BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group MC1: Medicinal Chemicals

A meeting of Expert Advisory Group (EAG): Medicinal Chemicals 1 (MC1) was held at 151 Buckingham Palace Road, London SW1W 9SZ on Tuesday 5 December 2017.

Present:
Professor A G Davidson *(Chairman),* Dr J C Berridge (*acting Chair for items MC1(17)32 – 37 and 39*), Dr E Bush, Mr A J Caws, Mr D Deutsch, Dr E Gray and Mr D Malpas.

In attendance: Ms H Corns, Dr K Radi, Mr H Makwana, Mr M Whaley, Mr R Griffiths and Ms F Lee.

Apologies: Professor D Cairns, Mr P Fleming and Dr J Lough.

495 **Welcome** The Chairman welcomed Mr H Makwana and Mr M Whaley, who attended the meeting as observers; and Ms F Lee and Mr R Griffiths from the BP Lab.

Members were informed that both Mr M Broughton and Mr A James had recently resigned from EAG MC1.

Members were saddened to learn of the death of Professor Derek Calam, a former Chair of the BP and EP Commissions.

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

Declaration of Interests Dr J C Berridge, Mr D Malpas and Mr A Caws declared interests in one or more agenda items and appropriate action was taken.

496 **Emergency evacuation procedure**

The emergency evacuation procedure for Buckingham Palace Road was noted.

497 **MINUTES**

The minutes and summary minutes of the meeting held on 15 June 2017 were confirmed.

498 **Matters Arising**

A list of 'Matters Arising' from the minutes of the meeting of EAG: MC1 held in June 2017 and those outstanding from previous meetings was presented.

499 **Mycophenolate Mofetil Preparations:**
Mycophenolate Mofetil Tablets (new)
Mycophenolate Mofetil Capsules (new)
Mycophenolate Mofetil for Infusion (new)
Mycophenolate Mofetil Oral Suspension (new)

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

500 Sodium Valproate preparations:
Sodium Valproate Tablets (revision)
Prolonged-release Sodium Valproate Tablets (revision)
Prolonged-release Sodium Valproate Capsules (revision)
Gastro-resistant Sodium Valproate Tablets (revision)
Sodium Valproate Oral Solution (revision)

Alternative methods for related substances and assay had been reviewed, following reports of low recovery of sodium valproate in the assay of Prolonged-release Sodium Valproate Tablets.

Related substances It was agreed the BP Laboratory should confirm that the current GC method was sufficiently sensitive and accurate where low recovery of the active and its related was encountered; and if not, to investigate alternative extraction solvents.

Assay It was agreed that the BP Laboratory should assess the alternative methods.

501 Doxepin Capsules (revision)

Related substances (other than Z-isomer) Reported issues regarding peak area measurements due to Z-isomer shoulder appearance were discussed. A revision proposal was investigated to allow better resolution of the shoulder peak. Adjustment of the mobile phase within permitted modifications under Appendix III Chromatographic Separation Techniques allowed the user to resolve the Z isomer, therefore it was agreed that no revisions would be implemented in the monograph method.

The presence of the shoulder peak affected peak symmetry. It was agreed that an exemption to the current peak symmetry requirement would be included in the monograph.

Degradation of impurity C was reported in the presence of sodium hydroxide. It was agreed that the statement '*Prepare the solutions immediately before use and protect them from light*.' would be included in the Doxepin Capsules monograph to minimise degradation of impurity C.

Additional unidentified peaks had been observed in the chromatogram obtained with the analysis of the Doxepin impurity standard BPCRS, which the BP Lab had investigated and eliminated.

502 Phenytoin preparations:
Phenytoin Capsules (revision)
Phenytoin Tablets (revision)

Dissolution Members agreed that a suitable dissolution test for these monographs should continue to be sought. However, it was recognised that a universal method may not be possible for these monographs.

503 Pyrimethamine Tablets (revision)

Dissolution A dissolution requirement of not less than 75% (Q) in 45 minutes had been included in the draft revised monograph, subject to stakeholder comments.

Related substances A solution to generate impurities 1,2 and 3 in-situ and a resolution requirement of at least 3.0 between the peaks due to impurities 1 and 2 had been included in the draft monograph.

A revised secondary peak limit, from 0.25% to 0.2%, was agreed subject to adoption of the revised Ph Eur Pyrimethamine monograph.

Further information regarding the detection of the impurities listed in the revised Ph Eur monograph when using the drafted Related substances method would be sought.

Assay The system suitability solution and requirement were accepted for the assay, as the method was harmonised with the related substances test.

504 Abacavir and Lamivudine Tablets (revision)

Related substances - impurity J limit A limit of 0.5% for impurity J had been requested. Further information was requested to support the impurity J limit increase.

Related substances – determination of impurities A request to limit the known lamivudine-related impurities against lamivudine, instead of limiting all impurities against abacavir had been made. Members agreed the revised approach to impurity determination, subject to confirmation of correction factors and sufficient information for users to identify lamivudine impurities.

505 BP 2019 new monographs:
Amlodipine Tablets
Amlodipine Oral Solution
Cinnarizine Tablets
Itraconazole Capsules
Itraconazole Sterile Concentrate
Itraconazole Oral Solution

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

506 Ranitidine liquid preparations:
Ranitidine Injection (revision)
Ranitidine Oral Solution (revision)

Ranitidine Injection – Related substances limits It was agreed that more data wsa needed before revised limits could be agreed.

Ranitidine Oral Solution – Content Based on data provided it was agreed to retain the limits of 90-105%.

Ranitidine Oral Solution – Related substances limits It was concluded there were insufficient stability data available to support the proposed revised limits at that point.

507 Carbimazole Tablets (revision)

Related substances Feasibility and validation reports to support an increase to the limit of thiamazole in the related substances test had been received. The justification was accepted and the proposed increase from the current 1% to 2.5% agreed.

508 Omeprazole preparations:
Gastro-resistant Omeprazole Tablets (revision)
Gastro-resistant Omeprazole Capsules (revision)

Impurity C Users had reported issues with the TLC test for impurity C. The test had been adopted from the Ph Eur Omeprazole monograph, and had been deleted from the Omeprazole monograph after the revision of the Related substances test allowed detection of impurity C. It was agreed to delete the test from the Omeprazole preparation monographs, following revision of the related substances procedure.
Related substances The LC test in the Omeprazole monograph had been revised to allow for the determination of impurity C.

509 Cetirizine preparations:
Cetirizine Tablets
Cetirizine Capsules
Cetirizine Oral Solution
Related substances Late-eluting peaks had been observed during BPCRS testing which appeared in subsequent analytical runs. No similar problems had been reported by users and therefore it was agreed that an extended hold at the end of the gradient would not be implemented until the nature of the late-eluting peak was investigated.

510 Nimodipine preparations:
Nimodipine Infusion (revision)
Nimodipine Tablets (revision)

Assay A user had reported that *nimodipine impurity A BPCRS* was supplied as a lower concentration solution than the concentration required in solution (3) of the assay. It was agreed that the system suitability solution concentrations used for related substances would be applied to the assay.

511 Digoxin preparations:
Digoxin Injection (revision)
Digoxin Tablets (revision)

It was agreed that laboratory work was necessary for identification, related substances and assay tests for both monographs.

512 Production statement for mesilates

Production statement A production statement to alert users to the potential formation of methanesulfonate esters in the presence of low molecular weight alcohols was agreed and recommended for consideration by BPC.

513 MC1 Work status and updates

The MC1 work programme was presented to members for information.

514 AOB

None raised

515 Date of next meeting

Friday 15 June (TBC)