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 13th May 2020.

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

In attendance: Ms H Corns, Dr H Bowden, Ms K Busuttil (BP Lab) and Ms M Nanasi (BP Lab).

Apologies: NA

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

452 Introductory Remarks

Welcome The Chairman welcomed members to the meeting and also welcomed Ms K Busuttil and Ms M Nanasi who attended from the BP Laboratory.

Expense Claims Members were invited to contact Mr Brian Delahunty (BP Secretariat) for enquires concerning expenses claims via email brian.delahunty@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 reminded that they are required to inform the Secretariat (Dr Fiona Swanson) of any changes to their interests throughout the year.

453 BP update

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

454 MINUTES

The minutes and summary minutes on the meeting held on the 22nd October 2019 were confirmed without amendment.

455 MATTERS ARISING FROM THE MINUTES

Matters arising and correspondence items from the meeting held on the 22nd October

2019 were noted.

MONOGRAPHS

456 **Chlorhexidine preparations:**
Chlorhexidine Gluconate Gel (for Acne) (New)
Chlorhexidine Gluconate Dental Gel (Revision)
Chlorhexidine Gluconate Gel (for Umbilical Cord Care) (New)
Chlorhexidine Irrigation Solution (Revision)
Chlorhexidine Mouthwash (Revision)

4-Chloroaniline (impurity P) limits (all monographs) It was acknowledged that a major challenge in the calculation of an ICH M7 aligned limit was that most chlorhexidine preparations were topically applied to affected areas, rather than ingested; therefore, dosing of the product and exposure to 4-chloroaniline were difficult to determine and that therefore Members agreed that in the absence of a patient safety driver and that these were long-established products, current published limits should be retained. Members also agreed that consistent expression of the 4-chloronaniline limit across the monographs would be beneficial and recommended that a limit relative to the amount of chlorhexidine in the product should be applied across the monograph family.

Chlorhexidine Gluconate Gel for Acne (New)

The new monographs would be included in a future publication of the BP subject to comments.

Chlorhexidine Gluconate Dental Gel (Revised)

Identification B and C As the combination of UV (Identification A) and peak comparison in the Assay (Identification C) were considered sufficient to confirm identity, members agreed that the colour change test should be deleted from the monograph.

4-Chloroaniline Members agreed to the deletion of the test for 4-chloroaniline, as the impurity was detected using the related substances procedure submitted by a manufacturer.

Related substances A gradient LC related substances test was accepted subject to further advice from manufacturers and comments from stakeholders.

Assay Members accepted the revised assay which was aligned with the related substances test.

Chlorhexidine Gluconate Gel for Umbilical Cord Care (New)

The new monographs would be included in a future publication of the BP subject to comments.

Chlorhexidine Irrigation Solution (Revised)

Identification A Members accepted the replacement of the published colour change test with the UV test from the Ph Int monograph for Chlorhexidine Digluconate Topical Solution.

4-Chloroaniline Members agreed the deletion of the test for 4-chloroaniline, as the impurity was detected using the related substances procedure submitted by the manufacturer.

Related substances An LC gradient method was accepted subject to laboratory evaluation and stakeholder comments.

Assay The Assay had been harmonised with the draft revised related substances test. The Secretariat would review the revised test in light of the comments made by members on the related substances method.

Chlorhexidine Mouthwash (Revised)

Identification A confirmatory identification test to complement the peak comparison in the Assay was agreed, subject to laboratory evaluation.

4-Chloroaniline Members agreed the deletion of the test for 4-chloroaniline, as the impurity was detected using the revised related substances procedure.

Related substances A gradient LC related substances test was agreed subject to laboratory evaluation and stakeholder comments.

Assay A revised assay harmonised with the draft revised related substances test, was accepted.

457 **Co-careldopa preparations:**

Co-careldopa Tablets (New)

Co-careldopa Prolonged-release Tablets (New)

The new monographs would be included in a future publication of the BP subject to comments.

458 **Ibuprofen preparations:**

Ibuprofen Effervescent Granules (New)

Ibuprofen Gel (Revised)

Ibuprofen Gel - Related substances

Minor amendments to the test conditions resulting in improved chromatography were endorsed by members.

Ibuprofen Effervescent Granules

The draft monograph would be included in a future BP publication.

4'-isobutylacetophenone BPCRS It was noted by the group that the identity of 4'-isobutylacetophenone BPCRS should be highlighted in the BPCRS leaflet as being equivalent to the Ph. Eur Impurity E. The Secretariat agreed to add this statement to the leaflet.

459 Adrenaline Injection preparations

The Adrenaline Injection preparations item was deferred to the next meeting.

460 Tranylcypromine preparations:

Tranylcypromine Sulfate (Revised)

Tranylcypromine Tablets (Revised)

Identification (Tablets) It was agreed by the EAG that the 3 current ID tests would be replaced with a UV-DAD comparison in the Assay, subject to public consultation and approval to adopt the test from BPC.

Dissolution (Tablets). The limit had been revised to 75% Q at 45 minutes, to bring in line with BP policy for dissolution test limits. The group agreed to accept this limit subject to stakeholder comments.

Related substances (Tranylcypromine Sulfate) The related substances method had been revised from gas chromatography to liquid chromatography And aligned with the USP Tranylcypromine Sulfate monograph.

The draft monograph limits impurities A-D at 0.5%. These were accepted by the EAG subject to public consultation.

Related substances (Tablets) The related substances method has been harmonised with the Tranylcypromine Sulfate monograph liquid chromatography method and limits impurities A-D at 0.5%. This was accepted by the group subject to public consultation.

Assay (Tablets) The assay method had been revised from a UV assay to harmonise with the new HPLC related substances method and was accepted by the group.

Impurities A transparency statement was included in the revised monographs.

461 Solifenacin Oral Suspension (New)

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

462 Naproxen preparations:

Naproxen Oral Suspension (Revised)
Naproxen Tablets (Revised)
Naproxen Gastro-Resistant Tablets (Revised)

Identification (Oral Suspension) The laboratory work confirmed that the revised IR sample preparation method was suitable.

Dissolution (Oral Suspension) Addition of a dissolution test was accepted by members, subject to stakeholder comments. A limit of not less than 80% (Q) in 15 minutes had been drafted.

Dissolution (Tablets) Members agreed to the proposal to update the dissolution limit to a harmonised acceptance value of 75% (Q), subject to stakeholder comments.

Related substances Laboratory evaluation confirmed that the Related substances method was suitable, and members agreed that the method should be adopted subject to stakeholder comments.

Assay Laboratory evaluation confirmed that the Related substances method was also suitable for assay purpose. Members agreed that the method should be adopted in the monographs, subject to stakeholder comments.

463 Rivastigmine preparations:
Rivastigmine Oral Solution (New)
Rivastigmine Capsules (New)
Rivastigmine Transdermal Patches (New)

The draft monographs would be included in a future publication of the BP, subject to comments.

464 Donepezil preparations:
Donepezil Oral solution (New)
Donepezil Orodispersible Tablets (New)
Donepezil Tablets (New)

The monographs would be included in a future publication of the BP, subject to comments.

465 Supplementary papers - February 2020

Nicorandil Tablets The Secretariat confirmed that members recommendations to remove the drafted revised production statement and to increase the limit for impurity D from 0.8% to 1% had been taken forward for publication in the BP 2021

Lisinopril preparations (Related substances) The laboratory had reported the success of an in-situ generation of the diketopiperazine impurity. This BPCRS had been a long term out of stock product. The revision had been drafted into the tablets and oral solution monographs and had been accepted by the EAG for publication in the BP 2021.

Co-beneldopa Capsules (Related substances) Members had agreed with the justification for the increase in the limit for benserazide impurity B from 0.5% to 0.7%. The Secretariat reported that the change was published in the BP 2021.

FOR INFORMATION

466 Out of Stock BPCRS

The updated long term out of stock BPCRS materials list was presented to the EAG.

467 MC2 Work status and updates

The MC2 work programme was presented to members for information.

468 Ph. Eur. Updates

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

469 ANY OTHER BUSINESS

No items raised.

470 NEXT MEETING

6th and 9th October 2020