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 and via videoconference on Wednesday 25 January 2023.

Present: Dr P Marshall *(Chair),* Dr J C Berridge *(Acting Vice Chair)*, Professor D Cairns (via videoconference), Mr A J Caws, Dr J Lough, Mr D Malpas, Mr S Nolan (via videoconference), Mr P Fleming and Dr F Pina.

In attendance: Ms G Li-Ship, Mr M Whaley, Ms M Dmitriieva, Mr S Greatorex (BP Lab) and Mr C Thompson (BP Lab).

Apologies: Dr G Lee, Dr Ed Bush (Vice Chair), Prof H Batchelor.

INTRODUCTORY REMARKS

694 **Welcome** The Chair welcomed members of the EAG to the meeting and extended a special welcome to Ms Dmitriieva, who had recently joined the MC1 Secretariat.

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. Members were reminded to inform the Secretariat (Dr Fiona Swanson) of any changes to their interests throughout the year.

Membership of the Group The Chair informed the group that Prof H Batchelor had offered her resignation from MC1 and thanked her for her contribution to the group.

695 **BP Update** **MC1(23)01**

Members were provided with an update on recent BP activities and personnel changes, including a new Government Fast Streamer who will be working on a project to look at ways that the BP can incorporate sustainability into BP operations and products, as well as at how to use the position of the BP to enable the sector to become more sustainable.

696 **MINUTES**

The minutes and summary minutes of the meeting held on 19 July 2022 were confirmed.

697 Matters Arising from the Minutes **MC1(23)02**

Matters arising from the 19 July 2022 meeting were noted, and the Secretariat highlighted 11 monographs had been posted on the BP website for public consultation, October to December 2022. Members had no additional comments.

MONOGRAPHS

698 PARACETAMOL PREPARATIONS: **MC1(23)03**

Paracetamol Capsules
Paracetamol Tablets
Paracetamol Dispersible Tablets
Paracetamol Effervescent Tablets
Paracetamol Soluble Tablets
Paracetamol Suppositories
Paediatric Paracetamol Oral Solution
Paracetamol Oral Suspension
Paediatric Paracetamol Oral Suspension
Paracetamol Oral Solution
Paracetamol Infusion

The reports from the laboratory evaluation were presented together with revisions to methods as appropriate. The Paracetamol Oral Suspension could not be progressed due to a lack of samples received for testing. In addition, no samples for the Paediatric Oral Solution were received and a “mock-up” of this formulation was tested by dilution of the sole Paracetamol Oral Solution sample.

Content (Paediatric Paracetamol Oral Solution) The group agreed to change the draft limit of % w/v (2.28 – 2.52) to the usual limit style of 95.0 – 105.0%.

Identification (Tablets) The non-specific Identification colour test B and melting point Identification test C had been omitted from the draft monograph. The IR identification test remained as a stand-alone test in the draft monograph.

Identification (Dispersible Tablets) The solubility test A, UV test B and TLC test C had been replaced in the draft monograph with an IR identification test, which had been assessed and found to be to be suitable by the laboratory and was approved by the EAG for inclusion in the draft monograph.

Identification (Effervescent Tablets, Soluble Tablets) The Identification tests A for solubility and effervescence in these monographs had been omitted from the draft monograph. An IR identification test had been assessed and found to be unsuitable by the laboratory; however, the alternative HPLC-UV/DAD test was found to be suitable and the EAG approved its inclusion in the draft revised monographs.

Identification (Suppositories, Paediatric Oral Solution) The non-specific colour test had been removed from the Suppositories and Paediatric Oral Solution monographs and replaced with a HPLC-DAD identification test, which was assessed by the laboratory and found to be suitable. The EAG agreed to the inclusion of the new method in the draft monographs.

Identification (Oral Solution)
The HPLC-UV/DAD test from the Assay test had been assessed by the laboratory and was found to be suitable and the EAG approved its inclusion in the draft monograph.

Identification (Infusion)
The draft monograph with an identification test would be included in a future BP publication, subject to comments from manufacturers.

Dissolution (Capsules, Tablets) The HPLC detection method from the Assay test was investigated as a replacement for the current UV method which used UV spectrophotometry. The assessed chromatographic conditions were found to be suitable by the laboratory for inclusion in the dissolution method.

Related substances (All Preparations) A draft HPLC gradient method which had been based on the Ph. Eur. method had been assessed by the laboratory.

It was agreed that the draft limit of 0.25% for “any other secondary peaks” limit would be changed to 0.10% to align with ICH guidelines, subject to stakeholder comments.

Related substances (Paediatric Oral Suspension, Suppositories) The HPLC-UV gradient method with modifications was found to be suitable. An additional wash step was added due to late-eluting excipients.

It was agreed that the reporting limit would be revised from 0.03% to 0.05% in line with ICH.

Related substances (Oral Solution) The HPLC-UV/DAD gradient method, as drafted, was found to be suitable by the laboratory with the inclusion of an additional wash step. The EAG agreed the method could be included in the draft monograph.

Related substances (Infusion)
The draft monograph with a Related substances test would be included in a future BP publication, subject to comments from manufacturers.

Assay (Tablets, Dispersible Tablets, Effervescent Tablets, Soluble Tablets, Suppositories, Paediatric Oral Solution, Paediatric Oral Suspension) The assay method which was based on the current capsules monograph was tested and found to be suitable and the EAG approved its inclusion in the draft monographs.

Assay (Oral Solution) The drafted HPLC-UV/DAD test, based upon the current capsules monograph, was found to be suitable and was adopted.

Assay (Infusion)
The draft monograph with an Assay test would be included in a future BP publication, subject to comments from manufacturers.

Storage (Dispersible Tablets, Capsules, Infusion)

It was noted that storage advice was inconsistent, and that the Secretariat would review storage advice for all formulations and harmonise.

699 DOXAZOSIN PREPARATIONS MC1(23)04

Doxazosin Tablets
Doxazosin Prolonged-release Tablets

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

700 TRAMADOL PREPARATIONS MC1(23)05

Tramadol Soluble Tablets
Tramadol Orodispersible Tablets

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

701 Itraconazole Capsules MC1(23)06

The Itraconazole Capsules monograph had been revised and a Laboratory report which investigated a user-reported unidentified impurity (impurity 1) was presented to the group.

The user who was based in ICH climatic zone IVb had requested a limit for impurity 1 of 0.5% should be included above the current unspecified impurities limit of 0.2%. At a previous meeting the group had agreed to the proposal to draft a limit for impurity 1 of 1%, which it was understood would cover all currently licensed products and a total impurities limit of 1.5%. The draft limits would be subject to confirmation of suitability.

Generation of Reference Chromatogram (Itraconazole Capsules) A sample had been provided for laboratory evaluation and a reference chromatogram had been generated. The resolution between itraconazole and impurity 1 and the correction factor for impurity 1 had been investigated.

The chromatogram from the system suitability solution was found to be suitable as a reference chromatogram for peak identification. The limit of 1% for impurity 1 and a revised limit of 1.5% for the sum of any secondary peaks would be reviewed. If it is acceptable, it was agreed that this revised monograph could be prepared for public consultation by correspondence.

Related substances - Numerical Limits The Secretariat will present a revised draft monograph to the group for comment should additional supporting data be available.

702 Dimercaprol Injection MC1(23)07

A request for the revision of the BP monograph for Dimercaprol Injection had been received from a user of the BP.

The user had noted that Dimercaprol Injection contained 5% w/v Dimercaprol in a “suitable vehicle” and interpreted this to mean that any “suitable vehicle” could be used in the formulation. This meant the defined limits in the current monograph and therefore the refractive index and weight per mL were not required.

Refractive index; Weight per mL The Secretariat noted that this monograph does not have an Identification test and therefore these tests stand in lieu of this. Removal of these tests would leave only a non-specific assay test.

The group agreed that there was insufficient justification for the removal of the tests by the user. It was highlighted the request was not from a manufacturer of the product and that the tests were in line with the sole UK manufacturer.

However, it was noted that the monograph could benefit from being revised in line with current pharmacopoeial requirements.

703 NITROFURANTOIN PREPARATIONS **MC1(23)08**

Nitrofurantoin monograph

The Secretariat presented the EAG with an update on work ongoing in a collaboration with the EDQM to help inform a revision to the drug substance monograph.

704 ASPIRIN PREPARATIONS **MC1(23)09**

Aspirin Dispersible Tablets
Aspirin Gastro-resistant Tablets
Aspirin Tablets
Aspirin monograph

The Secretariat presented the Aspirin monographs, summarizing comments made by correspondence, as there had been no time left to discuss these at the July 2022 meeting.

FOR INFORMATION

705 MC1 Work status and updates **MC1(23)10**

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

706 Ph. Eur. Updates **MC1(23)11**

Two draft Ph. Eur. texts that were published in Pharmeuropa 34.4 which are the responsibility of MC1 to review were presented to the group.

707 Appendix III Chromatographic Separation Techniques 2.2.46 - Update **MC1(23)12**

Appendix III the chapter on Chromatographic Separation Techniques (Ph. Eur. 2.2.46) which had been revised by means of the 11th edition in year update included many important changes.

The group were informed that one change introduced was a change to the sensitivity requirement which proposed to measure the signal-to-noise ratio based on a window of 20 times the peak width at half-height. EDQM had issued a notice that this requirement would not be implemented, and the change would be reverted by means of the Ph. Eur. 11.3 update (to be published in July 2023 and implemented on 1 January 2024).

The revised chapter would be reproduced in the BP at the earliest possible opportunity. BP users were being made aware of the change using a variety of methods including banners and a Notice of Intent on the associated web pages.

708 AOB

The Papaveratum monograph had been suggested for omission since there were no MAHs and morphine was preferred for prescribing by the BNF.