BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group MC1: Medicinal Chemicals

SUMMARY MINUTES

A meeting of Expert Advisory Group (EAG): Medicinal Chemicals 1 (MC1) was held via videoconference on Wednesday 14th July 2021.

Present: Professor A G Davidson *(Chair),* Professor D Cairns *(Vice-Chair),* Dr H Batchelor, Dr J C Berridge, Dr E Bush, Mr A J Caws, Mr D Deutsch, Dr E Gray, Mr P Fleming, Dr J Lough, and Mr D Malpas.

In attendance: Ms H Corns, Mr L Elanganathan, Mr R Smith, Mr D Darling (Senior Pharmaceutical Assessor for item 643), Ms K Busuttil (BP Lab) and Ms M Nanasi (BP Lab).

Apologies: Dr P Marshall and Dr S Bale.

Dr Bush, Mr Caws, Mr Fleming, and Dr Lough declared an interest in or more agenda items and appropriate action was taken.

INTRODUCTORY REMARKS

636 **Welcome** The Chair welcomed members, Mr D Darling, Ms K Busuttil and Ms M Nanasi to the meeting.

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. Members were reminded to inform the Secretariat of any changes to their interests throughout the year.

637 **BP Update**

Members were provided with an update on recent BP activities and personnel changes.

638 **MINUTES**

The minutes and summary minutes of the meeting held on 19 January 2021 were confirmed.

639 **Matters Arising from the Minutes**

Matters arising from the 19 January 2021 meeting were noted, and the Secretariat highlighted the following items:

Paracetamol Combinations – Minute 626 refers

The following draft monographs that were previously agreed (minute 600) were amended after discussions with the Chair and Vice Chair of MC1 upon receipt of subsequent laboratory data:

- Paracetamol and Caffeine Tablets
- Paracetamol and Caffeine Soluble Tablets
- Paracetamol, Codeine Phosphate and Caffeine Capsules
- Paracetamol, Codeine Phosphate and Caffeine Tablets

It was agreed that the control of impurity D (theobromine) should be omitted from the monograph due to the fact that inadequate separation was achieved for quantification. In addition, there were no toxicity concerns for this stable synthetic impurity which would not degrade in the product on storage. The proposed harmonised method used in the 'family of Paracetamol combination monographs' (Co-codamol and etc) was a major improvement to the currently published methods. The revised monographs were published in the BP 2022, in the absence of stakeholder comments.

MONOGRAPHS

640 Esomeprazole preparations (New):
Esomeprazole Gastro-Resistant Capsules
Esomeprazole Gastro-Resistant Granules
Esomeprazole Infusion
Esomeprazole Gastro-Resistant Tablets

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

641 Pioglitazone Tablets (New)

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

642 Paracetamol Preparations (Revisions):
Paracetamol Capsules
Paracetamol Tablets
Paracetamol Dispersible Tablets
Paracetamol Effervescent Tablets
Paracetamol Soluble Tablets
Paracetamol Oral Suspension
Paracetamol Suppositories
Paediatric Paracetamol Oral Solution
Paediatric Paracetamol Oral Suspension

Paracetamol Dispersible Tablets The Secretariat had observed that there were no longer any marketed Paracetamol Dispersible Tablets, only one registered Paracetamol orodispersible tablets product. Members agreed that the MAH should be contacted to ascertain whether a revision or a new monograph would be needed.

Identification Members agreed that Identification test A for testing solubility or effervescence in warm water should be removed in the Paracetamol Soluble Tablets/Effervescent Tablets monographs as it was covered in the Tablets general monograph.

Members also agreed that the suitability of a HPLC-UV/DAD method based on the respective revised Assay methods should be investigated where an infrared test was not suitable.

Dissolution (Paracetamol Tablets and Capsules) Members agreed that the suitability of HPLC quantification based on the respective Assay methods should be evaluated for the Paracetamol Tablets and Capsules monographs. Members also agreed that a limit of 75% (Q) in 45 minutes should be included for stakeholder comment.

Related substances A revised Related substances test, harmonised with the recently updated Ph Eur Paracetamol monograph test would be assessed for suitability for adoption in the Paracetamol preparation monographs. It was agreed that limits for impurities J & K should be aligned with the revised paracetamol combination products at 10 ppm & 100 ppm respectively, subject to stakeholder comments.

Assay The Secretariat proposed that the HPLC method that was currently in the published Paracetamol Capsules monograph was evaluated for the other monographs.

643 Phenytoin preparations (Revisions):
Phenytoin Capsules
Phenytoin Oral Suspension
Phenytoin Tablets

Content (Oral Suspension only) The content limit had been tightened to 95.0 – 105.0%, in-line with licensed specifications. Members accepted the change, subject to stakeholder comments.

Identification (Oral Suspension and Tablets only) Laboratory assessment had found that the alternative sample preparation procedures, which removed the use of chloroform from the tests, were suitable. Members accepted the recommendation made by the laboratory and the updated procedures were adopted.

Dissolution The laboratory assessment of the dissolution tests was discussed by members. A suitable test for the Capsules monograph had proved challenging, with a sampling time of 120 minutes required to accommodate licensed products. The rapid release of phenytoin was also a significant issue faced by applicants for new generic products and members agreed that retaining a production statement for dissolution in these monographs was the most appropriate action and requested that this recommendation was referred to EAG: PCN.

644 Sodium Cromoglicate Eye Drops

The Secretariat presented a proposal for revision to ensure that the monograph for this highly used product was fit-for-purpose by replacing the outdated analytical methods.

Identification It was agreed that a HPLC-UV/DAD identification method should replace the light absorption test in the monograph. The colour change test for sodium would be retained.

Related substances The corresponding test in the USP Cromolyn Sodium Ophthalmic Solution monograph would be evaluated for adoption in the BP monograph. Limits for specified and unspecified limits were drafted based on ICH limits, and the total impurities limit in line with the USP monograph.

Assay The HPLC method in the USP monograph was adopted for assay.

Impurities A transparency statement has been added following the inclusion of the new drafted method.

645 Zanamivir Inhalation Powder (New)

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

646 Nevirapine Preparations (New):
Nevirapine Tablets
Nevirapine Prolonged-release Tablets
Nevirapine Oral Suspension

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

647 Mycophenolate Mofetil preparations (Revised):
Mycophenolate Mofetil Capsules
Mycophenolate Mofetil For Infusion
Mycophenolate Mofetil Tablets

Content Trend analyses had been received from an MAH requesting wider content limits. Members agreed with the request to lower the content in the Tablets monograph to 94.0% and were open to the acceptance of wider limits for the Capsules and Infusion monographs, subject to further information.

648 Ketoconazole Preparations (Revised):
Ketoconazole Cream
Ketoconazole Shampoo

The Secretariat presented draft revised monographs following the completion of the agreed laboratory work to resolve issues reported by users.

Identification The laboratory had confirmed that replacing the published TLC methods with HPLC-UV/DAD using the Assay test in each monograph would be suitable, and members agreed the revised test should be adopted.

Related substances (Shampoo only) The laboratory had confirmed that the modifications proposed at a previous meeting (minute 587) successfully resolved the issues encountered by users. The system suitability test has also been revised to reflect the changes. The correction factor of impurity 2 had been amended to 1.5 in line with the

validated method. Members agreed to include the drafted revisions, subject to stakeholder comments.

Related substances and Assay (Cream only) Reports were received that the recommended column in the published monograph was not able to achieve adequate separation between the critical pair (impurity 1 and 2). The laboratory found that a different stationary phase (XBridge BEH) resolved this issue, and a resolution requirement of 1.5 between impurities 2 and 1 was agreed. The correction factor for impurity 2 had been amended to 1.5 in line with the method used in producing the published monograph. Members agreed for the inclusion of the amendments, subject to stakeholder comments.

In addition, the correction factor of impurity 2 had been amended in line with the method used in producing the published monograph. Impurity 1 had been included as a specified impurity, in line with the validated method and specifications.

649 Amlodipine Oral Solution (Revised)

Related substances Impurity D was reported as the main degradant and metabolite of amlodipine. A proposal to revise the limit to 3%had been received and was considered justified by stability data. Subsequent revision of the total impurities limit to 3.5% was also deemed justified based on the fact that a content limit of 95.0% to 105.0% was still maintained. Members agreed subject to confirmation from stakeholders that compliance with the content limit could be achieved.

650 MC1 Work status and updates

An update on the status of the MC1 work programme was presented to members for information.

651 MC1 BPCRS review

An update on the status of MC1 BPCRS was presented to members for information.

652 Pharmeuropa Update

An update on the status of Ph. Eur. monograph development was presented to members for information.