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 8th February 2022.

Present: Professor A G Davidson *(Chair),* Dr P Marshall *(Vice Chair)*, Dr J C Berridge, Dr E Bush, Professor D Cairns, Mr A J Caws and Dr E Gray.

In attendance: Ms H Corns, Mr L Elanganathan, Ms K Busuttil (BP Lab) and Mr C Thompson (BP Lab).

Apologies: Dr H Batchelor, Mr P Fleming, Dr J Lough, Mr D Malpas and Mr S Nolan.

Dr Bush and Mr Caws declared an interest in or more agenda items and appropriate action was taken.

INTRODUCTORY REMARKS

655 **Welcome** The Chair welcomed members, Ms K Busuttil and Mr C Thompson to the meeting.

Dr P Marshall was announced as the new Vice Chair. Prof. D Cairns was thanked for his contribution as the former Vice Chair, and his continued membership of EAG MC1.

Mr D Deutsch and Mr S Bale had both retired from membership of EAG MC1 and were thanked for their contributions.

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.

656 **BP Update**

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

657 **MINUTES**

The minutes and summary minutes of the meeting held on 14 July 2021 were confirmed.

658 **Matters Arising from the Minutes**

Matters arising from the 14 July 2021 meeting were noted and members had no additional comments.

The following monographs had been progressed for publication in the BP 2023 following public consultation:

- Metformin & Sitagliptin preparations (minute 623 refers)
- Cetirizine Capsules (minute 625 refers)
- Zanamivir Inhalation Powder (minute 645 refers)
- Nevirapine preparations (minute 646 refers)
- Ketoconazole preparations (minute 648 refers)
- Amlodipine Oral Solution (minute 649 refers)

MONOGRAPHS

659 Aripiprazole preparations (New):
Aripiprazole Tablets
Aripiprazole Orodispersible Tablets
Aripiprazole Oral Solution

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

660 Doxazosin preparations (New):
Doxazosin Tablets
Doxazosin Prolonged-release Tablets

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

661 Pioglitazone Tablets (New)

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

662 Trazodone preparations:
Trazodone Capsules (Revised)
Trazodone Oral Solution (New)
Trazodone Tablets (Revised)

The draft monograph for Trazodone Oral Solution would be included in a future BP publication, subject to amendments and comments from manufacturers.

Revisions to the Trazodone Capsules and Trazodone Tablets monographs were proposed.

Definition (Tablets) Members questioned whether the requirement for Trazodone Tablets to be coated was necessary. The Secretariat agreed to investigate and remove the coating requirement if it was not needed for a functional reason.

Production (Capsules and Tablets) Members discussed whether the production statement controlling the content of impurity F needed to be retained in the monographs. As impurity F was an upstream intermediate in the synthesis of Trazodone Hydrochloride and not reported to be a degradation product, members concurred that control in the drug substance was the most appropriate route. It was agreed that the statement would be removed from the monographs.

Dissolution (Capsules and Tablets) Members recommended that a target concentration of 0.0055% w/v of trazodone hydrochloride was added for the dissolution test solutions.

Related substances (Capsules and Tablets) The gradient LC method to be evaluated as part of the new Oral Solution monograph appeared to offer greater impurity control, with the addition of impurity H which was a potential degradation product, in a single method. Members accepted the proposal to replace related substances tests A and B with the gradient procedure, subject to laboratory assessment.

The reporting threshold had been brought in line with ICH (from 0.05% to 0.1%) and the limit for impurity D (0.3%) reduced the unspecified peak limit of 0.2%, as this was a synthetic impurity. Members agreed the revised limits, subject to stakeholder comments.

663 Sumatriptan preparations (Revised):
Sumatriptan
Sumatriptan Injection
Sumatriptan Nasal Spray
Sumatriptan Tablets

Related substances and Assay A number of user queries had been received regarding the variation in peak retention time and elution order in the Related substances tests between these monographs. The Secretariat had identified these monographs as a suitable project for investigation by the Analytical Quality by Design Working Party, with an aim to propose harmonised conditions for all monographs.

The Secretariat summarised the investigations that were carried out, which ranged from statistical modelling and laboratory studies. Based on the results obtained, the following revised parameters were agreed by the AQbD Working Party for consideration by EAG MC1:

- pH adjustment of the buffer to 7.1
- 22 volumes of acetonitrile and 78 volumes of buffer
- Ambient column temperature

In addition, the following system suitability controls were also proposed:

- Theoretical plate count of at least 6000 for the sumatriptan peak
- Minimum peak-to-valley ratio between the peaks due to impurities E and 1 of at least 4.0.

Members accepted the recommendations from the AQbD Working Party and supported the proposal that additional information was provided to aid users' understanding of the method, as part of the BP's aim to expand the application of AQbD concepts into monographs.

664 Esomeprazole preparations (New):
Esomeprazole Gastro-Resistant Capsules
Esomeprazole Gastro-Resistant Granules
Esomeprazole for Injection
Esomeprazole Gastro-Resistant Tablets

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

665 Bisacodyl Gastro-resistant Tablets

Related substances A number of technical and editorial changes were agreed, ranging from the removal of impurity D as a specified impurity, relevant EPCRS changes, through to revision of the secondary peaks and disregard limit from in line with ICH.

666 Loratadine Tablets

Dissolution Members accepted the proposal to introduce a dissolution test to the monograph, based on the USP Loratadine Tablets monograph. A release limit of NLT 75% (Q) in 45 minutes was agreed, subject to comments from stakeholders.

Impurity H Members agreed the recommendation to omit the test for impurity H from the monograph, as it was a synthesis-related impurity and controlled in the drug substance monograph. Finished product specifications had not shown increased limits for the impurity at the end of shelf-life.

Related substances Members agreed that the disregard limit should be increased to align with ICH.

667 Mycophenolate Mofetil for Infusion

Content A manufacturer reported that the 95.0 to 105.0% was too stringent for their product and requested a revision to 93.0 to 105.0%.

POST-MEETING NOTE: This was accepted on the basis of clinical advice from an MHRA assessor.

668 MC1 Work status and updates

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

669 BP 2023 Proposed Omissions

The Secretariat presented monographs that were under consideration for omission, pending stakeholder comments, to which members agreed to.

POST-MEETING NOTE: No monographs were omitted in the BP 2023 as further information was required.

670 MC1 Out of stock BPCRS review

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

671 Pharmeuropa Update

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