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 July 2022.

Present: Professor A G Davidson *(Chair),* Dr P Marshall *(Vice Chair)*, Prof H Batchelor, Dr J C Berridge, Dr E Bush, Professor D Cairns, Mr A J Caws, Dr J Lough, Mr D Malpas, Mr S Nolan, Dr G Lee and Ms F Pina.

In attendance: Ms H Corns, Mr L Elanganathan, Ms G Li-Ship, Mr M Whaley, Mr S Greatorex (BP Lab), Mr C Thompson (BP Lab), Ms M Guler (Observer) and Ms C Swann (Observer). Mr J Pound attended the opening part of the meeting.

Apologies: Mr P Fleming.

INTRODUCTORY REMARKS

674 **Welcome** The Chair welcomed members Dr G Lee and Ms F Pina to their first meeting as members of the EAG. Ms G Li-Ship and Mr M Whaley were also welcomed to the meeting, and it was explained that they would be inheriting the role of Secretariat to EAG MC1 from Ms Corns, Mr Elanganathan and Ms Bowden.

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. Members were reminded to inform the Secretariat (Dr Fiona Swanson) of any changes to their interests throughout the year.

Membership of the Group Mr J Pound paid tribute to Professor Alastair Davidson who would be stepping down as Chair of MC1 at the end of 2022.

The current EAG MC1 Vice-Chair Dr P Marshall would be appointed the new Chair as of January 2023.

675 **BP Update**

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

676 **MINUTES**

The minutes and summary minutes of the meeting held on 8 February 2022 were confirmed.

677 Matters Arising from the Minutes **MC1(22)17**

Matters arising from the 8 February 2022 meeting were noted. Members had no additional comments.

MONOGRAPHS

678 Levetiracetam preparations:
Levetiracetam Tablets
Levetiracetam Granules
Levetiracetam for Oral Solution
Levetiracetam Oral Solution
Levetiracetam Sterile Concentrate
Levetiracetam Infusion

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

679 Digoxin preparations
Digoxin Tablets
Paediatric Digoxin Oral Solution
Digoxin Injection

The laboratory evaluations had been completed and the monographs had been updated with the findings from the laboratory reports.

Content (Tablets only) Laboratory assessment indicated that a tightened lower content limit would cause compliance challenges for licensed products. Members agreed that the lower limit of 90.0% should be retained, with a tightened upper limit of 105.0%, subject to stakeholder comments.

Identification A (Tablets) The TLC identification test, adapted from the Ph. Eur. Digitoxin related substances procedure, was found to be suitable.

Identification (Oral Solution and Injection) The drafted TLC procedure was found to be unsuitable due to excipient interference. An alternative HPLC/UV-DAD identification test from the Assay test was found to be suitable and was endorsed by members.

Dissolution (Tablets only) The UPLC revised dissolution procedure was found to be suitable, however, the method gave rise to high back pressures. An isocratic HPLC method, adapted from the gradient related substances chromatographic conditions, was found to be suitable and was agreed for inclusion.

A revised limit of 75% (Q) in 45 minutes, aligned with the minimum expectation for an immediate release product had been included, as the samples tested were able to meet 70% (Q) within 30 minutes.

Related substances (Tablets, Injection and Oral Solution) The Ph. Eur. Digoxin monograph related substances method was found to be suitable for Digoxin Tablets and Digoxin Injection, with modifications. It was not found to be suitable for the Oral Solution monograph. In the absence of an alternative procedure, members agreed that the other revisions to the monograph should be taken forward while a suitable related substances method was sought

A correction factor of 0.7 for impurity C was required which had been included in the Tablets and Injection monographs.

Uniformity of content/Assay (Tablets only) The method was found to be suitable for uniformity of content testing and assay and was accepted by members.

Assay (Injection only) The method was found to be suitable for the assay and was accepted by members. The content expression was agreed to be changed to 95.0 – 105.0% of the stated amount instead of a % w/v range (0.0237 to 0.0263%).

Assay (Oral Solution only) The drafted method was found to be unsuitable for the Oral Solution Assay. The USP Digoxin Oral Solution monograph method was found to be suitable and a tightened 95.0 to 105.0% content limit, was accepted subject to stakeholder comments.

Impurities (Tablets and Injection) Impurities sections had been included in the monographs following the completion of the laboratory assessments, which were accepted by members.

680 Topiramate preparations:
Topiramate Tablets
Topiramate Capsules
Topiramate Oral Suspension

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

681 Metformin preparations:
Metformin Oral Solution
Metformin Tablets

Definition (Tablets) It was agreed there was no functional need for the tablet coating so this statement will be deleted from the monograph.

Dissolution (Tablets) The Dissolution test found to be suitable and the group endorsed the proposed limit of not less than 75% (Q) after 45 minutes.

Related substances (Tablets, Oral Solution) The originally drafted Related substances method aligned with the Ph. Eur. method was found to be unsuitable due to issues with tailing of the API peak.

An alternative method was found to be suitable for all assessed products with an adjustment to the mobile phase and was incorporated into the draft monograph.

Assay (Tablets) The Assay was found to be suitable and the group endorsed the limits of 95.0% to 105.0%.

Identification (Oral Solution) The LC/UV-DAD test was found to be suitable for inclusion in the monograph.

Acidity or Alkalinity (Oral Solution) It was agreed that in the absence of a strong rationale to retain the test it could be deleted.

The group endorsed the proposed limits of not more than 0.02% for Impurity A, not more than 0.3% for Impurity 1, not more than 0.10% for any other secondary peak and a limit of not more than 0.4% for the sum of all secondary peaks (excluding Impurity A and Impurity 1).

682 Esomeprazole for Injection (new)
Omeprazole for Injection (new)

Dr Bush & Dr Lough declared an interest.

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

683 Omeprazole preparations (revised):
Omeprazole Gastro-Resistant Capsules
Omeprazole Gastro-Resistant Tablets

Dr Bush & Dr Lough declared an interest.

Definition (Gastro-Resistant Tablets only) Products had been licensed which were manufactured using Omeprazole Magnesium and therefore members agreed to the proposal that the definition should be revised to include this drug substance in addition to Omeprazole.

Identification Members agreed to the proposal to replace the separate peak comparison in assay and UV absorption identification tests with a single LC/UV-DAD procedure.

Related substances The proposal to revise the secondary peak limit to 0.2% which aligned with ICH, subject to stakeholder comments, was agreed.

684 Aspirin preparations

Mr A J Caws declared an interest.

Aspirin Effervescent Soluble Tablets Due to the lack of marketed (non-combination) UK products, members endorsed the omission of this monograph in the BP 2024, subject to stakeholder consultation and BPC agreement.

Aspirin Dispersible Tablets, Aspirin Gastro-Resistant Tablets, Aspirin Tablets - Related substances

The group endorsed revising the monographs in the use of an external standard for the quantification of Impurities A to F and the use of a correction factor of 0.7 for the quantification of Impurity B against Impurity C.

A subtotal for unspecified impurities of not greater than 0.2% for the “sum of the areas of any other secondary peaks” was proposed and accepted by the group.

685 Propofol Injection (revised)

Identification The draft method had been revised from IR to a UV method due to user-reported issues. Propofol Injection has a distinctive UV spectrum and the test was endorsed for inclusion.

Lysolecithin A user had also questioned the chromatography in the current test for Lysolecithin which specified the use of “phosphatidylethanolamine from egg yolk EPCRS” as used in the Ph.Eur. monograph for Egg Phospholipids for Injection. This Ph. Eur. Monograph states that lysolecithin “may be eluted as 1 or 2 peaks” because lysolecithin exists as a mixture of 2 isomers.

A revision to the Propofol Injection monograph introducing wording to indicate that lysolecithin may be present as two peaks, both of which should be used for the calculation if present, was agreed by members.

686 Sodium Valproate Oral Solution

Mr D Malpas declared an interest.

Alkalinity Members agreed to endorse new pH limits of 7.0 – 8.5 into the monograph to reflect licensed specifications.

687 Warfarin Tablets

Dissolution Following previous recommendations that dissolution requirements are expressed as the internationally harmonised quantity, Q; a revised limit of 75% (Q) in 45 minutes was proposed and accepted for this monograph, subject to stakeholder comments.

Related substances A specified limit of 0.5% for impurity A had been proposed and accepted for inclusion in the monograph, subject to stakeholder comments.

688 MC1 Work status and updates

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

689 Chromatographic Separation Techniques 2.2.46 – PDG harmonisation

Members were informed that a revision to Ph. Eur. Chromatographic Separation Techniques (2.2.46) was being published in the 11th edition.

690 MC1 Out of stock BPCRS review

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

691 Pharmeuropa Update

An update on the status of the Ph.Eur. texts published in Pharmeuropa 34.2 was presented to members.