**BRITISH PHARMACOPOEIA COMMISSION**
**Expert Advisory Group (EAG): Medicinal Chemicals (MC1)**

**SUMMARY MINUTES**

A meeting of Expert Advisory Group (EAG): Medicinal Chemicals 1 (MC1) was held at 151 Buckingham Palace Road, London SW1W 9SZ on Thursday 15 June 2017.

**Present**:
Professor A G Davidson *(Chairman),* Dr J C Berridge, Dr E Bush, Mr A J Caws, Mr D Deutsch, Dr E Gray, Mr P Fleming, Dr J Lough and Mr D Malpas.

**In attendance**: Ms H Corns, Dr K Radi, Ms M-L Wall, Ms F Lee, Mr D Walker, Mr L Gibson and Ms E Cotterill

**Apologies:** Professor D Cairns, Mr M Broughton and Mr A James.

**470** **Welcome** The Chairman welcomed Mr D Deutsch and Dr E Gray, who attended their first meeting.

The Chairman also welcomed Dr K Radi, new Secretary to EAG MC1, Mr L Gibson and Ms E Cotterill, both attending as observers, and Ms F Lee and Mr D Walker.

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

**Declaration of Interests** Mr D Malpas, Dr E Bush, Dr Lough and Mr A Caws declared interests in one or more agenda items and appropriate action was taken.

**471** **Emergency evacuation procedure**

The emergency evacuation procedure for Buckingham Palace Road was noted.

**472** **MINUTES**

The minutes and summary minutes of the meeting held on 6 December 2016 were confirmed.

**473** **Matters Arising**

A list of 'Matters Arising' from the minutes of the meeting of EAG: MC1 held in December 2016 and those outstanding from previous meetings was presented.

**474** **Itraconazole Preparations:**
**Itraconazole Capsules (new)**
**Itraconazole Oral Solution (new)**
**Sterile Itraconazole Concentrate (new)**

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

**475** **Cinnarizine Tablets (new)**

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

from manufacturers.

**476 Amlodipine Preparations:**
**Amlodipine Oral Solution (new)**
**Amlodipine Tablets (new)**

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

**477 Paroxetine Tablets (revision)**

***Related substances*** The MHRA Laboratory had found that impurity A co-eluted with paroxetine when carrying out a survey of paroxetine tablet samples. Impurity A had been identified as a synthetic impurity and was specified at NMT 0.3% in the Ph Eur Paroxetine Hydrochloride and Paroxetine Hydrochloride Hemihydrate monographs. Members agreed that means of resolving impurity A from paroxetine should be investigated, and suggested that the Ph Eur Related substances test could be investigated as an alternative test. In the interim, it was agreed that both the limit and solution to identify impurity A would be retained in the Paroxetine Tablets monograph as the peaks may potentially be resolved with different brands of analytical columns.

**478 Primidone Tablets (revision)**
**[Primidone Oral Suspension (revision)]**

***Identification A*** It was agreed the requirement to use hot ethanol as an extraction solvent would be investigated.

***Dissolution*** A dissolution would be investigated for the revised monograph.

***Related substances*** An LC method capable of determining all Ph Eur impurities was proposed to replace the GC test for impurity A (2-ethyl-2-phenylmalonamide).

It was proposed that the current limit for impurity A (0.5%) should be retained, a limit of 0.2% for any unspecified impurities and a disregard limit of 0.05%, in-line with ICH guidelines, would be added subject to laboratory assessment and stakeholder comments.

***Assay*** An LC method with the same chromatographic conditions drafted for the Related Substances test was accepted subject to confirmation of suitability by laboratory assessment.

***Primidone Oral Suspension*** Revision of the analytical tests in the Primidone Oral Suspension monograph would also be investigated.

**479 Ritonavir Tablets (new)**

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

**480 Sodium Valproate Preparations:**

**Gastro-resistant Sodium Valproate Tablets (revision)**
**Prolonged-release Sodium Valproate Tablets (revision)**
**(Sodium Valproate Tablets (revision)**
**Prolonged-release Sodium Valproate Capsules (revision))**

***Dissolution (Gastro-resistant Tablets only)*** The LC procedure from the Sodium Valproate Tablets monograph would replace the UV determination following reports of problems with this analysis.

***Assay*** Problems had been reported with the extraction of sodium valproate from prolonged release tablet formulations when following the monograph method. An investigation to improve recovery was agreed. The scope of this investigation was extended to the Related substances test which applied the same extraction procedure.

**481 Co-codamol Preparations:**
**Co-codamol Tablets (revision)**
**Co-codamol Capsules (revision)**

***Identification Test B (Tablets only )*** It was agreed to substitute the use of chloroform with dichloromethane in the thin-layer chromatography test.

***Dissolution*** An additional requirement to determine the release of codeine as well as paracetamol was considered. Due to the high solubility of codeine phosphate, it was accepted that a further requirement would not add value to the monograph.

***Related substances A and B (Co-codamol Tablets only)*** It was agreed to substitute the use of chloroform with dichloromethane as a solvent for test A and the mobile phase of test B.

**482 Co-Dydramol Tablets (revision)**

A review of the monograph tests concluded that the analytical procedures would be fit for purpose if the monograph allowed for products containing 20 mg or 30 mg of codeine per 500 mg of paracetamol and chloroform was replaced with dichloromethane.

**483 Doxepin Capsules (revision)**

Members agreed to defer this item to the next meeting due to time constraints.

**484 Carboplatin Injection (revision)**

***Identification Test A*** The concentrations of solution (1) and (2) were reduced to 0.1% w/v following a recommendation from the BP Laboratory.

***Assay*** Difficulties meeting the system suitability requirement had been reported and data provided which supported a reduction to the injection volume, from 20 µL to 5 µL, as a resolution to the problem. The amendment was agreed for a future publication.

**485 Sumatriptan Preparations:**
**Sumatriptan Injection (revision)**
**Sumatriptan Nasal Spray (revision)**

***Related Substances*** Materials to support Sumatriptan Impurity Standard BPCRS were proving difficult to source. It was agreed that alternative ways to aid peak identification for impurities 1 and 2 would be investigated.

**486 Propofol Injection (revision)**

***Lysolecithin*** An alternative test for lysolecithin had been submitted and would be investigated by the BP Laboratory.

***Globule Size*** Revised wording for the Globule Size text, retaining the Coulter counter test, and allowing for alternative techniques listed in the Appendix XIII A to be used was agreed.

**487 Phenytoin Preparations:**
**Phenytoin Capsules (revision)**
**Phenytoin Injection (revision)**
**Phenytoin Oral Suspension (revision)**
**Phenytoin Tablets (revision)**

***Capsules – content*** Members agreed the revised content limits from 92.5% - 107.5% to 95.0% - 105.0% subject to stakeholder comments.

***Capsules – Identification*** It was agreed that IR was suitable as a standalone test. The incorporation of Identification B into the sample preparation for IR would provide assurance that phenytoin sodium was used to manufacture the capsules.

***Capsules – Dissolution*** A test based on the USP dissolution procedure for Extended Release Phenytoin Sodium Capsules had been assessed. Further investigation and input from stakeholders was needed before a dissolution test could be agreed.

***Capsules – Related substances*** The Ph Eur isocratic LC related substances test was found to be suitable for the monograph. Limits of NMT 0.3% for impurity E, NMT 0.2% for any other secondary peaks and a total impurity limit of 0.5% were agreed subject to stakeholder comments.

***Capsules – Assay*** An LC assay, based on the related substances test, was found to be suitable.

***Injection – Identification B*** The IR identification test was considered sufficiently discriminatory to be a standalone test. It was agreed that Identification B could be deleted.

***Injection – Related substances*** The Ph Eur isocratic LC related substances test was found to be a suitable replacement for the Benzil and Benzophenone test. Limits of NMT 0.3% for impurity E, NMT 0.2% for any other secondary peaks and a total impurity limit of 0.5% were agreed subject to stakeholder comments.

***Injection – Ethanol and propylene glycol*** A capillary GC test for ethanol and

propylene glycol, harmonised with the USP Phenytoin Sodium Injection test was accepted.

***Injection – Assay*** An LC assay, based on the related substances test, was adopted.

***Oral Suspension – Content*** Stakeholders would be asked to comment contents limits tighter than 90.0% - 110.0% limit could be met.

***Oral Suspension – Identification*** Investigation of a revised test which removed chloroform was recommended.

***Oral Suspension – Related substances*** The Ph Eur isocratic LC related substances test was found to be a suitable replacement for the Benzil and Benzophenone test. Limits of NMT 0.3% for impurity E, NMT 0.2% for any other secondary peaks and a total impurity limit of 0.5% were agreed subject to stakeholder comments.

***Oral Suspension – Assay*** An LC assay, based on the related substances test, was adopted.

***Tablets – Identification*** It was agreed that IR Identification A should be retained as a standalone test and the deletion of Identification tests B and C was agreed. The removal of chloroform from the test would be investigated.

***Tablets – Dissolution*** A test based on the USP dissolution procedure for Extended Release Phenytoin Sodium Capsules had been assessed. Further investigation and input from stakeholders was needed before a dissolution test could be agreed.

***Tablets – Related substances*** The Ph Eur isocratic LC related substances test was found to be suitable for the monograph. Limits of NMT 0.3% for impurity E, NMT 0.2% for any other secondary peaks and a total impurity limit of 0.5% were agreed subject to stakeholder comments.

***Tablets – Assay*** An LC assay, based on the related substances test, was adopted.

**488 Digoxin Preparations:**
**Digoxin Injection (revision)**
**Digoxin Tablets (revision)**

***Definition* (*Injection only)*** Revision to create an open strength monograph would be considered in conjunction with EAG ULM, who had responsibility for the Paediatric Digoxin Injection monograph.

***Identification* A** A TLC test, based on the Ph Eur Related substances test for *Digitoxin* was agreed.

***Identification B*** It was agreed that the colour change test would be deleted.

***Identification C*** The peak comparison in the Assay was confirmed as the second identification test and renamed as Identification B.

***Related substances*** A new HPLC test based on the Ph. Eur. Digoxin Related substances method was accepted by members. Limits in-line with the Ph Eur Digoxin monograph were agreed subject to stakeholder comments.

***Uniformity of content (Tablets only)*** An LC test, based on the revised Related substances test, was agreed.

***Assay (Injection only)*** An LC assay, based on the revised Related substances test, was agreed.

It was noted that an amendment to the standing time in the monograph, from 1 hour to 2 hours, had been agreed with the Chair and Vice-chair for the BP 2017 publication.

***Assay (Tablets only)*** An updated assay which referred to the average of the individual results obtained in the test for Uniformity of content was accepted.

**489 Quinine Dihydrochloride (revised)**

***Assay*** The International Pharmacopoeia had provided a report which investigated a replacement for mercury acetate. It was agreed that the titration assay method should be included in the BP monograph.

***Titratable cation*** It was agreed the Titratable cation test should be deleted following the inclusion of the updated Assay method.

**490 Amantadine Preparations:**
**Amantadine Capsules (revised)**
**Amantadine Oral Solution (revised)**

***Identification B*** The IR test (Identification A) was considered sufficiently discriminatory as a standalone identification test. The Chloride test in Amantadine Capsules and the Assay peak comparison test in Amantadine Oral Solution would be deleted.

***Related Substances*** An alternative GC method using a capillary column, based on the Ph. Eur. Amantadine Hydrochloride monograph was accepted.

Replacement of chloroform with toluene in the Amantadine Capsules monograph was agreed.

***Assay*** A revised test based on the proposed revision to the Related substances test would be investigated.

**491 MC1 Work status and updates**
The MC1 work programme was presented to members for information.

**492 PCY Update**
Members were provided with an update of the activities of EAG PCY.

**493 AOB**

**494 Date of next meeting**
Tuesday 5 December 2017