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 via videoconference on the 9th and 10th November 2022.

Present: Dr G Cook (*Chairman)*, Mr C Goddard (*Vice-Chairman*), Prof J Birchall, Ms K Boon, Mr J Cowie, Mr E Hook, Prof J Miller, Mr J Rickard and Mr N Wynne (9th November session only).

In attendance: Ms H Corns, Ms A Thomson, Ms C Swann, Mr K Rakowski (10th November session only), Mr S Greatorex (9th November session only) and Mr C Thompson (10th November session only).

Apologies: Dr K Foster, Dr A Ruggiero and Mr N Wynne (10th November session only).

547 Introductory Remarks

Welcome The Chairman welcomed members to the meeting, Mr J Rickard as a new member to MC2, Mr C Thompson and Mr S Greatorex from the BP Laboratory, and Ms C Swann from the Secretariat.

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.

548 BP Update **MC2(22)14**

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

549 MINUTES

The Minutes and Summary Minutes from the meeting held on the 10th and 13th May 2022 were confirmed without amendment.

550 MATTERS ARISING FROM THE MINUTES **MC2(22)15**

The following matters arising and correspondence items from the meeting held on the 10th and 13th May 2022 were noted.

MONOGRAPHS

Dr G Cook, Mr J Cowie, Mr E Hook and Mr N Wynne declared interests in one or more agenda items and appropriate action was taken.

551 Ephedrine preparations: MC2(22)16
Ephedrine Injection (Revised)
Ephedrine Nasal Drops (Revised)
Ephedrine Hydrochloride Tablets (Revised)
Ephedrine Elixir (Omission)

Ephedrine Elixir No UK licence holders for Ephedrine Elixir or Oral Solution had been identified. It was not listed in the BNF and there was no apparent usage of this product in the UK. Members agreed the proposed omission of the monograph, subject to comments from stakeholders and BPC approval.

Definition (Ephedrine Injection only) A proposal to broaden the definition to encompass the ready-to-use injection and a solution that may be further diluted, with deletion of the sub-monograph for Ephedrine Sterile Concentrate was accepted by members.

Content (Ephedrine Hydrochloride Tablets only) Members agreed that revised content limits of 95.0 to 105.0% should be consulted on.

Identification (Injection and Nasal Drops) The proposed revision of the identification tests to a LC/UV-DAD procedure was agreed.

Identification (Ephedrine Hydrochloride Tablets only) A revised extraction procedure for the IR identification test, based on the extraction in the Pseudoephedrine Tablets monograph, was accepted subject to confirmation of suitability.

Acidity or alkalinity (Injection and Nasal Drops) Members confirmed that the pH requirement should be removed from the Nasal Drops monograph and only retained in the Injection monograph if it was needed.

Dissolution (Ephedrine Hydrochloride Tablets only) A dissolution test, based on the USP procedure for Pseudoephedrine Hydrochloride Tablets had been drafted. Members advised that a release requirement of 75% (Q) in 45 minutes was unlikely to be discriminatory and recommended that 80% (Q) in 30 minutes included for stakeholders to comment on.

Related substances A revised method, provided by a manufacturer, had been included in the draft revised monographs, as the method in the Injection monograph was found not to be sufficiently selective for three additional impurities reported by an MAH; and impurities were controlled with a TLC test in the Nasal Drops and Tablets monographs. Members supported revision of the tests in the Ephedrine monographs, subject to further information being received and confirmation that the method was suitable for compendial use.

Assay The assay procedure had been harmonised with the related substances method, in line with the manufacturer's proposals, which was accepted by members.

Impurities A transparency statement had been added to the monographs which included the additional impurities reported by the manufacturer.

Ephedrine Sterile Concentrate (Ephedrine Injection only) Members confirmed the deletion of the sub-monograph with the adoption of the revised definition.

552 **Salbutamol preparations:** **MC2(22)17**
Salbutamol Nebuliser Solution (Revised)
Salbutamol Oral Solution (Revised)
Salbutamol Injection (Revised)
Salbutamol Tablets (Revised)
Salbutamol Inhalation Powder (Revised)
Salbutamol Inhalation Powder, pre-metered (Revised)
Salbutamol Pressurised Inhalation, Suspension (Revised)
Salbutamol Prolonged-release Capsules (Omission)

Content (Tablets) Members requested that tighter content limits of 95.0 – 105.0% were considered for the Tablets monograph, as this was achievable for the lower strength liquid formulations.

Related substances (Oral Solution) A review had identified that changes to the drafted limits could be required; tightening of the impurity C limit from 0.5% to 0.3% and the addition of four specified impurities (N,O, 1 and 2) at 0.3% each was proposed, which members accepted subject to stakeholder comments.

Related substances (Injection) A specified limit of 0.3% for impurity F had been included, aligned with the limit in the Ph. Eur. Salbutamol Sulfate monograph, which was agreed by members.

Related substances (Nebuliser Solution) A method had been received from a manufacturer and included in the draft revised monograph. Members supported the adoption of the method subject to the receipt of additional information from the manufacturer and stakeholder comments.

Assay (Nebuliser Solution) The method provided by the manufacturer had been included in the monograph, which was similar to the published Salbutamol Injection method.

Salbutamol Prolonged-release Capsules No UK licence holders for Salbutamol Prolonged-release Capsules had been identified. It was not listed in the BNF and there was no apparent usage of this product in the UK. Members agreed the proposed omission of the monograph, subject to comments from stakeholders and BPC approval.

553 Atenolol preparations: MC2(22)18

Atenolol Injection (Revised)
Atenolol Oral Solution (Revised)
Atenolol Tablets (Revised)
Co-tenidone Tablets (Revised)

Definition (Injection only) Members questioned whether it was necessary to specify citric acid monohydrate and sodium chloride in the definition. The Secretariat agreed to investigate further.

Content Members agreed that content limits should be revised to 95.0 to 105.0%, where achievable and subject to stakeholder comments.

Identification (Injection, Oral Solution and Co-tenidone Tablets) Members endorsed replacement of the published tests, which used chloroform, with LC/UV-DAD identification determined in the assay, where suitable.

Identification (Atenolol Tablets only) Members agreed the proposal for the laboratory to evaluate an alternative extraction procedure for the IR identification test, to remove chloroform from the monograph.

Acidity or alkalinity (Injection and Oral Solution) Members confirmed that the pH test should be removed from the Oral Solution monograph. It was recommended that the requirement in the Injection monograph was reviewed.

Dissolution (Tablets) Members accepted the proposals to include the USP Atenolol Tablets and Atenolol and Chlortalidone Tablets dissolution test conditions into the corresponding BP monographs. Members advised that limits of 80% (Q) in 30 minutes for Atenolol Tablets; and 80% (Q) for atenolol and 70% (Q) for chlortalidone in 45 minutes for Co-tenidone Tablets, aligned with the USP monographs, should be included subject to stakeholder comments.

Related substances The BP Lab had provided data that demonstrated quantitative limits could be applied to the published method which members accepted. Limits for individual unspecified impurities (NMT 0.2%) and a reporting threshold (0.1%) had been included, aligned with ICH. Members agreed that a total impurity limit of 1.0% should be included in all monographs, subject to stakeholder comments. An additional limit for Chlortalidone impurity B was included for Co-tenidone Tablets and excluded from the total impurity limit.

The system suitability test was revised to a resolution requirement of at least 1.5 between impurity E and impurity F peak 1, which replaced resemblance to the reference chromatogram provided with atenolol impurity standard.

Assay (Injection and Atenolol Tablets) Members confirmed that the non-specific assay procedures should be replaced with the HPLC procedure from the Oral Solution monograph.

Assay (Co-tenidone Tablets) It was agreed that the requirement to remove the film coating during the sample preparation should be deleted from the test.

Impurities Members endorsed the inclusion of the impurities section in the monographs.

554 Duloxetine Gastro-resistant Capsules (New) MC2(22)19

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

555 Indapamide preparations: MC2(22)20

Indapamide Tablets (Revised)
Indapamide Prolonged-release Tablets (Revised)

Definition (Tablets only) It was confirmed that the requirement for the tablets to be coated should be deleted.

Identification The BP Laboratory had found that HPLC-UV/DAD was suitable for identification. Members agreed that this test should replace the TLC procedure.

Impurity C (Tablets) The BP Laboratory reported that the Ph Eur test for impurity C was suitable with modifications to the solution concentrations and injection volume. The modified method was accepted by members.

Impurity C (Prolonged-release Tablets) The drafted method and Ph Eur method were both found to be unsuitable for the control of impurity C in prolonged-release tablets. In the absence of a suitable method, members agreed that the production statement, for a suitable test for impurity C to be carried out, should be retained.

Related substances A method provided by an MAH which offered improved separation of impurities was found to be suitable by the BP Lab. Correction factors of 0.6 for impurity B and 1.7 for impurity 2 were confirmed. Members endorsed the adoption of the revised test, subject to stakeholder comments.

Uniformity of content (Prolonged-release Tablets) The Lab confirmed that the related substances chromatographic conditions were suitable for uniformity of content testing for the prolonged-release tablets when reduced solution concentrations were used.

Assay The Lab confirmed that the related substances chromatographic conditions were suitable for use as an assay when reduced solution concentrations were used. All samples tested were able to comply with the limits.

556 Mirabegron Prolonged-release Tablets (New) MC2(22)21

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

557 Rivastigmine Transdermal Patches (Revised) MC2(22)22

Related substances A request had been received to increase of the limit for impurity A from 0.3% to 0.4%, to include an additional specified degradation impurity (impurity 1) to be controlled at 0.4%, and to increase of the total impurities threshold from 0.5% to 1.0%. The changes were approved by the group, based on the information provided and subject to stakeholder comments.

558 Chlorhexidine preparations: MC2(22)23
Chlorhexidine Gluconate Dental Gel (Revised)
Chlorhexidine Mouthwash (Revised)

Related substances (Dental Gel) During the stakeholder comment window, a MAH requested that the limit for 4-chloroaniline was revised to 0.25% from 0.2% and an unspecified impurity limit of 0.3%, compared to the drafted 0.2% limit, were included in the monograph. The numerical limit of 0.2% allowed up to 0.249%, which would be brought to the attention of the MAH. Members were not convinced that an increase to the unspecified impurity was justified by the information provided.

Related substances (Mouthwash) A MAH requested that the unspecified impurity limit was increased to 0.5%, compared to the drafted 0.2% limit. The increased unspecified impurity limit only appeared to be needed to accommodate one impurity seen at 0.3%, which could correspond to impurity K based on the relative retention. The Secretariat agreed to investigate whether a specified limit for impurity K would resolve this request with the MAH.

The MAH also requested that the total impurity limit, excluding impurity N, was increased from 2.0% to 2.5%, which members accepted based on the information provided.

559 Trandolapril Capsules (Revised) MC2(22)24

Identification B Members confirmed the proposal to delete identification test B, as the IR identification test was considered sufficiently discriminatory to be used as a standalone procedure.

Related substances A review had found that approved UK products contained limits of NMT 4.0% for impurity E and NMT 1.0% for impurity D, whereas the monograph had a limit of NMT 4.0% for impurity D and NMT 1.0% for impurity E. It was noted that the active metabolite, impurity E, was an intermediate in the formation of impurity D. Members highlighted that the formulation of the products could affect which was the predominant impurity. Members agreed that the limits in the monograph should be aligned with current approved UK limits, subject to stakeholder consultation. It was accepted that the monograph may require a combined limit for impurities D and E, to accommodate the potential for different impurity profiles due to product formulation.

560 Enalapril Tablets (Revised) MC2(22)25

Identification Members requested that an IR identification test was included in the monograph, if suitable, which the Secretariat agreed to investigate.

Dissolution Members noted that the dissolution test referred to the pre-Q value BP requirement and requested that the limit was updated to a Q value, in line with the policy to update pre-BP 2008 dissolution tests to include limits expressed in terms of the internationally harmonised quantity, Q. A limit of 80% (Q) in 30 minutes, harmonised with the USP, was agreed subject to stakeholder comments.

Related substances Justification for a widened limit of 2.0% for impurity C enalaprilat), from 1.5%, had been received. Members endorsed the increased limit, subject to stakeholder comments.

FOR INFORMATION

561 Out of Stock BPCRS MC2(22)26

The Secretariat reviewed the out-of-stock BPCRS for monographs relevant to EAG MC2 and presented these to the group.

562 MC2 Work status and updates MC2(22)27

The MC2 Work Programme was presented to members for information.

563 Ph. Eur. Updates MC2(22)28

The Secretariat thanked members for their contributions to the Pharmeuropa 34.3 review and confirmed that none of the texts in the Pharmeuropa 34.4 review had been assigned to MC2.

564 ANY OTHER BUSINESS

None.

565 NEXT MEETING

24 May 2023