BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group MC2: Medicinal Chemicals

SUMMARY MINUTES

A meeting of this Expert Advisory Group (EAG): Medicinal Chemicals 2 (MC2) was held virtually over two sessions on Tuesday 12 November and Thursday 14 November 2024.

Present: Dr G Cook *(Chair)*, Mr J Rickard (*Vice-Chair)*, Mr C Goddard (*Vice-Chair*), Mr M Ali, Prof J Birchall, Dr K Boon, Dr K Chan *(Observer)*, Mr J Cowie, Dr S Ho, Mr E Hook, Prof J Miller, Mr C Natarajan, Dr A Ruggiero and Dr Z Smith.

In attendance: Ms H Corns, Ms A Thomson, Mr R Legg (12th only), Ms R Feltham (12th only), Dr S Greatorex (BP Laboratory) and Mr D Crowe (BP Laboratory).

Apologies: Prof J Birchall (12th only), Dr K Foster and Mr C Natarajan.

623 Introductory Remarks

Welcome The Chair welcomed Dr Z Smith, a new member; Mr R Legg and Ms R Feltham, two new Secretariat members; and Dr K Chan, a new Commissioner attending as observer.

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 reminded that they are required to inform the BP Secretariat of any changes to their interests throughout the year via email to Agency's Committee Services Team.

624 BP update **MC2(24)14**

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

625 MINUTES

The minutes of the meeting held on 12 June 2024 were confirmed without amendment.

626 MATTERS ARISING FROM THE MINUTES **MC2(24)15**

Matters arising and correspondence items from the meeting held on 12 June 2024 were noted.

MONOGRAPHS

Mr M Ali, Dr G Cook, Mr E Hook and Dr A Ruggiero declared interests in one or more agenda items and appropriate action was taken.

627 Fludarabine preparations (New): MC2(24)16
Fludarabine Sterile Concentrate
Fludarabine for Injection
Fludarabine Tablets

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

628 Memantine preparations (New): MC2(24)17
Memantine Tablets
Memantine Orodispersible Tablets
Memantine Oral Solution

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

629 Ibuprofen Preparations: MC2(24)18
Ibuprofen Injection (New)
Ibuprofen Gel (Revised)
Ibuprofen Capsules (Revised)

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

Identification (Gel) Members noted the complexity of the infrared extraction procedure which required SPE extraction. A proposal to replace the test with HPLC UV-DAD, using the assay method, was accepted by members, subject to stakeholder comments.

Related substances (Gel) A report had been received which demonstrated that ibuprofen methyl, ethyl and propyl esters could be formed in the presence of the corresponding alcohols in Ibuprofen Gel products and which could be detected with the published related substance method. A request to limit ibuprofen ethyl ester at not more than 0.5% in the monograph was submitted with the report. It was confirmed that this limit had been approved by licence assessors and members endorsed the inclusion of the 0.5% limit for this impurity.

Related substances (Capsules) Correspondence had been received which reported peaks exceeding the any other secondary peak limit of 0.1% at early stages of stability studies. Through investigation, these peaks had been identified as ibuprofen sorbitol

and sorbitan esters, formed in the presence of liquid sorbitol. Members endorsed further investigation of these impurities with a view to revising the monograph to include structures and appropriate limits.

Supporting information for Assay The BP Lab had evaluated scaled column dimensions for the Assay method with acceptable results. Experts supported the inclusion of additional sustainability information on the BP website, under 'More Resources'.

630 Bumetanide preparations: MC2(24)19
Bumetanide Oral Solution (Revised)
Bumetanide Injection (Omission)

Identification (Oral Solution) The BP Lab had found standard and sample UV spectra to be concordant, with absorbance maxima at 222 nm and 334 nm. Members confirmed suitability of the HPLC/UV-DAD test for identification.

Related Substances (Oral Solution) In the absence of a suitable HPLC procedure, the Secretariat proposed adoption of a modified TLC procedure, replacing chloroform with dichloromethane in the mobile phase. The two plates were found by the BP Lab to be equivalent, with all secondary spots well resolved and their presence clearly identifiable. Members accepted the proposed modification.

Assay (Oral Solution) The BP Lab had found the Ph Eur Bumetanide related substances test to be fit for Assay purposes, with reduced solution concentrations to prevent blocking of the system and deterioration of the peak shape after injection. Solution (3) had been included for system suitability, with a resolution requirement of at least 2.0 between the peaks due to impurities A and B.

Members were satisfied that the draft monograph met all acceptance criteria, and the Assay results showed good repeatability. Members approved inclusion of the standard BP content requirement of 95.0% – 105.0% for website consultation.

Omission (Injection) The Secretariat proposed that the Bumetanide Injection monograph be considered for omission in the absence of a UK market authorisation holder. MHRA assessor advice had been sought, concluding there was no special use for the formulation. In light of this information, members approved the proposal to recommend omission from the BP 2026, subject to comments from stakeholders and BP Commission approval.

631 Propranolol preparations (Revised): MC2(24)20
Propranolol Prolonged-release Capsules
Propranolol Tablets

Identification The BP Laboratory had found that the simplified extraction procedure, using methanol was not suitable, due to excipient interference. Extraction with alternative solvents; ethanol, acetone and acetonitrile, was also found to be unsuitable. The Lab investigated the replacement of diethyl ether with petroleum ether

40 – 60° using the published IR procedure for Propranolol Tablets, which was successful. Members endorsed adoption of revised test in both monographs.

632 Olmesartan Tablets (Revised) MC2(24)21

Related Substances A request to increase the impurity A limit in the Olmesartan Tablets monograph, based on stability data and justification had been submitted. An increased impurity A limit of not more than 2.5% from 0.9% was endorsed by members, subject to stakeholder comment.

633 Latanoprost Eye Drops (New) MC2(24)22

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

634 Tranexamic Acid preparations (Revised): MC2(24)23

Tranexamic Acid Tablets
Tranexamic Acid Injection

Identification Members approved the proposal to delete identification B, a colour change test, and C, a melting point determination, with IR considered sufficiently discriminatory. Members endorsed the USP IR extraction procedure for BP Lab evaluation. An increased extraction volume was proposed by experts, with 1 mL unlikely to be suitable for the quantity of powdered tablets used in the procedure.

Dissolution A new test had been drafted based on the USP Tranexamic Acid Tablets monograph procedure, with the chromatographic conditions aligned with the related substances test. A limit of at least 75% (Q) in 30 minutes had been included which encompassed UK approved product specifications. Members approved the test and proposed limit for BP Lab evaluation.

Related substances Improvements to the published method, including a change to quantitative-style limits, was endorsed by members for BP Lab evaluation. Members approved a tightened 0.2% limit for impurity A, 0.8% for total impurities and a 0.05% reporting threshold in line with ICH.

Impurities C and D had been identified as synthetic impurities which were controlled at 0.05% in the drug substance monograph. Members accepted the proposal to remove the specified limits in the BP monograph. It was noted that impurities C and D were the closest eluting pair of peaks, which could be used to replace the existing system suitability requirement of resolution between impurity C and tranexamic acid. It was recommended that the BP Lab carried out an assessment of the separation of these peaks during their investigation.

Assay The replacement of the titration method with a LC procedure, harmonised with the BP Tranexamic Acid Injection chromatographic conditions and USP Tranexamic Acid Tablets monograph sample preparation was accepted by members.

Tranexamic Acid Injection Members endorsed inclusion of a simplified IR extraction procedure and quantitative limits for related substances, subject to BP Lab confirmation of suitability.

635 Pyridostigmine Tablets (Revised) MC2(24)24

Related Substances Tightening of the impurity B limit from 6.0 to 3.0% was endorsed by MHRA assessors and approved by members, subject to stakeholder comment.

636 Salbutamol preparations (Revised): MC2(24)25
Salbutamol Pressurised Inhalation, suspension
Salbutamol Oral Solution

Related substances (Pressurised Inhalation, suspension) The Secretariat had received user reports of difficulty obtaining the peak to valley ratio specified in the system suitability requirement when carrying out the revised test that was published in the BP 2025. Further investigation of the issues reported by monographs users was agreed by the experts.

Uniformity of delivered dose and Assay (Pressurised Inhalation, suspension) As no comments had been received on the revised method, it was agreed that the revised test would be adopted in the BP 2026.

FOR INFORMATION

637 MC2 Work status and updates MC2(24)26

The Secretariat presented the updated work programme to members for information.

638 Out of Stock BPCRS MC2(24)27

The Secretariat reviewed the out-of-stock BPCRS for monographs relevant to EAG MC2 and presented these to the group.

639 Ph Eur Updates MC2(24)28

The Secretariat thanked members for their ongoing support of Pharmeuropa, and confirmed update 36.4 was underway with seven MC2-allocated texts and a public deadline of 31 December 2024.

640 ANY OTHER BUSINESS

None raised.

641 NEXT MEETING

Members were informed that the next meeting would be held in-person at 10 South Colonnade in May 2025.