BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group MC2: Medicinal Chemicals

SUMMARY MINUTES

A meeting of this Expert Advisory Group was held at 151 Buckingham Palace Road, London SW1W 9SZ on Tuesday 24th October 2017.

Present: Dr G Cook (*Chairman)*, Mr C Goddard (*Vice-Chairman*), Prof J Miller, Mr N Wynne, Mr J Cowie, Dr J Lim and Dr K Bracht. Dr O Ní Ógáin was present for part of the meeting.

In attendance: Ms H Corns, Mr L Elanganathan, Ms S Gomersal (MHRA), Ms F Lee (BP Lab), Mrs C Galdino (BP Lab) and Ms N Ionescu (BP Lab).

Apologies: Dr D Edwards, Mr P Murray, and Mrs M Turgoose

350 Introductory Remarks

Welcome The Chairman welcomed Dr K Bracht who had been invited to observe the meeting as the proposed new Licensing representative on the group, to replace Dr A Ruggiero who had recently left the Agency. Dr A Ruggiero had been invited to submit an application to join EAG MC2 as an external expert, which would be considered at the next BPC meeting.

The Chairman also welcomed Fiona Lee, Carolina Galdino and Nicoleta Ionescu attending from the BP Lab.

BP Update Members were provided with an update on BP staff changes and recent BP and Agency-wide stakeholder engagement activities, including the release of the response to the MHRA biological standards consultation: https://www.gov.uk/government/consultations/strategy-for-pharmacopoeial-public-quality-standards-for-biological-medicines

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.

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

351 Emergency evacuation procedure

The emergency evacuation procedure for the building was provided.

I MINUTES

352 The minutes and summary minutes of the meeting held on 9th May 2017 were confirmed with no amendments.

II MATTERS ARISING FROM THE MINUTES

353 Matters arising and correspondence items from the meeting held on 9th May 2017 were noted.

Cyclophosphamide Preparations (Minute 328)

The Secretariat was awaiting further information before progressing the revision of these monographs.

Adrenaline Injection & Dilute Adrenaline Injection (minute 335)
The agreed amendments to the monographs were made for the BP 2018.

Further information to update the Related substances test was awaited before progressing the revision of these monographs.

Salbutamol Inhalation Powder; Salbutamol Inhalation Powder, Pre-Metered; Salbutamol Nebuliser Solution (minute 343)
The Secretariat was awaiting further information before progressing the revision of these monographs.

Chlorhexidine Preparations (minute 346)
The Secretariat was awaiting further information before progressing the revision of these monographs.

Flexible Collodion (minute 347)
The monograph was to be transferred to Panel CX.

COMMENTS ON TEXTS FROM PUBLIC CONSULTATION WINDOW

Galantamine Oral Solution; Galantamine Tablets; Galantamine Prolonged-release Capsules (minute 336)
The draft monograph would be included in a future BP publication.

Anastrozole Tablets (minute 337)
The draft monograph would be included in a future BP publication.

Clenbuterol Injection (minute 339)
The draft monograph would be included in a future BP publication.

III MONOGRAPHS

354 Liothyronine Preparations:
Liothyronine Tablets (revised)
Liothyronine for Injection (new)

Dissolution – Tablets Problems had been reported with the test and it was agreed that the test would be updated following a lab investigation.

Related substances – Tablets An alternative HPLC test had been provided which could identify an additional impurity formed from the presence of lactose. Members agreed that this method would be included in the monograph and the limits would be revised based on recommendations from the MHRA Licensing division.

Assay – Tablets The Secretariat agreed to investigate whether the test should be harmonised with the Related substances method in order to improve method selectivity to account for the high impurity levels.

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

355 Levothyroxine Preparations:

Levothyroxine Tablets (revised)
Levothyroxine Oral Solution (revised)

Identification – Tablets It was agreed that the peak comparison in the Related substances test would serve as a suitable replacement for Identification B.

Production – Tablets The production statement would be reviewed to ensure it was clear when the pentahydrate form should be used during the manufacturing process.

Dissolution – Tablets Difficulties with the test had been reported. As the test had undergone rigorous testing by the MHRA previously across available products, and there was insufficient evidence demonstrating the BP method was unsatisfactory, members agreed that no amendment to the method would be made at this time.

Related substances – Tablets It was agreed that an LC method that identified all the specified impurities and was shown to be suitable for two other marketed products would be included. The limits would be revised based on recommendations from the MHRA Licensing division.

Related substances – Oral Solution Members accepted the revision to the limits for the peak due to liothyronine, which was updated from 1.0% to 2.0%, and this peak was excluded from the sum of impurities limit.

Uniformity of content – Tablets & Oral Solution The Secretariat agreed to look into the use of the anhydrous and hydrate form of Levothyroxine, and to revise the concentration of solutions to account for the lowest strength products available.

356 **Ibuprofen Preparations:**
Ibuprofen Capsules (new)
Ibuprofen Gel (revised)
Ibuprofen Granules (new)
Ibuprofen Oral Suspension (revised)
Ibuprofen Tablets (revised)
Orodispersible Ibuprofen Tablets (new)
Prolonged-release Ibuprofen Capsules (revised)
Prolonged-release Ibuprofen Tablets (revised)

Ibuprofen Capsules; Orodispersible Ibuprofen Tablets; Ibuprofen Granules, Effervescent Ibuprofen Tablets; Ibuprofen Injection The draft monographs would be included in a future BP publication, subject to comments. No samples of the effervescent tablets or injection had been available for laboratory evaluation, therefore it was agreed to put development of these monographs on hold.

Ibuprofen Cream It was agreed that this monograph should be put forward to BPC for omission.

Identification – Ibuprofen Gel Members agreed that the IR procedure was suitable.

Identification – Ibuprofen Oral Suspension Members accepted the revision to Identification test A to replace chloroform with dichloromethane in the sample preparation. It was agreed that Identification test B would be deleted as the IR test was sufficiently discriminatory.

Related substances – Ibuprofen Tablets, Prolonged-release Tablets, Prolonged-release Capsules The draft LC method based on the Ph. Eur. parent monograph was found to be suitable by the lab and members accepted the inclusion of this test.

Related substances – Gel The lab found a number of unknown peaks at levels above the secondary peaks and the sum of secondary peaks limits. Members agreed that the draft

limits should be retained and further information would be sought from MAHs on the identity of the unknown peaks during public consultation.

Related substances – Oral Suspension The lab found a number of unknown peaks at levels above the secondary peaks and the sum of secondary peaks limits. Members agreed that the draft limits should be retained and further information would be sought from MAHs on the identity of the unknown peaks during public consultation.

Related substances – Limits Stakeholders would be given the opportunity to comment on the draft revised limits, which accommodated Ph Eur impurities limited about the secondary peak limit and ICH guidelines.
Related substances – System suitability Members agreed to increase the SST requirement to at least 5.0.

357 Candesartan Tablets (new)

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

358 Nicorandil Tablets (revision)

Polymeric impurities A lab investigation would be carried out to assess the suitability of methods to control polymeric impurities.

Assay Members agreed that a more specific assay should be investigated.

359 Tetracaine Hydrochloride Eye Drops (revised)

Content Content limits of 92.0 – 105.0% were agreed.

Acidity Members accepted the draft requirements of pH 3.3 to 4.4.

Related substances Limits had been drafted for impurity B at 0.5%, impurity A is controlled under any other secondary peaks limits, and a tighter limit of 1.5% was agreed for the sum of secondary peaks.

360 Galantamine Preparations
Prolonged-release Galantamine Capsules (new)
Galantamine Oral Solution (new)
Galantamine Tablets (new)

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

361 Temozolomide Preparations:
Temozolomide Capsules (new)
Temozolomide for Injection (new)

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

362 Ipratropium Preparations:
Ipratropium Pressurised Inhalation, Solution (revised)
Ipratropium Nebuliser Solution (revised)

Related substances test for Impurity A – Pressurised Inhalation, Solution Members accepted the inclusion of a TLC test to limit impurity 1 (Ph. Eur. impurity A).

Assay – Pressurised Inhalation, Solution The Secretariat agreed to update the Assay to refer to the average of the results obtained from the Uniformity of Delivered Dose test. It was also agreed that the content requirement should be updated to refer to the delivered dose (ex-actuator).

363 Salbutamol Pressurised Inhalation, Suspension (revised)

Content and Assay A delivered dose requirement of 85.0-115.0%, aligned with the revised BP policy for inhaled products was accepted.

Related substances Comments had been received indicating that the draft revised test was unsuitable, and an alternative method was agreed. Revised limits of 0.5% for impurities D, C, F and I were agreed.

Uniformity of Delivered Dose The method in the draft monograph had been shown unsuitable and an alternative method was agreed.

364 Salmeterol Inhaled preparations:
Salmeterol Pressurised Inhalation, Suspension (new)
Salmeterol Inhalation Powder, pre-metered (new)

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

365 Sertraline Tablets (revised)

Enantiomeric Purity Members agreed that the test should be deleted.

366 Propranolol Tablets (revised)

Related substances Poor chromatography had been reported due to the sample preparation solvent. The use of mobile phase for sample preparation resolved this issue, and members agreed the amendment.

367 Diclofenac Gel (revised)

Related substances and Assay Poor chromatography had been reported due to the sample preparation solvent. The use of mobile phase for sample preparation resolved this issue, and members agreed the amendment.

368 Phenindione (revised)

Content It was agreed that the limits would be widened to 98.0 – 102.0% to accommodate the change from a titration to an LC method.

Related substances Members accepted the draft revised test and the Secretariat agreed to make minor amendments as requested.

369 Indapamide Preparations:
Indapamide Tablets (revised)
Prolonged-release Indapamide Tablets (revised)

Impurity C A draft method to control impurity C had been included which members agreed should be investigated by the lab.

369 Pimobendan Preparations (VET):
Pimobendan Capsules (new)
Chewable Pimobendan Tablets (new)

This item was deferred to the next meeting due to time constraints.

370 Clenbuterol Injection (new)

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

371 MC2 Work status and updates

The MC2 work programme was presented to members for information.

VI ANY OTHER BUSINESS

None raised at the meeting.

VII DATE OF NEXT MEETING

The date of the next meeting is 24th April 2018.