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 Monday 8th February 2016.

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

In attendance: Mr M Whaley, Dr A Gardiner, Mr D Holcombe and Mr S Wilson

Apologies for absence were received from Mr E Flahive and Dr W Mann.

293 **Introductory Remarks**

Welcome The Chair and the Group recorded their thanks to Mr A Gibson and Mr B White, who had both resigned from the Group. It was noted that new members would be required and members were encouraged to refer any suitable candidates to the Secretariat. Additionally, thanks to Mr W Jeffries were noted as he would be retiring from his job as Pharmacopoeial Support Officer at the end of the month.

The Chair welcomed Mr D Holcombe and Mr S Wilson from the BP Laboratory to the meeting.

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

294 The minutes of the meeting held on 27th February 2015 were confirmed.

II GENERAL MATTERS ABS(16)01

295 **Changes to be Expenses Claims Policy** Experts were asked to note the changes to the expense claims policy, which had been updated for 2016.

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.

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(16)02

296 The following matters arising from the meeting held on 27th February 2015 were noted.

Norfloxacin Preparations (minute 229.4/ 260.1) The Secretariat reported that they continued to seek information regarding the potential inclusion of a test for Related substances.

Liposomal Amphotericin for Infusion (minute 266 refers) The Secretariat would look to recommence the elaboration of a monograph to cover Liposomal Amphotericin for Infusion products at the earliest opportunity.

Ciclosporin Preparations (minute 279 refers) Laboratory work to investigate the proposed method was due to be performed at the BP Laboratory. Results would be circulated to experts at the earliest opportunity.

Amikacin Injection (minute 284 refers) Lab work examining the suitability of the drafted method was still pending at the BP Laboratory. Results would be circulated to experts at the earliest opportunity.

IV REPORTS AND CORRESPONDENCE

297 **British Pharmacopoeia Publications** ABS(16)03

Members noted the new and revised monographs that were the responsibility of the EAG that had been included in the BP 2016 publications. Electronic updates would be added, as in-year updates, to the online BP 2016 to include the text of Ph. Eur. Supplements 8.6, 8.7 and 8.8.

298 **Work Programme** ABS(16)04

The Secretariat presented the Group an updated work programme.

Additions and Removals The British Pharmacopoeia Commission had agreed to add Azithromycin Eye Drops and Azithromycin Powder for Infusion to the EAG ABS work programme thus enabling five Azithromycin formulation monographs to be developed as a family. The proposal to add Moxifloxacin Tablets to the EAG ABS work programme had also been endorsed.

The British Pharmacopoeia Commission had endorsed the removal of the monograph for Cefradine Syrup from the work programme.

Monographs in progress Experts noted the list of monographs from the work programme which were actively being worked on

299 **Revision Programme** ABS(16)05

A list detailing the monographs currently undergoing revision by the group was noted.

Colistimethate Injection Experts endorsed that following the receipt of a proposal from a manufacturer; a revision to the BP monograph for Colistimethate Injection should be considered. The revision was in line with the agreed revision prioritisation criteria discussed at the previous meeting. The current BP monograph lacks a Related substances test and the parent monograph is currently being updated to include a Related substances test and a composition test. The proposal was discussed later in the meeting.

Erythromycin Preparations It was noted that the 5 Erythromycin Ph. Eur. monographs were under revision, and that that the BP currently contains 8 preparation monographs which contain Erythromycin (either in its base, estolate, ethylsuccinate, lactobionate or stearate forms). Five of these preparation monographs contained a microbiological assay.

Experts discussed the potential revision of the BP monographs. A member considered that this would be a significant piece of work for the Group and that revising the formulation monographs could be a challenge.

A member noted that it was important to revise these monographs in order to move away from the microbiological assay.

Experts endorsed a member's proposal that a strategy for the revision of the Erythromycin product monographs should be drafted by the Secretariat for discussion at the next meeting of the group.

300 **Bacterial Endotoxins** ABS(16)06

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

301 **BP Chemical Reference Substances** ABS(16)07

The Group reviewed the activity of the BP Laboratory between the meeting in February 2015 and the end of November 2015 relating to BPCRS used in monographs that are the responsibility of the Antibiotics EAG. The hard work performed by the BP Laboratory in supporting the work of this Group was noted.

302 **Nystatin Pessaries** ABS(16)08

Members were reminded that the Nystatin Pessaries monograph stated that "Nystatin Pessaries are vaginal tablets containing Nystatin", however the SPC of the product licensed in the UK described the pharmaceutical form as "Pessary". The Secretariat informed members that the Expert Advisory Group on Pharmacy agreed that separate monographs should be elaborated for pessaries and vaginal tablets. It had been clarified with the manufacturer of the product and the MHRA licensing division that Vaginal Tablets would be a more appropriate name for the preparation as the product is prepared by tabletting. The Secretariat therefore recommended to members that the title and definition of the Nystatin Pessaries monograph is revised to reflect the available product. A subsidiary title would be included. Members endorsed this proposal.

303 **Ph. Eur. Monograph Titles - Degree Of Hydration** ABS(16)09

Ph. Eur. degree of hydration proposal and Impact on BP Members discussed the proposal of the Ph. Eur. to explicitly include the degree of hydration in monograph titles and the possible impact on BP texts which are the responsibility of EAG ABS.

304 **Inhaled Products** ABS(16)10

British Pharmacopoeia Monographs for Inhaled Products Members were informed that the recommendations of the former Inhaled Products Working Party on the content and format of BP monographs for inhaled products had been revised to incorporate stakeholder feedback and the discussions of the Expert Advisory Group on Pharmacy and the BP Commission.

Impact on British Pharmacopoeia EAG ABS texts Two monographs that were the responsibility of EAG ABS would be impacted by the recommendations; Colistimethate Sodium Powder for Nebuliser Solution and Tobramycin Nebuliser Solution. Both of these monographs were currently undergoing revision and the definition statements were the only part of the texts that were to be affected by the policy. Members endorsed the changes proposed.

305 **Rifampicin Combination Preparations** ABS(16)11

The Secretariat had performed a review of the rifampicin combination product monographs published in the International Pharmacopoeia, to consider whether they might form the basis of BP monographs. Factors such as the number of UK MAH, hospital usage data and the current API and BP product monographs of the constituents were taken into account. Members endorsed the recommendation that the BPC could be asked to add the Rifampicin, Isoniazid and Pyrazinamide Tablets monograph to the EAG ABS work programme.

306 **Chlortetracycline Ointment And Eye Ointment** ABS(16)12

Diluent in Identification B The Secretariat informed the group that a Metacycline Hydrochloride BPCRS had been established to replace the discontinued EPCRS and during the testing of the new BPCRS, the Laboratory had found that water, currently used as a diluent in the TLC identification method (Identification B) in both monographs was unsuitable. The Laboratory instead successfully used methanol as the diluent, as specified in the other Chlortetracycline parent and product monographs and recommended that the monographs were amended accordingly.

Volume of hydrochloric acid in Identification B During the investigation of Identification B in the two monographs, it was noticed that solution (1) did not include a volume of 0.01M HCl. A review of the monograph history showed that previously 2 x 10 mL quantities of HCl had been specified, but this value was erroneously omitted during a revision. The group endorsed the reinstatement of the volume of 10 mL into the monographs.

307 **Doxorubicin Injection** ABS(16)13

Related substances BP2016 Revision At the previous meeting members had agreed to the removal of a system suitability criteria specifying adequate separation between doxorubicin aglycone and an excipient methyl 4-hydroxybenzoate. The excipient had been found to be no longer included in UK and centrally authorised products. The monograph had been revised by means of the BP2016 and a requirement for suitable resolution between the peaks due to doxorubicin and epirubicin had been retained.

Proposal from Manufacturer A manufacturer had previously proposed a revision to the published BP Related substances test method. At the February 2015 meeting the Group had agreed that the proposed method represented an improvement however it was agreed that it was preferable for the BP and EP monographs to remain harmonised. The Secretariat reported that they had contacted the manufacturer to propose that the method proposal could be forwarded to the EDQM for consideration. The manufacturer responded that they did not support the application of the method to the API at this time and so the method has not been passed to the EDQM and the BP monograph has not been revised.

Assay Limits At the previous meeting it had been noted that the published Assay limits for the ready-to-use solution and dry powder forms differed and the Group had questioned whether harmonised limits should be applied. The Secretariat had since reviewed the BP monograph limits.

The BP published monograph for Doxorubicin Injection provides limits for a ready to use product (95.0 to 110.0%) and a powder for injection or infusion product (90.0 to 110.0%). The Secretariat proposed that whilst it might be possible to harmonise the different limits the group should assess whether the current format of splitting the monograph into two sections Doxorubicin Injection (which is the ready to use solution) and Doxorubicin Hydrochloride for Injection (a sterile powder) was appropriate.

The Group were informed that Doxorubicin was available as a powder for injection, a sterile concentrate and a solution for infusion. A member considered that the Group should consider the elaboration of a standalone Sterile Doxorubicin Concentrate monograph and a separate monograph for Doxorubicin Infusion which would encompass both the powder and the solution for infusion products. The Secretariat agreed to present a draft revision at the earliest opportunity.

Acidity test Correspondence had been received from an overseas manufacturer of an Injection product requesting that the pH limit in the Doxorubicin Hydrochloride for Injection. Data had been requested to support this request but none had been received. The group agreed that during the process of the revision of this monograph manufacturers should be consulted on appropriate limits for this test.

308 **Ciprofloxacin Tablets** ABS(16)14

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 had 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 manufacturer used the USP method and had provided equivalence data which was presented to the Expert Advisory Group. The EAG agreed with the Secretariat proposal that, although equivalence is demonstrated by the supporting data, the dissolution method in the Ciprofloxacin Tablets monograph should not be revised due to the majority of users who use the BP method as published.

309 **Doxycycline Preparations** ABS(16)15

The two Doxycycline product monographs, Doxycycline Capsules and Dispersible Doxycycline Tablets used the APIs Doxycycline Hyclate and Doxycycline Monohydrate respectively. Both product monographs contained a Related substances method which was adapted from the Ph. Eur. method in 1997. This method limited impurities A and B at 2% and all other impurities at 0.5%. The Ph. Eur. had updated their Related substances method by way of the Ph. Eur. 8.4 supplement which additionally controlled impurities C and F.

Members were informed that a query had been received highlighting that impurity F was now controlled at a tighter limit in the product monographs than the parent monographs. The Secretariat asked the group whether the Related substances method in monographs should be revised in line with the new Ph. Eur. method. The group agreed that impurities should not have tighter limits in product monographs than parent monographs and endorsed the proposal to revise the method. Members also noted that these monographs would be subject to the ad-hoc name changes under the Ph. Eur. hydrates policy and advised the Secretariat to monitor the situation during the monograph revision.

310 **Vancomycin Infusion** ABS(16)16

Clarity of solution Members were informed that a request had been received from a manufacturer to increase the limit in the Clarity of solution test from not more than 0.1 to not more than 0.2.

Members felt that changing the limit would be concerning to patients as it would cause the infusion to be an unexpected colour. The group agreed that the licensed specification of the product should be investigated before a decision was reached.

Related substances Further communication had been received from a manufacturer regarding the Related substances test, highlighting the difficultly they have had with the frequent co-elution of monodechlorovancomycin and Vancomycin B. They explained that the peak due to monodechlorovancomycin can elute at differing times under the same chromatographic conditions, causing difficulty when calculating levels of unknown impurities. They requested that the BP include a similar statement to the USP, specifying that the fronting shoulder of the Vancomycin B peak should not be integrated separately.

Members were informed that the Ph. Eur. monograph was under revision and agreed that a revision to the BP monograph should be considered following the finalisation of the Ph. Eur. monograph.

V NEW MONOGRAPHS

311 **Marbofloxacin Preparations for Veterinary Use** ABS(16)17

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

312 **Moxifloxacin Tablets** ABS(16)18

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

313 **Tigecycline for Injection** ABS(16)19

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

314 **Sterile Amphotericin Concentrate** ABS(16)20

The group agreed the amount of practical work needed to progress this monograph could not at this stage be justified for a single marketed product. The development of this monograph would be put on hold until such time that more products are available and practical work could be justified. The manufacturer would be informed of the Group's decision.

315 **Azithromycin Preparations** ABS(16)21

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

316 **Benzoyl Peroxide and Clindamycin Gel** ABS(16)22

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

317 **Clarithromycin Granules for Oral Suspension** ABS(16)23

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

318 **Clindamycin Tablets for Veterinary use** ABS(16)24

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

319 **Tobramycin Nebuliser Solution** ABS(16)25

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

320 **Tobramycin Eye Drops** ABS(16)26

The Secretariat informed members that the draft monograph which had been presented to them previously, based on methods from the sole MAH, had not been validated for the product licensed in the UK. Prescription data showed low usage of the product. Members agreed that the monograph development should be put on hold.

Tobramycin and Dexamethasone eye drops The Secretariat noted that the MAH had a product licence for Tobramycin and Dexamethasone eye drops, which had higher usage data. Members endorsed the recommendation that the BPC should be asked to add the monograph to the EAG ABS work programme.

321 **Tylosin Premix** ABS(16)27

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

VII REVISION OF MONOGRAPHS

322 **Colistimethate Injection** ABS(16)28

The Secretariat presented the group with a proposal for the revision of the monograph which had been received from a manufacturer.

Identification A, B, C, & D The Group agreed with the proposal from the manufacturer that the existing identification tests, A (TLC), B (chemical reaction) and C (Sulfates) in the draft monograph could be replaced with a peak comparison with the chromatograms from the proposed composition test. It was agreed that the current Identification test D (sodium test) should be retained in the amended draft revision.

Acidity or alkalinity; Free colistin Experts agreed that the tests should be retained in the draft monograph.

Loss on drying The manufacturer had proposed widening the limit in line with the USP. Members agreed that this proposal could be included in the draft revision.

Bacterial endotoxins The manufacturer had proposed that the limit in the draft revision was changed based on their products maximum permissible dose. Experts agreed that in-line with the recent policy discussions at the BP Commission the test for bacterial endotoxins should be removed from the draft monograph. A test for bacterial endotoxins would still need to be performed as per the general monograph for Parenteral Preparations.

Composition and Related Substances The manufacturer had proposed the addition of a discriminatory and stability indicating UHPLC method based on the Ph. Eur. method in the Pharmeuropa 27.3 draft revision of the Colistimethate Sodium monograph.

The group agreed that the proposals could be included in the draft revision.

323 **Fusidic Acid and Sodium Fusidate Preparations** ABS(16)29

At the previous meeting members had been reminded that following the discontinuation of the 3-Ketofusidic Acid 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. It had been agreed that 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.

Following the previous meeting a manufacturer had been in contact with the Secretariat and indicated that they had no experience with the application of the Ph. Eur. Related Substances method to the drug products. Additionally, the manufacturer did not offer any alternative proposals to the TLC identification method which uses chloroform as a reagent.

Members were reminded that a university project had been initiated to examine the suitability of replacing the current Related substances method with the Ph. Eur. method. The work at Robert Gordon University was reported to be underway and results of the work would be presented at the earliest opportunity.

324 **Moxidectin Preparations for Veterinary Use** ABS(16)30

Following the previous meeting the Secretariat had updated the draft monographs for Moxidectin Injection, Moxidectin Oral Solution and Moxidectin Oromucosal Gel based on correspondence received from experts.

Moxidectin Injection – Related substances The sample preparation details had been updated to accommodate all sample strengths. The manufacturer had been asked to comment on the draft monograph and specifically on the identity (and nature) of the named impurities and to propose suitable limits.

Moxidectin Oral Solution – Related Substances The Secretariat reported that a question remained over the applicability of the sample preparation details in the method proposed by the manufacturer for the oral solution product. It was agreed the manufacturer would be asked to comment on the draft monograph and specifically on the necessary sample preparation details for oral solution, the identity (and nature) of the named impurities and to propose suitable limits.

Moxidectin Oromucosal Gel – Related Substances and Assay In the test for Related substances the sample preparation details had been updated. The assay sample preparation details had been revised to reduce the amount of gel needed to perform the test. Previously, as written the quantity of the gel needed had exceeded 1g. The manufacturer had been asked to comment on the draft monograph and specifically on the identity (and nature) of the named impurities and to propose suitable limits.

Moxidectin Pour On The manufacturer had previously stated that the pour-on solution specification did not include a Related substances test and that a method did not exist. Due to the nature of the preparation and because the manufacturer was currently the only MA holder for this product the group agreed that a revision to this monograph need not be progressed.

Consultation with the VMD As no further response had been received directly from the manufacturer, it was agreed that the VMD would also be asked to contact the manufacturer on behalf of the BP.

325 **Tobramycin Injection** ABS(16)31

The monograph had been revised according to discussions at the previous meeting and circulated to the MAH. A response had been received from one of the four MAH.

Identification A The published TLC method contained chloroform and was revised to be harmonised with the parent and Tobramycin Nebuliser drafted method.

Identification B A report was received from a UK manufacturer that the method was only successful if an hour is left prior to the addition of barium chloride. It was requested that a statement to this effect was included in the draft monograph. Members felt that this problem was specific to the formulation of the product and concluded that the statement was not necessary.

Related substances As suggested at the previous meeting, the Related substances method provided by a manufacturer for the Tobramycin Nebuliser monograph had been included in the draft monograph. The manufacturer which provided comments on the draft highlighted that the impurities used for the system suitability, nebramine and kanamycin B, both eluted at RRT 0.96 and asked how they could be distinguished. A statement indicating that the peak due to nebramine was observed to increase in solution (3) relative to solution (2), was included in the draft monograph. Members agreed with this approach. The stakeholder had no other objections with the draft method.

Members were asked for advice on the impurity limits that should be included in the draft monograph. Based on the registered specifications of marketed products, members agreed that limits of any individual impurity not more than 2.0%, total impurities not more than 3.0% should be included.

Members agreed that neither of the drafted methods would require laboratory investigation.

326 **European Matters** ABS(16)32

Experts were given the chance to raise any issues relating to the activity of the European Pharmacopoeia and to comment on the formal and informal reports on Group 7 which had been circulated in the members' area of the BP Website.

Membership Members were informed that a member had resigned from his position as the UK Expert on Group 7. Another member remained a UK Observer on the group however it was noted that it would be very helpful to have a replacement for the member who had retired. If members had an interest in being considered for membership of Group 7 they were invited to contact the Secretariat.

327 **Any Other Business**

None.

328 **Date of next meeting** 21st September 2016