MEDICINAL CHEMICALS GROUP 1 SUMMARY MINUTES

BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group MC1: Medicinal Chemicals

A meeting of Expert Advisory Group (EAG): Medicinal Chemicals 1 (MC1) was held remotely on Wednesday 29 January 2025.

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

In attendance: Mr M Whaley, Dr M Dmitriieva, Ms G Li-Ship, Mr Ross Legg, Ms P Mandalia (CST, MHRA) Mr S Greatorex (BP Lab), Ms Julia Portner (BP Lab), Mr D Crowe (BP Lab).

Observers: Mr S Hoare (Secretary & Scientific Director, BP), Ms H Hall (BP Commissioner)

Apologies: Mr P Fleming, Mr D Malpas

Mr D Crowe attended part of the meeting.

761 **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 and before discussion of each monograph item.

MINUTES OF THE PREVIOUS MEETING **MC1(25)01 & 02**

762 The minutes and summary minutes of the meeting held on 10 July 2024 were confirmed.

MATTERS ARISING **MC1(25)03**

763 Matters arising and correspondence items from the meeting held in previous meetings were noted and the group was updated on any progress.

Sustainability of Monograph Methods – scaling of pharmacopoeial Methods & alternative methods

Scaling of Monograph Methods

Following from the July 2023 meeting, the Secretariat collated criteria required for "scaling down" column sizes, flow rates and injection volume adjustments that are being

investigated by the BP Laboratory alongside drafted pharmacopoeial monograph methods. Solifenacin Oral Suspension, published in BP2025, was highlighted as an example together with qualifying supporting information for the scaled Dissolution and Assay methods in the “More Resources” tab.

The criteria to reduce environmental impact through scaling were given as below:

Criteria	***(Delete as appropriate)***
Assay or dissolution or content test	✓*or* ✗
Isocratic	✓*or* ✗
Injection volume <100 uL	✓*or* ✗
Column dimensions are big enough to allow for scaling reductions down towards: - ***2.5 um particle size and 7.5 cm column length, or*** - ***2.1mm internal diameter***	✓*or* ✗
Test is not harmonised with the related substances test*	✓*or* ✗

The criterion for the Assay test not being harmonised with the Related substances test was explained as being designed to avoid working on scaling of a harmonised method which may have several potentially interfering peaks.

The Secretariat aimed to incorporate sustainability into method evaluations of monographs for future meetings, including identifying and developing creating metrics to measure sustainability efforts.

Aripiprazole Preparations

Following the Oral Solution MAH feedback, the Secretariat have prepared the monographs for review by the BP Commission for publication in BP2026, subject to BPC approval.

Tramadol Preparations The Soluble Tablets, Orodispersible Tablets and Dispersible Tablets monographs had been prepared for public consultation (Oct – Dec 2024) and no significant technical issues were received.

The monographs have been prepared for review by the BP Commission for publication in BP2026, subject to BPC approval.

Levetiracetam Preparations (Tablets, Sterile Concentrate)

The monographs have been prepared for review by the BP Commission for publication in BP2026, subject to BPC approval.

Nifedipine Preparations

No comments were received from the public consultation (Oct – Dec 2024). The monographs have been prepared for review by the BP Commission for publication in BP2026, subject to BPC approval.

Trazodone Preparations (Minutes 754 refers) The Tablets, Soluble Tablets, Capsules and Oral Solution monographs had been prepared for public consultation (Jan – March 2025) and subject to no significant comments being received, will be prepared for review by the BP Commission for publication in BP2026, subject to BPC approval.

REPORTS AND CORRESPONDENCE

764 BP Update **MC1(25)04**

Members were provided with an update on recent BP activities including the appointment of a new MHRA Chair, BPC reappointments and MC1 Secretariat staff changes.

765 Colchicine Tablets **MC1(25)05**

The BP Secretariat had received a query from a user who highlighted that the Ph Eur intended to remove the reference standard, Colchicine for System Suitability A EPCRS from the Colchicine monograph.

The BP monograph for Colchicine Tablets referred to Colchicine for System Suitability A EPCRS which was used in the system suitability test to determine suitable resolution between Colchicine and Impurity A.

The Ph Eur standard, Colchicine for System Suitability A EPCRS, contained impurities A, E and G whereas the new Colchicine for System Suitability B EPCRS, published in the Ph Eur 11.6 supplement, contained impurities A, E, G and H.

The Ph Eur 11.6 Related substances method for Colchicine API included modifications to the stationary phase and the column temperature to help separate impurity G from impurity H.

It was highlighted that the Ph Eur standard would remain available whilst stocks lasted and would be kept visible in the EPCRS catalogue until the 1st January 2026.

It was agreed that the Secretariat should contact the user to ask whether they had any practical experience with the use of Colchicine for System Suitability B EPCRS. It was also proposed that the BP Laboratory should be asked to assess the new EPCRS using the BP's Colchicine Tablets Related substances method.

766 Pregabalin Capsules **MC1(25)06**

The Secretariat had received correspondence from three users that they could not achieve the required resolution for the Related substances system suitability test (SST) even though the permitted adjustments of Appendix III had been applied.

The monograph had been introduced in BP2022 and revised in BP2025 for the Dissolution test. The Related substances test had been based on an MAH data package. The method had been verified in the laboratory resulting in the current

resolution requirement for the SST of NLT 14 between the peaks due to pregabalin and impurity 1. However, the BP users had found it too strict and unachievable.

Members agreed with the Secretariat proposal to decrease the SST resolution requirements from NLT 14 to NLT 10. This which would still be sufficient to resolve the critical pair of impurities 1 and 2 for a reliable determination, as their resolution was expected to decrease from 3.5 to NLT 2.

767 Esomeprazole for Injection and Omeprazole for Injection MC1(25)07

Previous meeting At the previous meeting it had been agreed to amend the two monographs to introduce a correction to the preparation of the Assay mobile phase Letters of Intent had been published on the BP website to give notice to users that the monographs will be revised.

User feedback Following the publication of the letters detailing the correction the BP Secretariat had received queries from users of the BP monographs for Esomeprazole for Injection and Omeprazole for Injection who were highlighting difficulties with meeting the system suitability requirements in the Assay tests.

The Assay in both the current BP monographs contained the following System Suitability requirements.

> *System suitability*
> *The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peaks due to impurity D and omeprazole is greater than 5.0.*

One user reported that the peaks due to Omeprazole and Impurity D had approximately the same retention time and even with modification of the mobile phase, in line with Appendix III Chromatographic Separation Techniques, the resolution criteria cannot be met (Annex 1).

Another user reported that, whilst there was resolution (~3.7) between the peaks due to Omeprazole and Impurity D, the criteria of greater than 5.0 was not achieved.

Experts agreed to laboratory investigation of the assay system suitability test.

768 Hydroxychloroquine Tablets MC1(25)08

Following the publication of a revised monograph in BP 2022, correspondence had been received on several sections of the monograph, which the Expert Advisory Group was asked to consider.

Dissolution Two users of the BP independently noted that, in the dissolution test, the concentration of the standard in solution (2) of 0.022% w/v of hydroxychloroquine sulfate BPCRS resulted in strong absorbance of more than 2.0.

The Dissolution method adopted in BP2022 had been based on a user's request to align with the USP monograph method. Neither the USP method nor the user's request had specified an appropriate solution strength.

A request from a user, supported by a validation package, had recommended that the concentration of the standard solution should be adjusted to 0.002% w/v of hydroxychloroquine.

Members supported this request.

Related substances and Assay (Gradient Table) Two users had been in correspondence with the BP Secretariat about their experiences with the chromatographic conditions in the Related substances test and the Assay in Hydroxychloroquine Tablets monograph.

Both users highlighted issues with the elution of peaks. One user noted that the retention time they had been experiencing for the peak due to the active in the Assay differs from that in the monograph and another user noted that in the Related substances test the peak due to Impurity G does not elute as expected.

Members agreed with the proposal to correct the gradient table by adding the 4th isocratic step which had been inadvertently deleted when the monograph had been editorially restyled in BP2022.

NEW MONOGRAPHS

769 Baclofen Preparations **MC1(25)09**
Baclofen Injection - new
Baclofen Tablets – revised
Baclofen Oral Solution - revised

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

Identification (Tablets, Oral Solution) Members agreed to replace the TLC method with a HPLC-UV DAD test, subject to evaluation by the laboratory.

Dissolution (Tablets) Members agreed to revise the dissolution sampling time from 45 minutes to 30 minutes and move to a Q (%) limit of 70%, in line with BP policy for revising suitable monographs.

Impurity A / Related substances (Tablets and Oral solution) Members agreed with replacing the specific impurity A test with a Related substances test.

Related substances Members discussed the proposed unspecified impurity and the total impurity limits.

Based on available stability data from some of the MAHs, the drafted limits were agreed, subject to laboratory evaluation and stakeholder comment.

770 Ondansetron Oral Solution **MC1(25)10**

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

771 Diltiazem Prolonged-Release Capsules **MC1(25)11**

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

NEW MONOGRAPHS IN PROGRESS

772 Topiramate Tablets **MC1(25)12**

The Secretariat presented the draft monograph following completion of the laboratory assessment. The monograph would be published in a future publication subject to amendments and stakeholder comment.

REVISION OF MONOGRAPHS

773 Felodipine Prolonged-Release Tablets **MC1(25)13**

Content The current content is 92.0 – 105.0% and the revised draft had proposed moving to 95.0% - 105.0%.

Members were concerned that only half of the MAH specifications would be able to meet the proposed drafted limits and requested that the current limits be retained subject to further stability data from MAHs. The Secretariat agreed to retain the current content limits.

Identification Members accepted that the current published method would not be revised at this time as the Ph.Eur. Felodipine monograph comments were being reviewed for the revision of the first and second identification tests.

Related substances The current published method is an isocratic HPLC-UV method which can detect impurities A, B & C, based on Ph.Eur. 9.0 update drug substance monograph. The Ph.Eur. felodipine monograph had been revised in 2023 (11.1 update) with separate limits for impurities B & C of NMT 0.5% for each impurity, from a combined limit of 1.0% for impurities B + C.

The Secretariat proposed keeping the current published method whilst harmonising with the updated Ph. 11.1 related substances limits for the separate impurities B & C. In line with the BP policy, the laboratory will also be asked to provide background data to move to numerical limits.

There was limited stability data available and the Secretariat agreed to reach out to MAHs for further information to inform proposed limits.

Sustainability An evaluation showed that this monograph could potentially be scaled for sustainability, despite being harmonised the related substances test with the assay test.

774 Warfarin Tablets **MC1(25)14**

Related substances In response to a customer query and following the EAG recommendation, the drafted procedure based on the USP Warfarin Sodium Tablets Related Substances method had been investigated in the Laboratory. The procedure had been found to be fit for purpose with some modifications. The monograph would be published in a future publication subject to amendments and stakeholder comment.

775 Bisacodyl Suppositories **MC1(25)15**

As part of a restyling exercise the BP Secretariat presented a revised draft monograph for Bisacodyl Suppositories which had been brought up to date with the current BP editorial style.

The monograph included the use of Chloroform in the Identification test which Experts agreed should be replaced if possible. The Related substances test used a thin-layer chromatography method which the Experts felt should be updated. The assay was highlighted as not using a chromatographic method which the EAG thought could be updated if possible.

Experts agreed with the Secretariat's proposal that the editorially restyled monograph could be technically restyled at the earliest opportunity and manufacturers of Bisacodyl Suppositories would be contacted to ask for data packages which could support the technical revision of this monograph.

776 *EUROPEAN PHARMACOPOEIA*

Members were provided with an update on Ph Eur monographs which concerned MC1 monographs. Due to time constraints, this was not discussed in the meeting.

ANY OTHER BUSINESS

777 Proposed BP2026 Omission **MC1(25)17**

A verbal update was given by the Secretariat correcting the proposed omission for Aspirin Soluble Effervescent Tablets as further information was provided by the assessors that there are two active UK MAHs. The Secretariat would reach out to the MAHs for samples for laboratory evaluation to enable revision of this monograph in line with other revised aspirin monographs published in the BP2025.

778 BPCRS Update **MC1(25)18**

Members were provided with an update on BPCRS reports since the last meeting. There were no out-of-stock BPCRS. Due to time constraints, this was not discussed in the meeting.

779 Work Programme **MC1(25)19**

Members were provided a copy of the current MC1 programme to the group. Due to time constraints, this was not discussed in the meeting.

780 Metformin and Sitagliptin Tablets **MC1(25)20**

Identification, Assay and Related substances (correspondence)

The Secretariat had received correspondence from a user highlighted a discrepancy between the recorded UV spectrum under Identification Test A (210 – 400 nm) for the Assay whereas the Assay detection wavelength is 205 nm.

Members agreed to revise the Identification Test A UV spectrum range from 210 – 400 nm to 190 – 400 nm.in the Metformin and Sitagliptin Tablets monograph for the BP2026 publication.

790 Loperamide Orodispersible Tablets **MC1(25)21**

Content limits The Secretariat had received correspondence from a BP user to extend monograph content limit from 95.0% – 105.0% to 95.0% – 107.5% based on their low tablets weight (17 mg) manufactured by lyophilisation.

The Secretariat had replied that there was no justification to revise the BP content limit for the Loperamide Orodispersible Tablets as using a sample from 20 powdered tablets would mitigate any deviation due uniformity of mass in content determination.

However, the customer had continued to request a content extension referring to the available USP monographs (Loperamide tablets, Loperamide Capsules and Loperamide Oral Suspension), which have assay limits of 90.0% to 110.0%, and to the Australian (TGA) OTC monograph having an assay limit 95.0% to 107.5%.

The Secretariat had received data from the assessors for 4 other approved Loperamide Orodispersible tablets, with assay limits of 95 – 105%, including one product manufactured by lyophilisation with a tablet weight of 150 mg.

Members agreed there was no need to revise the monograph and to retain published the content limit.

791 Chlorphenamine Preparations The group was informed that a laboratory project had successfully resolved chlorphenamine from related substances and parabens using a Luna-3-C18 (150 mm x 4.6 mm) column with the same mobile phase components as the published BP Oral Solution monograph.

Chromatographic gradient conditions had been developed for the Oral Solution and isocratic HPLC chromatographic conditions for the assay, providing suitable specificity and run times. Validation work on linearity and LOQ for related substances was pending.

Next Meeting **MC1(25)22**

The next meeting was planned to be held in person on 23 July 2025.