For BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group: Anti Infective Medicines

SUMMARY MINUTES

A meeting of Expert Advisory Group: Anti Infective Medicines was held virtually on Wednesday, 11th September 2024.

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

Apologies: Mr V Jaitely.

In attendance: Ms S Bowles, Mr K Rakowski, Mr O Waddington, Mr R Legg, Mr D Crowe and Mr S Greatorex.

596. INTRODUCTORY REMARKS

Welcome The Chair welcomed members to the meeting as well as Mr Sam Greatorex and Mr David Crowe from the BP Laboratory.

597. GENERAL MATTERS **AIM(24)14**

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

Declaration of Interests Members were reminded of the requirement to declare specific interests via correspondence with the Secretariat, 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 Freedom of Information (FOI) requests they receive to the Secretariat.

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

I MINUTES **AIM(24)15**

598. The minutes of the meeting held on 15th April 2024 were confirmed.

II MATTERS ARISING FROM THE MINUTES **AIM(24)16**

599. The following matters arising from the meeting held on 15th April 2024 were noted.

Clarithromycin Preparations (minute 584 refers) Clarithromycin methods had been reviewed by members and it had been accepted that Solutions A and B were the correct way around. A member raised the question regarding whether there should be a system suitability test for the Assay. The European Pharmacopoeia (Ph. Eur.), chapter 2.2.46, stipulates system suitability should be employed for the Assay for drug substances. The use of the system suitability test with the Assay, would be reviewed by the Secretariat.

Bleomycin (minute 585 refers) The gradient table had been added to the Bleomycin monograph as actioned previously, and the monograph published in BP2025. Further comments that were received as part of the Document Review Tool (DRT), would be updated in a future publication.

Flucloxacillin Oral Solution (minute 586 refers) Flucloxacillin methods had been scheduled for public consultation as agreed previously.

Oxytetracycline Preparations (minute 587 refers) The Secretariat had confirmed that Impurity A was an active metabolite, and the content limits were suitable. The monographs were being reviewed at Public Consultation.

A Manufacturing Authorisation Holder (MAH), had made a query regarding the decrease in Dissolution time from 45 to 30 minutes. They were experiencing difficulties passing the test using that time point. However, the MAH were also conducting an ongoing investigation into their product, as they had an unusual formulation containing gelatin. No action was to proceed prior to the investigation being completed.

Erythromycin Stearate Tablets (minute 588 refers) Laboratory work had been scheduled to investigate whether an MAH result for Impurity S could be replicated and verify the methanol to buffer ratio, and whether the dissolution results of the MAH could be replicated.

III MONOGRAPHS FOR THE BP 2026+

600. Marbofloxacin Preparations (NEW) **AIM(24)17**
Marbofloxacin Tablets
Marbofloxacin Injection
Marbofloxacin Powder for Injection

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

601. METRONIDAZOLE PREPARATIONS (REVISED) **AIM(24)18**
Metronidazole Tablets
Metronidazole Infusion
Metronidazole Suppositories

The Metronidazole family of monographs were previously discussed at the September 2022 meeting, where they were agreed to be updated and modernised in line with current BP policies and style guide. The Laboratory had completed their assessment for Metronidazole Tablets, Metronidazole Infusion and Metronidazole Suppositories monographs.

Identification (Tablets)

The experts were made aware of an error in the laboratory report, where the IR spectra were incorrect. The corrected IR spectra were shared via the Forum and presented during the meeting. The proposed IR identification method from the draft Metronidazole Tablets monograph was investigated but was found unsuitable due to the standard and sample spectra being non-concordant. An alternative HPLC-DAD method was investigated and found to be suitable as a compendial method. Members endorsed the method.

Dissolution (Tablets)

The proposed dissolution procedure based on the USP monograph for Tablets was found to be suitable as a compendial method and endorsed by the members. The members agreed to tighten the limit to 80% (Q) in 30 minutes due to metronidazole being BCS class 1.

Related substances (Tablets, Infusion, Suppositories)

The HPLC Related substances procedure was harmonised with the Ph. Eur., assessed by the Laboratory, and found to be suitable as a compendial method. Members endorsed the method, subject to editorial corrections.

Assay (Tablets, Infusion, Suppositories)

The proposed HPLC Assay procedure was investigated. Concentrations of solutions 1 and 2 were halved to improve peak shape. The procedure was found to be suitable as a compendial method. Members endorsed the method, subject to editorial corrections.

Members discussed the content limit for the Metronidazole Infusion monograph, querying why it was set to 95 – 110%. It was agreed that this should be investigated and amended to 95 – 105%, if possible.

602. TRIMETHOPRIM PREPARATIONS (REVISED) AIM(24)19
Trimethoprim Tablets
Trimethoprim Oral Suspension

Dissolution (Tablets, Oral Suspension)

A dissolution procedure based on the USP monograph for Tablets was investigated by the Laboratory. All samples complied with the draft monograph criteria at level S1, and the amount of metronidazole released after the final stage was not less than 75% (Q) of the stated amount. The method was found to be suitable as a compendial method. Members endorsed the method for public consultation, subject to editorial corrections.

For the Oral Suspension monograph, the chromatographic conditions from the draft Trimethoprim Tablets monograph were used. The mobile phase composition was modified to improve peak separation (allowable adjustment as per BP appendix III). The procedure was found to be suitable as a compendial method. The Laboratory also investigated whether the sampling time could be reduced. It was found that 15 minutes time interval would be suitable to be incorporated into the monograph.

Members noted that the procedure evaluates a volume equivalent to 18 mg of Trimethoprim, rather than a volume equivalent to a single dose (100 mg). It was agreed that the Laboratory will repeat the dissolution procedure using a single dose. Members endorsed the method, subject to the results of the laboratory investigation and minor corrections.

Related substances (Tablets, Oral Suspension)

The draft method met the acceptance criteria and the samples tested met the proposed limits, for the Tablets monograph. The related substances test in the draft Trimethoprim Tablets monograph was found to be suitable for use as a compendial method.

The HPLC Related substances method was investigated but was found to be unsuitable due to co-elution of trimethoprim and an excipient peak, for the Oral Suspension monograph. The related substances method from the draft Trimethoprim Tablets monograph was used instead.

The mobile phase composition was modified to improve peak separation between the trimethoprim peak and an excipient peak in the test solutions (allowable adjustment as per BP appendix III). The draft monograph method met the acceptance criteria and the samples tested met the proposed limits. The related substances test in the draft Trimethoprim Oral Suspension monograph, using the chromatographic conditions from the related substances test in the draft Trimethoprim Tablets monograph with a modified mobile phase composition, was found to be suitable as a compendial method.

Members asked that the relative retentions times were included, if possible. The procedures were endorsed for the Tablets and Oral Suspension monographs, subject to minor corrections.

Assay (Tablets)

The HPLC assay method from the draft Trimethoprim Tablets monograph was investigated. The concentration of the solutions was reduced from 0.4% w/v to 0.002% w/v to improve peak shape. The draft monograph method met the acceptance criteria. The assay test in the draft Trimethoprim Tablets monograph was found to be suitable for use as a compendial method, with modifications.

Members endorsed the procedure for public consultation.

603. MOXIDECTIN PREPARATIONS (REVISED) AIM(24)20
Moxidectin Injection
Moxidectin Oral Solution
Moxidectin Oromucosal Gel

Related Substances

Moxidectin preparations were revised in BP 2018 to include Related Substances tests, based on methods supplied by an MAH. The Secretariat received a query from an MAH indicating that several impurity limits in the Moxidectin BP Injection monograph were stricter than those in the Ph. Eur drug substance monograph. This issue also affected the Oral Solution and Oromucosal Gel monographs. The secondary peak limit of 1% in the BP was tighter than the limits for impurities D, A, C, G, E, and F in the Moxidectin API monograph.

The Secretariat explained that this was potentially an oversight when writing the monograph which was based on an email from the MAH in 2016 which proposed that all impurities should be controlled via the Ph. Eur monograph for Moxidectin and not the BP finished product monographs. Members agreed that the impurity limits in the product monographs should not be tighter than the limits in the API. Members endorsed that the impurity limits in the Ph. Eur monographs, be added to the BP product monographs.

A member explained that the MAH was the innovator MAH and due to the age of their products, they did not have any degradation impurities listed in their finished product specifications. However, newer products from different MAHs control impurities to the EP limits and have additional limits for the 23-keto-FA impurity and Impurity L, both of which are controlled at NMT 1.5%, based on a toxicological assessment. These two

impurities were not controlled in the EP monograph. Members agreed that Impurity L and 23-keto-FA should both be specified at NMT 1.5% in the BP product monographs.

Members questioned whether the BP gradient method was intended to bridge together the two Ph. Eur isocratic methods and whether it could identify all listed impurities. The Secretariat noted that as no BP laboratory work had been completed to date, it was difficult to confirm whether all impurities could be identified by the BP method. Members agreed that it would be sensible to conduct laboratory work to confirm what impurities the BP method could identify, with particular focus on Impurity L and 23-keto-FA. It was questioned whether reference standards were required for these impurities or whether their RRTs were distinctive enough. The Secretariat agreed to investigate this further.

One member questioned whether specifications were the same for different strengths of the injections. It was noted that there are 1%, 2%, and 10% injections as well as non-aqueous injections, which could have a different degradation profile, but did not have any data on these injections. It was noted that they may not have a degradation profile due to the age of the products, but the Secretariat agreed to contact the MAH for more information.

Content

A member questioned why the content limits in the BP products were 90 to 110% when the pioneer MAH had assay limits of 95 to 110% in their specifications. It was noted that in the email from the MAH, they had indicated that the product was stable, but a content limit of 110% was claimed as a stability overage in some products. Members questioned whether the BP content limits were appropriate and suggested they may need review. One member also questioned how MAHs had seen elevated levels of Impurity L when the MAH had claimed the substance to be stable. Members explained that the active substance was often refrigerated but sometimes it was stored at room temperature, affecting the stability. It was suggested the substance might not be as stable as claimed by the MAH. The Secretariat and a member would review the data of authorised specifications and investigate this further.

604. EPIRUBICIN INJECTION (REVISED) AIM(20)21

A request was received from an MAH to revise the Epirubicin Injection Assay and Related Substances methods. They requested changes to the HPLC column, diluent/mobile phase, and the Impurity limits. The Epirubicin injection monograph had first been published in BP2013 and used the Ph. Eur Related Substances method. It had not been revised since.

Assay and Related Substances

The Assay and Related Substances methods both instructed to “Use a stainless-steel column (25 cm × 4.6 mm) packed with trimethylsilyl silica gel for chromatography (6 µm) (Zorbax TMS is suitable)”. However, the user expressed that this column was not available on the market, which the Secretariat had confirmed with the column manufacturer. The Ph. Eur Epirubicin Hydrochloride monograph used the same column but with a 5 µm particle size, which was readily available on the market. The Ph. Eur Epirubicin Hydrochloride monograph was revised in 2021 from a 6 µm to a 5 µm column. However, the BP injection monograph had not made this update. EDQM CRS reports showed that a 5 µm column had always been used in place of the 6 µm column, even before the monograph was updated. Members agreed that the column could be changed to a 5 µm particle size, without the need for laboratory work.

The user also reported issues with precipitation during sample preparation, which they claimed was due to sodium dodecyl sulfate in the diluent and the presence of sodium chloride in the formulation. The BP had received similar queries reporting precipitation issues. The MAH found that removing SDS from the diluent solved their precipitation issue. The user referenced the USP monograph, which used the same method but did not use SDS in the diluent. Members agreed that as this is consistent with the USP method, SDS could be removed from the diluent.

The user requested a revision to the Impurity limits, specifically Impurity F (Epidaunorubicin) and Impurity G (Epirubicin dimer). These were controlled by the "any other secondary peaks" limit of 0.5%. The user referenced the USP method which specifies that these impurities were not controlled individually but were in included in the total impurities limit (3.9%). The user did not provide any data or justification for a revision to the impurity limits, other than them being different to the USP limits. The secretariat requested that supporting data is required if a change to the limits was to be investigated. Members agreed that no further action was required.

Identification

One member proposed changing the identification test from light absorption and retention time, to an HPLC UV-DAD test. However, it was pointed out that this would necessitate additional laboratory work. Since the group had previously decided that such work was unnecessary for the column and diluent changes, it was deemed not appropriate to increase the laboratory's workload at this time. The secretariat agreed to document the suggestion and would consider updating the test if future laboratory work became necessary.

605. TACROLIMUS PREPARATIONS (NEW) AIM(24)22
Tacrolimus Capsules
Tacrolimus Granules for Oral Suspension
Tacrolimus Prolonged Release Capsules
Tacrolimus Prolonged Release Tablets
Tacrolimus Sterile Concentrate
Tacrolimus Ointment

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

606. FLUCONAZOLE CAPSULES (REVISED) AIM(24)23

Dissolution

A query suggested that the concentrations of solutions in the current Dissolution test for Fluconazole Capsules resulted in low absorption (0.12 at 261 nm), which was outside of the querier's usual range of 0.2 – 0.8. This was also outside of the BP Laboratory's internal range limit of 0.3 to 1.5 A, as defined in their SOP.

To investigate, the BP Laboratory ran the UV spectrum of Fluconazole BPCRS at two concentrations (0.0056% w/v – the currently used concentration, and 0.011% w/v) and found comparable results to the querier. The higher concentration resulted in 0.24 A, still below the Laboratory's internal SOP limits, but an improvement to the current result.

During the monograph's development, the concentration of solutions in this test was lowered to accommodate the lowest product strength on the UK market (50 mg). It was noted that the donor method differentiated between lower (50 and 100 mg) and higher (150 and 200 mg) strength capsules, where the lower strengths were dissolved in 500 ml of media, and higher strengths in 900 ml.

It was proposed that the Dissolution test be divided into two separate procedures based on the capsule's strength. Based on the Laboratory's initial findings, the concentration of solutions in the lower strength procedure (0.01% w/v) should result in ~0.24 A. While this was still below the BP Laboratory's procedure, an increase in absorbance was favourable.

Members suggested that an HPLC procedure could be used. It was agreed that the Secretariat would request 50 mg samples from the querier and run the dissolution procedure at 500 ml and 900 ml.

607. Out of Stock BPCRS report **AIM(24)24**

There were no out of stock BPCRS reported.

608. AIM WORK PROGRAMME **AIM(24)25**

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.

Prioritised Monographs

The prioritised monographs identified in 2021 were continuing to be worked on. An additional list of further priorities had been devised in January 2024. These had been added to the Work Programme. Metronidazole, Marbofloxacin, and Trimethoprim, had been discussed at this meeting, and were expected to be published in BP 2026. Tacrolimus, which also had a high priority rating, was planned for the BP2027 publication.

Laboratory Work Plan

The Laboratory work programme was discussed. Erythromycin Stearate Tablets was currently being investigated by the laboratory. Laboratory requisitions for Tacrolimus, Moxidectin, Clarithromycin, Fluconazole Capsules, Rifampicin, Rifaximin, Ciclosporin and Clotrimazole, were planned to go to the Laboratory in November 2024.

609. BRITISH PHARMACOPOEIA MATTERS **AIM(24)26**

The BP 2025 Publication became available on time and in full as planned on 1st August. It will be legally effective on 1st January 2025. A Continuous Improvement (CI) plan had been implemented for work on the website and would continue to evolve throughout 2025 and 2026. Features that had already been implemented included live webchat, a feedback button on every page and a personalised dashboard for all users.

V EUROPEAN PHARMACOPOEIA **AIM(24)27**

Group of Experts 7

A verbal update on the actions from the 175th meeting, which took place in April 2024, was provided. A written report would be provided at a later date. Comments were received for the 35.4 Pharmeuropa consultation.

Pharmeuropa
Comments on the updates to consultation 36.3, had been made.

VI ANY OTHER BUSINESS

Antimicrobial Resistance
An update on the work the MHRA were undertaking for Antimicrobial resistance (AMR) measures was provided. The Secretariat confirmed that in September 2023, a cross-agency group had been set up to work on this and were in consultation with the National Action Plan group on AMR.

VII NEXT MEETING

The date of the next meeting was proposed as 15th April 2025, to avoid clashes with the British Pharmacopoeia Commission meeting. This would be confirmed via invite.