BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group MC1: Medicinal Chemicals

SUMMARY MINUTES

A meeting of Expert Advisory Group (EAG): Medicinal Chemicals 1 (MC1) was via videoconference on Thursday 20 July 2023.

Present: Dr P Marshall *(Chair),* Dr E Bush (Vice Chair), Dr J C Berridge, Professor D Cairns, Mr A J Caws, Dr J Lough, Mr D Malpas and Dr F Pina (Authorisation Lifecycle, MHRA).

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

Apologies: Dr G Lee (Authorisation Lifecycle, MHRA), Mr S Nolan, Mr P Fleming.

INTRODUCTORY REMARKS

709 **Welcome** The Chair welcomed members of the EAG to the meeting.

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.

MINUTES OF THE PREVIOUS MEETING

710 The minutes and summary minutes of the meeting held on 25 January 2023 were confirmed with a minor post-meeting note highlighted for Action (3) under paracetamol preparations, Minute 698 refers.

MATTERS ARISING **MC1(23)13**

711 Matters arising from the July 2022 and Jan 2023 meeting were noted and the group updated on their progress.

REPORTS AND CORRESPONDENCE

712 **BP Update** **MC1(23)14**

Members were provided with an update on recent BP activities and personnel changes. Mr Steve Hoare had taken up the role of Head of Standards and Regulatory Governance (including the role of Secretary & Scientific Director of the BPC). Mr Peter Crowley had been appointed as Head of BP and Labs (including the role of Editor-in-Chief). Mr Adrian Evans of the MC3 and PCN groups had been seconded to the MHRA's Defective Medicines Reporting Centre.

BPC and EAG membership

A call for British Pharmacopoeia Commission membership had been opened with the deadline for applications now being closed (13th July).

The term of office for all current members of the Expert Advisory Groups, Panels of Experts and Working Parties of the BP Commission is due to end on 31st December 2023. A review of the membership of these groups will be required and the group was encouraged to circulate EAG membership to interested parties when this is publicised.

MHRA Corporate Plan 2023 to 2026

The MHRA had recently published the agency's strategic direction on the gov.uk website, outlining the four strategic priorities of:

1. Maintain public trust through transparency and proactive communication;
2. Enable healthcare access to safe and effective medical products;
3. Deliver scientific and regulatory excellence through strategic partnerships;
4. Become an agency where people flourish alongside a responsive customer service culture.

713 Sustainability of Monograph Methods MC1(23)15

Ms Estlin presented a paper on how the BP can reduce the environmental impacts associated with BP operations and products in line with the MHRA's net zero ambitions. One of the initiatives being considered was the proposal, where appropriate, to consider scaling down column sizes used in monograph methods with flow rates and injection volumes adjustments used in monograph methods with the aid of online calculators. These calculators would provide an indication of the method "greenness" which could be used in the creation of laboratory requisitions. Isocratic methods would be initially investigated as they are less sensitive to scaling changes and the BP Laboratory would be asked to compare the scaled method against the original column dimensions for performance.

714 Trihexyphenidyl Tablets MC1(23)16

Related substances The Secretariat had received an observation from the MHRA Laboratory that the SST resolution requirements of > 4.0, as written in the BP2023 related substances test for the monograph, was difficult to achieve. The chromatographic conditions for the Related Substances, Assay, and Uniformity of Content tests for the Trihexyphenidyl Tablets monograph in the BP2023 were the same except for the concentration of the system suitability solutions. Based on this observation, the Secretariat proposed to harmonise the concentrations of the SST solutions throughout all three tests and to amend the mobile phase preparation, to reflect the mobile phase from the Related Substances test of the Ph. Eur. API monograph upon which the BP Tablets monograph was based.

The group agreed to provide comment by correspondence following the meeting on both the specific proposal for the Trihexyphenidyl Tablets Related Substances system suitability test and their preferred general approach to the concentrations used in system suitability tests in monographs of the British Pharmacopoeia.

POST-MEETING NOTE: A preference for keeping the SST resolution solution concentration for the Related Substances test whilst changing the requirements was

expressed. The group agreed to harmonise the concentrations of the system suitability resolution solutions between the Assay and Uniformity of Content based on the Assay method's SST solution concentration. It was also agreed that amendments would be made to the order of the mobile phase preparation.

Identification The TLC Identification method uses chloroform as a solvent.
The group agreed to consider the replacement of the TLC Identification procedure with the HPLC-DAD test subject to confirmation of its suitability from the MHRA Laboratory.

715 Pregabalin Capsules **MC1(23)17**

The Secretariat had received correspondence from two users of the BP monograph who had independently highlighted that the response of the test solution in the Dissolution test was very low.

It was suggested that the published injection volume in the dissolution test of 10 µL may be an error and the injection volume should be 100 µL.

The monograph for Pregabalin Capsules had been introduced into the BP in BP2022 and the dissolution test had been based on a MAH data package. The method had not assessed by the MHRA Laboratory.

The experts believed that the injection volume of 10 µL was likely to be an error and agreed with the proposal that the injection volume should be revised to 100 µL in line with the MAHs validated method and the observations and data provided by the users.

716 Cyclizine Injection **MC1(23)18**

The Secretariat had received a question from an Authorisation Lifecycle colleague regarding revision of the Characteristics of the Injection from "A clear, colourless solution" to "A clear, colourless to slightly yellow solution" as there were at least 2 MAHs having these as part of their product description.

An MAH variation submission had requested this revision as there was a change in colouration of the product after terminal sterilisation.

As the Characteristics section is not an official requirement, the group did not object to the requested revision if it could be confirmed that the change in colour.ation was not due to degradation before proceeding.

NEW MONOGRAPHS

717 Pemetrexed Preparations **MC1(23)19**

Pemetrexed Sterile Concentrate
Pemetrexed Infusion
Pemetrexed for Infusion
Three new monographs had been prepared for Pemetrexed products.

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

718 Domperidone Preparations: MC1(23)20

Domperidone Oral Suspension (new)
Domperidone Tablets (revised)
A new monograph for the Oral Suspension had been drafted based on a MAH method and validation data. The draft new monograph would be included in a future BP publication, subject to laboratory evaluation and stakeholder comment.

The Tablets monograph had been revised with the addition of dissolution Q values.

Dissolution (Tablets) The Secretariat had drafted dissolution values as NLT 80% (Q) in 30 minutes, based on MAH specifications.

719 Alfentanil Injection MC1(23)21

A new monograph had been drafted based on a validated MAH method.

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

720 Paracetamol preparations: MC1(23)22

Paracetamol Capsules (revised)
Paracetamol Tablets (revised)
Paracetamol Dispersible Tablets (revised)
Paracetamol Effervescent Tablets (revised)
Paracetamol Soluble Tablets (revised)
Paracetamol Suppositories (revised)
Paediatric Paracetamol Oral Solution (revised)
Paediatric Paracetamol Oral Suspension (revised)
Paracetamol Oral Solution (new)
Paracetamol Infusion (new)

Dr P Marshall and Mr A Caws both declared an interest. They participated in the discussion.

The draft new monographs for Paracetamol Oral Solution and Paracetamol Infusion would be included in a future BP publication, subject to stakeholder comment.

Related substances The experts reviewed a draft monograph including a proposal from the Secretariat to return to the “old” style limits from the numerical limits in the previous draft monographs because the Secretariat did not have access to linearity data for the particular intervals of the impurities’ concentration around the limits.

The group advocated continuing with numerical limits and putting the limits in line with the ICH guideline. The Secretariat responded with the proposal to contact the EDQM Lab to get the linearity data for the API impurities which is limited mainly at the same level; this could prove the linearity for impurities in the preparations at the needed level. The group agreed with the proposal.

The Secretariat has contacted two MAHs regarding the results that were found to be outside of the drafted impurities limits during the BP Laboratory investigation into the suitability of the draft methods. One MAH had provided confirmation that the impurity was misidentified, and another asked the Secretariat for further time to complete their investigation. The drafted requirements were not expected to affect the MAHs.

POST-MEETING NOTE: The linearity data appeared to be available in the BP Laboratory as the linearity happened to be examined but the data was not included in the final report because it was out of the scope of the requisition in the preparation for the analysis. As a consequence the Secretariat would include numerical limits in the next version of the draft monograph.

Storage conditions The Secretariat proposed to eliminate the statement "Should be protected from light" from all monographs since finished drug products are already protected from the light, being packed in the secondary package for the entire duration of their presence on the market. The same approach is applied in the monographs for paracetamol finished drug products of other pharmacopoeias (USP).

The group did not agree with this proposal and preferred to keep the statement for informative purposes as this quality attribute is not mandatory and is included in the monograph for information.

REVISION OF MONOGRAPHS

721 Nifedipine Capsules MC1(23)23

Technical and editorial (style) revisions to the Capsules monograph were proposed.

Identification The monograph has both an IR and TLC tests for identification and the Secretariat proposed to delete the TLC test. Members endorsed this proposal.

Dissolution There were a number of manufacturers and based on product specifications the Secretariat proposal had revised the method with dissolution Q value of 75% (Q) in 45 minutes. Based on disintegration specifications of 20 and 30 minutes, a dissolution time of 30 minutes was accepted.

Related substances The nitro-(Ph.Eur. Impurity A) and nitroso-phenylpyridine (Ph.Eur. Impurity B) analogues test was proposed to be renamed as Related substances in line with the Prolonged-release Tablets and the Prolonged-release Capsules. It was requested if the limit of Ph.Eur. impurity A could be tightened from 1% to 0.5% for one of the MAHs to align with the PR tablets and capsules limit. In addition, the limit of "any other secondary peak" was proposed to be tightened to 0.2%, in line with ICH limit, subject to stakeholder comment. Members requested that the specified impurities A & B limits is included in the "total impurities" limits. The Secretariat had drafted the disregard limit / reporting threshold at 0.1% in line with ICH guidelines but noted that other nifedipine monographs had a disregard limit of 0.05%. Members agreed that the disregard limit / reporting threshold should be harmonised across the family of monographs.

The modified draft monograph was asked to be presented at a future meeting together with the other family of monographs.

722 Loperamide Capsules MC1(23)24

Dr Lough declared an interest. He participated in the discussion.

Revisions to the Capsules monograph were proposed.

Dissolution The monograph was drafted with a revised dissolution value of 75% (Q) in 45 minutes, which was in line with the Loperamide Tablets monograph dissolution Q limit. Members endorsed this for the BP2025, subject to stakeholder comment.

723 Allopurinol Tablets **MC1(23)25**

Revisions to the monograph were proposed.

Content The current monograph was drafted as 92.5 to 107.5% and one member asked if it was possible to update this to contemporary standards of 95.0 to 105.0% or if this needed to be retained. The Secretariat agreed to investigate this and amend as necessary.

Identification The method had been revised to delete Test A of the UV spectrum and Test B precipitate with an IR test from a validated MAH method. However, the MAH method has a qualifier for the spectrum, "the spectrum of standard and sample solutions should show a significant wave number at 1595 ± 10 cm^{-1} and 1700 ± 10 cm^{-1}." The Secretariat agreed to investigate if the IR spectrum is sufficiently discriminating or whether to include the retention time from the HPLC assay.

Dissolution An isocratic dissolution test had been added using a validated MAH's method. As not all manufacturers contained a dissolution test in their finished product specification, members agreed that laboratory evaluation was required for the HPLC procedure. As the manufacturers without a dissolution test have disintegration times of not more than 15 minutes, it was agreed that the dissolution time could be acceptably amended from 75% (Q) to 30 minutes.

Assay
Members agreed to replace the non-specific assay with the dissolution test conditions, subject to laboratory evaluation.

Impurities The impurities transparency statement had been revised. It was noted that the disregard limit of 0.02% was very low for the MDD, which should nominally be set at 0.1%. It was agreed to review this to determine if the impurities for this product are particularly toxic, which may inform the setting of this historical disregard limit.

724 Sodium Valproate preparations **MC1(23)26**

Sodium Valproate Tablets
Sodium Valproate Prolonged-release Tablets
Sodium Valproate Gastro-resistant Tablets
Sodium Valproate Prolonged-release Capsules
Sodium Valproate Oral Solution

Members discussed the Secretariat proposal to amend the wording of the Identification Test B to clarify its purpose in the family of sodium valproate monographs. Test B is a precipitate test for the counter-ion as the Test A is for the valproic acid. It is not clear if test B is unequivocally characteristic for the sodium counter-ion. Both the Ph.Eur. Sodium Valproate and USP Sodium Valproate Injection monographs have a counter-ion Identification.

Historical data indicated that an additional test yielding reactions characteristic of sodium and their salts, Appendix VI, had previously been present in older versions of the monographs but which was then deleted due to unsatisfactory results in laboratory evaluations.

The need for a test for the counter-ion, the sodium salts available for the formulations, (GR capsules contains the semi-sodium salt) were discussed. Members agreed to leave Test B unchanged and record the discussion.

Dissolution (Gastro-resistant Tablets) The test was revised to include a Q value (65%) after 60 minutes (Stage II) and this was accepted by members.

725 EUROPEAN PHARMACOPOEIA **MC1(23)27**

An update on the status of Ph.Eur. monograph development (Pharmeuropa 35.2) was presented to members for information.

ANY OTHER BUSINESS

726 Work Programme **MC1(23)28**

Annex 1

The Secretariat presented a copy of the current MC1 programme to the Expert Advisory Group. The monographs being targeted for the BP2024 and BP2025 publications were highlighted.

727 BPCRS Update **MC1(23)29**

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