BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group: Antibiotics

SUMMARY MINUTES

A meeting of Expert Advisory Group: Antibiotics was held via videoconference on Tuesday 12th October 2021.

Present: Dr R Horder *(Chairman),* Mr G Blake, Dr G Clarke, Mr E Flahive, Dr V Jaitely, Prof J Miller, Dr M Pires and Mr J Sumal.

Apologies: Dr G Cook (Vice-chairman), Dr W Mann and Mr I Williams.

In attendance: Mr P Crowley, Ms A Thomson and Ms D Ballottin.

516 Introductory remarks

Welcome The Chair welcomed members to the meeting and Ms Ballottin from the BP Laboratory.

517 General Matters **ABS(21)14**

Declaration of Interests Members were reminded about the introduction of Survey Monkey to declare specific interests, and to inform the Secretariat of any changes to their interests throughout the year.

No interests were declared for any of the agenda items.

Confidentiality The confidential nature of the papers, discussions, and minutes of the meeting was highlighted. In view of this aspect of the work all papers were marked OFFICIAL-SENSITIVE and papers were made available by posting on the website.

Freedom of Information Members were asked to refer any FOI queries that they receive from the media to the Secretariat.

Membership Members were asked to inform the Secretariat if amendments were required to their contact details. It was noted that a review of BP advisory group memberships was scheduled to take place in 2022.

Duties of members of Expert Advisory Groups The duties of members, as stated in the British Pharmacopoeia, were provided for members information.

I MINUTES **ABS(21)15**

518 The minutes and summary minutes for the meeting held on 04th March 2021 were confirmed without comment.

II MATTERS ARISING FROM THE MINUTES **ABS(21)16**

519 The following matters arising from the meeting held on 04th March 2021 were noted.

Oxytetracycline Preparations (minute 507) These monographs had been published in the BP 2022.

Ciprofloxacin Preparations (minute 508) These monographs had been published in the BP 2022.

Tylosin Injection (minute 509) The Secretariat had progressed the Tylosin Injection monograph, in collaboration with VMD, with a view to publishing in the BP 2023 subject to stakeholder comment.

Clindamycin Injection (minute 510) This monograph had been published in the BP 2022.

Erythromycin Stearate Tablets (Minute 511) The MAH had been informed that more detailed characterisation of impurity S was required.

III MONOGRAPHS FOR THE BP 2023

520 PIVMECILLINAM TABLETS (New) ABS(21)17

The draft monograph would be included in a future publication subject to resolution of any outstanding points.

521 TEICOPLANIN FOR INJECTION (New) ABS(21)18

The draft monograph would be included in a future publication subject to resolution of any outstanding points.

522 VANCOMYCIN PREPARATIONS
ABS(21)19
Vancomycin Capsules (Revision)
Vancomycin for Infusion (Revision)
Vancomycin for Oral Solution (Omission)

At the September 2020 meeting of this EAG members were presented a risk-based review of the ABS lab queue. The group chose to progress the Vancomycin for Oral Solution and Vancomycin for Infusion monographs without laboratory work as the formulations did not contain excipients. No comments had been received on the draft monographs during the public consultation window.

During finalisation, differences were noted in the text when compared to the donor method which required correction and so these monographs were marked to be held back from publication in the BP 2022. These monographs were however published in error, although not included in the BP introduction.

As the Vancomycin Capsules products contained various excipients it had been agreed that laboratory work should be undertaken. The laboratory had completed their assessment and the monographs were presented with a view to publication in the BP 2023 subject to comments from the public consultation.

Definition (for Oral Solution and for Infusion) It was noted that “Hydrochloride” had inadvertently been included in the title of the monograph in the definition and so this had been corrected.

Content The Secretariat noted that once reconstituted, some oral solution products had a shelf life of 96 hours when stored at 2-8ºC and so a standard content statement

of not more than 120% when freshly reconstituted and not less than 80% when stored may have been appropriate. Members highlighted however the oral solution was not licensed as a standalone product. Instead some infusion products had a secondary indication for use as oral solutions.

Members agreed that the oral solution monograph should be omitted, but that reference should be made to the oral solution in the for infusion monograph through use of a subsidiary title and updated definition. It was recognised that this would need to be carefully constructed such that when used for oral solution, only the oral liquids general monograph would apply, as additional requirements like sterility were needed for the infusion.

Identification Members had previously agreed to include the use of LC-DAD identification of both concordant retention time and spectra for the vancomycin peak in solutions (1) and (2) of the Related substance and Vancomycin B test. This had been included in the published monograph.

Acidity (for Oral Solution and for Infusion) Members agreed to retain the test for acidity in the monographs.

Colour and clarity (for Oral Solution and for Infusion) It was noted that the colour and clarity requirement could also be formulation dependent. As the “for infusion” products did not contain excipients however, it was agreed it should be retained as an indicator of degradation. It was noted that the procedure for this test was based on the solution absorbance rather than the usual comparison to colour and clarity standard solutions.

Dissolution (Capsules only) A production statement was included in the published Capsules monograph mandating that a suitable dissolution test was to be performed by manufacturers. It was noted that the USP capsules monograph included dissolution parameters and a limit of Q=85% in 45 minutes, but that the microbiological assay <81> was used for quantification which would be onerous for manufacturers to perform.

The USP specification was however included in all licensed specifications, and so the Secretariat had drafted a procedure in line with this approach. It was confirmed that the concentration of vancomycin in the dissolution vessel for the lowest strength capsule would be a suitable concentration for the microbiological assay.

Members discussed if there might be an alternative to the microbiological assay used for quantification. It was however noted that as products were labelled in terms of international units, and that the Ph Eur parent monograph determined potency in terms of IU using the microbiological assay, it would not be possible to introduce an LC quantification until they had been revised.

Vancomycin B and Related substances It was noted that the Vancomycin for Infusion and Oral Solution monographs published in the BP 2022 contained a number of differences to the donor method. Prior to the laboratory assessing the suitability of the Vancomycin B and Related Substances procedure for the Capsules, the Secretariat had prepared corrected drafts and the laboratory had found this procedure to be suitable. The laboratory reported however that both the capsules products tested had failed the limits for Vancomycin B and for total known and unknown impurities. The manufacturer of these products did not state impurity limits in their specification and so it was proposed that in the absence of any other data, the limits for the capsules would be set in line with the reported results.

For the infusion products, a review of licensed specifications demonstrated variety in impurities limits and it was noted the USP used different specifications across their product monographs. Members agreed that the Ph Eur limits should be stated in the drafts, which had been posted for public consultation, as this was in line with expectations for new licensed products. It was requested that manufacturers be approached to specifically comment on the limits and provide batch data justifying wider limits if required.

Water Members agreed to retain the test for water in the infusion monographs but omit from the Capsules.

Assay The microbiological assay of antibiotics was referenced in all product monographs and had not been revised.

Impurities It was noted that the monograph limited impurities listed under the Ph Eur Vancomycin Hydrochloride monograph and so an impurity statement had been included for transparency.

Next steps Members agreed that letters of intent should be published advising users of the corrections to be implemented in the BP 2023.

IV MONOGRAPHS FOR THE BP 2024

523 CEFALEXIN PREPARATIONS ABS(21)20

Cefalexin Capsules (Revised)
Cefalexin Oral Suspension (Revised)
Cefalexin Tablets (Revised)

The Secretariat had reviewed the Capsules and Tablets monographs as well as drafted procedures for the Oral Suspension monograph with a view to publishing in the BP 2024 pending any comments arising from public consultation.

Content Members had previously queried if the drafted content limits of 92.5 – 110.0% were suitable for the capsules and tablets and the Secretariat had reviewed licensed content limits noting there were a number below the 95.0% limit but few above the usual 105.0% limit. Members agreed that manufacturers of Capsules and Tablets should be asked to confirm if limits of 95.0-105.0% were suitable for their products.

Members noted that manufacturers had licensed tighter limits than the BP's standard reconstitution shelf-life limits for oral suspensions of 80-120%. It was noted that the upper limit was particularly high as overages for stability purposes were not generally acceptable in licensing submissions.

Identification Members had previously agreed at the March 2020 meeting of this EAG to remove identification tests B and C: a thin-layer chromatography procedure and a chemical colour test from the Capsules and Tablets monographs.

It had also been agreed that the chemical colour test in the Oral Suspension monograph should be replaced with a concordant retention in the Assay.

Acidity/Alkalinity Unlike the parenteral preparations, members agreed that a pH requirement was not required for the Cefalexin monographs as pH would clearly be impacted by the different formulations and there were no pH safety concerns with these

preparations.

Antimicrobials Members had previously queried if a test for Antimicrobials was required in the Oral Solution monograph. The Secretariat noted that the general monograph for Oral Liquids contained a production statement stating that the efficacy of antimicrobial preservation should be assessed where the formulation contained an antimicrobial preservative. Members agreed that if the Oral Suspension was to be retained as a standalone monograph, a specific test would not therefore have been required.

Dissolution At the previous meeting of this EAG, procedures had been included in the draft Capsules and Tablets monographs which were erroneously thought to be based on manufacturers specifications. On final review during the finalisation of these texts, it was noted that there were some differences to the licensed specifications and that the procedure had not been included in the tablets monograph posted for consultation in October 2020 (the existing disintegration test was retained).

The dissolution procedure had been confirmed to be from data on the Capsules only. The drafted procedure however prescribed LC quantification harmonised with the Assay instead of the UV quantification at 262nm. The USP included the same dissolution test in their monographs for Capsules and Tablets under the name Cephalexin and that these tests utilised the same dissolution conditions as described in the drafts but with UV quantification. The Secretariat had therefore replaced the LC quantification in the Capsules and Tablets monographs with the UV quantification in line with the original procedure and USP monographs with limits of 80% release in 30 minutes based on licensed specifications.

Manufacturers did not include a specification for the Oral Suspension products and so a procedure and limits had been drafted harmonised with the Capsules and Tablets with a view to review receiving comments from the public consultation. It was noted however that excipients in the oral suspension could cause interference.

Related substances The HPLC related substances procedure had been included in the public consultation for which no comments had been received from manufacturers. The drafted limits had been based on that for the existing TLC procedure (1% for impurity A, B and for any other impurity) with the total limit of 4% based on the widest specification. The Secretariat noted that a number of manufacturers however had lower total limits of 3%, and some also control the limit for unknown impurities at 0.1%. Members agreed that the tighter limits should be included in the drafts for public consultation with a view to manufacturers commenting on their suitability and providing batch data to support wider limits.

It was also noted that relative retentions had been included for Impurity A, Impurity B and Cefotaxime based on chromatograms from a recent Ph Eur CRS report. Retentions for Dimethylformamide and dimethylacetamide were not identified in Ph Eur reports but a solution had been included to identify these peaks such that they could be disregarded.

3 additional impurities were specified and controlled by manufacturers and it was noted that it may be necessary to specify them in the monographs and that the laboratory may need to verify if these impurities can be controlled by the method. It was agreed to defer a decision on laboratory work pending comments from manufacturers.

524 CLARITHROMYCIN PREPARATIONS ABS(21)21

Clarithromycin for Infusion (Revised)
Clarithromycin Granules for Oral Suspension (Revised)
Clarithromycin Prolonged Release Tablets (Revised)
Clarithromycin Tablets (Revised)

Members had previously approved publication of the Infusion, Prolonged-release Tablets and Tablets monographs in the BP 2022. When finalising for publication however, a number of differences to the donor method had been noted with the related substances which had been corrected in the updated drafts.

It had also been agreed that the BP Laboratory should verify procedures for the Oral Suspension products due to the complexity of their extraction. The Secretariat had since updated the monograph based on a procedure donated by a manufacturer and proposed to work with manufacturers to confirm the sample extraction for their products with a view to publishing in the BP 2024, rather than ask the laboratory to develop and validate a suitable extraction.

Content It was noted that manufacturers had adopted tighter specifications that those normally used for Granules for Oral Suspension.

Dissolution The dissolution test in the Tablets monograph had been updated based on a review of licensed specifications to include a dissolution limit of not less than 80% (Q) in 30 minutes. It was noted that this limit was in line with the USP Tablets monograph and quantification was harmonised with the LC Assay.

Dissolution criteria had been included for the Granules for Oral Suspension based on licensed specifications with quantification harmonised with the Assay as per the tablets monograph. Members agreed that manufacturers should be asked to comment on the suitability of the procedure during public consultation.

Acidity Members agreed that the pH requirement should be retained in the Infusion monograph for safety and solubility reasons.

It was also noted that due to the very bitter taste of clarithromycin, the granules for oral suspension had a coating masking the taste which was designed to provide gastric release and so also pH dependent. It was therefore agreed that pH should be retained in the Granules for Oral Suspension monograph.

Clarity and colour Members noted that the colour and clarity requirement could also be formulation dependent. As the “for infusion” products did not contain excipients however, it was agreed it should be retained as an indicator of degradation.

Related substances Members had previously agreed to include a related substance procedure in all product monographs based on that donated by a manufacturer of the Granules for Oral Suspension. On review of the clarithromycin product monographs against the donor method prior to publishing in the BP 2022, a number of differences had been noted resulting in the deferral of publishing these monographs.

The Secretariat highlighted differences in the correction factors between the current published procedure and the new procedure despite both specifying the same wavelength, 205nm, for quantification. As members could not justify why correction factors should be different at the same wavelength based on the data provided, it was agreed that the manufacturer be requested to explain this difference.

While some manufacturers had introduced tighter limits for some impurities that those currently published, it was agreed the limits in BP monographs could not be tightened more than the Ph Eur limits. The limits in the Granules for Oral Suspension monograph would be simplified however to remove the specific limits for impurity I/A and D which were aligned with the published limit for any other impurity.

Water Members agreed to retain the test for water in the monographs pending confirmation of a policy regarding its inclusion in BP monographs.

Assay The Secretariat had retained the Assay procedures included in the published monographs as previously agreed by members, which date back to 2008. It was noted that although the procedure in the Tablets and Prolonged-release Tablets monographs were harmonised, there were some differences applied to the procedure in the other preparation monographs.

The procedure for the Infusion had a minor modification to the mobile phase composition with slightly less organic content, a slower flow rate, and although the column chemistry was the same, a different column was stated as suitable.

In the Granules for Oral Suspension, modified conditions were stated with a non-end capped C18 column, altered flow rate and a mobile phase with even lower organic content.

Members agreed that these modifications were likely required due to the differences in formulation and so no changes were necessary at this time.

525 TETRACYCLINE PREPARATIONS ABS(18)22
Tetracycline Capsules (Revised)
Tetracycline Tablets (Revised)

The Secretariat proposed a significant revision to the Tetracycline Capsules and Tablets monographs with a view to publishing in the BP 2024.

Content Members endorsed retaining the existing limits with a view to manufacturers commenting on them during the public consultation.

Identification Members recommended replacing the existing TLC procedure with LC/DAD spectra and HPLC retention time for identification purposes with a view to modernisation. It was noted that the UV spectra of tetracycline appeared to be significantly impacted by in solution pH dependent epimerisation to 4-epitetracycline, potentially impacting the need for laboratory evaluation to ensure suitability across licensed products.

Dissolution The existing dissolution parameters had been retained and the layout updated in line with new BP styling. Members endorsed proposals for the standard BP limit of NLT 70 % (Q) in 45 minutes to be included in both monographs, which was in line with licensed specifications.

Related substances Members supported the inclusion of a new related substances procedure to control all known impurities, based on the USP Capsules monograph. This approach had been taken for both the Tablets and Capsules BP monographs. It was noted that the USP did not specify the retention time for tacrolimus and so minor practical work would be required to confirm this.

Limits of 3.0% for impurity A, 1.0% for impurity D and 0.5% for impurity C were approved by members for the purpose of public consultation. Members were concerned that there was not data to support a limit for total impurities and agreed that manufacturers could be asked to comment and provide batch data as part of the monographs public consultation. The unspecified impurities limit and reporting threshold were drafted in line with ICH guidelines.

Loss on drying Members approved removal of the loss on drying requirement from the draft monograph based on recent discussion at the BP Commission regarding the relevance of these tests in determining product quality where different formulations exist.

Assay Members agreed for the chromatographic conditions to be harmonised with the new related substances procedure for analytical convenience.

V FOR INFORMATION

526 OUT OF STOCK BPCRS REVIEW ABS(21)23

It was noted that only 2 BPCRS that were the responsibility of this EAG were currently out of stock. Although the Secretariat had been provided an expected availability date for the Cefradine BPCRS, concern had been raised regarding the quality of the standard procured for its establishment, with significant degradation observed.

527 WORK PROGRAMME ABS(21)24

The EAG ABS work programme was presented to the members for discussion.

528 BRITISH PHARMACOPOEIA MATTERS ABS(21)25

Change Proposal Website Consultations A series of short consultations had been published to the BP website throughout Q3-2020. The items list the addition of new tests for identification and Related substances/Assay in monographs and a proposal for change to numerical limits for related substances. The consultations closed on 30 September 2020, and stakeholder responses were broadly supportive of the change proposals. BPC endorsed the change proposals in November 2020 and experts can expect to see: LC/UV-DAD in identification tests from BP 2022; Quantitative limits in chromatographic related substances tests from BP 2023; PAD for related substances and Assay from BP 2024 (predominantly for antibiotic monograph use). Outcomes to the consultations could be found on the consultations page of the BP website.

BPC Membership Professor Kevin Taylor's appointment as Chair of the British Pharmacopoeia Commission (BPC) had been extended for one year, from 1 October 2021.

Members of the BPC were appointed by the Department of Health and Social Care's Appointments Team, on behalf of the Secretary of State and the Northern Ireland Minister. This involved a formal application and interview process, governed by the DHSC Appointments Team.

It was noted that Professor Kevin Taylor had written an article about his time in the role of BPC Chair on the MHRA inspectorate blog.

Analytical Quality by Design The AQbD working party had prepared a supplementary chapter which had been published in the BP 2022.

As the work of the Analytical Quality by Design Working Party continued into its next phase, the British Pharmacopoeia Commission was looking to extend the professional membership of this Working Party with experts from a range of stakeholders.

A joint webinar with the USP on the real world application of AQbD and the analytical procedure life cycle management had taken place on 30th September – 1st October.

Biologicals The BP had been building on the consultation outcomes identified in the MHRA Strategy for pharmacopoeial public quality standards for Advanced Therapy Medicinal Products. Authoritative, non-mandatory, best practice guidance for standardising the application of flow cytometry (and other topics) were being developed through the BP's ATMP working party.

A consultation on best practice guidance on the application of flow cytometry for the cell and gene therapy community for the cell and gene therapy community had been released in May 2021 and was followed by a consultation on vector copy number quantification in July 2021. The outcomes of these consultations would be published to the BP website shortly.

BP Product Improvements It was highlighted that the Revision History project (aka Annotations - making monograph revision history available to online users) had been launched with the online BP 2022 and provided users a rationale for changes made to BP texts.

COVID-19 Update It was recognised that Members would be aware of the ongoing developments and the MHRA's ongoing involvement in assessing and authorising vaccine. The Agency continued to be very busy in responding to the Covid-19 pandemic and there remained a large demand on resource from across the Agency to support the wider healthcare system.

Remote working was likely to continue for some time, some colleagues had been returning to the office, but the numbers were minimal. The BP Lab remained operational. It was anticipated that all EAG meetings would be held remotely for the time being.

End of Transition Period The BP website content had been updated at the start of the year to reflect the new arrangements on 1st January 2021.

The British Pharmacopoeia continued to be a full and participating member of the European Pharmacopoeia Commission and expert groups, and the OMCL network.

It was noted that the British Pharmacopoeia continued to monitor for any impacts as customers make adjustment. For example, our process for shipping BPCRS orders to EU customers had been updated by adding customs tariff codes, EORI number and statement on Origin of Goods to international invoices and shipping documents to assist with customs processes.

BPC Annual Report It was noted that the 2020 Annual Report of the Human Medicines Regulations 2012 Advisory Bodies, which included the report of the BP Commission, had been published. The report included a foreword from Lord Bethell

thanking all those involved and highlighting how their professional expertise, commitment and hard work plays a vital role in ensuring that the medicines we take continue to meet the highest standards of safety, quality and efficacy.

VI EUROPEAN PHARMACOPOEIA **ABS(21)26; Annexes 1 to 3**

529 **Group of Experts 7 – Antibiotics** An informal report from the 169th meeting of experts Group 7 was presented to the EAG.

Pharmeuropa Draft monographs for Ampicillin Sodium (0578) and Tazobactam (2210) had been made available for comment in PharmEuropa 33.4 with a public deadline for comments of 31st December 2021.

Members were thanked for their continued support to the work of the UK Delegation to the European Pharmacopoeia.

European Commission The 171st Session was scheduled to take place on 23rd and 24th November 2021.

VII ANY OTHER BUSINESS

530 None

VIII NEXT MEETING

531 The date of the next meeting was confirmed as the 22nd February 2022.