BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group MC1: Medicinal Chemicals

SUMMARY MINUTES

A meeting of Expert Advisory Group (EAG): Medicinal Chemicals 1 (MC1) was held in person, with some experts attending remotely on Wednesday 10 July 2024.

Present: Dr P Marshall *(Chair),* Dr E Bush (*Vice-Chair*), Dr Varada Bapat, Dr J C Berridge, Mr S Boland, Professor D Cairns, Mr D Malpas, Mr S Nolan, Dr G Lee (Population Health, MHRA) and Dr F Pina (Population Health, MHRA).

In attendance: Mr M Whaley, Dr M Dmitriieva, Dr C Swann, Mr S Greatorex (BP Lab), Mrs Yasmine El Dabh (BP Lab), Mr D Crowe (BP Lab).

Apologies: Mr P Fleming, Mr A J Caws, Dr J Lough.

Mr D Crowe attended part of the meeting.

745 INTRODUCTORY REMARKS

Welcome Dr Marshall welcomed all those present to the meeting and gave the attendees the opportunity to give a brief introduction of their background and experience.

Expense Claims Members were asked to note that expenses claims should be submitted electronically to committeeservicesteam@mhra.gov.uk.

Confidentiality Members were reminded that all papers and minutes were confidential and should not be disclosed outside the BP Commission.

Declaration of Interests Members were thanked for providing their interests prior to the meeting. Committee Services also reminded members that holding shares in companies in the pharmaceutical industry is an interest that should be declared.

Dr Bapat, Dr Bush, Mr Caws and Dr Lough declared interests in one or more agenda items and appropriate action was taken.

MINUTES OF THE PREVIOUS MEETING **MC1(24)17**

746 The minutes and summary minutes of the meeting held on 31st January 2024 were confirmed subject to the Secretariat correcting the title of Summary Minutes to include the word “summary”.

MATTERS ARISING **MC1(24)18**

747 Matters arising and correspondence items from the meeting held on the 31st of January 2024 were noted. Members agreed that whilst discussing the BPs sustainability initiative that the BP Secretariat should circulate the details of the BP Webinar which would include a presentation on sustainability. Members had no additional comments.

REPORTS AND CORRESPONDENCE

748 BP Update **MC1(24)19**

Members were provided with an update on recent BP activities including the appointment of new members of the BP Commission, the pre-election guidance, an update on the BP website and some temporary staff changes.

749 Cetirizine Oral Solution **MC1(24)20**

The Secretariat had received a query from within the MHRA about the published shelf-life pH limit of 4.0 to 5.0. The query highlighted discrepancies between the registered pH limits of already approved, products and the current BP monograph limits of 4.5 to 5.5.

The Chair concluded the groups discussions and asked the Secretariat to investigate revising the BP related substances method to detect the ester impurities and if possible, make proposals for appropriate limits. The pH limits could then be widened or revised based on the updated impurity detection capabilities of the Related substances method.

Experts also requested that whilst the Related substances test was being considered as a means of limiting ester impurities the BP Secretariat should investigate and check if the current disregard limit was appropriate

750 Leflunomide Tablets **MC1(24)21**

Members were informed about two potential issues with the published Leflunomide Tablets monograph. An observation from a BP user had led to the BP Secretariat highlighting a need for potential amendments to the Leflunomide Tablets monograph.

Experts discussed and agreed with the proposal from the Secretariat that the limit section of the related substances test should be revised to read “The area of any other secondary peak is not greater than the area of the principal peak in the chromatogram obtained with Solution (5) (0.2%)”.

Members discussed whether to revise the total impurities limit to exclude Impurity B from the total impurities limit. After consideration, Experts agreed these were now established pharmacopoeial limits and consensus was reached to not revise the impurity specification limits.

751 Mycophenolate Mofetil Tablets and Capsules **MC1(24)22**

The BP Secretariat had received correspondence from a user of the BP who had highlighted difficulty, when using the Mycophenolate Mofetil Tablets monograph. The user was unable to achieve the expected resolution requirement, between the peaks due to the drug substance and Impurity C, which is used as the system suitability test in the Related substances test.

The Secretariat reported that there appeared to be an error in the published monograph which was likely to be the cause of the user’s difficulty. The buffer used in the mobile phase of both the Related substances and the Assay tests in the monograph contained an error resulting in the concentrations of both the triethylamine and orthophosphoric acid portions of the buffer being ten times less concentrated than the validated method the monograph was based upon.

In contrast to the published monograph, the example chromatogram published on the pharmacopoeia.com website, which was prepared by the BP Laboratory and reflected practical assessment carried out, included the correct preparation of the mobile phase.

The Experts considered the data presented and agreed that the monographs for Mycophenolate Mofetil Tablets and Mycophenolate Mofetil Capsules should be corrected so the mobile phase in both the Related substances and Assay tests should read:

200 volumes of a solution containing 0.5% v/v of orthophosphoric acid and 1.0% v/v of triethylamine in water, adjusted to pH 5.4 with orthophosphoric acid or 1M potassium hydroxide, 350 volumes of acetonitrile and 450 volumes of water.

There was only one UK MAH licensed formulation upon which the Dissolution test was based; the user who sent the request for revision was not a UK MAH. No further complaints had been received from other users.

Members agreed that no action was needed, and the Dissolution test would not be revised.

752 Warfarin Tablets **MC1(24)23**

The BP Secretariat had received a query from a user of the BP who had experienced difficulties achieving the appropriate separation in the recently revised BP 2024 monograph. The user experienced poor separation between Impurity A and the drug substance peak although the system suitability test of resolution between Impurity B and C could be met with a large margin.

It was agreed the current procedure should be investigated in the laboratory to improve it as soon as possible.

NEW MONOGRAPHS

753 Lercanidipine Tablets **MC1(24)24**

The draft new monograph would be included in a future BP publication, subject to laboratory evaluation and stakeholder comment.

NEW MONOGRAPHS IN PROGRESS

754 Trazodone Preparations: **MC1(24)25**

Trazodone Capsules (Revision)
Trazodone Oral Solution (New)
Trazodone Tablets (Revision)
The draft new monograph for Trazodone Oral Solution would be included in a future BP publication, subject to laboratory evaluation and stakeholder comment.

The Action and Use statements in the monographs for Trazodone Capsules and Trazodone Tablets would be considered for revision after the BP Secretariat sought further advice on the suitability of the current statement.

The Experts agreed to revisions to the Related substances tests in the monographs for Trazodone Capsules and Trazodone Tablets.

It was noted by the Experts that the Identification test of the Trazodone Tablets monograph included instruction to remove the film coating. Experts asked the BP Secretariat to seek more information about whether this detail was necessary.

The Secretariat were asked to consider the feasibility of including extra impurities (Impurities A and H) in the existing Trazodone Hydrochloride Impurity Standard BPCRS.

All proposed revisions to the monographs for Trazodone Capsules and Trazodone Tablets would be subject to public consultation.

REVISION OF MONOGRAPHS

755 Chlorphenamine Preparations: MC1(24)26
Chlorphenamine Injection
Chlorphenamine Oral Solution
Chlorphenamine Tablets

The three monographs were being revised by the Group.

It was highlighted to the Group that the three monographs had not been revised since before 2014 and all three monographs used chloroform in an ID and/or TLC Related substances tests. Both the Tablets and Injection monographs used non-specific Assay UV tests whilst the Oral Solution monograph used a GC Assay with chloroform. Additionally, the Tablets monograph did not have a Dissolution test.

Content There were different content specifications for UK licensed products. The Secretariat explained to the Experts that this discrepancy may have been because of the previously used UV specific absorption value for the assay procedure.

The Group agreed that a harmonised draft limit should be included in the draft monographs.

Identification The Identification method which used chloroform had been replaced by a draft method using the retention time and UV spectrum to confirm identity. The experts agreed that if an IR was not feasible the laboratory could be asked to evaluate the suitability of the retention time and UV DAD method as the ID method.

Dissolution An isocratic HPLC-UV dissolution test had been drafted based on a validated method. The laboratory would be asked to evaluate the use of paddle method, the suitability of the methods and the draft limits.

Related substances – The Secretariat had proposed that the TLC related substances tests using chloroform in the three monographs was replaced.

Experts discussed the draft monographs and requested that updated draft monographs were circulated for the group to reflect the BP Secretariat's latest proposals. The Experts would review the revised drafts prior to laboratory work being planned. It was requested by the experts that, as per the Ph. Eur. monograph, any peaks due to Maleic Acid should be disregarded.

Assay - The experts discussed the proposals to revise the Assay tests in the monographs and requested that it should be assessed whether a new HPLC Assay method could be used in all three monographs. The Secretariat agreed to provide updated draft monographs and circulate for the group to review prior to laboratory work being planned.

756 Esomeprazole and Omeprazole for Injection MC1(24)27

Experts were asked to consider both a correction to the mobile phase in the two monographs and a request for the amendment to the limit for the test for Alkalinity in the monograph for Omeprazole for Injection.

Assay: Esomeprazole for Injection and Omeprazole for Injection The BP Secretariat had received correspondence from users of the BP 2024 monographs for Esomeprazole for Injection and Omeprazole for Injection who had highlighted an issue with the preparation of the mobile phase. The Experts agreed with the proposal to change the mobile phase section of the Assay, and the Secretariat would prepare letters of intent to revise these monographs which would be published on the website until the corrections to the monographs were published and effective. This correction would be targeted for the earliest possible publication, BP2026.

Omeprazole for Injection – Alkalinity (Request for Revision) The BP Secretariat had received a request for the revision of the BP2024 monograph which contained a test for Alkalinity with a limit of 9.0 to 11.0%. A manufacturer submitted a request for the revision of the limits and provided their justification for the revision and some batch data.

The Experts reviewed the information available, and it was agreed that there was insufficient justification and data to suggest that current limit was not achievable. The Secretariat would contact the user to inform them of the EAG's decision.

757 Esomeprazole Gastro-resistant Granules MC1(24)28

Members of the EAG were reminded that at the previous meeting the EAG considered correspondence from a manufacturer who had requested changes to the Dissolution, Related substances and Assay tests.

At the January 2024 meeting, Experts had agreed to the harmonisation of the dissolution sample and reference standard concentrations.

Related substances - Mobile Phase Composition
The Experts agreed that the mobile phase section should be corrected and that both mobile phase A and mobile phase B should be prepared using the same buffer component. The Secretariat would prepare a letter of intent to inform BP users of the error and revise this monograph at the earliest opportunity.

Use of Solution A as a diluent Following the request for revision, the Experts considered two courses of action to address the request for revision, which were (a) revising the method of preparation to harmonize with the USP solution, as per customers request and (b) Taking no action and keeping solution A as published, harmonized with the other Esomeprazole preparation monographs, based on its demonstrated suitability in the laboratory work performed on Gastro Resistant Capsules and Tablets formulation.

Experts agreed to keep the existing BP diluent as this had been demonstrated to be suitable in the practical work performed in support of the Gastro Resistant Capsules and Tablets monograph.

758 *EUROPEAN PHARMACOPOEIA* **MC1(24)29**

The Secretariat gave an update on the activities of the European Pharmacopeia and highlighted that the UK Delegation had, since the previous meeting of MC1, attended the 178th and 179th sessions of the European Pharmacopoeia Commission.

Experts were presented with a list of Ph Eur draft monographs that were published in Pharmeuropa 36.3.

ANY OTHER BUSINESS

759 Work Programme **MC1(24)30**

The Secretariat provided a verbal update on the work programme, highlighting new and revised monographs that had been published in BP2025 and noting the monographs that were targeted for BP2026, BP2027 and beyond.

The Secretariat agreed to circulate a paper detailing the work programme following the meeting.

760 BPCRS Update **MC1(24)31**

The Secretariat provided an update on the BPCRS reports since the last meeting. There were no out-of-stock BPCRSs for any active MC1 monographs, but the BP Laboratory were looking for replacement candidate material to support the Etodolac Capsules monograph.

NEXT MEETING **MC1(24)32**

The next meeting was planned to be held by teleconference in January 2025.