

# BRITISH PHARMACOPOEIA COMMISSION

## Expert Advisory Group ABS: Antibiotics

### SUMMARY MINUTES

A meeting of the Expert Advisory Group on Antibiotics was held at 151 Buckingham Palace Road, London, SW1W 9SZ on Friday 27<sup>th</sup> February 2015.

**Present:** Dr R L Horder (*Chair*), Dr G Cook (*Vice-Chair*), Mr P Ellis, Mr E Flahive, Mr A Gibson, Dr V Jaitely, Dr W Mann, Professor J Miller and Mr I R Williams.

**In attendance:** Mr A Gibb, Mr M Whaley. Mr S Young attended part of the meeting.

Apologies for absence were received from Mr B White.

#### 257 **Introductory Remarks**

**Welcome** The Chair and the Group recorded their thanks to Dr A Livingstone and Ms N Thomas, who had both retired from the Group, for their help and guidance over the years.

The Chair welcomed two new members to the Group, Mr Andy Gibson and Mr Eamon Flahive.

**BP 2015** The Chair highlighted the publication of the BP 2015. Members were asked to contact the Secretariat if they had not received their preferred versions of the BP 2015.

**Expenses** Experts were reminded of the correct procedure for claiming fees and expenses.

**Confidentiality** Experts were reminded of the sensitive nature of the papers and discussions.

**Declaration of Interests** Experts were reminded to declare any specific interests at the start of the relevant discussions during the meeting.

#### **I MINUTES**

258 The minutes of the meeting held on 18<sup>th</sup> February 2014 were confirmed.

#### **II GENERAL MATTERS**

ABS(15)01

259 **Fire Evacuation Procedure** Experts were reminded of the evacuation procedure in the event of a fire alarm.

**Freedom of Information** Experts were reminded that any FOI queries that they received from the media were to be referred to the Secretariat.

**Data Handling Guidance** Experts were presented with a data handling guidance document and were reminded of the responsibilities of both the Secretariat and Experts when dealing with official sensitive documents.

**Electronic Working** Before the meeting members had been informed that the BP Commission had agreed to trial providing members with only electronic papers. The Secretariat would circulate a survey following the meeting to give members a chance to provide feedback on the new way of working.

**Membership** A copy of the current membership list was provided for information. Members were asked to inform the Secretariat if any of their details were incorrect and reminded to notify the Secretariat in the event of any future changes.

### III MATTERS ARISING FROM THE MINUTES

ABS(15)02

260 The following matters arising from the meeting held on 18<sup>th</sup> February 2014 were noted.

**Norfloxacin Preparations (minute 229.4)** The Secretariat reported that they continued to seek information regarding the potential inclusion of a test for Related substances.

**Ciprofloxacin Tablets (minute 252.2 refers)** Because the Group had noted that the General Notices of the Pharmacopoeia allowed the use of alternative validated methods, a manufacturer had been informed of the outcome of the Group's decision not to revise the dissolution test to specifically accommodate the automated dissolution equipment the manufacturer used.

**Teicoplanin Injection (minute 243 refers)** The Group had previously discussed the need for a monograph for Teicoplanin Injection and it had been proposed that a monograph was worked on in parallel with the revision to the Ph. Eur. parent monograph. The revision of the Ph. Eur. monograph was still ongoing and once the Ph. Eur. proposals were finalised the work on the BP monograph would recommence at the earliest opportunity.

### IV REPORTS AND CORRESPONDENCE

#### 261 Publications - Update

ABS(15)03

Members noted the new and revised monographs that were the responsibility of the EAG that had been included in the BP 2015 publications. Electronic updates would be added, as in-year updates, to the online BP 2015 to include the text of Ph. Eur. Supplements 8.3, 8.4 and 8.5.

#### 262 Work Programme

ABS(15)04

The Secretariat presented the Group an updated work programme.

**Removals** The BPC had endorsed that the monographs for Milbemycin Tablets and Milbemycin Chewable Tablets should be removed from the work programme due to an absence of UK licenses.

**Additions** The BPC had endorsed that the monographs for Milbemycin and Lufenuron Tablets, Milbemycin and Praziquantel Tablets, Milbemycin and Praziquantel Chewable Tablets and Milbemycin and Spinosad Chewable Tablets were added to the work programme.

**Re-initiation** In addition to the monographs in progress which were to be discussed later in the meeting, the Secretariat updated the Experts on the status of the other monographs on the work programme. The majority of the human medicines on the current work programme had been initiated but may require re-initiation. The Secretariat informed the Group that the number of MA holders were used as a guide to where re-initiation should be targeted. However, due to number of monographs currently requiring assessment at the BP Laboratory the Secretariat would also continue to work on monographs from the work programme where there was only one MA holder and as a consequence BP Laboratory work may not be necessary. The aim of this mixed approach to re-initiation and prioritisation was to ensure that EAG ABS continued to be able to elaborate new monographs without overburdening the capacity of the BP Laboratory.

**Azithromycin Preparations** During the re-initiation of monographs for Azithromycin products it had been discovered that eye-drops and powder for infusion products also existed. It was proposed by the Secretariat that the BPC should be asked to add Azithromycin Eye Drops and Azithromycin Powder for Infusion to the work programme. The Group endorsed the proposal.

**Moxifloxacin Tablets** The Secretariat reported that the International Pharmacopoeia had expressed an interest in the elaboration of a monograph for Moxifloxacin Tablets. In order to assist the work of the International Pharmacopoeia it was proposed that the BPC were asked to add this item, which had 2 UK MA holders, to the work programme of the EAG. The monograph could then be initiated with a view to producing a monograph harmonised between the International Pharmacopoeia and British Pharmacopoeia in the future. The Group endorsed the proposal.

263 **Revision Prioritisation** ABS(15)05

The Secretariat presented a summary list of the current BP monographs which were undergoing revision. The Group agreed with the proposal from the Secretariat to prioritise revisions based on reports from users experiencing difficulties with published methods; monographs which lack related substances tests; monographs for preparations which contain superseded Ph. Eur. test methods; monographs for which the parent monograph was undergoing revision; monographs with methods which contained chloroform.

264 **Bacterial Endotoxins** ABS(15)06

**Bacterial endotoxin policy** The newly adopted Ph. Eur. policy on the inclusion of the test for bacterial endotoxins in monographs for substances for pharmaceutical use and a proposal for a new BP policy for inclusion of the test in formulated preparations were discussed.

**Test for Pyrogens** The Secretariat reported that they continued to contact manufacturers of Flucloxacillin Injection, Colistimethate Injection and Amikacin Injection products in order to request data to support a request to revise the Ph. Eur. parent monographs to remove, if appropriate, the test for pyrogens.

265 **British Pharmacopoeia Chemical Reference Substances** ABS(15)07

The Group received a report for information detailing the testing and replacement of BPCRS, performed since the February 2014 meeting, which supported EAG ABS monographs.

The published monograph for Amphotericin for Infusion had been elaborated to specifically exclude liposomal Amphotericin for Infusion products. The sole manufacturer of the liposomal product had previously been unwilling to support the elaboration of a monograph due to the proprietary nature of their product. The Group were asked to discuss whether, at such time that a monograph for a liposomal product could be prepared, it should be incorporated under the umbrella of the existing monograph or whether the Ph. Eur. should be asked to elaborate a general monograph for Liposomal Preparations and a new BP monograph should be elaborated.

The Chair reported that the EDQM's Group 12 were in the process of considering the addition of the term liposomes to the Glossary entry for colloidal dispersion.

A member said that the liposomal nature of the product in question could be critical to the pharmacokinetics of the medicine and he also noted that generic liposomal products were likely being developed.

It was agreed that whilst a company might not be willing to assist in the elaboration of a monograph for proprietary reasons, this was not necessarily a reason why a monograph could not continue to be developed. It was proposed that the monograph for the liposomal product should continue to be progressed as far as possible.

**Amphotericin Lozenges & Amphotericin Oral Solution** The Secretariat reported that, as had been agreed at the 2014 meeting of the Expert Advisory Group, the monographs for Amphotericin Lozenges and Amphotericin Oral Solution had been omitted from the BP by means of the publication of the 2015 edition. The Nystatin EPCRS did not have the necessary declared content of tetraenes and the BP Laboratory had been unable to establish a Nystatin BPCRS which would support the monographs. Neither product was licensed in the UK.

**Content of Tetraenes** At the previous meeting the purpose of the content of tetraenes test was discussed and members discussed whether or not it might be necessary to include this test in other amphotericin product monographs. Following the meeting the Secretariat had reviewed the relevant monograph files and now reported that the test was originally included in the monographs for Amphotericin Lozenges & Amphotericin Oral Solution as a means of controlling these manufacturing impurities. The Group agreed that the Related substances test in both the Ph. Eur. parent monograph and the BP monograph for Amphotericin for Infusion sufficiently controlled these impurities.

It had been confirmed that the published monograph for Cefradine Oral Suspension suitably covered all licensed oral suspension products, which were supplied as a dry powder for reconstitution before administration. This included those described as a 'syrup'. It had been confirmed that licenced or previously licensed Cefradine products described as 'syrups' had incorrectly applied the term.

Cefradine Syrup had previously been included on the work programme as a new monograph for development. It was agreed that a monograph was not required and the item be removed from the work programme.

269 **Doxorubicin Injection**

ABS (15)11

**Related substances (system suitability)** A system suitability resolution requirement had previously been introduced to the monograph to ensure adequate separation between doxorubicin aglycone and the excipient methyl 4-hydroxybenzoate. The excipient was no longer included in UK and Centrally Authorised products. It was noted that the excipient could be used abroad but it was recognised that BP monographs focus was on UK products. A member noted parabens would not normally be used in single-use injectable, such as Doxorubicin Injection and the requirement reflected historical products.

The requirement would be removed from the monograph with the retained doxorubicin and epirubicin resolution requirement being used to confirm the system suitability.

It was noted that the EMA had held a public consultation in 2013 on the use of parabens and the outcomes of this were still to be published.

**Assay** The published Assay limits for the ready-to-use solution and dry powder forms differed and members questioned if harmonised limits should be applied. The differences in the limits was likely to reflect the historical situation at the time of monograph elaboration. The limits would be reviewed for a future meeting.

**Related substances (manufacturer proposals)** A manufacturer had previously proposed an alternative method consisting of a modified version of the BP/Ph. Eur. methodology. Approval had been requested from the manufacturer to forward this method onto the EDQM for review and a response was awaited.

270 **Clarithromycin Preparations**

ABS(15)12

Correspondence had been received from users highlighting that the suitable column referenced in the related substances test in the monographs for Clarithromycin for Infusion, Clarithromycin Tablets and Prolonged-release Clarithromycin Tablets was no longer available. The Group agreed that the brand of column currently referenced in the monograph should be replaced to reflect the column used most recently by the BP Laboratory (Phenomenex Hypersil BDS) which met the requirements of the monograph.

271 **Fusidic Acid Oral Suspension**

ABS(15)13

Experts were asked to note that EAG PCY had carried out a review of the clinical appropriateness of statements relating to dispensing and supply within BP monographs, which followed a discussion on monograph structure. EAG PCY recommended that the following statement in the monograph for Fusidic Acid Oral Suspension was retained for consistency with the BNF and because the only licensed product was of the same strength as that in the statement.

*“When Fusidic Acid Oral Suspension is prescribed or demanded, no strength being stated, an Oral Suspension containing the equivalent of 250 mg of anhydrous fusidic acid in 5 mL shall be dispensed or supplied”.*

The Group endorsed the retention of this statement.

272 **Rifampicin Preparations**

ABS(15)14

At both the 2013 and 2014 meetings of the Group, the published limits for related substances in the BP monographs for Rifampicin Capsules and Rifampicin Oral Suspension were discussed. Experts had questioned the reason for the differences between the limits in the Ph. Eur. method and the BP monographs and the ten-fold difference between the limit for 3-formyl rifamycin in the capsules and the oral suspension monograph.

A member confirmed no reports of any issues with the existing limits in the BP monographs.

A member noted also noted that rifampicin products were increasingly formulated as combination products. Another member highlighted that the International Pharmacopoeia contained monographs for rifampicin combination products that could be used for the elaboration of BP combination monographs.

The absence of a specific limit for 3-formyl rifamycin in the Ph. Eur. monograph was discussed. The BP monographs for Rifampicin Capsules and Rifampicin Oral Suspension contained limits of not more than 0.5% and not more than 5% 3-formyl rifamycin. Currently the Ph. Eur. monograph would control this and any other impurities other than impurity A at not more than 1.0%. Experts considered a request for the revision of the Ph. Eur. monograph to include a specific limit could be made however a member considered this revision was not necessary and given that the Secretariat had not received any reports that this was a problem the Group agreed that no action was necessary.

273 **Vancomycin Potency**

ABS(15)15

It had become apparent that there were discrepancies in the declaration of strength, in terms of IU, for vancomycin drug products. Changes to the Ph. Eur. monograph for Vancomycin Hydrochloride had been made over time to reflect an increase in potency over time. Some manufacturers had maintained the use of an equivalence of 1000 IU to 1mg, whereas others used an equivalence of 1050 IU to 1mg. The products were labelled in terms of mg and IU but were dispensed in terms of mg, it was therefore important to ensure manufacturers implemented the correct potency.

The EMA Quality Working Party (QWP) had discussed the issue and a draft Q&A document relating to the wording on the issue with specific guidance on labelling instructions was provided to members. The labelling advice was intended to clarify the issue but not to impact on clinical practice. It was suggested that inclusion of an example wording could strengthen the guidance and a member agreed to make the suggestion to the QWP.

It was agreed that, due to the existing wording used, no revisions were required to the published BP formulation monographs based on the draft QWP document.

**V NEW MONOGRAPHS**

274 **Azithromycin Preparations**

ABS(15)16

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

275 **Benzoyl Peroxide and Clindamycin Gel** ABS(15)17

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

276 **Clindamycin Tablets for Veterinary Use** ABS(15)18

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

277 **Tylosin Granules for Veterinary Use** ABS(15)19

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

## VI **MONOGRAPHS IN PROGRESS**

278 **Sterile Amphotericin Concentrate** ABS(15)20

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

279 **Ciclosporin Preparations** ABS(15)21

The draft monograph for Ciclosporin Capsules would be included in a future BP publication, subject to comments from manufacturers.

**Ciclosporin Oral Solution** The monograph was published in the BP 2015 without a Related substances test. The laboratory work to be undertaken would also address applying a method to the oral solution.

**Sterile Ciclosporin Concentrate** The monograph had been published in the BP 2015 and included the Ph. Eur. Related substances method, which had been found suitable for this formulation. No changes were proposed to the published method and Laboratory work on this product was not planned.

280 **Clarithromycin Granules for Suspension** ABS(15)22

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

281 **Tobramycin Eye Drops** ABS(15)23

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

282 **Tobramycin Nebuliser Solution** ABS(15)24

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

## VII **REVISION OF MONOGRAPHS**

283 **Replacement of Microbiological Assays** ABS(15)25

The Secretariat gave an update on the monographs which still contained a microbiological assay.

A number of BP Erythromycin preparation monographs still contained a microbiological assay and a member updated the Group on the revision of the Ph. Eur. monograph for Erythromycin. He reported that the assay method needed validation before it was published in Pharmeuropa.

A member described the current general approach to microbiological assays at both Group 7 and at the EMA's QWP.

284 **Amikacin Injection** ABS(15)26

Practical assessment of the suitability of the Ph. Eur. methods in the Amikacin monograph for inclusion in the BP injection monograph was awaited at the BP Laboratory. Previously this work was on hold due to a lack of suitable detector electrodes. The Laboratory now had the correct equipment and work would be progressed at the earliest opportunity.

285 **Apramycin Preparations** ABS(15)27

**Apramycin Sulfate; Apramycin Injection** As agreed previously the monograph for Apramycin Injection had been omitted from the BP (Vet) 2015. Consequential changes to remove reference to parenteral preparations in the BP monograph for Apramycin Sulfate had also been published in the BP (Vet) 2015.

**Apramycin BPCRS** The agreed changes to the leaflet, to include reference to the correction factor following revisions made to the BP (Vet) 2014 had been deferred. The BPCRS had remained out-of-stock, the leaflet was to be revised on release of the replacement batch.

**Apramycin Oral Powder; Apramycin Premix** A member noted that these preparations were available. Apramycin products were not widely used and no generics were available, and addition to the work programme was not considered at this time.

286 **3-Ketofusidic Acid EPCRS** ABS(15)28

Members were reminded that following the discontinuation of this EPCRS, the BP monographs for Fusidic Acid Cream, Fusidic Acid Eye Drops, Fusidic Acid Oral Suspension and Sodium Fusidate Ointment had been revised to amend the system suitability sections of these monographs. The revisions were to be a temporary stop-gap and manufacturers had been invited to comment on the suitability of the Ph. Eur. related substances method or to propose alternatives. Detailed responses were awaited.

The Secretariat also reported that a university project had been initiated to examine the suitability of replacing the current related substances method with the Ph. Eur. method.

**Assay** At the previous meeting an expert had questioned whether the current titrimetric assay method in the Ph. Eur. monographs had replaced an HPLC method. Upon review the Secretariat confirmed that the assay in the monograph for Fusidic Acid had been a titrimetric method as far back as the BP 1988.

**Test for light absorbing impurities** The Secretariat reminded the Group of the reports that had been received from users who had struggled to meet the requirements of the test. The UK had submitted a request for the revision of the Ph. Eur. parent monograph which also contained the test and Group 7 had previously indicated that the request to remove this test could be accepted. However the revision of the Ph. Eur. monograph encompassed a number of elements and was still not finalised. The EAG was presented with an extract from correspondence with the Ph. Eur. Secretariat who passed on the opinion of a Group 7 member who indicated it was their opinion that the related substances test adequately supersedes the test for light absorbing impurities. Two members agreed that there was still a lot of discussion to be had at Group 7, which did not relate to the test for light absorbing impurities, before the monograph for Lymecycline could be finalised.

The Group agreed that in light of continued reports from users about the difficulty performing this test, the information received from the Ph. Eur. Secretariat and the length of time before the Ph. Eur. monograph could be finalised, the test for light absorbing impurities could be removed from the BP monograph for Lymecycline Capsules.

**Ph. Eur. Revision** The Group agreed that once the progress of the revision of the rest of the Ph. Eur. monograph became clearer the BP should look to consider the revision of the BP Capsules monograph.

At the previous meeting the Secretariat informed the EAG that it was continuing to seek further information from manufacturers to allow the inclusion of a test for related substances. The Secretariat presented the Group with updated draft monographs for Moxidectin Injection, Moxidectin Oral Solution and Moxidectin Oromucosal Gel based on a response received from the sole MA holder of all but one of the authorised moxidectin veterinary product in the UK. The manufacturer had submitted two related substances methods to cover three of the BP monographs.

It was requested that experts send in their comments on the draft monographs by correspondence.

**Moxidectin Pour-on** The manufacturer had informed the Secretariat that the finished product specification did not include a test for related substances. A member considered that the absence of a related substance test was in this case acceptable because parasiticides were exempted from GMP requirements. The Head of Analytical Science also believed there was precedence for the absence of related substances tests in monographs for topical products. The Group agreed that, in this case, the test for related substances was not necessary and the revision need not be pursued.

**Identification** The published TLC method included the use of chloroform. It was agreed that the method be replaced with the Ph. Eur. monograph method for Tobramycin and circulated to manufacturers for comment. Subject to these comments, the need for laboratory work to confirm the suitability of the method would be considered.

**Related substances** Manufacturers had been invited to submit proposals to replace the published TLC method with a HPLC method but no responses had been received.

Previous assessment at the BP Laboratory demonstrated that the HPLC Assay method was unsuitable for determination of impurities. It was agreed that the application of the HPLC Related substances method provided for the draft monograph for Tobramycin Nebuliser Solution should be investigated. A draft revision to include the method would be prepared and circulated to manufacturers for comment and to the BP Laboratory for assessment.

The USP monograph for Tobramycin Inhalation Solution was noted to include a test for Related substances but investigation of this method was not considered necessary. Investigation of the chosen method would assist in harmonisation between BP monographs.

## VIII EUROPEAN PHARMACOPOEIA

290 **Current Ph. Eur. Matters of Interest** ABS(15)32

**Group of Experts No.7** A member had retired as the UK representative of Group of Experts No. 7 and members asked that their thanks for his contributions be recorded in the minutes.

Copies of the Summary of Decisions from the March, June, November 2014 and January 2015 meetings of Ph. Eur. Group of Experts No.7 were provided for information. Copies of the informal reports provided by UK representative following the meetings would be included in future EAG papers.

**Colistimethate sodium** The Ph. Eur. monograph was under revision and a UPLC method was under consideration. Future consideration would be given to any changes required to Colistimethate containing BP monographs.

**EMA guideline** Group of Experts No. 7 had been working on revising monographs based on the published EMA Guideline on setting specifications for related impurities in antibiotics and two members gave a verbal update to the EAG on issues experienced in the implementation of the guideline for Ph. Eur. monographs.

### ANY OTHER BUSINESS

291 **EDQM Standard Terms**

Access to the EDQM's Standard Terms was now freely available to all users following registration on the EDQM's Standard Terms portal: <https://standardterms.edqm.eu>.

292 **Date of next meeting** To be arranged.