BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group: Anti Infective Medicines

SUMMARY MINUTES

A meeting of Expert Advisory Group: Anti Infective Medicines was held via videoconference on Thursday 7th September 2023.

Present: Dr R Horder (*Chair*), Dr G Cook (*Vice-chair*), Dr G Clarke, Mr E Flahive, Mr V Jaitely, Mr S Jones, Prof J Miller, Mr J Sumal, and Mr I Williams.

Apologies: Mr G Blake.

In attendance: Mr P Crowley, Ms S Bowles, Ms M Guler, Mr K Rakowski, Mr D Tong, and Mr C Thompson.

568 Introductory remarks

Welcome The Chair welcomed members to the meeting as well as Mr C Thompson from the BP Laboratory.

569 General Matters **AIM(23)01**

Expense Claims Members were informed that expense claims, and any queries about expenses, should be emailed to Committee Support.

Declaration of Interests Members were reminded of the requirement to declare specific interests via Microsoft Forms, and as they arose during the meeting.

Confidentiality Members were reminded of the confidential nature of discussions and minutes of the meeting, with all papers marked OFFICIAL-SENSITIVE.

Freedom of Information Members were asked to refer any FOI requests they receive to the Secretariat.

Membership Members were asked to inform the Secretariat if their contact details had changed. It was noted that Warren Mann had resigned from this EAG at the end of 2022.

Members were thanked for their service and asked to confirm with the Secretariat if they wished to continue their membership. Members were also encouraged to approach potential candidate EAG/Panel members to express their interest via the BP website.

I MINUTES **AIM(23)02**

The minutes of the meeting held on 13th September 2022 were confirmed.

II MATTERS ARISING FROM THE MINUTES **AIM(23)03**

The following matters arising from the meeting held on 13 September 2022 were noted.

Clarithromycin Granules for Oral Suspension (minute 535 refers) Laboratory evaluation of the revised dissolution and related substances procedures had started. A laboratory report was pending and would be reported at a future meeting of this EAG. It was noted that although the other product monographs had been reviewed by this EAG previously, it was preferable to publish the family once the laboratory had completed its assessment as this may lead to changes to the harmonised methods.

Tacrolimus preparations (minute 551 refers) The draft monographs would be included in a future publication, subject to resolution of any outstanding points.

Chloramphenicol Preparations, Cefalexin Oral Suspension, Erythromycin preparations, Tigecycline for infusion, Tetracycline preparations, Rifaximin tablets, Doxycycline preparations (minutes 551, 552, 555, 556, 557, 558 and 559 refer respectively) These revised monographs had been published in the BP 2024.

Levofloxacin Preparations, Enrofloxacin preparations (minutes 551 and 554 refer respectively) These new monographs had been published in the BP 2024.

Ciclosporin Preparations (minute 553 refers) A follow up laboratory investigation had found that the Related substances procedure was not suitable for the control of a key degradant, impurity C. The Secretariat would present these findings and proposals at a future meeting.

Metronidazole Preparations (minute 560 refers) A laboratory report was pending for the assessment of the ID, Dissolution, Acidity, Related substances, and Assay procedures.

Out of Stock BPCRS (minute 562 refers) Members were informed that there were no out of stock BPCRSs related to this EAG.

III MONOGRAPHS FOR THE BP 2025

572 FLUCLOXACILLIN PREPARATIONS (REVISED) AIM(23)04

Flucloxacillin Capsules
Flucloxacillin for Injection
Flucloxacillin Oral Solution
Flucloxacillin Oral Suspension

The Flucloxacillin family of monographs had last been reviewed in the March 2020 meeting of this EAG. The monographs had been updated and modernised with the current BP policies and style guide. It had been agreed that the BP Laboratory should assess the drafted Identification, Dissolution, Related substances, and Assay procedures for all relevant Flucloxacillin preparations.

The Laboratory had completed their assessment for Flucloxacillin Capsules, Flucloxacillin Injection, and Flucloxacillin Oral Solution monographs. Due to the unavailability of samples for the Flucloxacillin Oral Suspension monograph, the laboratory could not investigate its drafted methods. Based on the 2022 Prescription Cost Analysis data, there were only 7 prescriptions for Flucloxacillin Oral Suspension products. Members confirmed that as there was only very low use in the UK, it should be retained as a BP monograph but not updated at this time.

Identification (Oral Solution) The published monographs for Flucloxacillin Oral Solution and Flucloxacillin Oral Suspension use an identification by Thin-Layer

Chromatography (TLC) procedure. This procedure utilised Iodine Vapour which was classed as extremely harmful to aquatic life and a known irritant. An HPLC-DAD (Diode Array Detection) method had been drafted and performed by the laboratory for the Oral Solution and found to be fit for purpose. However, although the retention time and UV spectra were concordant between the sample and standard solutions, the UV spectrum of flucloxacillin lacked characteristic features of UV identification. In accordance with BP policy, the use of LC/DAD may only be included as a stand-alone test if the UV spectrum is characteristic. Therefore, the HPLC-DAD method may not be considered specific enough as an identification test.

Members discussed the suitability of the method. Some members supported the move to the LC-DAD method, suggesting that the combination of retention time and UV spectrum should suffice. Other members were not supportive of the move due to concerns regarding the specificity and the ability of labs to use the LC-DAD method. It was proposed that the laboratory investigate alternative methods, but members agreed to retain the TLC procedure.

Dissolution (Capsules) A dissolution procedure had been drafted based on limited licensing information. The method utilised paddles at 50 rpm and water as the dissolution medium, with a Q value of 85% in 15 minutes. The laboratory had investigated the procedure and confirmed its suitability. A Q value of 97% had been obtained on average from 6 trials. The results supported the proposed limit of 85% (Q) in 15 minutes and members accepted to publish the dissolution procedure as drafted.

Related substances (Capsules, Injection and Oral Solution) An LC procedure based on the Ph Eur Flucloxacillin Sodium draft monograph (PharmEuropa 31.3) had been drafted, which applied gradient, reversed-phase elution and detection at 225 nm. The new methodology reflected an improvement in analytical capabilities over the past 20 years and provided control for a number of additional named impurities and a tighter control for un-identified impurities. Drafted limits have been assessed against the licensed products. In line with ICH Q3B(R2), the disregard has been set at 0.05% as the maximum daily dose was greater than 1g. The limit for any other impurities was set to be greater than the identification threshold, but in line with the drug substance.

The laboratory had assessed the LC method for Flucloxacillin Capsules, Flucloxacillin Injection and Flucloxacillin Oral Solution monographs. All samples tested for the Flucloxacillin Capsules and Flucloxacillin Injection monographs passed the drafted limits and the procedure was found to be suitable as a compendial method. It was recommended for all the preparations that the signal to noise requirement for the disregard solution to be at least 42 due to impurity C having a correction factor of 4.2. The signal to noise value determined from the analysis was 132.

For the Oral Solution monograph, three out of four samples passed the limits for specified impurities but contained individual specified impurities up to 0.39%. One of the samples failed to meet the limit for impurity A, as well as containing individual impurities up to 0.57% and total impurities up to 5.68%. It was noted that these would also fail the MAH licensed specification.

The laboratory also noted that impurity C co-eluted with a number of unspecified peaks. Despite injecting solutions of excipients, the laboratory was unable to identify all of the peaks. However, given that impurity C is a synthetic impurity, it was proposed to be disregarded in the Oral Solution monograph as it would be controlled in the Ph. Eur. drug substance monograph.

Members reviewed the limits for Flucloxacillin Capsules and Flucloxacillin for Injection monographs and agreed they should be published for public consultation as drafted.

Members discussed limits for Oral Solution and agreed the total impurities limit should be increased from 7.5% to 10% for the public consultation based current licensing expectations.

Assay (Capsules, Injection and Oral Solution) An LC procedure largely harmonised with the Related substances had been drafted in the interest of analytical convenience. The procedure was based on the Ph. Eur. Assay which used sample concentration tenfold more dilute than related substances. The content limits for the individual monographs had been drafted in-line with current policy and licensed specifications.

The laboratory found the method to be suitable as a compendial method. The Assay results showed good repeatability and all samples tested passed the proposed limits.

It was noted that the content limits for Flucloxacillin Capsules monograph were set at 92.5% to 110%, which was wider than the normal 95% to 105%. Members agreed that the content limits should be set as 95% to 105% for public consultation, with a possibility to bring the lower limit to 92.5% based on the response.

There was a discussion on the Bacterial Endotoxin limit of 3.5 IU/mg. It was proposed that this was higher than acceptable. The members agreed to review the limit in line with the MAH product specifications.

573 Phenoxymethylpenicillin Oral Solution (Revised) AIM(23)05

The Phenoxymethylpenicillin family of monographs were last reviewed by members at the February 2019 meeting of this EAG following a laboratory assessment confirming the methods suitability for the range of products tested. The monographs were published in BP 2020 after a public consultation window during 2019 Q1.

The Secretariat had since received correspondence from an MAH of the Oral Solution requesting the BP review and widen the limits of impurities.

Related substances An MAH had provided batch data of different formulations and different strengths with expiry dates between November 2023 and January 2024. The MAH had requested a widened limit of 4.0% from 1.0% for impurity E (sum of penicilloic acid isomers of phenoxymethylpenicillin), 6.0% from 1.0% for impurity F (sum of penilloic acid isomers of phenoxymethylpenicillin) and 10.0% from 4.0% for total impurities (excluding impurity D).

Members commented the MAH did not provide enough justification on the proposed limits based on the batch data. Members also questioned the large difference of impurity F between batches which may indicate the MAH is having difficulties in the analysis or when applying the BP method. The members and the Secretariat agreed to contact the MAH and ask for a more comprehensive data package, details of the analytical procedure and better justification on the proposed limits.

574 Nystatin Oral Suspension (Revised) AIM(23)06

The Nystatin family of monographs were last reviewed by members at the February 2019 meeting of this EAG. It had been agreed that the BP Laboratory should assess suitability of the procedures on marketed oral suspension products. The Laboratory had completed their assessment, finding the methods to be suitable with modifications outlined below.

Composition The composition procedure was drafted based on the Ph Eur drug substance monograph, utilising HPLC gradient elution with DAD detection at 305 nm. The Laboratory performed the test on one of the two licensed products in the UK due to difficulties encountered while asking for sample donations. It was noted that these products have comparable formulations in terms of parabens which had been demonstrated to interfere with chromatography. Therefore, it was anticipated that the drafted method would be applicable to the other formulation. The Laboratory had found that the drafted method met the acceptance criteria and the samples tested met the proposed limits. Therefore, the method was accepted as fit for purpose and suitable for use as a compendial method.

One member questioned the need to inject the system suitability solution immediately after the stated period of time. The Laboratory explained this was due to rapid decomposition of the impurities. Members noted this observation and suggested that it should also happen in the Nystatin drug substance monograph and suggested the Secretariat to notify EDQM of the observation.

Members agreed to keep the suggested injection condition in the monograph and suggested the Secretariat to provide sample chromatograms for the composition test due to the complexity of the chromatogram obtained.

Related substances The Laboratory had found that the drafted method met the acceptance criteria and the samples tested met the proposed limits, therefore the method was accepted as fit for purpose and suitable for use as a compendial method. Members agreed to adopt nitrogen as the carrier gas due to ease of access and its equivalent performance to helium. Members also agreed to adopt the 5 head-space parameters proposed by the Laboratory for the gas chromatographic conditions.

One member questioned the relations of Tiglic aldehyde and mesityl oxide to the drug substance and hence the need for testing these compounds. The Secretariat noted that it had been the consensus of the group to have a Related substances test for a BP monograph, and the test method came from an old product dossier. The Secretariat agreed to reconfirm the rationale for why these compounds were controlled and to look at the current products in the market before putting the monograph for public consultation. If the test was retained, it was agreed the title should be changed to Tiglic aldehyde and mesityl oxide.

IV FOR INFORMATION

575 AIM WORK PROGRAMME AIM(23)07

A paper was presented outlining progress with the AIM work programme focussing on targets for the next publication, progress of monographs prioritised for development, and progress of monographs which required laboratory assessment.

576 BRITISH PHARMACOPOEIA MATTERS AIM(23)08

BPC Membership Review A call for new BPC members closed on the 13th July. Applicants were being shortlisted with interviews expected to take place later in the year with the expectation that successful candidates will be in post in the new year.

EAG Membership Review The term of office for all current members of the Expert Advisory Groups, Panels of Experts and Working Parties of the BP Commission was due to end on 31st December 2023.

A call for expressions of interest was expected to be released on the BP Website and our MHRA media channels shortly. Members were encouraged to share with their networks and encourage people to get involved.

BP and Lab Services team - staff changes A number of staff changes within the BP Secretariat were flagged for members information.

New Look Website A new Beta version of the BP website had been in development for a number of months. Intended to replace the legacy site, they were expected to run concurrently until for a number of months when the legacy site will be shut down. Members were encouraged to use the beta site and provide feedback.

MHRA Corporate Plan 2023 to 2026 A plan outlining the agency's strategic direction over the next three years had been launched and could be found on the following website:

https://www.gov.uk/government/publications/mhra-corporate-plan-2023-to-2026

The following four strategic priorities for the agency were:
1. Maintain public trust through transparency and proactive communication;
2. Enable healthcare access to safe and effective medical products;
3. Deliver scientific and regulatory excellence through strategic partnerships;
4. Become an agency where people flourish alongside a responsive customer service culture.

V EUROPEAN PHARMACOPOEIA AIM(23)09

Group of Experts 7 Group 7 had held their 172nd and 173rd meetings on Dec 22 and Apr 23 respectively and reports of these meetings were discussed.

Pharmeuropa The Secretariat thanked members for their continuing support for the work of the UK delegation to the European Pharmacopoeia.

Since the September 2022 meeting, monographs had been posted for review on Pharmeuropa 34.4, 35.1, 35.2, and 35.3. Many of the revisions were due to changes made to the pyrogens test to facilitate the replacement of the rabbit-based test.

It was noted that several of the proposed revised monographs falling under the remit of EAG AIM were expected to impact related BP monographs including the Oxytetracycline dihydrate and Chloroquine phosphate families. Members supported adding these to the work programme.

VI ANY OTHER BUSINESS

A member asked about the possibility of holding the next meeting in person. An agreement was made on a meeting a year being virtual, and one in person. This will enable all the new members of the group to meet face to face.

VII NEXT MEETING

The date of the next meeting was confirmed as the March 2024. Exact date to be confirmed