BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group: Antibiotics

SUMMARY MINUTES

A meeting of Expert Advisory Group: Antibiotics was held at 151 Buckingham Palace Road, London SW1W 9SZ on Thursday 21st September 2017.

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

Apologies: None

In attendance: Mr P Crowley, Mr L Elanganathan, Mr S Maddocks, Mrs Fiona Lee (BP Lab), Ms Carolina Galdino (BP Lab) and Mr Michael Threadgold (BP Lab).

362 Introductory remarks

Welcome
The Chair welcomed members to the meeting. A special welcome was extended to Dr Melanie Pires, who was attending her first meeting as a new member, and to Mrs F Lee, Ms C Galdino and Mr M Threadgold from the BP Laboratory.

Membership
Mr Vikas Jaitely had left the MHRA but continued his membership of EAG ABS as an external expert. Dr Pires was the new representative from the Licensing Division.

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.

363 General Matters **ABS(17)01**

Emergency evacuation procedure
Members were reminded of the evacuation procedure in the event of a fire alarm.

I MINUTES **ABS(17)02**

364 The minutes of the meeting held on 21st September 2017 were confirmed.

II MATTERS ARISING FROM THE MINUTES

365 The following matters arising from the meeting held on 21st September 2016 were noted.

Teicoplanin Injection (minute 260 refers) The Secretariat were awaiting finalisation of the Ph Eur parent monograph before further developing this monograph.
Lymecycline Capsules (minute 287 refers) The test for light absorbing impurities had been removed from the monograph in the BP 2016. The Secretariat were awaiting finalisation of the Ph Eur parent monograph before further developing the monograph.

Liposomal Amphotericin for Infusion (minute 296 refers) The Secretariat would present proposals for a draft monograph at a future meeting.

Tylosin Premix (minute 321 refers) The Secretariat were awaiting finalisation of the Ph. Eur. Parent monograph prior to revising the monograph.

Norfloxacin Preparations (minute 332 refers) The Secretariat had received data supporting a revised related substances procedure. A draft monograph would be presented at a future meeting.

Azithromycin Preparations (minute 332 refers) The Secretariat would be presenting proposals for new monographs for Eye Drops and Powder for Oral Solution at a future meeting.

Tobramycin Sulfate (minute 336 refers) Comments from members on the draft monographs had been provided to EAG ULM for consideration at their November meeting.

Doxycycline Preparations (minutes 338 and 339 refer) A laboratory report was pending for method assessments

Minocycline Preparations (minutes 341 and 342 refer) A laboratory report was pending for the assessment of the methods.

Ceftiofur Hydrochloride Suspension for Injection (minute 343 refers) Specifications and comments had been requested from VMD and a laboratory report was pending for the assessment of the methods.

Tigecycline for Infusion (minute 347 refers) The Tigecycline for Infusion monograph was expected to be published in the BP 2019.

Fusidic Acid & Sodium Fusidate Preparations (minute 348 refers) The Secretariat were investigating the feasibility of commissioning a MSc project to carry out the assessment of the monographs.

Marbofloxacin Preparations (minute 349 refers) The monographs were to be published for public consultation with a view to publishing in the BP 2019.

Clindamycin Tablets for Veterinary Use (minute 350 refers) A laboratory report was pending for the assessment of the methods.

Moxidectin Preparations (minute 351 refers) The Secretariat were reviewing comments received from a manufacturer which will be presented at a future meeting with a view to publishing in the BP 2019.

Bacterial Endotoxins (minute 352 refers) The Secretariat were seeking clarification on the additional information required to remove pyrogens test from remaining Ph. Eur. parent monographs.

Vancomycin Infusion (minute 355 refers) The Secretariat were awaiting finalisation of the Ph. Eur. Drug substance monograph prior to the progression of the monograph.

Co-amoxiclav Injection (minute 356 refers) The revised monograph was intended to be updated in the BP 2019.

III MONOGRAPHS FOR THE BP 2019

366 Amikacin Injection (Revision) ABS(17)03

Members had agreed at the February 2013 meeting that the BP laboratory assess the suitability of the new Ph Eur pulsed amperometric detection (PAD) related substances method, and the revised Assay. This was in response to correspondence received from a manufacturer highlighting difficulties using the current methods.

This work was now complete and the Secretariat outlined the observations and conclusions from the laboratory report.

Related Substances
The laboratory had experienced difficulties establishing a stable system, with long equilibration times and retention time shifts. The chromatographic conditions and sample concentrations had been optimised to enhance the sensitivity of the method, but it was not found to be achievable for the disregard solution.

A report on the collaborative work carried out by the EDQM, revealed that the three participating labs had been able to achieve sensitivity and it was to be noted that the three labs used dedicated HPLC-PAD systems. As the BP laboratory did not have dedicated system, a chromatographic system had been replicated by supplementing existing HPLC equipment with a PAD detector and an external pump for the inline addition of a post column solution.

The laboratory had found a published paper which carried out the analysis using very similar chromatographic conditions and detector settings. They noted that high concentrations of Amikacin were analysed, and although the LOD and LOQ was not reported, it indicated that the method may not be suitable at low concentrations.

Members discussed possible reasons for the difference in sensitivity and concluded that as the manufacturers and laboratories in the EDQM collaborative work used dedicated instrumentation for PAD methods, they would not observe as much chromatographic noise so attaining better signal to noise ratios. It is likely that more methods for ABS would be developed using the PAD technology and so expertise of this technique should be developed within the BP Laboratory.

Members agreed that until the Ph Eur procedure had been assessed, the current method for related substances should be retained.

Assay
The method included in the Ph. Eur. monograph was found to be suitable for all products tested.

Members agreed that the draft Assay method is put forward for public consultation with a view of publishing in BP 2019.

367 Benzoyl Peroxide & Clindamycin Gel (Revision)

This monograph was first published in the BP 2018 but the Secretariat had developed further improvements.

Identification
Members agreed that the BP Laboratory should confirm the suitability of substituting

chloroform with dichloromethane.

Impurities
The Secretariat provided for comment a paper to be presented to the Nomenclature Expert Advisory Group, which requested advice on the naming of the remaining unidentified impurities.

368 Colistimethate Preparations ABS(17)05
Colistimethate for Injection (revision)
Colistimethate Powder for Nebuliser Solution (Revision)
Colistimethate Inhalation Powder, hard capsule (New)

A new policy for inhaled products has been agreed by the BP Commission and therefore a revised draft monograph for the Colistimethate Powder for Nebuliser Solution was also presented for consideration. A manufacturer had provided data in support of this revision.

A draft monograph for Colistimethate dry powder inhaler, hard capsule would be included in a future publication subject to a public consultation.

It was highlighted that the Ph. Eur. Colistimethate Sodium monograph had been revised to include the manufacturers proposed Composition and related Substances procedures and was published in supplement 9.2. A revision to replace the Pyrogens test with the bacterial endotoxins test was currently at an early stage.

Title
As Colistimethate Sodium was the only salt that is used in the preparation of these products, reference to sodium has been deleted from the titles in line with BP policy.

As all injection products were supplied as a powder for Injection, the title had been updated to reflect this. As the Powders for injection were also labelled as powders for infusion, a subsidiary title of Colistimethate for Infusion had also been included.

Definition
As all injection products were supplied as a powder for injection, the definition for the ready to use solution had been omitted.

Content
As all products were defined in terms of international units, members agreed that no content statement should be included. Instead this would be defined in the microbiological assay as per antibiotics policy.

Identification
The powder for nebuliser solution monograph had also been revised to harmonise the identification tests, replacing the TLC, Chemical reaction and Sulfates tests with concordant retention time in the Composition Test.

Uniformity of content
Members discussed whether a uniformity of content test was required for inclusion in the powder for nebuliser solution monograph. This would be reviewed when the policy has been confirmed.

Aciditiy or Alkilinity
The test and limits from the Injection had been harmonised across all monographs. Members endorsed widening the lower limit from 6.5 to 6.2.

Free Colistin
Members agreed the already harmonised tests and limits from the injection and powder for nebuliser solution monographs should be included across the whole family of monographs.

Loss on drying
Members had previously agreed to a limit of 7.0% for the Injection as proposed by the manufacturer.

Composition
As all products had the same formulation, the LC Composition test previously agreed for the Injection monograph, which applied gradient conditions and quantification at 210nm, had been harmonised across all other product monographs.

The limits agreed for the injection monograph had been harmonised across all products and manufacturers would be asked to comment on their suitability. Members expressed a preference to retaining the Ph Eur limits, which the Secretariat agreed to confirm with the manufacturers and licensing division.

The Secretariat noted that as each component was specified in the composition test, the previously included limit of disregard was not required and so had been deleted from this test. The requirement to identify peaks due to EC1 and EC2 had been moved to the related substances test as they were not referenced in the Composition test. Members also agreed that the instruction to integrate all peaks greater than 0.05% should be retained as the normalised limits were based on the inclusion of these peaks.

Related Substances
As agreed for the injection monograph, the chromatographic conditions for the related substances were cross referred to the test for Composition in all monographs.

The limits drafted for the Injection monograph had also been harmonised in the absence of any other manufacturers impurity specification. Limits for unspecified and total impurities were based on the manufacturers recommendations. A limit of disregard of 0.50% and an instruction to disregard any peaks related to Colistimethate Sodium EC1 or EC2 had also been included.

Assay
The microbiological assay of antibiotics had been retained in the injection and powder for nebuliser solution monographs.

Members agreed that the amended drafted monographs should be posted to the BP website for public consultation with a view to publishing in the BP 2019.

369 Doxorubicin Preparations ABS(17)06
Doxorubicin for Infusion (Revision)
Doxorubicin Sterile Concentrate (Revision)

Revised monographs for Doxorubicin for infusion and Sterile Doxorubicin Concentrate were published in the BP 2018 in order to split the powder and solution forms contained in the previous Doxorubicin Injection monograph. Following a request from a

manufacturer to harmonise limits in the Sterile Doxorubicin Concentrate monograph with the latest USP monographs, the Secretariat had performed a review of UK licensed impurity limits, and revised the monograph accordingly. The Doxorubicin for Infusion monograph had been revised accordingly and both monographs were presented for discussion.

Members were informed that the Doxorubicin Hydrochloride Injection USP revision became effective as of 1st March 2017 as part of an Interim Revision Announcement (IRA).

Title
The Secretariat had conducted a review of UK licensed products for Doxorubicin which identified 5 different pharmaceutical forms. It was noted that the Doxorubicin for Infusion monograph was also applicable to the powder for injection product and members agreed to include a subsidiary title of Doxorubicin for Injection.

All solution formulations were comparable containing the same excipients. Members agreed that the Sterile Doxorubicin Concentrate monograph should include subsidiary titles of Doxorubicin Injection and Doxorubicin Infusion. The Chair noted it had been recently agreed by the Pharmacy expert advisory group that standard terms should not be split, and so the monograph title should be updated to Doxorubicin Sterile Concentrate.

Related substances
The Related substance procedure published in the Doxorubicin monographs was harmonised with that in the Ph Eur drug substance monograph for doxorubicin hydrochloride. The Secretariat noted that the column diameter was slightly larger in the BP monographs however and that this has been corrected in the interests of harmonisation.

Following the request from the manufacturer, the Secretariat had reviewed licensed limits for both powder and solution presentations as well as the limits included in USP and Ph Eur. Members discussed the draft limits and agreed they should be harmonised with the USP where possible.

The limit solutions in the related substances tests of both monographs had been amended to be a dilution of the test solution rather than the published standard solution, which was in line with BP policy.

Impurities
As the related substance procedure was harmonised with the Ph Eur drug substance monograph, an impurities statement had been included for transparency.

370 Griseofulvin Tablets (Revision) ABS(17)07

The Secretariat had received a request from a manufacturer to replace the GC related Substances in the Griseofulvin Tablets monograph with their internal HPLC procedure, validation data had been provided.

It was highlighted that the proposed revision to the Ph. Eur. Griseofulvin monograph included a new gradient HPLC related substances method and had been published in Pharmeuropa 28.4.

Related Substances
The manufacturer had highlighted that they, and other public testing laboratories, had encountered issues with the current GC related substances method. They had submitted a HPLC method with a full validation package to the British Pharmacopoeia for revision of the Griseofulvin Tablets monograph.

The method, which applied isocratic conditions and quantification at 290nm, had been drafted into the revised monograph. The limits specified for the latest draft of the Ph Eur Parent monograph have been adopted, with the exception for the unspecified impurity limit which has been increased in line with ICH Q2B (R2).

Members expressed a preference to harmonise with the new Ph Eur procedure and it was agreed to postpone any revision of the monograph until this procedure was confirmed.

Assay
Members stated a preference to harmonise with the related substances but that this should be confirmed when this procedure had been agreed.

371 Moxifloxacin Tablets (New) ABS(17)08

A draft monograph would be included in a future publication subject to a public consultation.

372 Oxytetracycline Preparations ABS(17)09
Oxytetracycline Calcium (Revision)
Oxytetracycline Capsules (Revision)
Oxytetracycline Veterinary Oral Powder (Revision
Oxytetracycline Tablets (Revision)

The Secretariat had received queries regarding the availability of *4-epioxytetracycline EPCRS* used in the Assay for Oxytetracycline Tablets and Oxytetracycline Calcium BP monographs. The Secretariat noted that the EDQM had discontinued the production of this material which was required for the system suitability test.

The Ph. Eur. had recently revised the HPLC related substances test and the paper in addition to proposing a solution to the discontinued EPCRS, also outlined a proposal to include the revised procedure in the BP monographs.

Related substances
Impurities in the Ph Eur drug substance monograph had been previously controlled by a non-specific light absorbing impurities test, but it had been recently revised to include a new HPLC procedure which provided specific control of several impurities. The Secretariat proposed that this procedure should be included in the BP product monographs to control the known degradants, impurities D, E and F as well as the fermentation impurities C and B.

As the licensed specifications did not include any impurity limits, limits had been drafted in line with those from the Ph Eur and (V)ICH guidelines and members agreed that the suitability of the procedure should be investigated by the BP laboratory.

Assay
The Secretariat noted that the current Assay method was based on a previous related substances test from the Ph. Eur. Oxytetracycline Hydrochloride and Oxytetracycline

Dihydrate monographs, which used *4-epioxytetracycline EPCRS* as a measure of system suitability. A new *oxytetracycline for system suitability EPRCS* (containing impurities A to E) had been developed for use with the new procedure and the *4-epioxytetracycline EPCRS* discontinued.

Members agreed that 4-epioxytetracycline should be added as a reagent in the BP 2019 with a purity greater than 95% as it was used for identification purposes only. It was also agreed that the laboratory should investigate the suitability of the new related substances procedure to harmonise conditions with the Assay for a future publication.

373 Tobramycin Preparations ABS(17)10
Tobramycin Injection (Revision)
Tobramycin Nebuliser Solution (Revision)
Tobramycin Inhalation Powder, hard capsule (New)
Tobramycin Eye Drops (New)

The Tobramycin Injection and Nebuliser Solution monographs were published in the BP 2017 and included a related Substances procedure provided by a manufacturer. The Secretariat had received correspondence from a different manufacturer highlighting a high level of observed unknown impurities in both sample and BPCRS. On investigation, it was noted that an instruction to disregard in the manufacturers original method had been omitted from the monographs.

Draft monographs for Tobramycin Inhalation Powder, hard capsule and Tobramycin Eye Drops would be included in a future publication subject to a public consultation.

Related substances
The Secretariat noted that instructions to disregard unknown peaks identified in a degraded standard solution and to perform a blank subtraction were missing and members agreed to update the monograph accordingly.

IV MONOGRAPHS FOR THE BP 2020+

374 Cefoxitin Injection (Revision) ABS(17)11

An analyst query had been received requesting advice on obtaining the column specified in the BP monograph for Cefoxitin Injection. Upon investigating which products are covered by the monograph, it was found that there were not any products licensed in the UK or in Europe.

Omission
The Secretariat noted that there were no licenced products available according to the MHRA and EMA databases. Information was not available in the BNF, but reference was found in “Martindale: The Complete Drug Reference” that these products were no longer marketed or manufactured in the UK or Europe. It was noted however that as a query had been received, there was evidence of the monograph being used internationally.

Members agreed that the monograph should be omitted following consultation with relevant health authorities.

Related substances
The query regarded the description of the column packing material, which the analyst had found not to be available. Additional detail specifying surface area and pore size

had been included for the packing description as per the previous Ph. Eur. monograph. The Secretariat had confirmed with the supplier that this material was only manufactured to 8 nm and not 7 nm. As it was understood that only one pore size was available from the supplier, members agreed that this detail was removed from the monograph in the BP 2019, prior to it being omitted.

375 Clarithromycin Granules for Oral Suspension (Revision) ABS(17)12

The monograph for Clarithromycin granules for Oral Suspension had been developed from analytical procedures and validation data provided by a collaborating manufacturer, and was first published in the BP 2017. The Secretariat presented additional comments from a collaborating manufacturer regarding the infrared Identification procedure and related substances, which were the subject of this paper.

The Secretariat noted that there were a number of other published product monographs within the Clarithromycin family and that the collaborating manufacturer was in the process of validating an improved related substances procedure which they would provide to the BP.

Identification
The infrared identification test was based on that from the Clarithromycin Tablets and Prolonged-release Clarithromycin Tablets monograph and had been assessed by the BP Laboratory. The manufacturer had raised concerns that the IR spectra for Clarithromycin closely resembled that of hypromellose which was used as an excipient in a new product they had developed.

Members requested that the BP laboratory verify the spectra and if necessary develop a TLC identification. Members agreed to retain the current test until this investigation was complete.

Related Substances
The related substances test was based on the analytical procedure provided by a manufacturer and the BP laboratory had found it to be suitable for the samples tested. The same manufacturer had made a number of comments relating to the interpretation of the sample preparation.

Members agreed to include additional wording instructing the user to centrifuge samples prior to performing the final dilution step. It was noted that this could be included as an alternative procedure which the Secretariat agreed to investigate.

Members also agreed that the solution of impurity E used in solution (4) should be prepared in methanol to a concentration of 0.0045% w/v as per the manufacturers method, and that the concentration of solution (5), the peak identification solution, should be reduced to 0.05% w/v.

Members recommended that the resolution in the system suitability requirement should be increased from 1.0 to 1.5, and the Secretariat agreed to look into the feasibility of this change with the laboratory.

376 Erythromycin Preparations ABS(17)13
Gastro-resistant Erythromycin Capsules (Revision)
Gastro-resistant Erythromycin Tablets (Revision)
Erythromycin Lactobionate Infusion (Revision)
Erythromycin and Zinc Acetate Lotion (Revision)

Erythromycin Ethyl Succinate Tablets (Revision)
Erythromycin Ethyl Succinate Oral Suspension (Revision)
Erythromycin Stearate Tablets (Revision)

Members had previously discussed an approach to revising the Erythromycin preparation monographs based on updated related substances procedures published in the 9.0 edition of the Ph Eur for the drug substance monographs. It was highlighted that lab work to assess the new methods was scheduled to be complete by March 2018. The Secretariat had prepared draft monographs based on the agreed approach which were presented for comment.

Title
Members noted that the Erythromycin Ethyl Succinate Oral Suspension products were only available as a powder for oral suspension and so the monograph should be updated accordingly

Content
The Secretariat presented a summary of content specifications for all products from the current BP monograph, the Ph Eur drug substance as well as licensed specifications. The proposed specifications were generally harmonised with the drug substance so as not to impose tighter controls on the product. Members noted however, that the purity of the drug substance would be taken into account when manufacturing the drug products and so standard limits of 95-105% would be suitable. Additionally, it was agreed that the content in all monographs should be declared in terms of erythromycin.

It was noted that for the powder for oral suspension / solution products, the content statement should control the product when freshly constituted and at end of shelf life as for the Co-Amoxiclav Oral Suspension monograph. The Secretariat agreed to propose suitable wording in line with BP policy.

Identification
The existing IR tests had been retained. Reference to secondary tests had been removed and replaced with a cross reference to the Assay HPLC retention time. No changes were planned for the Erythromycin and Zinc Acetate Lotion monograph.

Dissolution
A number of different approaches had been drafted for each individual monograph, which were based on introducing a HPLC procedure for quantification. Members noted that as Erythromycin is likely to degrade in an acidic dissolution media, a non-specific coulometric test would be preferable to minimise this effect.

Related Substances
Members had previously agreed to adopt the harmonised related substances procedure from the Ph. Eur. parent monographs which included a unique gradient system, modified by the user based on the retention time of erythromycin B. The requisition for laboratory assessment of this procedure had been drafted and monographs revised accordingly.

The new HPLC method controlled a number of specific impurities which were previously controlled by wide limits for unspecified and total impurities. Based on the increased specificity, limits had been specified for impurities A, B, C, D, E, F, H, L and M (in line with Ph. Eur.), and the limit reduced the any other impurities to 0.4% across all monographs. A disregard limit of 0.05% had been drafted for all monographs in line with ICH guidelines.

A statement limiting the content of erythromycin B and C to 5% each was currently published in the Erythromycin Lactobionate Infusion monograph. This statement had been included in all other product monographs.

The Secretariat noted that the new HPLC method for the Erythromycin Ethyl Succinate drug substance monograph had been retracted by the Ph Eur on 1st March 2017 due to issues identified by manufacturers.

EP Group 7 were currently carrying out remedial work on the method and had reinstated the previous method from the Ph. Eur. 8.0.

It was agreed that the Secretariat would monitor progress with this monograph and provide updated procedures to the BP laboratory prior to the completion of their investigations.

A member noted that the chromatographic gradient was overly complicated and could be simplified for the benefit of users. It was agreed that he would provide updated conditions for assessment by the BP laboratory.

Assay
The Assay HPLC method was harmonised with the related substances method, except for a 10-fold dilution of the test solution to allow quantification of the principal peak. Members agreed that the laboratory should develop an isocratic version of the gradient conditions, confirming separation of Erythromycin A, B & C using available standards.

It was noted that for the Erythromycin Ethyl Succinate and Erythromycin Stearate monographs, this test replaced a microbiological Assay procedure.

Impurities (Ethyl Succinate Tablets, Ethyl Succinate Oral Suspension, Stearate Tablets)
The Secretariat had drafted an impurity statement for these monographs in the interest of transparency.

V FOR INFORMATION

377 Work Programme ABS(17)13

The work programme had been updated since the previous meeting and was presented to the members. The Secretariat highlighted several areas that had been changed and invited the members to comment on the suitability of the format and also to suggest possible improvements.

A summary of updates to Ph Eur antibiotic monographs and potential affects to BP monographs as well as the BP laboratory work plan were presented for information.

The members agreed on the format of the new work programme with no extra suggestions for improvements and thanked the Secretariat for their hard work in ensuring the programme is progressive.

378 British Pharmacopoeia Matters ABS(17)15

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

The chair provided a verbal update of the latest EAG PCY from 12th September.

VIII EUROPEAN PHARMACOPOEIA

379 European Matters ABS(17)16

Members were informed of recent Group 7 meetings and that the MHRA had provided a new member for the group.

Monographs on Pharmeuropa were highlighted and the deadline for comments noted by members.

380 Any Other Business

There was no other business noted by the members.

359 Date of next meeting

The date of the next meeting is TBC.