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 Tuesday 19 January 2021.

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

In attendance: Ms H Corns, Mr L Elanganathan, Ms A S Thomson, Mr D Jones (Expert Non-Clinical Assessor), Mr M Whaley (Lab Services Manager), Ms K Busuttil (BP Lab) and Ms M Nanasi (BP Lab).

Apologies: Dr S Bale, Dr E Bush and Mr S Nolan.

Prof. D Cairns and Mr D Malpas declared an interest in one or more agenda items and appropriate action was taken.

INTRODUCTORY REMARKS

615 **Welcome** The Chair welcomed members, Mr D Jones, Mr M Whaley, Ms K Busuttil and Ms M Nanasi to the meeting. Dr P Marshall was introduced as a new member of EAG MC1.

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.

616 BP Update

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

617 MINUTES

The minutes and summary minutes of the meeting held on 30 June 2020 were confirmed.

618 Matters Arising from the Minutes

Matters arising from the 30 June 2020 meeting were noted and members had no additional comments.

MONOGRAPHS

619 Tramadol preparations:
Tramadol Injection (New)
Tramadol Oral Drops (New)
Tramadol Dispersible Tablets (New)
Tramadol Effervescent Tablets (New)
Tramadol Capsules (Revised)
Tramadol Prolonged-release Capsules (Revised)
Tramadol Prolonged-release Tablets (Revised)

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

Tramadol Capsules – Dissolution A test had been drafted based on the methods submitted by manufacturers, with a draft release limit of not less than 75% (Q) in 30 minutes. The drafted test and limit were accepted by members, subject to stakeholder comments.

Tramadol Capsules, Prolonged-release Capsules and Prolonged-release Tablets – Related substances Quantitative limits had been introduced based on the adoption of such limits in the Ph Eur Tramadol Hydrochloride monograph and supporting data from a BPCRS replacement report. Members supported the revision as the related substances methods in the BP monographs were harmonised with the Ph Eur test.

Tramadol Capsules, Prolonged-release Capsules and Prolonged-release Tablets – Impurities The transparency statement had been revised to exclude impurity E, as this was not controlled in the related substances test.

BPCRS review A review of the BPCRS requirements across the family of monographs was presented to members to consider any action required for maintenance.

620 Itraconazole Capsules (Revised)

The Secretariat presented a proposal to include a new specified degradation impurity in the Related substances test following a user request.

A user had submitted supporting information of a degradant observed at a level above the unspecified impurities limit (0.2%). Members agreed for the inclusion of the impurity based on the supporting information, and the Secretariat agreed to confirm a suitable limit with the Licensing Division.

621 Bendroflumethiazide Tablets (Revised)

The Secretariat presented the draft monograph following completion of the laboratory assessment. The draft revised monograph had been posted on the BP website for stakeholder consultation on 1 January 2021, no comments had been received before the meeting was held.

Identification Members accepted the laboratory recommendation that a HPLC/UV-DAD identification test was included in the revised monograph.

Dissolution Members accepted the laboratory recommendations regarding the dissolution and chromatographic conditions.

Related substances Members accepted the laboratory recommendations regarding the method, and agreed to the draft revised limits, subject to comments received from stakeholders.

Assay Members accepted the laboratory recommendations, and agreed that the revised test should be adopted with the revised content limits of 95.0 – 105.0%.

622 Metformin preparations:
Metformin Tablets (Revised)
Metformin Oral Solution (Revised)

Due to time constraints, this item was not discussed during the meeting and members were requested to submit comments via correspondence following the meeting. The comments and recommendations from members were discussed with the Chair and Vice-Chair on Monday 1 February 2021 and recorded below.

Post-meeting note:

Dissolution (Metformin Tablets) Members agreed for the inclusion of the drafted limit of 75% (Q) in 45 minutes to be circulated for stakeholder comment.

Related substances (Metformin Tablets) The Secretariat proposed that laboratory evaluation was carried out to assess the suitability of a revision to the column following user queries. Members agreed with the proposal and the proposed limits.

Related substances (Metformin Oral Solution) Members agreed that the suitability of the published test should be evaluated following queries received regarding the identical column specified in the Metformin Tablets.

The published monograph included a limit of 0.15% for unspecified peaks, and a user queried this as this was not in line with ICH guidelines (0.2% for Metformin). It was noted that manufacturers had a specified drug product degradant impurity above this limit, and the Secretariat therefore proposed that the laboratory evaluate whether this impurity is detected. The Licensing division confirmed that a draft limit of 0.3% was suitable, and The Secretariat agreed to initiate BPCRS development if required.

Acidity/Alkalinity (Metformin Oral Solution) The Secretariat agreed to reconsider the pH limit due to the effect on product stability. The Licensing Division also recommended that a general consideration of the need for pH limits in monographs should be conducted, as it was thought that pH controls should only be used in monographs if they provide a control that the rest of the monograph does not provide.

623 Metformin & Sitagliptin preparations:
Metformin & Sitagliptin Tablets (New)
Metformin & Sitagliptin Prolonged-release Tablets (New)

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

624 Etodolac preparations:
Etodolac Prolonged-release Tablets (New)
Etodolac Capsules (Omission)

Due to time constraints, this item was not discussed during the meeting and members were requested to submit comments via the DRT. The comments and recommendations from members were discussed with the Chair and Vice-Chair on Monday 1 February 2021 and recorded below.

Post-meeting note:

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

Omission of Etodolac Capsules Members agreed with the proposal to omit the monograph from the BP 2022, subject to international stakeholder comments, as it had been confirmed that they were no longer marketed in the UK,

625 Cetirizine Capsules (Revision)

Due to time constraints, this item was not discussed during the meeting and members were requested to submit comments via the DRT following the meeting. The comments and recommendations from members were discussed with the Chair and Vice-Chair on Monday 1 February 2021 and recorded below.

Post-meeting note:

Dissolution The Secretariat presented a draft revision to the Dissolution test following a user's request, as significant interference was observed with the UV method due to the capsule shell excipients. The user had confirmed that the chromatographic conditions in the published HPLC Assay method was suitable, and therefore members agreed with the proposal subject to stakeholder comment.

626 Paracetamol Combination Preparations (Revisions)

Due to time constraints, this item was not discussed during the meeting and members were requested to submit comments via the DRT following the meeting. The comments and recommendations from members were discussed with the Chair and Vice-Chair on Monday 1 February 2021 and recorded below.

Post-meeting note:

Members agreed for the following monographs to be published in the BP 2022, as no adverse comments had been received from stakeholders:

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

Dissolution (Co-codamol Capsules and Tablets) An MAH had reported that their product may not comply the drafted dissolution limit of 75% (Q) in 45 minutes, based on their registered specification of 70% in 45 minutes. Members agreed that the proposed limit

should be retained as it had been noted that the drafted dissolution limit should be easily met based on experience of these products, and that the product would still comply at the S2 level.

Related substances (Co-codamol Capsules) It was previously agreed that a draft limit of 0.2% for unspecified peaks due to codeine should be included, despite the presence of an unknown peak at 0.3% during laboratory evaluation of a capsules product.

The MAH had reported that a corresponding unknown peak at a level of 0.1% was observed during an investigation, and would further investigate its identity. As the peak was detected at a level below the unspecified limit, the Secretariat proposed that the drafted limits were included for publication in the BP 2022. Members agreed, and noted that a revision could be made if this was warranted.

Related substances (Co-dydramol Tablets) The Secretariat previously agreed to contact MAHs following the observation of a number of unknown peaks above the unspecified peaks limit during laboratory evaluation. This was based on quantification of unknown peaks against dihydrocodeine, but the Secretariat had since noted that an investigation in the laboratory report supported the quantification against paracetamol, which would mean that they were detected below the disregard limit. Members agreed for the monographs to be progressed as drafted for publication in the BP 2022.

Labelling statements (Co-codamol Capsules, Co-codamol Effervescent Tablets, Co-codamol Tablets) The Secretariat informed members that EAG PCY had yet to receive input from the Department of Health and Social Care. Members agreed that the labelling statements should be retained until an approach to removing them was agreed.

627 Mycophenolate Mofetil preparations (Revisions):
Mycophenolate Mofetil for Infusion
Mycophenolate Mofetil Capsules
Mycophenolate Mofetil Tablets
Mycophenolate Mofetil Oral Suspension

Due to time constraints, this item was not discussed during the meeting and members were requested to submit comments via the DRT following the meeting. The comments and recommendations from members were discussed with the Chair and Vice-Chair on Monday 1 February 2021 and recorded below.

Post-meeting note:

Mycophenolate Mofetil for Infusion, Capsules and Tablets – Content A wider content limit of 93.0 to 105.0% for the Infusion, Capsules and Tabletshad been requested by a manufacturer who provided stability data trend analyses for their products.

Members concurred that the data did not convincingly support the need for wider limits in the monographs, and requested that a significant trend requiring lower limits was demonstrated before revision request could be agreed.

Mycophenolate Mofetil Capsules, Infusion and Tablets – Related substances
Members accepted the request from a manufacturer to include impurity F in the total impurity limit.

Mycophenolate Mofetil Oral Suspension – Related substances & Assay An error in the preparation of solution (1) had been identified and the monograph had been revised to

read: ‘Shake a weighed quantity of the oral suspension containing 0.8 g of Mycophenolate Mofetil with 100 mL… ‘.

628 Trazodone Hydrochloride (Revision)

In November 2010, a Production statement was added to tighten the limit of impurity F to not more than 2.5 ppm based on toxicological data. A letter from a user requested a reversal of this decision and toxicological data in support of this had been provided.

A MHRA Expert Non-Clinical Assessor, presented an overview of the two toxicological reports to the experts. The assessor was minded to accept the non-mutagenicity of impurity F findings of the second report, as he had concluded that there was no compelling evidence of a genotoxic effect. It was also confirmed that there were no strongly problematic features of the impurity F structure.

Experts proposed that the Secretariat contact the USP to understand the inclusion of the 2.5 ppm limit in their monograph, and were prepared to accept the recommendation of the assessor subject to the response from USP and stakeholder confirmation.

Post-meeting note: The USP reported that the 2.5 ppm limit had been included based on the documentation provided by the monograph sponsor. The Secretariat have proposed to investigate further and report to a future meeting.

629 Hydroxychloroquine Tablets (Revised)

The draft revised monograph was made available on the BP website between 1 October and 31 December 2020. No comments were received.

Due to time constraints, this item was not discussed during the meeting and members were requested to submit comments via the DRT following the meeting. The comments and recommendations from members were discussed with the Chair and Vice-Chair on Monday 1 February 2021 and recorded below.

Post-meeting note:

Related substances The development of a replacement batch of 2-[4-[(7-chloro-4-quinolinyl)amino] pentyl] amino ethanol BPCRS (impurity C) raised a discrepancy between the BPCRS name and how the limit for impurity C was presented in the monograph, as the BPCRS name did not include ‘sulfate’.

It was agreed that the BPCRS name would be amended to include the salt form, and that the concentration of solution (3) should be amended from 0.00005% to 0.00004% w/v, and that the expression of the limit would be amended from 0.5% to 0.4% as the sulfate in line with the Ph Eur monograph limit.

630 Supplementary papers

Decisions made by members via correspondence on revisions to the following monographs for publication in the BP 2022, subject to stakeholder comments during Q1 of 2021, were reported for official record:

- Aciclovir Preparations: revision to the specified impurities in the Related substances test in line with Aciclovir European Pharmacopoeia monograph.
- Diltiazem Prolonged-Release Tablets: revision to solution concentrations in the Related substances test to optimise chromatography.
- Nicotine Preparations: revision to the disregard limit in the Related substances test in line with ICH guidelines.
- Sumatriptan, Sumatriptan Tablets: Revision to the diluent in the Impurities A and H, Related substances, and Assay tests to optimise chromatography.

631 MC1 Work status and updates

The MC1 work programme was presented to members for information.

632 MC1 Out of stock BPCRS review

The Secretariat outlined the only BPCRS that was out of stock long term, and provided an update of the options available to either re-establish or discontinue the BPCRS.

633 Pharmeuropa Update

The Secretariat notified members of BP monographs that would require revision following proposed revisions to the drug substance monographs on Pharmeuropa 32.3 and 32.4.