**For BRITISH PHARMACOPOEIA COMMISSION**

**Expert Advisory Group: Anti Infective Medicines**

**SUMMARY MINUTES**

A meeting of Expert Advisory Group: Anti Infective Medicines was held in person at 10SC, Canary Wharf on Monday, 15th April 2024.

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

**Apologies: N/A**.

**In attendance**: Ms S Bowles, Mr K Rakowski, Mr O Waddington, Ms M Guler and Mr S Greatorex.

**580 Introductory remarks**

580.1 **Welcome** The Chair welcomed members to the meeting as well as Mr Sam Greatorex from the BP Laboratory.

**581 General Matters AIM(24)01**

581.1 **Expense Claims** Members were informed that expense claims, and any queries about expenses, should be emailed to Ms M Guler.

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

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

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

581.5 **Membership** Members were asked to inform the Secretariat if their contact details had changed.

**I MINUTES AIM(24)02**

582 The minutes of the meeting held on 7th September 2023 were confirmed.

**II MATTERS ARISING FROM THE MINUTES AIM(24)03**

583 The following matters arising from the meeting held on 07th September 2023 were noted.

583.1 **Metronidazole preparations** (Minute 560 refers).

Metronidazole preparations are being processed in the laboratory for identification, dissolution, acidity, related substances and assay tests. The secretariat will report the results at a future meeting.

583.2 **Flucloxacillin oral solution** (Minute 572 refers).

End of re-constituted self-life testing was discussed at the British Pharmacopoeia Commission (BPC) meeting on the 4th March 2024. Members commented that the British Pharmacopoeia states that manufacturers should perform end of shelf-life testing as part of stability studies. However, batch release testing is performed on freshly reconstituted material. It was proposed that related substances testing was performed on product at the end of reconstituted shelf-life as well. A member commented that there needs to be consideration of the different types of antibiotics that this would have an impact on e.g. Clarithromycin granules for oral solution. The question was raised as to what the other Pharmacopoeias stipulate. Members agreed that monographs should not be changed until the BPC had reached a decision in the July meeting.

583.3 **Phenoxymethylpenicillin oral solution** (Minute 573 refers).

A change of limits had been proposed by a marketing authorisation holder (MAH), for Phenoxymethylpenicillin oral solution. However, when they were asked for validation and test paperwork, they did not reply. Members agreed on the Secretariat's decision not to progress this further.

583.4 **Nystatin oral suspension** (Minute 574 refers).

The Secretariat notified the EDQM on the decomposition of impurities generated in the system suitability solution of the Composition test for Nystatin oral suspension. Controlling Tiglic aldehyde and Mesityl Oxide was discussed. Members agreed that the Related Substances test would not be added to the Nystatin monographs for the BP2025. The only addition would be the Composition test for this publication.

## III MONOGRAPHS FOR THE BP 2025

**584 CLARITHROMYCIN PREPARATIONS (REVISED)** **AIM(24)04**
**Clarithromycin for Infusion**
**Clarithromycin Granules for Oral Suspension**
**Clarithromycin Prolonged Release Tablets**
**Clarithromycin Tablets**

584.1 **Out of Stock Impurity E BPCRS**

Clarithromycin preparations were discussed during the September 2023 EAG meeting. It was decided that the preparations should all be published together once the laboratory work on the Granules for Oral Suspension had been completed. In the interim, there was a difficulty ensuring the supply of Clarithromycin impurity E BPCRS. Clarithromycin impurity E BPCRS was used in the Dissolution test and Assay for Tablets; and the Assay for Prolonged Release Tablets and Infusion. It was also used for the Related Substances test for the Granules for Oral Suspension.

Members discussed the use of impurity E BPCRS in the assay test. The laboratory representative confirmed that there was no reason not to include the clarithromycin for peak identification EPCRS as an alternative to the impurity E BPCRS. The resolution was found to be comparable: around 5.5, versus 5.8 achieved with the impurity E BPRCS.

A member asked what the alternative would be for a system suitability test on the Assay. The laboratory representative commented that there are tests such as theoretical plate counts. Another member asked where the impurity E in the system

suitability had come from. The Secretariat confirmed this was historical . A member asked if impurity E was a degradation impurity. Members confirmed it was a synthetic impurity. Another member commented that it is unusual to have a separation time to prove results within limits and that it should be a retention time instead. A further member commented that the system suitability does not affect the Dissolution and the Related Substances were controlled already; therefore, if you named the impurity E retention time, using the peak identification EPCRS, that would assist people with achieving the correct result.

Members agreed that the laboratory report showed equivalency and supported the proposal to replace impurity E BPCRS with Clarithromycin for peak identification EPCRS. A member enquired that when the monographs were updated, that there still would be a system suitability test, but that it would be related to retention time. The Chair suggested that the monograph should include a statement that the test is not valid unless the expected retention time matches the peak identification. This change would occur for all the monographs for Assay and Dissolution, but the current system suitability would remain for the Related Substances. I.e. the resolution between impurity F and H is between 3 and 8, and the signal to noise ratio is at least 10. Members agreed.

584.2 **Dissolution**

The second part of the Clarithromycin paper was a discussion on the Clarithromycin Granules for Oral Suspension. The laboratory work had been completed. However, fifty percent of the samples tested failed to achieve passing Dissolution results. Several MAH products failed the mean label claim of 98% after forty-five minutes, and even when it was extended to sixty minutes they still failed. The laboratory had no samples left to continue further investigation. The Secretariat had contacted MAHs to obtain further samples; however, none had returned the request. The Secretariat proposed that the test could be repeated using 75rpm paddle rotation speed once sample had been obtained. The Secretariat asked for members input with any further suggestions.

A member suggested that the pH seemed high and that with a higher pH the solubility would be reduced. The coating on the Granules is provided to overcome a taste problem with the drug. The coating dissolves, not entirely in the stomach because of the acid liability of macrolides, but soon after leaving the stomach. Therefore, the members wondered if the pH of the phosphate buffer was too high. A member suggested that 98% for the limit was too high for Dissolution, as this would suggest complete dissolution. They suggested a more appropriate limit would be 80% dissolution. A member suggested that the limits were over discriminating, and that conditions and limits should be more in line with those of the Tablets monograph, which were a pH of 5 and a Dissolution limit of 80% within thirty minutes. However, they were unaware of the coating and queried whether this would be sufficient. A member confirmed that the coating needs to come off to release Clarithromycin. However, a pH of 5 would probably be sufficient to dissolve the coating as well.

A member expressed concern that the centrifuging and separation of particles in the method seemed complicated. Another member expressed their concern over laboratories being able to accurately measure the very precise volumes in the method. Members agreed that the volumes specified should ideally allow the use of bulb pipettes. A member further pointed out that, since the concentration of injection for the HPLC is only half of what it is for the Tablets method, it would be appropriate to standardise the methods. A member pointed out there were further problems with the method in that the dilutions were peculiar volumes and resulted in solution

concentrations which were different. They suggested using whole numbers for the dilutions.

A member queried whether all the samples were taken from the same container. The laboratory representative explained that they were only provided with one container of each sample. The member commented that therefore the work performed was a repeatability test and yet there was a 10% variation in results, which was high for repeatability. They suggested that testing using more than one container should be considered. The Secretariat explained that there had been an issue with obtaining samples from manufacturers, and that although permission had been granted to approach the wholesaler, it was unlikely that greater than one container would be available. Members suggested that the dissolution of suspensions of generic products submitted for approval could also be evaluated, as more than one container of the same samples should be used.

A further member commented that Dissolution tests for suspensions are more complicated than for solid dosage forms. The method that has been used was very complicated, and more work is needed on the Dissolution test.

584.3 **Related Substances**

The proposed changes to the Related Substances test were discussed. A member raised concerns regarding solution A and B. Solution A was used to remove the excipients from the sample, so that only Clarithromycin is left. Solution B was used to make the Clarithromycin solution. However, Solution A was at pH 5, which should have dissolved all the Clarithromycin, and Solution B (dipotassium salt) was at a higher pH and the Clarithromycin would have a lower solubility. The member wondered if the solutions were switched between the draft monograph and manufacturers method. The current monograph only used solution B to wash the sample and used acetonitrile to dissolve the residue in Clarithromycin. Members suggested the method was incorrect and may have resulted in very poor recovery. The laboratory representative confirmed that the donor method called Solution A ‘washing solution’ and Solution B ‘extraction solution’. Since members still had concerns the Chair suggested that once the laboratory had more sample, they should confirm the methods and results. Members also queried the use of a mesh in the method and how users would know the type of mesh required. The laboratory confirmed it was for separating the excipient and collecting the coated particles, and that it was a coarse filter that they had readily procured and was available for laboratory use.

A member mentioned that the chromatogram for system suitability had a poor baseline, and queried whether this could be improved. The Laboratory representative explained that a recovery of 95% had been achieved.

A member suggested exploring whether there were other licenced methods in addition to the donor method for comparison and that there might be a more conventional method that may work.

It was concluded that there was more work to be performed on the method from both the laboratory and the donor to achieve a suitable method, and that the Granules for Oral Suspension should be published without the Dissolution method for BP2025 to address the impurity E BPCRS stock challenge.

**585 BLEOMYCIN FOR INJECTION (Revised) AIM(24)05**

585.1 The Secretariat explained that there were difficulties supplying Bleomycin Sulfate BPCRS and proposed a remedial action of using Bleomycin Sulfate EPCRS as an alternative. The laboratory report showed that the EPCRS was a suitable equivalent to the BPCRS, with a change required to the buffer and gradient. The column particle size was also reduced from 7µm to 5µm. The Secretariat updated the draft monograph in line with the current BP style. A member queried that the gradient table was missing from the draft monograph. Members agreed this should be added. Members noted that there were several comments on the DRT regarding the storage conditions dictated in the draft monograph. A member suggested the retention time of Bleomycin B should also be included. The Secretariat confirmed laboratory work would be required for this, and, in view of the BPCRS supply issue, members agreed that the monograph could be printed as drafted, and the monograph updated with the Bleomycin retention time in the future.

**586 FLUCLOXACILLIN ORAL SOLUTION (Revised) AIM(24)06**

586.1 The revision of the Oral Solution Identification test was deferred at the September 2023 meeting, due to the proposed HPLC-DAD test not being sufficiently characteristic. It was agreed that further investigation should be carried out by the BP Laboratory to find a suitable alternative to the published TLC procedure.

The Secretariat explained that the BP Laboratory had developed a suitable alternative TLC method which used a fluorescent coated plate and visualisation under UV light, instead of derivatisation with iodine vapour. The method was found to be fit for purpose and all samples tested met the acceptance criteria.

A member queried the style of the limits in the draft monograph and that the expected retention time was missing. The Secretariat confirmed that the style would be changed for the BP2025 publication, but the retention time would be published in BP2026.

The members agreed that the procedure should be published as drafted for public consultation.

**587 OXYTRETRACYCLINE (Revised) AIM(24)07**
**Oxytetracycline Tablets**
**Oxytetracycline Capsules**

587.1 The Secretariat explained that the Ph. Eur was adopting changes for Oxytetracycline dihydrate (0199) and Oxytetracycline hydrochloride (0198) for publication in EP 11.6. New impurities had been added to the Related Substances test that impacted the BP Tablets and Capsules monographs. The Oxytetracycline capsules contain hydrochloride and the oxytetracycline tablets contain dihydrate. The BP had received a query from an MAH, which questioned a discrepancy in the Impurity A limits between the Ph. Eur Oxytetracycline dihydrate and the BP Oxytetracycline Tablet monographs.

The changes proposed to the related substances test on the dihydrate monograph, were the introduction of impurity G, which was found to co-elute with impurity A, so a

limit was added. A new EPCRS was also added to allow for identification of the peak due to impurity G. This utilised epitetracycline hydrochloride CRS (impurity G).

The change proposed to the hydrochloride monograph was the introduction of impurity F as a specified impurity. This was present in current batches at levels above the limit for any other impurity. As the impurity was found to degrade into impurities D and E, a limit for the sum of impurities D, E and F was introduced. The total limit of these impurities was set to 0.4%, with a 0.2% limit per impurity.

Members agreed that the finished product impurity A limit should be changed because it should not be tighter than the Ph. Eur API limit. The Secretariat, together with experts, will review whether 0.7% is an appropriate limit for the Tablets and 0.5% is appropriate for the Capsules.

A member questioned whether impurity A was a degradant. The Secretariat confirmed it was and agreed an action for stability data to be reviewed to determine appropriate limits. Members also suggested the Capsules should have a limit for impurities D, E and F of 1% so they matched the tablets. Members questioned whether the content limits of 95 to 110% were appropriate when the total impurities limit was set to 4% and it was agreed that consideration should be given to revising the content limits.

## 588 ERYTHROMYCIN STEARATE TABLETS (Revised) AIM(24)08

588.1 the Erythromycin family of monographs underwent revisions in BP2021, which included updates to Dissolution, Related Substances, and Assay methodologies based on laboratory assessments of the relevant Ph Eur drug substance procedures. Post the BP2021 update to this monograph, there were questions regarding whether impurity S was in fact stearic acid. The Secretariat confirmed that the identity of impurity S remained unclear and needs to be resolved.

588.2 **Related Substances**

At the end of 2023, an MAH raised concerns about the Related Substances test for Erythromycin Stearate Tablets, as their finished product failed to meet the specification limit for Impurity S. However, when they used the Ph. Eur API method, the material passed. They suspected that differences in methods, such as diluent composition and impurity level calculations, may have contributed to elevated impurity levels when using the BP method.

Members discussed whether differences in tablet formulations (e.g. inclusion of magnesium hydroxide or sodium citrate, different buffer ratios) could give rise to different results. Originally for all Erythromycin preparations, the percentage claim limit was for erythromycin, irrespective of whether it was stearate, ethyl succinate, estolate or the lactobionate.

Members agreed that work should be carried out in the laboratory to evaluate whether the MAH results could be repeated using the monograph method.

588.3 **Dissolution**

A procurement agency had informed the BP that their manufacturers used Methanol instead of the dissolution medium to prepare the standard in the Dissolution test. They found that the use of methanol for solution preparation resulted in around a 10- 12% higher dissolution rate result compared to use of dissolution medium.

Members felt that the MAH's findings were counterintuitive, as methanol would likely enhance the solubility of the standard, potentially resulting in lower sample results.

Members queried the differences in methanol/buffer ratios between the Ph. Eur and the BP. The Secretariat agreed that further laboratory work was needed to investigate buffer ratios and the identification of Impurity S and/or Stearic acid.

Members agreed that the laboratory should try to replicate the MAH's findings by preparing standards in dissolution media and methanol.

**589 CHLOROQUINE PHOSPHATE TABLETS (Revised) AIM(24)09**

589.1 The Secretariat explained that the Ph. Eur was adopting changes to the Related Substances method in the Chloroquine Phosphate (0544) monograph in publication 11.6. The thin-layer chromatography method had been replaced by a liquid chromatography method. The list of impurities and their specifications had been updated, with five impurities now listed, and impurity A specified at 0.5 per cent. A revised monograph had been drafted, with impurity limits being aligned with the Ph. Eur limits.

589.2 **Identification**

A member noted that the current Identification (ID) A test uses chloroform and that this should be changed to dichloromethane or ethylene dichloride, as these were more environmentally friendly. It was also agreed that the ID test B should be removed, as melting point is no longer considered a useful test for identification.

589.3 **Related Substances**

Members discussed whether the impurities were degradants and the potential impact on stability data/shelf life. Licensing agreed to evaluate the approved product licences and potential impact on manufacturers.

589.4 **Assay**

It was noted that the assay uses chloroform and was also a titration which was not a favoured method of analysis. As the Related Substances will use a HPLC method it was agreed that a HPLC method should be developed for the Assay. A member questioned the contents limits as to whether there was a rationale for including an overage; and that it would be more appropriate to align with the Ph. Eur instead. Licensing committed to check for appropriate content limits.

Members agreed that the monograph would need to be submitted for public consultation.

## IV FOR INFORMATION

### 590 Out of Stock BPCRS report AIM(24)10

There were two out of stock British Pharmacopeia chemical reference standards (BPCRSs), which were discussed previously in the meeting.

Members noted the continued reduction in out of stock BPCRS and complimented the team working on this.

### 591 AIM WORK PROGRAMME AIM(24)11

The Secretariat presented a paper 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.

#### 591.1 Work Programme Overview

An updated version of the work programme had been provided which highlighted all revised monographs which had been planned for publishing in BP2025.

#### 591.2 Prioritised Monographs

The prioritised monographs identified in 2021 were continuing to be worked on.

#### 591.3 Laboratory Work Plan

The Laboratory work programme continued for monographs intended for the BP2026 and BP 2027 publications.

### 592 BRITISH PHARMACOPOEIA MATTERS AIM(24)12

#### 592.1 BPC Membership Review

The Committee Services Team (CST) has confirmed the new term of office for all members of the BP Commission.

#### 592.2 EAG Membership Review

The Committee Services Team (CST) has confirmed the new term of office for all members of the EAG.

#### 592.3 BP and Lab Services team - staff changes

Several staff changes since the September 2023 meeting of this EAG, were noted.

#### 592.4 New Look Website

The new Beta website went live on the 13th December 2023 and the legacy site no longer existed. The Secretariat encouraged members to continue to provide feedback so that further improvements may be made.

## V EUROPEAN PHARMACOPOEIA AIM(24)13

593.1 **Group of Experts 7**

A verbal update on the 174th meeting, held in October 2023, was provided and the meeting report discussed.

593.2 **Pharmeuropa**

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

Since the September 2023 meeting, monographs have been posted for review on Pharmeuropa 35.4 and 36.1. It was noted that Ivermectin may be affected by these revisions and members supported adding it to the work programme.

## VI ANY OTHER BUSINESS

594 **Antimicrobial Resistance**

Members noted that antibiotic resistance continues to be a concern and queried if the EAG could support efforts in this area. The Secretariat confirmed that they had attended the Westminster Health Forum on antimicrobial resistance (AMR) on 24th January 2024 and that the MHRA is working closely with the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR), and an internal AMR group is working with MHRA partners.

## VII NEXT MEETING

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