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 at 10 South Colonnade, London E14 4PU on Thursday 13 June 2019.

Present: Dr G Cook (*Chairman)*, Mr C Goddard (*Vice-Chairman*), Prof J Birchall, Dr K Boon (nee Bracht), Mr J Cowie, Dr K Foster, Mr E Hook, Prof J Miller and Dr A Ruggiero.

In attendance: Ms H Corns, Mr L Elanganathan, Mr S Maddocks, Ms K Busuttil (BP Lab), Ms P Makhomu (BP Lab) and Ms M Nanasi (BP Lab).

Apologies: Mr N Wynne

Mr Goddard, Mr Cowie and Dr Ruggiero declared interests in one or more agenda items and appropriate action was taken

411 Introductory Remarks

Welcome The Chair welcomed members to the meeting and introduced the new experts for the Expert Advisory Group on Medicines Chemicals 2 (EAG MC2).

The Chairman also welcomed Scientists from the BP Laboratory; and Mr L Elanganathan, who had recently re-joined the BP Secretariat and Mr S Maddocks as new secretariat support to the EAG.

Expense Claims Members were invited to contact Mr Brian Delahunty (BP Secretariat) for enquires concerning expenses claims either via email brian.delahunty@mhra.gov.uk or on 020 3080 6144.

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 Secretariat of any changes to their interests throughout the year.

412 Emergency evacuation procedure **MC2(19)01**

The emergency evacuation procedure for the building was provided.

413 BP Update **MC2(19)02**

The launch of the recent consultation on Analytical Quality by Design (deadline for comments 31 August 2019) was brought to the attention of members: (https://www.gov.uk/government/consultations/consultation-on-the-application-of-analytical-quality-by-design-aqbd-principles-to-pharmacopoeial-standards-for-medicines). Dr Cook highlighted the unique nature of the AQbD project and encouraged all to comment.

A ‘How to use the BP’ companion guide had recently been developed to help users become more familiar with the content and application of BP and was available on the website (https://www.pharmacopoeia.com/how-to-use-the-bp). Feedback on the guide was welcomed, as the guide would be updated over time.

414 MINUTES

The minutes and summary minutes of the meeting held on 24 October 2018 were confirmed without amendment.

415 MATTERS ARISING FROM THE MINUTES

The following matters arising and correspondence items from the meeting held on 24 October 2018 were noted and members had no additional comments.

Chlorhexidine preparations Discussions were on-going the BP Secretariat and the MHRA Licensing Division regarding the limit for 4-chloroaniline.

Galantamine preparations Correction factors for impurities were investigated during BPCRS establishment work. A correction factor of 0.5 had been applied to impurity A in the monographs, published in the BP 2020, as a result.

Bisoprolol Tablets The members had previously queried differences in the system suitability requirements. The Secretariat confirmed that the Symmetry factor of 0.8 – 1.6 was suitable, confirmed by the associated Laboratory report. The Secretariat also confirmed that the Assay and Dissolution system suitability requirements were different as these are harmonised with the USP monograph.

Phenoxybenzamine Hydrochloride and preparations Further information had been received from a manufacturer and a Licensing Assessor had concluded the variation application assessment. Recommendations would be presented at a future meeting.

Cyclophosphamide preparations Advice on the inclusion of a conductivity detector for the LC related substances method was awaited.

Clenbuterol preparations The draft monographs would be published in a future edition of the BP.

Ibuprofen preparations The Ibuprofen Capsules monograph had been amended as discussed via the BP Forum, and progressed for publication in the BP 2020.

The acidity specification in the Ibuprofen Gel monograph was amended in line with licensed specifications, and progressed for publication in the BP 2020.

The additional laboratory work for the Ibuprofen Granules and Ibuprofen Oral Solution monographs, was scheduled for the 2019/2020 financial year.

Bumetanide preparations Members previous comments on the monographs have been addressed by the Secretariat, the monographs would be circulated to manufacturers and a paper be presented at a future meeting of the EAG.

MONOGRAPHS

416 Levothyroxine Tablets (revised) MC2(19)03

A market survey had been completed by the BP Laboratory which was undertaken on behalf of the MHRA Licensing division and BP to understand the levels of the Maillard impurity seen in UK products and to support the revision of the Levothyroxine Tablets monograph to include a Related substances test.

Related substances – Maillard impurity (impurity 1) The market survey had shown that the drafted related substances method was suitable for controlling the Maillard impurity and that it was present in all UK marketed products formulated with lactose. The Secretariat

reported that the Licensing division were working closely with manufacturers to determine an appropriate limit.

Related substances – other impurities The reports produced by the lab showed the method was suitable for the monograph. A secondary peak limit of 1.0% and a total impurity limit of 5.0%, excluding impurity 1, were proposed which took into account the results of the survey, the Ph Eur drug substance monograph, ICH guidelines and advice from Licensing, which members accepted subject to stakeholder comments.

417 Liothyronine Tablets (revised) **MC2(19)04; MC2(19)04b**

A market survey had been completed by the BP Laboratory which was undertaken on behalf of the MHRA Licensing division and BP to understand the levels of the Maillard impurity seen in UK products and to support the revision of the Levothyroxine Tablets monograph to include a Related substances test.

Content Members recommended that the upper limit was reduced from 110.0% to 105.0%. Advice on the proposal would be sought from the Licensing division and through public consultation. if that was acceptable to the Licensing division.

Identification B A second identification test, a peak comparison in Related substances which used a different stationary phase chemistry to the Uniformity of content test, was accepted by members.

Dissolution Insufficient data was available to determine whether water or a pH 10 borate buffer should be selected as the dissolution medium for the monograph test. As water was more physiologically relevant and, in the limited data available, appeared to be more discriminatory; it was agreed that this medium would be included in the draft made available for public consultation.

Related substances – Maillard impurity (impurity 1) The market survey had shown that the drafted related substances method was suitable for controlling the Maillard impurity and that it was present in all UK marketed products formulated with lactose. As for Levothyroxine Tablets, Secretariat reported that the Licensing division were working to determine an appropriate limit.

Related substances – other impurities The reports produced by the lab showed the method was suitable for the monograph. A secondary peak limit of 1.0% and a total impurity limit of 3.5%, excluding impurity 1, were proposed which took into account the results of the survey, ICH guidelines, the Ph Eur drug substance monograph and advice from Licensing colleagues, which members accepted subject to stakeholder comments.

Uniformity of content Members accepted the inclusion of a system suitability requirement which was harmonised with the Assay.

418 Carbocisteine preparations: **MC2(19)05;**
Carbocisteine Capsules (new)
Carbocisteine Oral Solution (new)

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

419 Methylphenidate Prolonged-release preparations: (new) **MC2(19)06;**
Methylphenidate Prolonged-release Capsules (new)
Methylphenidate Prolonged-release Tablets (new)

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

420 **Furosemide preparations:** **MC2(19)07;**
Furosemide Tablets (revised)
Furosemide Injection (revised)
Furosemide Oral Solution (new)

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

Dissolution (Tablets) The exclusion of tablets containing more than 100 mg of Furosemide was removed from the dissolution test, subject to stakeholder comments.

Related Substances . Additional information had been received from a manufacturer confirming the suitability of the test for the monographs. It was agreed that stakeholder comments should be sought prior to publication of the revised monographs.

421 **Tamsulosin Prolonged-release preparations (revised):** **MC2(19)08;**
Tamsulosin Prolonged-release Capsules
Tamsulosin Prolonged-release Tablets

Related substances The proposed method was assessed by the BP laboratory and found to be suitable for compendial use for both the capsules and the tablets, however a slight modification to the sample solvent was required for the tablets. It was agreed that the Secretariat would work with the Licensing Division, individual Manufacturers and the BP laboratory to provide full justification for impurity limits prior to publication of the revised monograph.

422 **Mebeverine preparations:** **MC2(19)09;**
Mebeverine Tablets (revised)
Mebeverine Prolonged-release Capsules (new)

Following the publication of the Mebeverine Hydrochloride monograph in European Pharmacopoeia 9.8 supplement, the BP monograph for Mebeverine Hydrochloride was omitted from the BP 2020. Data packages had been received by the Secretariat for the Tablets and Prolonged-release Capsules formulations. The draft monograph for Mebeverine Prolonged-release Capsules would be included in a future BP publication, subject to comments.

Identification (Tablets) The replacement of chloroform in the IR extraction would be investigated. It was agreed that the identification test B in this monograph was not required as ID by infra-red spectroscopy was sufficiently discriminatory. The Secretariat agreed to remove this test from the draft Furosemide Tablets monograph.

Identification B (Tablets) The light absorption test would be deleted from a future publication as IR was considered suitably discriminatory.

Dissolution It was agreed that a dissolution test would be added to the monograph. The test utilised 0.01M HCl as the medium and used Apparatus 2 with a 75 revolutions per minute for 45 minutes. A limit of 80% (Q) was adopted.

Related Substances The TLC related substances test would be replaced by an LC procedure, following confirmation that the test was suitable for compendial purposes by the BP laboratory. The proposed limits were at 0.2% for impurities C, D and Unspecified. The total impurities limit was agreed at 1.0%

Assay The assay would be updated with a more specific LC procedure, if found suitable by the BP Laboratory.

423 **Modafinil Tablets (new)** **MC2(19)10;**

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

424 Simvastatin preparations: MC2(19)11;
Simvastatin Oral Suspension (revised)
Simvastatin Tablets (revised)

Due to an update in the Simvastatin parent monograph, the Simvastatin for peak identification EPCRS was no longer available. This was replaced the monographs with the new Simvastatin for System Suitability EPCRS for the BP 2020. The new EPCRS contained a number of new impurities (I and J) as well as the existing impurities (A, B, C, D, E, F and G).

Related Substances The updated Ph . Eur. HPLC procedure was drafted in to the related substances procedures in both monographs. The extraction solvents and procedures have remained the same as the published monographs as they were still compatible with the mobile phase. Members agreed that the similarity in the methods allowed the direct replacement of the published methods with the new API method and the monographs should be placed on the website for public consultation following editorial modifications.

425 Nicorandil Tablets (revised) MC2(19)12;

Public consultation on the draft revised monograph had been completed. No substantive comments were received and one manufacturer had sought clarification on the amendments made. It was agreed that the draft revised monograph could be taken forward for publication.

426 Oxybutynin Tablets (revised) MC2(19)13;

This paper was deferred to a future meeting of the EAG due to the Secretariat requiring further information from the collaborating manufacturer.

427 Atenolol Tablets (revised) MC2(19)14;

Customer queries had prompted a review of the Atenolol Tablets monograph. The customer queries surrounded an issue where the main peak during the related substances procedure was splitting during the chromatography. A change had been made to the monograph to indicate a more suitable column manufacturer without changing the stationary phase.

428 MC2 Work status and updates MC1(19)15;

The MC2 work programme was presented to members for information.

429 Ph. Eur. Updates MC2(19)16;

An update on changes to Ph. Eur. monographs that affected MC2 monographs was presented to members.

430 ANY OTHER BUSINESS MC2(19)17

No items were raised.

431 DATE OF NEXT MEETING

Tuesday 22 October 2019