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,15th April 2025.

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, Mr V Jaitely and Mr F Ali.

Apologies: N/A

In attendance: Ms S Bowles, Mr K Rakowski, Mr O Waddington, Ms B Bahsoun and Mr S Greatorex.

613. INTRODUCTORY REMARKS

Welcome The Chair welcomed members to the meeting as well as Mr Sam Greatorex from the BP Laboratory. A welcome was extended to Ms B Bahsoun, who joined a new member of the Anti-infective Medicines Secretariat.

614. GENERAL MATTERS **AIM(25) 01**

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(25) 02**

615. The minutes of the meeting held on 11th September 2024 were confirmed.

II MATTERS ARISING FROM THE MINUTES **AIM(25) 03**

616. The following matters arising from the meeting held on 11th September 2024 were noted.

Marbofloxacin Preparations (minute 200 refers)
The Marbofloxacin preparation draft monographs were updated with revised veterinary limits as discussed at the previous meeting. However, upon review

alternative limits were suggested in line with VMD and product specifications. The newly updated monograph would be circulated for public consultation, aiming to be published in BP2027.

Metronidazole Preparations (minute 601 refers)
The draft monographs were updated with the tightened Dissolution and Content limits, as per the September 2024 discussion. They were published for public consultation in January 2024 and are to be published in BP2026.

Trimethoprim Preparations (minute 602 refers)
Relative retention times were added to the Related Substances test, as per the September 2024 discussion and the draft monographs published for public consultation. They are to be published in BP2026.

Moxidectin Preparations (minute 603 refers)
The Veterinary expert provided the details of approved specifications as discussed in September 2024 and laboratory work was scheduled with the updated limits. The Secretariat would report results at a future meeting.

Epirubicin Injection (minute 604 refers)
Changes to the column size and removal of SDS were updated on the draft monograph as discussed at the September 2024 meeting. The monograph will be published in BP2026.

III MONOGRAPHS FOR THE BP 2026+

617. Flucloxacillin Oral Solution (Revised) AIM(25) 04

Since the March 2024 EAG AIM meeting, the Flucloxacillin Oral Solution monograph had been revised with a new related substances test and published in the BP 2025. In December 2024, the Secretariat received communications from one of the MAHs querying the Related substances limits; the MAH's products were not able to meet the outlined limits.

A letter of intent was prepared and uploaded to the website to guide BP users to use their registered specification limits for the related substances test. The Secretariat drafted a new set of limits for the related substances test based on the available licensed data and data provided by the querying MAH. A monograph with the proposed limits was drafted, approved by the Chair and Vice Chair of EAG AIM, and shared with all licensed MAHs, asking for feedback. No feedback was received after 3 months.

Members were presented with the newly drafted limits, which were subsequently endorsed for the upcoming BP 2026 publication.

IV MONOGRAPHS FOR THE BP 2027+

618. Erythromycin Stearate Tablets (Revised) AIM(25) 05

Erythromycin Stearate tablets were discussed at the April 2024 meeting, in response to queries regarding the Related Substances and the Dissolution test. The BP Laboratory investigated both methods.

Dissolution
The Secretariat received a query from a user claiming that they used methanol instead of dissolution media to prepare the standard, as it resulted in around a 10-12% higher dissolution rate. The laboratory investigated the current BP method using both dissolution media and methanol to prepare the standard. The results were consistent with the MAH; showing an average increase of 11.5% for the methanol standard compared to the dissolution media standard. Members discussed the findings. However, there was no conclusion on how this had occurred or how to explain the higher dissolution results when using methanol to prepare the standard.

The laboratory investigated an alternative method using the HPLC conditions from the dissolution test for Erythromycin Gastro-resistant Tablets. However, results were lower than those obtained by UV-vis. Members agreed this could cause compliance issues, making the HPLC method unsuitable.

One member proposed that the discrepancy in results could be related to the differences in labelling between Erythromycin and Erythromycin Stearate. However, members agreed that additional investigations were not the best use of the laboratories limited resources. Members agreed that there should be no change to the current method at this time.

Related Substances
An MAH reported that their finished product failed to meet the specification limit for impurity S using the BP method but would pass using the Ph. Eur. drug substance method. They suspected that differences in the methods, such as diluent composition and impurity level calculations, may have contributed to elevated impurity levels when using the BP method. The laboratory investigated both methods to determine if these results could be replicated.

The identity of impurity S was determined not to be stearic acid by comparison with injections of stearic acid and sodium stearate solutions.

The laboratory confirmed that the BP method gave a higher result for impurity S than the Ph. Eur. method. Members noted that the BP diluent could be giving a more valid result than the Ph. Eur as it dissolves the impurities more effectively. Members agreed that the diluent should not be changed at this time.

619. Bleomycin for Injection AIM(25) 06

Bleomycin was updated in 2024 due to BPCRS changes. Upon review it was noted that other parts of the monograph could be updated. The Secretariat drafted proposed changes based on the current style guide.

Members agreed the title of the monograph should be Bleomycin Powder for Injection and that the title of the monograph and the definition, should match.

The Secretariat had suggested that the loss on drying (LOD) test could be removed in line with BP style. However, the members agreed that as Bleomycin was a

lyophilised powder and water was used in the last stages of manufacture, there could be an impact on stability. The LOD test would be retained with a limit reflecting the API monograph.

For identification, the published monograph had three tests included. The Secretariat had drafted the monograph with the IR and the sulfates test, as IR was the preferred option of the Secretariat. Members commented that there was no infrared sample preparation drafted and that this was acceptable for products without excipients, but that one MAH had excipients added. Members agreed that the BP should match the European Pharmacopoeia and that the Identification tests should be the Composition test and the sulfates test.

The Secretariat had drafted the monograph without the Acidity test, in line with BP style. Members agreed this should be kept as pH can affect the stability, and one MAH had declared sodium hydroxide as an excipient, which would indicate a pH adjustment was required. Members agreed to keep the test, as it was in all MAH specifications.

The Secretariat had drafted that the colour and clarity test remained. Members agreed that due to the lack of a Related Substances test, and the colour and clarity test providing an indication of stability, it should remain.

For the related substances test, the members agreed that the test should reflect the European Pharmacopoeia.

The members approved the Bleomycin monograph for public consultation, with the above changes made.

620. Voriconazole Preparations (new) **AIM(25) 07**
Voriconazole Tablets
Voriconazole for Infusion

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

621 Entecavir Tablets (New) **AIM(20) 08**

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

622. Phenoxymethylpenicillin Oral Solution (Revised) **AIM(20) 09**

A request was received from an MAH to widen impurity limits in the Phenoxymethylpenicillin Oral Solution Related Substances test, which was discussed at the September 2023 meeting. Members agreed that further batch data and justification for their proposal was required. The MAH had provided additional data to support their proposal.

Related Substances
The MAH results were discussed at length. The Secretariat proposed that the higher impurity levels experienced by the MAH could be related to the more acidic nature of their product. The MAH had a lower pH specification compared to other licensed MAHs, suggesting their product is more acidic. Members agreed that the MAH should investigate their results further and that no changes should be made to the monograph at this time.

623. Tylosin Injection (Vet) (Revised) AIM(20) 10

A Tylosin Injection monograph revision was published in BP2023. The updates to the 2023 publication were technical changes described as the following:

- Composition test updated to mirror Ph. Eur. and harmonise with related substances.
- Related substances - Included due to test being added to Ph. Eur.
- Assay - Updated fiducial limits based on MAH specifications.

Post publication, the BP received queries from customers about the related substances test, highlighting that there was a limit for Impurity D and Impurity B, however there were no recorded relative retention times (RRT) for either. The monograph stated an RRT for Tylosin D at 0.78. However, this is not Impurity D. All MAHs recorded an unknown impurity in their product specifications, and when using an HPLC method, this produced an RRT of about 0.78.

Members indicated that Tylosin's A, B, C and D and the associated impurities found upon analysis should be clearly defined in the monograph to assist the user.

Members agreed to proceed with laboratory work to establish whether the unknown impurity could be identified and provide an RRT. The monograph would be updated in a future publication.

624. PIPERACILLIN AND TAZOBACTAM FOR INFUSION (NEW) AIM(25) 11

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

625. TACROLIMUS PREPARATIONS (New) AIM(25) 12

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

626. OXYTETRACYCLINE CALCIUM (Revision) AIM(25) 13

The Secretariat received a request for a limit change for the Oxytetracycline Calcium monograph, in June 2024. The request was to reduce the calcium content. The manufacturing authorisation holder (MAH), then further requested to change the overall content. A further request was then made by the MAH to further increase the range of limit of the calcium content to 3.5 – 4.5%. The limit of 3.9 – 4.3% for calcium content had been the same prior to 2014.

The MAH had provided several reports to support their request, including statistical analysis of their results since 2022. This showed variation in their results for calcium content and the overall content of oxytetracycline calcium. Despite their efforts, no conclusion was reached regarding the cause of the variability in the results, or why they had started to fail specification since 2022. There was no evidence in the reports as to why the levels of content and calcium content were falling, or if they had undertaken corrective or preventative actions to mitigate the problem.

Members discussed the provided reports at length. The discussion focused on the impact of changing the limits and whether there was enough justification to do so.

Members discussed that the content level had been changed in 2022 from 90.0 - 100.5% to 94.5 - 102.0% to aligned with the Ph. Eur monograph content limits for Oxytetracycline dihydrate. The MAH was experiencing inconsistencies in results for the content level and were on the edge of failure for several batches since the limit had been changed. The MAH requested to revert to the content limits that were in place previously. They reasoned that there should be no consequential impact on efficacy or quality from reverting to the previous limits. The MAH had not been specifically consulted about the change in limits for the 2022 monograph revision.

Members discussed that most of the calcium assays in the BP are water soluble and there is a digestion step required when the product is insoluble in water. Potentially this leads to a higher inherent variability in the sample preparation. Variability in results could also occur because the colour change for the end point of the titration might be relatively subtle; e.g. different shades of blue.

Members felt there was nothing in the reports to show an evaluation of the assay or show where it may not be working or may be providing spurious results. A suggestion was made to test the batches using the United States Pharmacopoeia (USP) assay, which has the same limits, but uses a different technique, for comparison.

Members discussed the production process flow outline provided by the manufacturer and noted that the data provided indicated that the manufacturing process was not in a state of control. Members discussed whether monocalcium oxytetracycline might be partially formed in the manufacturing process, but the manufacturer and MAH had not provided details of their investigations to try to find a root cause for the variable results.

Members agreed there was not enough information on the root cause of the variation in results, and more investigation was required by the MAH. Consequently, members did not support the request to revise the specification.

627. Out of Stock BPCRS report **AIM(25)14**

There were no out of stock BPCRS reported.

628. AIM WORK PROGRAMME **AIM(25)15**

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.

629. BRITISH PHARMACOPOEIA MATTERS AIM(25)16

The Secretariat explained about the plans to change the prices and package format of the BP2026 publication.

The Secretariat presented the plans for the continuous improvement of the website; including:

- implementing two factor authentication for licence managers
- improving the search function of the website
- looking into 'bot' hunting throughout the site.

The Secretariat presented the changes to the BP Team.

630. Sustainability

The Secretariat provided a paper on the advances the BP team were making in using sustainable methods throughout the monographs.

V EUROPEAN PHARMACOPOEIA AIM(25)17

Group of Experts 7
A verbal update on the actions from the 176th and 177th meetings, which took place in October 2024 and March 2025, respectively, was provided.

Pharmeuropa
The Secretariat thanked members for their contributions to the Pharmeuropa 36.4 and Pharmeuropa 37.1 review.

VI ANY OTHER BUSINESS

The Secretariat informed the group that the wavelength for the Doxycycline Capsules dissolution method had been changed from 276nm to 345nm for the BP2026. This was following a query which found that the monograph stated "at the maximum at 276 nm" despite 276nm not being the maximum. The monograph was incorrectly harmonised with the Doxycycline Tablets monograph which used a different dissolution medium and therefore had a different maximum. The laboratory had tested 345nm which was also used in the donor MAH method.

VII NEXT MEETING

The date of the next meeting was proposed as the end of September 2025/ beginning of October 2025. This would be confirmed via invite.