BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group MC2: Medicinal Chemicals

SUMMARY MINUTES

A meeting of this Expert Advisory Group was held at 10 South Colonnade, London E14 4PU on Wednesday 24 October 2018.

Present: Dr G Cook (*Chairman)*, Mr C Goddard (*Vice-Chairman*), Prof J Miller, Mr N Wynne, Mr J Cowie, Dr A Ruggiero and Dr K Bracht.

In attendance: Ms H Corns, Ms S Gomersal, Ms N Clothier, Ms M Rueda (BP Lab) and Ms R Ravishankar (BP Lab). Mr S Maddocks attended for part of the meeting for the Dissolution item.

Apologies: Dr J Lim and Mrs M Turgoose.

391 Introductory Remarks

Welcome The Chairman welcomed Ms N Clothier, the new BP fast-streamer, who observed the meeting.

The Chairman also welcomed Ms M Rueda and Ms R Ravishankar who attended from the BP Lab.

BP Update Members were provided with an update on BP staff changes.

Confidentiality Members were reminded that all papers and minutes were confidential and should not be disclosed outside the BP Commission.

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

392 Emergency evacuation procedure

The emergency evacuation procedure for the building was provided.

393 Dissolution policy update (PCY)

Mr Maddocks provided a verbal update on the work EAG Pharmacy (PCY) had completed looking at the BP's policy on Dissolution for solid oral dosages forms. A response to the consultation was yet to be made public but the key points from the draft response were highlighted to members.

I MINUTES

394 The minutes and summary minutes of the meeting held on 24 April 2018 were confirmed with minor amendments.

II MATTERS ARISING FROM THE MINUTES

395 Matters arising from the 24 April 2019 meeting were noted.

III MONOGRAPHS

396 Co-beneldopa preparations:
Dispersible Tablets (revised)
Capsules (revised)
Prolonged-release Capsules (revised)
Related substances test A The method in the Prolonged-release Capsules

monograph would replace the current procedure in the Capsules and Dispersible Tablets monograph due to reported difficulty in quantifying impurity B. The updated monographs would be made available for public consultation.

Test for Levodopa (Related substances test B) The need for a separate test in the Dispersible Tablets and Capsules monographs was considered. Members agreed that the test should be retained in these monographs until a lab investigation confirmed that levodopa related impurities could be observed under the updated LC conditions in Related substances test A.

397 Nicorandil Tablets (revision)

Production As polymeric impurities could be controlled through the revised related substances the production statement would be revised to reflect this.

Dissolution A dissolution procedure based on a method provided by a manufacturer would be included, subject to stakeholder comments, with limits of 80% (Q) in 30 minutes.

Related substances The BP lab had confirmed that an alternative method offered improved control of related substances.

Based on the laboratory results revised limits were included, subject to stakeholder comments:

- impurity D (3-(4,5-dihydro-1,3-oxazol-2-yl)pyridine) not more than 0.8%;
- impurity 4 (nicorandil dimer) not more than 0.5%;
- any secondary peak not more than 0.2%;
- the sum of the areas of any secondary peaks not more than 2%

An in-situ degradation standard had been included to aid users with peak identification.

Assay The assay method would be harmonised with the related substances test. The new method was specific for polymeric impurities.

398 Ibuprofen Preparations:
Gel (revised)
Capsules (new)
Orodispersible Tablets (new)

Identification As the Ph. Eur. monograph contained additional ID tests in support of the IR test for Identification, the Secretariat agreed to check with the Ph. Eur. to understand whether supporting tests would be needed in the BP monographs.

Ibuprofen Gel – Acidity The pH requirement of 3.6 – 4.6 would be reviewed alongside current marketed product specifications.

Ibuprofen Gel – Related substances Supporting information identifying an unknown peak observed during BP Lab investigation confirmed the unknown peak as benzyl alcohol. As this was an excipient no amendment to the monograph would be required and the monograph would be published in the BP 2020.

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

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

399 Letrozole Tablets (new)

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

400 Bisoprolol Tablets

Content Data was provided which supported widened content limits of 90.0 – 105.0%.

Related substances The revised limits had been confirmed as suitable during public consultation and would be included in the revised monograph.

Assay An amendment to the concentration of solution (2) was accepted to bring the concentration in line with the test solution.

401 Phenoxybenzamine Hydrochloride
Phenoxybenzamine Capsules
Phenoxybenzamine Sterile Concentrate

Related substances – elution order Data had been submitted which appeared to show a different elution order for the tertiary amine and closely eluting peak. It was recommended that the BP laboratory should investigate the elution order of the impurities, and that an impurity standard containing visibly different ratios of the impurities could aid correct peak identification.

Related substances – tertiary amine impurity limit Justification and stability data had been submitted in support of a request to increase the tertiary amine impurity limit, from 1.0% to 1.5% in the BP drug substance and Capsules monographs.

The data available did not indicate an increased tertiary amine limit was needed in the Phenoxybenzamine Hydrochloride. The limit in the Capsules monograph would be considered after an MHRA license review had been completed.

402 Valsartan

Members were provided with a brief update of the continued investigation and actions related to the detection of nitrosamine impurities in Valsartan API. Members agreed that revision of BP finished product Valsartan monographs would be considered based on the outcome of completed investigations.

403 Bumetanide Preparations:
Bumetanide Tablets (revised)
Bumetanide Oral Solution (revised)
Bumetanide Injection (revised)

Identification A – Oral Solution The test would be updated in line with the changes to the Related substances test.

Dissolution – Tablets The method in the USP monograph had been included, with UV detection. A limit of not less than 80% (Q) in 30 minutes was agreed, subject to stakeholder comments.

Related substances The current TLC test would be replaced with the LC method from the parent Ph. Eur. monograph.

The below limits for impurities were proposed for the Tablets:

- Impurity B and C – 0.3% each
- Unspecified impurities – 0.2%
- Total impurities – 1.0%

The below limits for impurities were proposed for the Oral Solution:

- Impurity B – 0.5%
- Unspecified impurities – 0.2%
- Total impurities – 1.0%

There were no UK MAHs for the Injection and no change to the impurity limits were proposed for this monograph.

Assay – Tablets Harmonisation with the method in the Related substances test was proposed and would be added to the lab work for the Related substances test to determine the method's suitability as an Assay.

404 Cyclophosphamide Preparations:
Injection (revised)
Tablets (revised)
Title – Injection Two sets of data had been provided for regular injection (non-lyophilised, without excipients) and lyophilised (with excipients) products. The monograph would apply to both products.

Content – Injection Separate content requirements for the non-lyophilised (at 95.0 to 105.0%) and lyophilised (at 90.0 – 110.0%) products were agreed.

Identification – Injection; Tablets Test A was updated in both monographs with the IR method from the lyophilised product data which avoided the use of chloroform. As IR is sufficient as a standalone test, test B was removed in both monographs. Suitability of the test would be confirmed.

Determination of water – Injection A test had been included as the amount of water present affected product stability.

Related substances – Injection The current TLC method was replaced with an LC method. Draft revised limits for impurities were agreed, as listed below, subject to stakeholder comments.

- Impurity 1 and 4 – 2.0% each
- Impurity 7 – 1.0%
- Impurity 5, 8 and 9 – 0.5% each
- Impurity 2 – 0.25%
- Impurity 6 – 0.3%
- Unspecified impurities – 0.2%
- Total impurities, excluding impurity 3 – 4.0%

Impurity 3 – Injection A separate LC test for the degradation product was included, as this impurity culd not be controlled using the related substances method due to interference.

Assay – Injection The method in the USP Cyclophosphamide for Injection monograph had been found suitable for both lyophilised and non-lyophilised products and had been included in the draft revised monograph.

Content – Tablets The statement was updated to refer to the content of anhydrous cyclophosphamide and the requirement tightened to 95.0 – 105.0% (from 93.5 – 107.5%) based on the product specifications.

Dissolution – Tablets A new test would be included based on that in the USP Cyclophosphamide Tablets monograph. It was suggested to harmonise the LC method with that in the Assay test. Members accepted the draft limit of Q = 75%.

Acidity – Tablets Members agreed that as the results of acidity would be affected by excipients, the test was not suitable for compendial purposes and would be deleted.

Related substances – Tablets A manufacturer had put forward a more sensitive

TLC method than that in the current monograph but it was agreed that an alternative TLC method would not offer significant improvement to the monograph. Revision to this test would be progressed once a suitable alternative to TLC was available.

Assay – Tablets The titration method would be updated to a LC procedure.

405 Alendronic Acid Tablets (revised)

Phosphate and Phosphite The title of the test would be updated to align with the respective parent monograph test, "Impurities B and C".

4-aminobutanoic acid The title of the test would be updated to 'related substances' as it used conditions harmonised with the Ph. Eur. parent monograph test of that name. An unspecified impurities limit of 0.1% would be included.

Assay The Declaration of content would be corrected to reflect the declared content of the BPCRS:

> "Calculate the content of $C_4H_{13}NO_7P_2$ in the tablets using the declared content of $C_4H_{12}NNaO_7P_2$ in *sodium alendronate BPCRS.* Each mg of $C_4H_{12}NNaO_7P_2$ is equivalent to 0.9189 mg of $C_4H_{13}NO_7P_2$."

406 Temozolomide Capsules (new)

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

407 Phenindione (revised)

Related substances A request had been received to widen the limits for impurities 1 and 2 and data provided. The following limits were agreed, pending confirmation from the manufacturer:

- Impurity 1: 0.5%
- Impurity 2: 0.3%
- Unspecified impurities: 0.2%
- Total impurities: 1.5%

408 Clenbuterol Preparations (VET):
Oral Solution (new)
Granules (new)

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

389 MC2 Work Status and Updates

The MC2 work programme was presented to members for information.

390 Ph. Eur. Updates

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

VI ANY OTHER BUSINESS

None raised at the meeting.

VII DATE OF NEXT MEETING

Thursday 13 June 2019