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 Tuesday 18th February 2014.

Present: Dr R L Horder (*Chairman*), Dr G Cook (*Vice-Chairman*), Mr P Ellis, Dr V Jaitely, Dr A Livingstone, Dr W Mann, Professor J Miller, Ms N Thomas, and Mr I R Williams.

In attendance: Mr A Gibb, Mr N Patel, Ms D Russell, and Mr M Whaley.

Apologies for absence were received from Mr B White.

226 **Introductory Remarks**

Welcome The Chairman welcomed Mr Patel and Ms Russell (a new analyst of the BP Laboratory) to the meeting.

Secretariat Following changes in the responsibilities of BP Secretariat staff members, the role of Secretary to the EAG had been transferred from Dr Fiona Swanson to Mr Michael Whaley. Dr Swanson had been involved with the work of EAG ABS and its former incarnation of Committee E for a considerable number of years and Members recorded their thanks for her contribution to the work of the EAG.

Alistair Gibb and Helen Corns of the Secretariat had been promoted to Senior Pharmacopoeial Scientists following completion of their training grades.

BP 2014 The Chairman highlighted the publication of the BP 2014. Members were asked to contact the Secretariat if they had not received their preferred versions of the BP 2014.

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

Confidentiality Members were reminded of the restricted nature of the papers and discussions.

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

I MINUTES

227 The minutes of the meeting held on 18th February 2013 were confirmed.

II GENERAL MATTERS ABS(14)1

228 **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.

Changes to the MHRA A presentation outlining the changes to the structure of the agency was supplied to members.

New Chair of the British Pharmacopoeia Commission In October 2013 Professor Kevin Taylor had been appointed as the new Chair of the British Pharmacopoeia Commission. Professor Taylor was Head of Pharmaceutics at University College London School of Pharmacy.

New Chief Executive of the Agency Dr Ian Hudson had been appointed as Chief Executive of the MHRA. Dr Hudson had previously been the head of the MHRA Licensing Division.

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.

A full review of membership of all the BP EAGs, Panels and Working Parties was to be undertaken in 2014 as part of the membership appointment cycle.

III MATTERS ARISING FROM THE MINUTES ABS(14)2

229 The following matters arising from the meeting held on 18th February 2013 were noted.

Cefradine Syrup (minute 206) The Secretariat had been making enquiries to ascertain if the formulation was covered by the existing monograph for Cefradine Oral Suspension or if a replacement (or additional) monograph for the syrup was required. The manufacturer had been contacted but had stated that they were unable to assist.

Moxidectin Preparations (minute 211 & 219) The Secretariat was continuing to seek further information from manufacturers and the Veterinary Medicines Directorate to allow the consideration of the inclusion of a test for Related substances in the monographs.

Use of Chloroform; Ph. Eur. Harmonisation (minute 214) A prioritised revision programme was to be produced at the earliest opportunity.

Norfloxacin Preparations (minute 220) The Secretariat were seeking further information regarding the potential inclusion of a test for Related substances. There were a limited number of generic products available.

Rifampicin Preparations (minute 221) The Secretariat were seeking further information from manufacturers regarding the test for Related substances. A member referred to additional details included in the USP monographs that may be of assistance. Further rifampicin combination products were also available and members supported the addition of these to the work programme at a later date.

IV REPORTS AND CORRESPONDENCE

230 Publications - Update ABS(14)3

Members noted the new and revised monographs that were the responsibility of the EAG that had been included in the BP 2014 publications. Electronic updates would be added to the online BP 2014 to include the text of Ph. Eur. 8th edition and Supplements 8.1 and 8.2 as in-year updates.

231 Vancomycin Potency ABS(14)4

Dr Jaitely updated members on discussions held at the EMA Quality Working Party concerning the potency of vancomycin. It was reported that it had become apparent that there were discrepancies in the declaration of strength, in terms of IU, for vancomycin drug products. There had been an increase in potency of the active over time, attributed to improvements in the fermentation process. This change had been reflected by a number of revisions to the Ph. Eur. parent monograph to require a minimum potency of 1050 IU/mg, from the original of 900 IU/mg. Some manufacturers had maintained the use of an equivalence of 1000 IU to 1mg, whereas others used an equivalence of 1050 IU to 1mg. From the information available no revision appeared necessary to the BP vancomycin formulation monographs as all included microbiological assays, specified limits in terms of the stated IU and did not include a weight equivalence statement.

Dr Jaitely undertook to review the Vancomycin monographs and provide proposals for any necessary revisions to the BP Secretariat. It was noted that the potency of the material was in terms of vancomycin hydrochloride, not vancomycin, but that the sample preparation instructions for BP Vancomycin formulation monographs referred to the use of '[…] IU of vancomycin' and this would be checked.

232 Bacterial endotoxins ABS(14)5

BP/Ph. Eur. policy The establishment of a formal BP policy, on the inclusion of the test for Bacterial endotoxins in individual monographs or reliance on the requirements included in the relevant General Monograph, had been deferred until similar discussions at the EDQM had been completed.

Test for Pyrogens – Ph. Eur. Monographs A number of Ph. Eur. parent monographs retained the test for Pyrogens whereas the BP formulation monographs specified the use of Bacterial endotoxins. The Secretariat would continue to contact manufacturers in order to obtain data that could be provided to the Ph. Eur. Secretariat to allow consideration towards the replacement of the test.

233 **Cefotaxime Injection** ABS(13)6

A query had been received from a user questioning the inclusion of the Loss on drying test in the monograph for Cefotaxime Injection, whereas the test for Water was applied in the Ph. Eur. monograph for Cefotaxime Sodium. The Ph. Eur. monograph had previously specified the use of Loss on drying but this had been subsequently revised to replace the test for Loss on drying with that for Water and Ethanol. As all Cefotaxime Injection products in the UK consisted of the bulk material without excipients, it was agreed the monograph would be harmonised with Ph. Eur. monograph methods and limits.

The monograph for Cefotaxime Sodium also included tests for two residual solvents (2-Ethylhexanoic acid and *N*,*N*-Dimethylaniline). In accordance with the usual BP policy regarding the control of residual solvents these tests would not be added to the BP monograph.

234 **Doxorubicin Injection** ABS(13)7

Related substances The BP Laboratory had recently carried out work to check the robustness of the system suitability resolution requirement between doxorubicin aglycone and the excipient methyl 4-hydroxybenzoate. The Laboratory had carried out work on two different systems using separate columns and mobile phases. The necessary resolution was achieved on both systems but the elution order differed. As the resolution was achieved it was agreed no change was necessary.

An expert queried a manufacturer's formulation because they believed the use of benzoates was discouraged. Ms Thomas noted that there had been a review of the use of benzoates in formulations and undertook to provide details to the Secretariat.

Proposals from a manufacturer An alternative Related substances method had been proposed by a manufacturer. This was a modified version of that included in the BP/Ph. Eur. method and was stated to allow the separation and detection of 3 additional impurities. They had been unable to comment on the applicability of the method to products containing methyl 4-hydroxybenzoate. Members agreed that the proposed method represented an improvement but that it would be preferable for the BP and Ph. Eur. methods to remain harmonised. Subject to approval from the manufacturer, the proposed method would be forwarded to the EDQM for review.

235 **3-Ketofusidic Acid EPCRS** ABS(14)8

Related substances The BP monographs for Fusidic Acid Cream, Eye Drops & Oral Suspension and Sodium Fusidate Ointment specify the use of 3-ketofusidic acid EPCRS in the Related substances system suitability test. The method was based on that formerly included in the Ph. Eur. monographs for Fusidic Acid and Sodium Fusidate. Following the revision of the Ph. Eur. monographs the EPCRS was no longer available. A news item explaining the discontinuation of the EPCRS had been posted on the BP website.

The Secretariat had prepared draft revisions to remove the affected system suitability requirements and these were accepted. Additionally, it was agreed that the requirement for theoretical plates included in the Assay methods should also be included. It was recognised that this approach was suitable only as a temporary stop-gap, to ensure there was no absence of system suitability criteria. Details on the retention times of Fusidic Acid and 3-ketofusidic acid would be added to the revised monographs.

Manufacturers would be contacted to seek advice on the suitability of the current Ph. Eur. Related substances method for use in the BP preparation monograph or, where appropriate, to request alternative proposals.

Assay A member noted the use of a titrimetric Assay in the Ph. Eur. monographs and questioned if this had replaced an HPLC method. The Secretariat would check the background of the Ph. Eur. monograph.

236 **Fusidic Acid Eye Drops** ABS(13)9

The Secretariat had received correspondence from a stakeholder who queried whether or not the monograph was applicable to ophthalmic suspension products as the published definition referred to the product as a solution. The original data upon which the monograph was based referred to the product as a semi-solid eye preparation and the only UK licence holders product was described as a ‘white to off-white, slightly thick liquid’.

A draft amendment to the monograph had been prepared to revise the monograph definition to refer to a suspension and include a test for Particle size. This was accepted subject to the test for Particle size being removed as this aspect was sufficiently controlled by the General Monograph.

237 **Ivermectin Oral Solution** ABS(13)10

At the previous meeting members had requested information concerning the identity of process and degradation impurities. The EDQM had responded, but had been unable to provide any further information. Information had been received from a manufacturer of Ivermectin Tablets who used a method for their API which was equivalent to the Ph. Eur. related substances method. From the information provided it appeared that Ph. Eur. impurities A, B, D, H, G, I and J were degradation impurities.

238 **Amphotericin for Infusion** ABS(14)11

It had been agreed at the previous meeting that because the published monograph for Amphotericin for Infusion applied only to non-liposomal complexed products (e.g. sodium deoxycholate complexed product) the manufacturer of the liposomal product should be contacted for assistance with the elaboration of a monograph specifically for liposomal products. The manufacturer had responded negatively to the request citing the proprietary nature and intellectual property rights pertaining to the analytical tests and controls of their product. It was acknowledged by experts that the tests included in a liposomal product monograph were likely to be product specific and assistance from manufacturers was necessary. The importance of physical tests and the difficulty of characterising liposomal products was highlighted by a member.

Work on the monograph would be put on hold and reviewed at a future time subject to the development of further liposomal amphotericin products.

239 **Cefuroxime Axetil and Preparations** ABS(14)12

A manufacturer had proposed a revised Assay method to allow the use of octyl silane columns in place of a trimethyl silyl column, based on reported difficulties sourcing the specified column. As trimethyl silyl columns were available commercially no change to the monograph would be made.

240 **Nystatin BPCRS: Amphotericin Preparations** ABS(14)13

The BP Laboratory had been working to establish nystatin BPCRS for use in the monographs for Amphotericin Lozenges and Amphotericin Oral Solution. Upon circulation of the laboratory report it had been noted that the standard did not give a declared content of tetraenes and as such would not be suitable for use as a reference substance in the Content of tetraenes test. It had also been noted that nystatin EPCRS did not contain a declared content of tetraenes. As a result the tests in the monograph were not currently suitable for use. As both Amphotericin Lozenges and Oral Solution were no longer licensed in the UK it was agreed that the monographs should be omitted.

Members questioned the purpose of the test for Content of tetraenes and if control of these substances was also required in the BP monograph for Amphotericin for Infusion, which did not include the test. The limit of 13.3% in the monographs that included the test was also noted to be unusual for an impurity. The Secretariat agreed to check these aspects.

241 **British Pharmacopoeia Chemical Reference Substances** ABS(14)14

Members noted the various reference materials relating to monographs that were the responsibility of this EAG that had been adopted since the last meeting in February 2013.

V NEW MONOGRAPHS

242 **Work Programme** ABS(14)15

A table indicating the status of current new monographs for EAG ABS was provided for information.

The Secretariat intended to review the work programme and include details of the number of MA holders on the work programme to aid in prioritisation. Following a question, the Secretariat explained that work was usually prioritised based on the number of manufacturers, community prescribing figures and hospital purchasing data. Members supported this and highlighted that consideration should be given to the limited benefits a monograph would bring for products where there was only one licensed manufacturer. However it was also noted that monographs, even where there is just one licensed manufacturer, were always useful and could support innovation. Based on the review the Secretariat was to commence a programme of re-initiation.

The revision of old monographs was highlighted as still being of importance, especially as the prevalence of antibiotic resistance was resulting in the increased use of older products, for example colistin. Existing BP monographs would be reviewed with the intention of developing proposals for a targeted programme of monograph revision to ensure monographs remained fit for purpose.

Products for the treatment of HIV were noted as being an important area but were outside the remit of the EAG.

243 **Teicoplanin Injection** ABS(14)16

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

244 **Ciclosporin Preparations** ABS(14)17

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

245 **Clarithromycin Granules for Suspension** ABS(14)18

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

246 **Tobramycin Preparations: Infusion; Nebuliser Solution; Eye Drops** ABS(14)19

The draft monographs for Tobramycin Nebuliser Solution and Tobramycin Eye Drops would be included in a future BP publication, subject to comments from manufacturers.

Tobramycin Infusion was not licensed in the UK and the monograph would be removed from the work programme.

VI MONOGRAPHS IN PROGRESS

247 **Sterile Amphotericin Concentrate** ABS(14)20

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

248 **Neomycin and Chlorhexidine Nasal Cream** ABS(14)21

The draft monograph would not be progressed due to practical concerns with the feasibility of elaborating methods for both components of the formulation.

VII REVISION OF MONOGRAPHS

249 **Replacement of Microbiological Assays** ABS(14)22

Members were supplied with an update on the review of monographs that contained a test for microbiological assay. The Ph. Eur. revision of the Erythromycin monographs was ongoing. Upon adoption of a revised method the BP Laboratory would be asked to examine the suitability of the method to the relevant formulations.

ACTION The BP Laboratory to examine the revised Ph. Eur. Method following adoption.

250 **Amikacin Injection** ABS(14)23

Laboratory work to examine the suitability of the Ph. Eur. HPLC Related substances and Assay method, using pulsed amperometric detection, to the injection was still to be carried out. The BP Laboratory did not have access to the required detector to run the method. Mr Patel reported that the necessary detector was to be ordered.

251 **Apramycin Preparations** ABS(14)24

Apramycin Sulfate; Apramycin Injection The Veterinary Medicines Directorate had previously recommended that the monograph for Apramycin Injection should be omitted from the BP (Vet) as there were currently no UK licensed injection preparations. Omission of the monograph had been deferred pending revisions to all BP Apramycin monographs regarding the expression of impurity limits. These amendments had been published in the BP(Vet) 2014 and members agreed that the monograph for Apramycin Injection be omitted by means of a future BP(Vet) publication

The BP monograph for Apramycin Sulfate included separate requirements for material intended for use in the manufacture of a parenteral dosage form. A consequential revision to delete these requirements on the omission of the injection monograph had been prepared and was accepted. In the event of a need for a monograph for the Injection formulation in the future, the need to include separate limits for potency and impurities would be reconsidered.

Apramycin BPCRS The agreed amendments to the leaflet accompanying the BPCRS, following the publication of the revised formulation monographs, were still to be made. The BPCRS was out of stock and the Laboratory intended to update the leaflet upon release of the replacement batch.

252 **Ciprofloxacin Tablets** ABS(14)25

Dissolution (medium) A manufacturer had previously requested that the dissolution medium be changed from water to 0.01M hydrochloric acid, in line with the USP, but had provided insufficient data to support revision of the monograph. The Secretariat has contacted all UK licence holders to confirm the Dissolution method used and request data regarding the equivalence for any alternative methods used. Responses had been received from seven manufacturers, six of whom used the BP method and had no reports of difficulties implementing it. One used the USP method but no supporting data had been supplied prior to the meeting.

As no equivalency information had been supplied and any change would impact on other manufacturers it was agreed that no revision should be made.

Dissolution (detection wavelength) The manufacturer, who had provided the BP monograph method, confirmed the suitability of the BP method but noted that it was not suitable for automated Dissolution equipment. This was due to the high response at the specified detection wavelength and the need for a dilution step. The manufacturer requested that an alternate wavelength (350 nm) outside of the maximum UV response also be included in the monograph and had provided supporting validation data. As the General Notices of the Pharmacopoeia allowed the use of alternate validated methods it agreed that no change was required. The Secretariat undertook to contact the manufacturer to explain the outcome of the EAG's discussions.

253 **Lymecycline Capsules** ABS(14)26

Light-absorbing impurities Requests for the removal for the test for Light-absorbing impurities or relaxation of the limits had been previously considered but not accepted. The nature of the impurities controlled was unclear, however the test was included in the Ph. Eur. monograph for Lymecycline.
Members advised that changes to the BP monograph be postponed until the revisions to the Ph. Eur. monograph had been finalised as other consequential changes may need to be considered.

254 **Tobramycin Injection** ABS(14)27

Related substances The monograph retained a TLC Related substances test as the HPLC Assay method had previously been found unsuitable for determination of impurities by the BP Laboratory. Manufacturers of the Injection product had not responded to requests for suitable methods. A manufacturer had committed to supply proposals for the Tobramycin Nebuliser Solution monograph and members considered that any method included may also be suitable for the injection product. The USP monograph for Tobramycin Inhalation Solution also included an HPLC gradient method, utilising the derivatisation used in the BP Tobramycin Injection Assay.

The Laboratory highlighted the difficulty in applying derivatisation methods. The proposals from the manufacturer were to be awaited and the Laboratory were to be asked to investigate either these or the USP method, depending on which looked to be most suitable.

Identification The use of chloroform in the TLC Identification test was noted and it was suggested that the method should be replaced with that used in the TLC Related substances test in this monograph.

[SECRETARIAT NOTE *The published identification test included the use of kanamycin monosulfate BPCRS and neomycin sulfate BPCRS, in order that the test be sufficiently discriminatory. As it was unclear how these substances would elute in the proposed replacement test the suitability of the method would be checked prior to making any changes.*]

Tobramycin BPCRS Following reports of problems with the application of semi-micro determination of water to Tobramycin BPCRS the BP Laboratory had confirmed the suitability of an oven coulometric method to the material. Due to the hygroscopic nature of the material, the user was required to carry out a test for water to determine the declared content and instructions were provided in the BPCRS leaflet, which had been amended. As semi-micro determination of water was specified in the Ph. Eur. monograph for Tobramycin, members agreed that a request for revision be submitted to the Ph. Eur. Commission to replace the method.

VIII EUROPEAN PHARMACOPOEIA

255 **Current Ph. Eur. Matters of Interest** ABS(14)28

Group of Experts No. 7 Mr White had stepped down as UK representative of Ph. Eur. Group of Experts No. 7 and the Secretariat recorded their thanks for his contributions. Mr Gibson replaced Mr White as the new UK Representative. Dr Jaitely had also been appointed as a specialist to the group following requests from the EDQM that a representative from a European licensing authority also be nominated.

Copies of the Summary of Decisions from the 146th, 147th and 148th meetings of Ph. Eur. Group of Experts No.7 were provided for information.

VIII ANY OTHER BUSINESS

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