BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group MC2: Medicinal Chemicals

MINUTES

A meeting of this Expert Advisory Group (EAG): Medicinal Chemicals 2 (MC2) was held at 10 South Colonnade, London E14 4PU on Tuesday 22 October 2019.

Present: Dr G Cook (*Chairman)*, Mr C Goddard (*Vice-Chairman*), Prof J Birchall, 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, Mr S Maddocks, Mr Ryan Smith, Ms K Busuttil (BP Lab) and Mr C Thompson (BP Lab).

Apologies: Dr K Boon.

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

432 Introductory Remarks

Welcome The Chairman welcomed members to the meeting and also welcomed Ms K Busuttil and Mr C Thompson who attended from the BP Laboratory; and Dr H Bowden and Mr R Smith who have both recently joined the BP 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.

433 Emergency evacuation procedure

The emergency evacuation procedure for the building was provided.

434 BP Update

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

435 MINUTES

The minutes and summary minutes of the meeting held on 13 June 2019 were confirmed without amendment.

436 MATTERS ARISING FROM THE MINUTES

Matters arising and correspondence items from the meeting held on 13 June 2019 were noted.

MONOGRAPHS

437 Portfolio review

A set of general principles and measures had been developed by the Secretariat to support a broad and systematic review of the BP monograph portfolio. The following monographs were proposed for omission from the BP 2021, which were accepted subject to comments from

stakeholders and confirmation from BPC:

Bretylium Tosilate	Bretylium Injection	
Colestipol Hydrochloride	Colestipol Granules	
Metipranolol	Metipranolol Eye Drops	
Dipivefrine Eye Drops	Flurbiprofen Suppositories	
Clemastine Oral Solution	Mexiletine Injection	
Sulfaquinoxaline	Sulfadoxine and Trimethoprim Injection	
Sterile Phenoxybenzamine Concentrate		

438 Adrenaline Injection preparations:
Adrenaline Injection / Epinephrine Injection
Dilute Adrenaline Injection 1 in 10,000 / Dilute Epinephrine Injection 1 in 10,000

Laboratory assessment of options to improve the Related substances test and of a chiral assay had been completed and were reported to the group.

Content Members advised that wording of the content requirement should be changed from 'and not less than 0.0850% w/v is L-adrenaline' to 'of which at least 0.0850% w/v is L-adrenaline', as this would be clearer to users.

Related substances Following laboratory work it was agreed that the improved control of impurity F, a degradation product, was more important than a second control on the synthetic impurities D and E, which were already limited in the Ph. Eur. drug substance monographs.

Members noted that it was not clear that the total impurities limit of 16% applied to the combined results of the D-adrenaline and related substances tests. The Secretariat agreed to investigate means to distinguish this limit from the related substances test limits.

Assay The laboratory assessment had found that the results for the chiral assay were inconsistent with results of the related substances test. Members agreed that the current test should be retained and that calculation instructions for the L-adrenaline content should be included in the monograph. Further work on a chiral assay for the monographs was recommended.

439 Chlorhexidine Gluconate Gel preparations

Monograph titles 3 separate monographs covering gel for acne treatment, dental gel and gel for umbilical cord care were recommended for development by licensing and agreed by MC2. The names for these monographs should be advised by EAGs NOM and PCY.

MC2 confirmed that the Chlorhexidine Gluconate Gel published monograph should be changed to Chlorhexidine Gluconate Dental Gel at the earliest opportunity. The Secretariat agreed to investigate whether the currently published name presents potential risk to availability of the umbilical cord care and options to implement an immediate revision, if required.

440 Innovation Board

An update on BP website improvement projects was presented to the group.

441 Ibuprofen preparations;
Ibuprofen Effervescent Granules
Ibuprofen Oral Suspension

Additional lab work had been completed by the BP lab and was presented to members. The draft monograph for Ibuprofen Effervescent Granules would be included in a future publication, subject to comments from manufacturers.

Dissolution (Granules) The Secretariat agreed to review the requirements of the general monograph for Granules and to work with Licensing colleagues, to investigate whether a dissolution test was needed. It was recommended that the analytical conditions were harmonised with the Assay if possible.

Dissolution (Oral suspension) The group accepted the addition of the proposed dissolution test.
Related substances Following a laboratory investigation it was confirmed that the impurities detected in the ibuprofen products were not related to ibuprofen. The Secretariat agreed to investigate this via public consultation on the draft revised monograph.

Assay (Granules) Members expressed concern over the lab report and it was agreed that the secretariat would investigate the chromatography before taking the monograph forward for publication.

442 Phenoxybenzamine preparations:
Phenoxybenzamine Capsules
Sterile Phenoxybenzamine Concentrate

Content (Capsules) Members queried whether the content limits could be tightened to 95.0 – 105.0% from 92.5 – 107.5%. The Secretariat agreed to investigate this via public consultation on the draft revised monograph.

Related substances – chromatographic conditions (Capsules)
The group accepted the reduction of the flow rate from 1-0.6 mL/min to improve the separation of the impurities and the Secretariat agreed to review the run time and amend, as appropriate.

Related substances – limits (Capsules)
Members agreed that limits of NMT 1.5% and NMT 1.0% for impurity B (as named in the draft Ph. Eur. Phenoxybenzamine Hydrochloride monograph) and Impurity 1 (phenoxybenzamine tertiary amine) respectively should be added to the monograph.

Assay (Capsules) Members agreed that the system suitability requirement should be deleted, as the unknown peak referenced in the monograph was not always found to be present.

Impurities (Capsules) The inclusion of an impurities section was agreed, which cross-referenced the impurities in the draft Ph. Eur. monograph for Phenoxybenzamine Hydrochloride.

Sterile Phenoxybenzamine Concentrate As there were no licensed sterile concentrate products, members agreed that the monograph should be put forward to BPC for omission, subject to advice from international stakeholders and EAG ULM.

443 Solifenacin preparations:
Solifenacin Oral Suspension
Solifenacin Tablets

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

444 Diclofenac preparations:
Diclofenac Diethylamine
Diclofenac Gastro-resistant Tablets
Diclofenac Gel
Diclofenac Prolonged-release Capsules
Diclofenac Prolonged-release Tablets

Related substances
Diclofenac Gastro-resistant Tablets and Prolonged-release Tablets monographs had been revised to maintain harmonisation with the Ph. Eur. Diclofenac Potassium and Diclofenac Sodium monographs. Members accepted the column change from C8 to C18 and the correction factors for impurities A and F, and also recommended that a means to identify impurity F in solution (1) was included in the monographs.

Information would be sought regarding the need for correction factors for impurities A and F in the Prolonged-release Capsules, Diclofenac Diethylamine and Diclofenac Gel monographs, before revision of these monographs can be proposed.

445 Mexiletine preparations:
Mexiletine Capsules
Mexiletine Injection

Content (Capsules) A product had been licensed by the EMA with the expression of strength in terms of the active moiety, not in terms of mexiletine hydrochloride, as stated in the BP monograph. There were no national licences for mexiletine preparations Members accepted the draft revision to express the content in the BP monograph in terms of the active moiety, subject to comments from stakeholders.

Dissolution (Capsules) Members accepted the drafted dissolution test, based on the USP monograph for Mexiletine Hydrochloride Capsules, subject to stakeholder comments.

Mexiletine Injection Members agreed that the monograph should be put forward to BPC for omission, subject to advice from international stakeholders and EAG ULM.

446 Propranolol preparations:
Propranolol Injection
Propranolol Oral Solution
Propranolol Prolonged-release Capsules
Propranolol Tablets

Related Substances MC2 accepted the proposal to harmonise the chromatographic conditions with the Ph. Eur. 10.0 update of the Propranolol Hydrochloride monograph. Manufacturers would have the opportunity to comment on the revisions to the monographs prior to publication.

Identification (Injection, Oral solution, Tablets) The group agreed to remove the second identification test from the monographs that contained an IR identification method.

Assay (Injection, Tablets, Prolonged release capsules) The Secretariat agreed to add the update of the Assay to LC to the MC2 work programme.

447 Out of stock BPCRS

Long term out of stock BPCRS materials brought to the attention of the group for comment and advice regarding the sourcing of the materials.

448 MC2 Work status and update

The MC2 work programme was presented to members for information.

449 Ph. Eur. Updates

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

450 ANY OTHER BUSINESS

The definition in the monograph for Ipratropium Nebuliser Solution monograph has changed to allow the use of “a suitable vehicle” for the product rather than “water for injections”.

451 DATE OF NEXT MEETING

Wednesday 13 May 2020