procedure and for the assessment of the Related substance and Assay procedures.

**Co-Amoxiclav Preparations (minute 400 refers)** A laboratory report was pending for the assessment of the Related substance procedure.

**Enrofloxacin Preparations (minute 401 refers)** The monographs would be included in a future publication.

**Rifampicin Preparations (minute 402 refers)** A laboratory report was pending for the assessment of the Identification, Related substance and Assay procedures.

**Amoxicillin Preparations (minute 409 refers)** A laboratory report was pending for the assessment of the Related substance procedure.

**Lymecycline Capsules (minute 417 refers)** The Secretariat were awaiting finalisation of the Ph Eur parent monograph before further developing the Related substances procedure in this monograph.

**Tylosin Premix (minute 417 refers)** The monograph would be included in a future publication.

**Bacterial Endotoxins (minute 417 refers)** The Secretariat were seeking clarification on the additional information required to remove pyrogens test from remaining Ph. Eur. parent monographs.

**Amikacin Injection (minute 417 refers)** The Secretariat were looking at options for the assessment of the PAD Related substances procedure with a contract laboratory. The Secretariat had contacted an expert in EDQM regarding the use of PAD to explore potential for training and knowledge transfer to the BP laboratory.

**Benzylpenicillin Injection (minute 417 refers)** The monograph was intended to be published in the BP 2020.

**Clindamycin Preparations (minute 417 refers)** A laboratory report was pending for the assessment of the Identification, Related substance and Assay procedures.

**Minocycline Preparations (minute 417 refers)** The monographs were intended to be published in the BP 2020.

**Caspofungin for Injection (minute 417 refers)** The monograph would be included in a future publication.

**Ciclosporin Preparations (minute 417 refers)** The monographs were awaiting finalisation of the Ciclosporin API monograph before proceeding with laboratory work.

**Rifampicin Combination Preparations (minute 417 refers)** The monographs would be included in a future publication.

**Azithromycin Eye Drops (minute 419 refers)** The monograph was intended to be published in the BP 2020.

**Cilastatin and Imipenem for Injection (minute 420 refers)** The monograph was intended to be published in the BP 2020.

**Co-amoxiclav Injection (minute 421 refers)** The monograph was intended to be published in the BP 2020

**Colistimethate Inhalation Powder, Hard Capsule (minute 422 refers)** The monograph was intended to be published in the BP 2020.

**Erythromycin Preparations (minute 424 refers)** A laboratory report was pending for the assessment of Identification, Dissolution, Related substances and Assay procedures.

**Griseofulvin Preparations (minute 425 refers)** The monographs were intended to be published in the BP 2020.

**Tobramycin Preparations (minute 426 refers)** The monographs were intended to be published in the BP 2020.

**Vancomycin Preparations (minute 427 refers)** A laboratory report was pending for the assessment of the Related substance and Vancomycin B procedures.

**Chloramphenicol Preparations (minute 428 refers)** A laboratory report was pending for the development of an Identification procedure and for the assessment of the Dissolution, Related substance and Assay procedures.

## III MONOGRAPHS FOR THE BP 2020

**442 Clindamycin Preparations** **ABS(19)04**
**Clindamycin Capsules (Revised)**
**Clindamycin Injection (Revised)**

Members had previously approved laboratory work on a range of Clindamycin

monographs, which had been completed for the two clindamycin monographs that were under revision, Clindamycin Injection and Clindamycin Capsules. The laboratory reports were introduced by the Laboratory.

The draft monographs for the Tablets, Gel, Solution, Lotion and Cream would be included in a future BP publication, subject to comments from manufacturers.

**Identification (Capsules)**
The laboratory report confirmed that the use of dichloromethane in place of chloroform was suitable if the volume of the solvent was increased from 15 mL to 50 mL. The Secretariat had made the required changes and placed the draft monograph on the website for public consultation in Q1 2019.

**Dissolution (Capsules)**
The method and acceptance criteria for dissolution of Clindamycin Capsules had been found to be satisfactory with limits of Q = 80% after 30 minutes. All samples tested complied with the limits.

**Related Substances (Injection)**
The LC procedure from the published clindamycin phosphate monograph had been investigated for its applicability to assess the related substances of Clindamycin Injection. The method applied gradient conditions and quantification at 210nm. Members approved the drafted limits which had been found to be suitable for the sample tested.

**Assay (Injection)**
The LC procedure from the published clindamycin phosphate monograph, harmonised with the related substances procedure had been assessed by the laboratory and found to be suitable. The method applied isocratic/gradient conditions and quantification at 210nm.

Members agreed to the publication of the monographs in the BP 2020 subject to further comment by manufacturers.

**443 Phenoxymethylpenicillin Preparations ABS(19)05**
**Phenoxymethylpenicillin Oral Solution (Revision)**
**Phenoxymethylpenicillin Tablets (Revision)**

Members had previously approved laboratory work on Phenoxymethylpenicillin Tablets and Oral Solution monographs. This has since been completed and the laboratory reports were introduced by the laboratory. The draft monographs had been amended in-line with the laboratory findings and placed on the website for the public consultation in Q1 2019.

**Content**
The content statement was formed of the combination of Phenoxymethylpenicillin and Impurity D, as previously agreed. The Related substances test was to be utilised to quantify the amount of impurity D in the product. All content results obtained from the combination of the Assay value and the impurity D value had passed the limits comfortably.

Members discussed that as Impurity D was an active moiety, it should not be referred to as an impurity. The Secretariat noted that this was harmonised with the Ph Eur and members proposed that a request for revision be prepared for the UK Delegation to the European Pharmacopoeia Commission to see this changed in the drug substance monograph.

Members agreed to the limits drafted in-line with current policy but requested that the BP Commission reviewed the policy for Oral Solution limits as there was an expectation that these could be tightened.

**Dissolution**
Members noted that the BP Commission had recently confirmed that dissolution requirements in all BP monographs should be stated in terms of the internationally harmonised quantity, Q, of active substance dissolved in a specified time. It was agreed that the acceptance criteria in the tablets monograph should be updated to Q= 75% in-line with this policy.

**Related substances**
The Related substances method had been found suitable for the Phenoxymethylpenicillin Tablets formulations tested within the laboratory. For the Oral Solution monograph, an additional system suitability criterion for resolution between sodium benzoate and impurity E1 had been included due to several excipients in the formulations. The resolution limit had been set based on injections of the additional system suitability solution. The Secretariat had also included an additional criterion for the disregard of peaks based on the laboratory data.

Members agreed to the system suitability criteria and impurity limits based on the laboratory data.

**Assay**
The drafted Assay methods in the monographs were assessed by the laboratory and found to be suitable for all products tested. The solution concentration had been reduced in the monograph from 0.1% to 0.05% w/v to ensure the peak asymmetry for the standard and sample chromatograms was less than 1.8.

Members agreed to the publication of the monographs in the BP 2020 subject to further comment by manufacturers.

**MONOGRAPHS FOR THE BP 2021**

**444 Colistin Tablets (Revision) ABS(19)06**

At the September 2018 meeting of the EAG, the members agreed that Colistin Tablets should be transferred to EAG ULM following a revision to incorporate an update in methodology from the Ph. Eur. (supplement 9.6). Monographs transferred to ULM required confirmation by the originator EAG prior to transfer. Members agreed that the Tablets monograph should be transferred to EAG: ULM.

**Identification**
Members agreed that the use of Cromatropic acid in the Identification test (B) was not acceptable and the test should be replaced with test (C) from the Ph. Eur. Colistin Sulfate monograph.

**Composition**
The Secretariat had revised the composition and Related substances tests in the draft monographs to harmonise with the Ph. Eur.

The draft procedure provided improved control of a number of compounds with activity similar to Colistin. The method utilised HPLC with UV characterisation at 215nm and

quantification through normalisation. In the absence of manufacturers specifications, limits had been drafted in-line with the Ph Eur drug substance monograph, but it was expected that the suitability of the limits would be confirmed by EAG ULM.

**Related substances**
The Related substances procedure was harmonised with the Composition procedure in the draft monograph. Limits had been drafted in-line with the Ph Eur drug substance monograph, but it was expected that the suitability of the limits would be confirmed by EAG ULM.

**445 Norfloxacin Preparations ABS(19)07**
**Norfloxacin Eye Drops (Omission)**
**Norfloxacin Tablets (Revision)**

The Secretariat highlighted that the tablets monograph had been previously discussed at the February 2018 meeting of this EAG regarding a revision to the identification test. At the time, members had requested that the Ph Eur Related substances procedure be incorporated into these monographs.

Although there was a marketing authorisation holder for the tablets when discussed, this had been withdrawn and there were no licensed products. The BNF noted that the tablets were available from special-order manufacturers and there was evidence of use of the tablets in the prescription data but there was no evidence of use of the eye drops. Members agreed that the Tablets monograph should be transferred to EAG: ULM and that the Eye Drops monograph be omitted from the BP 2020.

On review, members agreed that the chloroform should be replaced with dichloromethane in the TLC Identification mobile phase and that Q acceptance criteria should be used in the test for Dissolution.

**Related Substances**
For the Tablets monograph, the Secretariat had drafted a new test for Related substances using the LC procedure from the Ph Eur drug substance monograph. This procedure employed gradient elution and quantification at 265 nm. In the absence of manufacturers specifications, limits had been drafted in-line with the Ph Eur drug substance monograph, but it was expected that the suitability of the limits would be confirmed by EAG ULM.

**446 Streptomycin Injection (Revision) ABS(19)08**

The name of the streptomycin sulphate EPCRS had been changed to streptomycin sulphate for identification EPCRS by the European Pharmacopoeia. This change had been included in the Streptomycin Sulphate monograph published in Pharmeuropa 20.4, along with the replacement of a colorimetric test for specific absorbance. Group 7 were reviewing a number of comments regarding the revised monograph and it had not yet been scheduled for publication.

The streptomycin sulphate EPCRS was used in the Streptomycin Injection BP monograph which included requirements for the dry powder and solution for injection. The Secretariat noted that there were no marketing authorisation holders or evidence of use for either the powder or solution but that the BNF indicated streptomycin for use in the treatment of Tuberculosis and that a powder for solution for injection was available from unlicensed manufacturers. A member highlighted that a license was active for a solution for injection product for veterinary use. Members agreed that the Powder for Injection monograph

should be transferred to EAG: ULM and that the Solution for Injection be moved to the BP Vet.

The Secretariat had drafted the Powder for Solution monograph, renaming the EPCRS and removing the Solution for Injection requirement but retaining critical tests like TLC identification and streptomycin B. Members agreed that the Solution for Injection monograph should be drafted in the same manner.

## IV MONOGRAPHS FOR THE BP 2022+

**447 Florfenicol Preparations** **ABS(19)09**
**Florfenicol Injection (New)**
**Florfenicol Premix (New)**
**Florfenicol Solution for Use in Drinking Water (New)**
**Florfenicol Veterinary Oral Powder (New)**

The draft monographs would be included in a future BP publication, subject to comments from manufacturers.

**448 Nystatin Preparations** **ABS(19)10**
**Nystatin Ointment (Revision)**
**Nystatin Oral Suspension (Revision)**
**Nystatin Pastilles (Omission)**
**Nystatin Tablets (Revision)**
**Nystatin Vaginal Tablets (Revision)**

A significant update to the Nystatin family of monographs had not been undertaken since 1980, where a UV identification test was added to the existing microbiological Assay, Acidity and Loss on drying specifications for the 1983 addendum.

The Nystatin monograph family had been proposed for informal harmonisation by the USP as part of their modernisation programme as the monographs did not contain a Related substances test. Although the USP were leading this development, the Secretariat had prepared revised drafts for discussion with UK stakeholders, including the Composition test from the Ph Eur Nystatin monograph for the control of impurities as a Related substances procedure was not available. On consideration, members requested the Secretariat to investigate alternative methodology to control impurities in addition to consulting with manufacturers.

Although the BNF listed the Oral Suspension as the sole licensed formulation, licenses were available for the Tablets and Vaginal tablets. Members agreed that the Ointment should be transferred to EAG ULM as there was prescription volume but that the Pastilles should be omitted as there was no evidence of use.

**Composition**
The Secretariat had drafted a new test for Composition harmonised with the LC procedure from the Ph Eur drug substance monograph. This procedure employed gradient elution and quantification by normalisation at 305 nm.

In the absence of any licensed shelf life data for nystatin composition, limits were drafted in line with the Ph Eur drug substance monograph, but manufacturers would be asked to comment on their suitability. Members noted that the identity of the principle peaks should be specified.

The Secretariat noted that all three Oral suspension products contained parabens as well as a number of other excipients which were likely to interfere with the chromatography. Members agreed that a laboratory assessment of the method should be undertaken to assess the suitability of the procedure and limits for the available products.

**449 Polymyxin and Bacitracin Preparations ABS(19)11**
**Polymyxin and Bacitracin Eye Ointment (Revision)**
**Polymyxin and Bacitracin Ointment (Revision)**

The Secretariat and USP had recently discussed the informal harmonisation of the Polymyxin and Bacitracin monograph family based on the recent update to the Bacitracin zinc drug substance monograph in Ph Eur 9.6. It had been agreed that the product monographs could be improved and would be good candidates for collaboration.

The Secretariat noted that the Polymyxin B Sulfate monograph was also under revision and that there were no licensed products for the Polymyxin and Bacitracin Eye Ointment. Members agreed that as there was no evidence of use of this product, this monograph should be omitted.

Members noted that Chloroform used in the Identification and both Assay procedures should be replaced with Dichloromethane as part of the revision.

**Composition & Related substances (Polymyxin B Sulfate)**
The Ph Eur had created a new test for composition in the Polymyxin B Sulfate monograph using the existing chromatographic conditions in the Related substances. The Related substances procedure in the ointment and eye ointment monographs was harmonised with that of the Ph Eur. Members considered if the composition limits should be included in the drug product monograph but agreed they were not necessary and so no changes were required.

**Composition & Related substances (Bacitracin Zinc)**
The Ph Eur Bacitracin Zinc monograph had been updated with a new procedure and limits for the Composition and Related substances tests, replacing the existing Composition, Related peptides and Impurity E tests.

The BP product draft monographs had been updated accordingly to replace the Related peptides and Impurity E tests with the new Related substances procedure. This applied isocratic conditions and quantification by normalisation at 254nm. The Secretariat noted that the disregard was lower than that specified by ICH Q3B (R2), but this had been harmonised with the Ph Eur in order to maintain the impurity limits obtained by the normalisation procedure.

The Secretariat noted that the updated procedure used similar chromatographic conditions to the Impurity E test and so the existing diluent and extraction procedure was expected to be suitable. It was expected that the differentiation of impurities due to Polymyxin B Sulfate and Bacitracin Zinc would be complex and so a laboratory assessment would be required.

**450 Teicoplanin Injection (New) ABS(19)12**

The draft monograph would be included in a future BP publication, subject to comments

from manufacturers.

## V FOR INFORMATION

### 451 Liposomal Formulations ABS(19)13

The addition of monographs for Liposomal formulations to the work programme had been discussed at the September 2018 meeting of this EAG following a review of liposomal finished products. The Secretariat provided a brief update on the evolving situation regarding the naming of the drug products. Members discussed factors to be considered in the development of a template for liposomal product monographs.

### 452 Antimicrobial Resistance ABS(19)14

Members discussed the implications of Antimicrobial resistance (AMR), an area of growing global concern for antibiotic products. The Secretariat highlighted that following the independent review on Antimicrobial Resistance chaired by Jim O'Neill (https://amr-review.org/), the UK Government had published a 20-year vision for antimicrobial resistance and resulting five year national action plan for AMR. This detailed a broad approach to tackling AMR, focussing on reducing unnecessary use and supporting new research, but also recognising the importance of improved quality assurance of antimicrobial products in the prevention of AMR.

Pharmacopoeial standards support the security of the UK's supply chain as part of the regulatory system blocking substandard products. The USP support this in their position paper on AMR highlighting that pharmacopoeial standards maintain the quality of antimicrobials at all stages of the product lifecycle.

New EU rules on medicated feed banning preventative use of antibiotics in groups of animals and placing restrictions on metaphylactic use of antibiotics to control the spread of a disease will come into force in 2022 and are likely to have an impact on the use of Premix and Solution for drinking water products.

Members agreed that a general review of antibiotic monographs would be beneficial to maintain alignment with current standards and licensing expectations. Data like the WHOs list of Critically Important Antimicrobials for Human Medicine could be used to prioritise the revision of antibiotic monographs from an international perspective.

Members were supportive of the Secretariat working with colleagues in the wider agency to identify how British Pharmacopoeia standards can help manufacturers develop new antibiotics quicker, which would be critical in the prevention of AMR, and ensure that the environmental impact from manufacturing, particularly from manufacturing waste, is minimised. This could include changes to how antibiotic monographs are initiated and the development of manufacturing advice in supplementary chapters.

### 453 Out of stock BPCRS Review ABS(19)15

The Secretariat presented a paper on out of stock BPCRS that were used in monographs that were under the remit of the EAG

### 454 Work Programme ABS(19)16

The ABS work programme was presented to members for information.

Members confirmed the addition of the following revisions to monographs to the work programme:

Cefalexin Capsules, Cefalexin Tablets, Cefalexin Oral Suspension, Co-fluampicil Capsules, Flucloxacillin Capsules, Flucloxacillin Oral Solution, Tetracycline Tablets.

Members confirmed the addition of the following new monographs to the work programme, subject to approval via the BP Commission initiations route:

Levofloxacin Tablets, Pivmecillinam Tablets, Ofloxacin Tablets, Rifaximin Tablets.

**455 British Pharmacopoeia Matters ABS(19)17**

A summary of the minutes from the latest BPC meeting was presented for information.

**VI European Pharmacopoeia ABS(19)18**

456 An update on changes to Ph. Eur. monographs that affected ABS monographs was presented to members.

**VII Any Other Business**

457 **Ear Preparations**
The Chair opened a discussion on the value of including a Uniformity of Delivered Dose test for Ear Sprays in the general monograph for Ear Preparations. Members considered that as a spray into the ear was a topical application it was not necessary from a quality perspective but agreed it would be beneficial from a manufacturing perspective to ensure that a device delivers the stated number of metered doses.

**VIII Date of Next Meeting**

To be arranged.