BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group: Antibiotics

SUMMARY MINUTES

A meeting of Expert Advisory Group: Antibiotics was held via teleconference on Monday 9th December 2019.

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

Apologies: Dr G Clarke

In attendance: Mr P Crowley, Mr S Maddocks, Ms K Busuttil and Ms M Nanasi. Mr I Jenkins from the VMD attended the meeting as an invited expert.

459 Introductory remarks

Welcome
The Chair welcomed Mr Jenkins to the meeting, who was attending as an invited expert, as well as 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.

460 General Matters **ABS(19)19**

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(19)20**

461 The minutes and summary minutes for the meeting held on 7th February 2019 were confirmed pending the addition of a note under any other business concerning instances of regulators classing antibiotics derived from fermentation as biologics.

II MATTERS ARISING FROM THE MINUTES **ABS(19)21**

462 The following matters arising from the meeting held on 7th February 2019 were noted.

Marbofloxacin Preparations (minute 365 refers) Draft monographs would be published in a future publication of the Pharmacopoeia.

Ceftiofur Hydrochloride Suspension for Injection (minute 365 refers) A draft monograph would be published in a future publication of the Pharmacopoeia.

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) Draft monographs would be published in a future publication of the Pharmacopoeia.

Rifampicin Preparations (minute 402 refers) Draft monographs would be published in a future publication of the Pharmacopoeia.

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) A draft monograph would be published in a future publication of the Pharmacopoeia.

Amikacin Injection (minute 417 refers) The Secretariat were looking at options for the assessment of the PAD Related substances procedure with a contract laboratory.

Caspofungin for Injection (minute 417 refers) A draft monograph would be published in a future publication of the Pharmacopoeia.

Ciclosporin Preparations (minute 417 refers) The monographs had been amended as agreed and were awaiting finalisation of the Ciclosporin API monograph before proceeding with laboratory work.

Rifampicin Combination Preparations (minute 417 refers) Draft monographs would be published in a future publication of the Pharmacopoeia.

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.

Colistin Tablets (minute 444 refers) The Secretariat were to revise the monograph and propose its transfer to ULM.

Norfloxacin Tablets (minute 445 refers) The Secretariat were to revise the monograph and propose its transfer to ULM.

Streptomycin Injection (minute 446 refers) The Secretariat were to amend the monograph for Streptomycin Injection for inclusion in the BP(Vet) and to create a separate monograph for the powder for injection requirement which would be proposed for transfer to EAG: ULM.

Florfenicol Preparations (minute 447 refers) Draft monographs would be published in a future publication of the Pharmacopoeia.

Nystatin Preparations (minute 448 refers) The Secretariat were to amend the monographs as previously agreed and circulate to manufacturers and the USP for comments. The ointment monograph would be proposed for transfer to EAG: ULM.

Polymyxin and Bacitracin Ointment (minute 449 refers) The Secretariat were to amend the Ointment monographs as agreed and circulate to manufacturers for comment.

Teicoplanin Injection (minute 450 refers) A draft monograph would be published in a future publication of the Pharmacopoeia.

III MONOGRAPHS FOR THE BP 2021

463 Erythromycin Preparations — ABS(19)22

Erythromycin Lactobionate Infusion (Revision)
Erythromycin Gastro-resistant Capsules (Revision)
Erythromycin Gastro-resistant Tablets (Revision)
Erythromycin Stearate Tablets (Revision)
Erythromycin and Zinc Acetate Lotion (Revision)

The BP Laboratory had investigated updated methodology for the dissolution, related substances and Assay procedures for the Erythromycin family of monographs.

The laboratory report for Erythromycin Ethyl Succinate for Oral Suspension monograph demonstrated poor reproducibility of retention time for impurity P resulting in issues affecting the quantification of Erythromycin B. It was noted that the European Pharmacopoeia had reverted back to the previous version of the monograph for Erythromycin Ethylsuccinate and members agreed that the methods were not suitable for publication. It was agreed that the monograph would be revisited when a more appropriate method was available.

Dissolution
The methods for dissolution had been updated based on laboratory investigations. The laboratory found that Erythromycin degraded in 0.06M hydrochloric acid and was therefore not able to be quantified under the conditions set out for the first stage of the dissolution test.

The second stage of the dissolution test was drafted using a medium of pH 6.8 phosphate buffer, the Erythromycin release was quantified using isocratic HPLC separation and UV quantitation at 210 nm. The limit was drafted as 75% (Q) after 60 minutes.

Members discussed the limits and were concerned that acid resistance was only inferred by release in the second medium as it was not possible to quantify in the first. It was noted that only the second stage was quantified in the existing Erythromycin Gastro-resistant Capsules monograph. Members agreed that the procedures represented a significant improvement and were suitable for publication, but that manufacturers should be contacted with regard to sourcing a method for quantifying the amount of Erythromycin released at the first stage.

Related Substances
The laboratory had successfully completed assessment of the Related Substances procedure for the Gastro-resistant Capsules, Gastro-resistant Tablets, Lactobionate for Infusion, Stearate Tablets and Zinc Acetate Lotion products.

The BP laboratory experienced a number of issues when performing the verification, including an increase in system pressure after a number of injections, solubility and stability of Erythromycin in solution and excipient interference. Members noted the issues and agreed the methods were a significant improvement on the existing methods.

Members reviewed the drafted impurity limits and agreed they were suitable based on the licensed specifications and results from the laboratory reports.

It was agreed that the Secretariat would contact manufacturers to seek comment on the impurity limits.

Assay (All monographs)
The laboratory had successfully completed an assessment of the Assay procedure for the Gastro-resistant Capsules, Gastro-resistant Tablets, Lactobionate for Infusion, Stearate Tablets and Zinc Acetate Lotion products.

Members discussed the opportunity for the method to be shortened to the isocratic portion of the gradient. The Secretariat confirmed that late eluting impurities could cause interference with the active peak and so the gradient was required.

It was agreed that the methods should be made available for public comment in Q1 2020 with a view to publishing in the BP 2021.

464 Clindamycin Preparations **ABS(19)23**
Clindamycin Chewable Tablets (New)
Clindamycin Gel (New)
Clindamycin Injection (Revision)
Clindamycin Lotion (New)
Clindamycin Solution (New)
Clindamycin Tablets (New)

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

Members previously reviewed draft monographs for Clindamycin Capsules and Injection, based on completed laboratory assessments. The Clindamycin Capsules monograph had been published in the BP 2020, but the Clindamycin Injection monograph was deferred due to concerns from manufacturers regarding the impurity specifications.

Related Substances

The LC procedure from the published clindamycin phosphate monograph had been found to be suitable for Clindamycin Injection products and was confirmed by members at the last meeting of this EAG. During the public consultation between January and March 2019, manufacturers raised concerns regarding the limits, providing data to support new limits. The Secretariat had therefore redrafted the limits accordingly. Members requested that during the public consultation, manufacturers attention be drawn to the limits, particularly for impurity F which was noted to be lower than in the licensed specifications.

465 Fusidic acid/Sodium Fusidate Preparations ABS(19)24
Fusidic acid Cream (Revision)
Fusidic Acid Eye Drops (Revision)
Fusidic Acid Oral Suspension (Revision)
Sodium Fusidate Ointment (Revision)
Sodium Fusidate Tablets (New)

The monograph for Sodium Fusidate Tablets would be published in a future publication of the Pharmacopoeia, subject to comment from manfacturers.

The BP Laboratory had successfully completed an assessment of the identification, related substances and Assay procedures for the Fusidic Acid Cream and Fusidic Acid Eye Drops monographs which were based on the European Pharmacopoeia methods for Fusidic Acid. The monographs for Fusidic Acid Oral Suspension and Sodium Fusidate Ointment had been revised based on the laboratory findings for the Cream and Eye Drops.

Identification
The TLC identification method for the Cream and Eye Drops had been revised to replace chloroform with dichloromethane which had been found to be suitable by the BP Laboratory.

Dissolution
A dissolution test for the Fusidic Acid Oral Suspension monograph had not been sourced but members agreed that the monograph should be published in BP 2021. The Secretariat would continue to request manufacturers provide a suitable procedure and the monographs would be revised at a future date.

Related Substances
The related substances method had been updated in all monographs based on the laboratory work performed for the Cream and Eye Drops products. The method utilised reversed phase Liquid chromatography with a Water Symmetry C18 stationary phase and quantification at 235nm. The impurity limits were drafted in-line with registered specifications and agreed for adoption by the EAG.

Members queried the need for solution (4), Butylhydroxyanisole, in the Fusidic Acid Cream monograph but it was concluded that it was necessary to ensure separation of this excipient from Impurity A.

Assay
The Assay procedure, which was harmonised with the related substances, had been updated in all monographs based on the laboratory work performed for the Cream and Eye Drops products. Members confirmed the procedure as suitable.

IV FOR INFORMATION

466 Portfolio Review ABS(19)25

A set of general principles and measures had been developed by the Secretariat to support a broad and systematic review of the BP portfolio. Proposals for rationalising BPCRS use were considered by members. Phase one of the review had used sales of BPCRS over 5 years as an indicator of value of the monograph and standard to users to identify monographs that could be omitted or revised.

Monographs for omission
The Secretariat did not recommend any monographs for omission. It was however noted that the monographs for Erythromycin Estolate Capsules had previously been agreed for omission and therefore did not fall under the remit of this review.

Monographs for revision
It was agreed that the need for the Cefalotin Sodium BPCRS could be removed by harmonising the Cefalonium (VET) API monograph with the Cefalonium Intramammary Infusion (Dry Cow) monograph, which contained superior methodology.

Members also supported replacing Chloramphenicol Sodium Succinate BPCRS with its EPCRS equivalent in the Chloramphenicol Sodium Succinate Injection monograph. It was noted that there was an increase in marketed products for Chloramphenicol Sodium Succinate Injection and so a more thorough review of the monograph was agreed to be undertaken at a later date.

The ongoing revisions to the monographs for Erythromycin Ethyl Succinate Capsules and Erythromycin Ethyl Succinate oral suspension would seek to remove the need for the Erythromycin Estolate BPCRS.

467 BP 2020 Update ABS(19)26

It was noted that the British pharmacopoeia 2020 had been published in August 2019 and would come into effect on 1st January 2020. The BP 2020 contained all the text from the 9th edition of the European Pharmacopoeia, together with Supplements from 9.1 to 9.8. The 10th edition of the European Pharmacopoeia was published in July and the content of the new edition was to be incorporated into the BP online in December, prior to its implementation on 1st January 2020.

The Secretariat highlighted that 7 new monographs, 9 revisions to current monographs and 3 monograph omissions, all under the remit of EAG ABS had been incorporated in the BP 2020.

468 British Pharmacopoeia Matters ABS(19)27

The Secretariat highlighted the recent work of the British Pharmacopoeia as well as recent items that had been discussed at British Pharmacopoeia Commission meetings.

Assay for Liquid Formulations; Weight per mL
The current policy for Assay of liquid formulations had been confirmed. For a formulation that could be easily pipetted, sampling by volume would have been acceptable and there would be no need for a weight per mL determination to be carried out. However, if a formulation was viscous and could not be accurately measured by pipette, it had been

agreed that sampling should be done by weight, and a weight per mL requirement be included in the monograph.

Related substances: Use of correction factors
Following a request to include correction factors for all impurities specified in monographs, the Commission had confirmed the current policy as stated in Appendix III: Chromatographic Separation Techniques as suitable. This specified that correction factors are only applied when the response of an impurity compared to that of the active substances was outside the range “0.8 to 1.2”.

Assay for Capsules
Attention had been drawn to inconsistencies in the method of sample preparation in the Assay for tablets and capsules formulations. The approach for tablets was to “Weigh and powder 20 tablets”, the usual approach for capsules was to use the “mixed contents of 20 capsules” without an explicit weighing step. The Commission had confirmed that in line with the approach in the International Pharmacopoeia and the United States Pharmacopeia a weighing step should be included and had agreed a form of words that would encompass powder-, granule- and liquid-filled capsules. The new wording was to be included in all new capsule monographs going forward as well as in those that were undergoing revision.

AQbD Consultation
The consultation had gained a total of 25 responses, which covered 3 separate continents and at-least 1 respondent from each of the key stakeholder groups. These included: large pharma; small/medium pharma; generics; academia; consultancy and other regulatory agencies.

The overall response had been positive and largely encouraged the use of AQbD concepts within the pharmacopoeia. The Secretariat was preparing an official response, which was expected in Q1 2020 which would detail a strategy, ensuring the project remained world leading and aligned with industry and regulatory practices.

BP User Guide
In response to comments from users, a guide had been developed to help our users become more familiar with the requirements of the BP. This was located on the BP website (https://www.pharmacopoeia.com/how-to-use-the-bp).

BP Website
A number of improvements had been made to the BP website. A “timeline” feature was introduced in the BP 2020, which highlighted the editions in which changes had been made to individual monographs (https://www.pharmacopoeia.com/enhancements-to-the-BP-timeline). Work was ongoing to improve the website search function and a track-changes feature was to be included to identify amendments in each new edition.

469 European Pharmacopoeia Matters **ABS(19)28**

Mr Sumal reported back on the meetings of group 7 and noted that the issue of replacing the pyrogens test with BET had been considered again, but that their equivalence was understood to be a complex and ongoing matter.

Members were thanked for their contributions to the work of the European Pharmacopoeia, specifically to their ongoing support of Group 7 monographs.

There were no monographs under the remit of the EAG that were up for comment on PharmEuropa 31.4.

V ANY OTHER BUSINESS

Teicoplanin Injection
Members discussed reports that the colour of teicoplanin injection products were changing colour and noted several academic papers which had been published on the subject.

VI DATE OF NEXT MEETING

Tuesday 31st March 2020.