

**BRITISH PHARMACOPOEIA COMMISSION  
EXPERT ADVISORY GROUP (EAG): MEDICINAL CHEMICALS 1 (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 Monday, 15<sup>th</sup> December 2014.

**Present:** Professor A G Davidson (*Chairman*), Professor D Cairns (*Vice-chairman*), Dr. M Ahmed, Dr. J C Berridge, Mr. A J Caws, Mr. P Fleming, Dr. V Loh, Dr. J Lough and Mr. D Malpas.

**Apologies:** Mr. M Broughton.

**In attendance:** Mrs. M Barrett, Ms. H Corns, Dr. H Schmidt, Mr. A Panchal and Ms. C Marcolan.

**291 Welcome**

The Chairman welcomed everyone especially Dr. H Schmidt from the International Pharmacopoeia, who was observing BP practices, and Mr. A Panchal and Ms. C Marcolan from the BP Laboratory.

**I GENERAL MATTERS**

**292 Minutes**

The minutes and summary minutes of the meeting held on 11<sup>th</sup> June 2014 were confirmed.

**293 Emergency evacuation procedure** MC1 (14) 27

The emergency evacuation procedure for Buckingham Palace Road was noted.

**294 Declaration of interests** MC1 (14) 28

Members had declared their interests prior to the meeting and these would be noted in the minutes.

**295 Issues arising from the BP Commission** MC1 (14) 29

Members were provided with an update on matters recently discussed by the BP Commission.

**Government security classifications** From 2<sup>nd</sup> April 2014 the six-tier system for indicating sensitivity of information had been replaced by a three-tier system, Official, Secret and Top Secret.

**Electronic cigarettes (e-cigarettes)** Members were informed that the BPC had agreed that a BP monograph would be established by Medicinal Chemicals 1 for e-cigarettes containing nicotine.

**Application of ICH disregard limits in BP monographs** BPC had agreed that the preferred policy for disregard limits should be to follow the ICH guidelines when applying a limit of disregard in a BP monograph but a flexible approach to the limit could be adopted where justified.

## Expert Advisory Group Medicinal Chemicals 1

15<sup>th</sup> December 2014

### II MATTERS ARISING FROM THE MINUTES

**296 Matters arising** MC1 (14) 30

A list of 'Matters Arising' from the minutes of the meeting of EAG: MC1 held in June 2014 and those outstanding from previous meetings was circulated with the papers for the meeting. A copy is appended (Annex 1). The following was noted.

**Prolonged-release Metformin Tablets** Members were informed that, following the receipt of additional information from a manufacturer, the BP Laboratory would carry out further assessment on Prolonged-release Metformin Tablets.

**297 MC1 status update** MC1 (14) 31

A document outlining the BP work schedule was presented for information.

**298 Opening statement in monographs for Anti-epileptic Drugs** MC1 (14) 32

Following the recommendation by the BP Commission, that non-interchangeability statements should be included in both category 1 and category 2 monographs for anti-epileptics, the statement that category 1 products "are not interchangeable" and a statement that category 2 products "may not be interchangeable" had been drafted in the relevant MC1-related monographs.

All of the affected monographs had been amended, to include the appropriate opening statement, for BP 2016. The MC1-related category 1 monographs were for Carbamazepine, Phenytoin and Primidone products. Category 2 monographs included Sodium Valproate and Lamotrigine products.

On the recommendation of the Commission on Human Medicines only medicines for oral use would be revised to include the non-interchangeability statement. Medicines for parenteral use did not apply. Phenytoin Injection had not been amended.

**299 Pessaries and Vaginal Tablets** MC1 (14) 33

Following discussions held at the June 2014 MC1 meeting the Secretariat had sought advice from the Pharmacy Expert Group, EAG: PCY, on whether BP monographs for Pessaries should be revised to remove any reference to Vaginal Tablets and if individual monographs for vaginal pessaries and tablets should be published.

**Standard terms** EAG: PCY had stated that Pessaries and Vaginal Tablets had different standard terms and that the general monograph for Vaginal Preparations included different disintegration requirements for each type of preparation. The Pharmacy Group stated that it was important to use the correct dosage form in the title and in the definition of the monograph.

**Clotrimazole Vaginal preparations** EAG: PCY had recommended that 3 monographs should be published for Clotrimazole Vaginal preparations: Clotrimazole Pessaries, Clotrimazole Vaginal Tablets and Clotrimazole Vaginal Capsules.

**Clotrimazole Pessaries** The current monograph for Clotrimazole Pessaries had been revised to refer to pessaries only.

**Clotrimazole Vaginal Tablets** A new monograph for Clotrimazole Vaginal Tablets was presented to members.

**Clotrimazole Vaginal Capsules** Manufacturers would be asked to send batch and stability data to elaborate a new monograph for Clotrimazole Vaginal Capsules.

## Expert Advisory Group Medicinal Chemicals 1

15<sup>th</sup> December 2014

**Econazole Pessaries** Members were informed that the Definition in the current monograph for Econazole pessaries stated that they were either moulded pessaries or vaginal tablets. On the recommendation of EAG:PCY the definition had been amended to remove any reference to vaginal tablets and to only refer to moulded pessaries as referenced in all of the Summaries of Product characteristics (SPCs) for these products in the UK.

**Econazole Pessaries – chloroform** Members agreed that chloroform would be replaced by dichloromethane in Identification test A subject to agreement from manufacturers.

**Soft gel Econazole Pessaries** It was stated that there were also soft gel pessaries on the UK market. The Secretariat would ask manufacturers for information on soft gel Econazole Pessaries and if data was received, a new monograph to be drafted.

### III NEW MONOGRAPHS

**300 Prolonged-release Sodium Valproate Capsules** MC1 (14) 34

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

**301 Prolonged-release Sodium Valproate Tablets** MC1 (14) 35

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

**302 Gastro-resistant Acamprostate (Calcium)Tablets** MC1 (14)36

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

**303 Clotrimazole Vaginal Tablets** MC1 (14) 33

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

**304 Fluconazole Capsules** MC1 (14) 37

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

**305 Fluconazole Infusion** MC1 (14) 38

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

**306 Fluconazole Oral Suspension** MC1 (14) 39

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

**307 Amlodipine Tablets** MC1 (14) 40

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

## Expert Advisory Group Medicinal Chemicals 1

15<sup>th</sup> December 2014

### IV MONOGRAPHS IN PROGRESS

308 **Zidovudine preparations** MC1 (14) 41

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

309 **Zidovudine Infusion  
(Zidovudine for Infusion)** MC1 (14) 42

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

310 **Ketoconazole Cream** MC1 (14) 43

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

311 **Ketoconazole Shampoo** MC1 (14) 44

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

### V REVISION OF MONOGRAPHS

312 **Piperonyl Butoxide BP (Vet)** MC1 (14) 45

A manufacturer had informed the Secretariat that a more robust Related substances test was available and had provided batch and stability data for the test.

**Action and Use** It was noted that Piperonyl Butoxide was an insecticide synergist. After discussion it was agreed that the action and use statement, *insecticide*, as published in the BAN 2012 would be retained.

**Definition** The definition in BP 2014 was *Piperonyl Butoxide is 5-[2-(2-butoxyethoxy)ethoxymethyl]-6-propyl-1,3-benzodioxole. It contains not less than 94.0% of C<sub>19</sub>H<sub>30</sub>O<sub>5</sub>*. No upper limit had been published in the assay as peak normalization was used to determine the content of the active in the current publication. Members proposed that an upper limit of 102.0% was drafted as the revised method of assay included an assay standard. Manufacturers would be asked to provide batch and stability data if requesting different limits.

**Characteristics** The statement *Very slightly soluble in water; with ethanol (96%) with ether and with petroleum oils* was agreed. Reference to miscibility with chloroform was deleted.

**Identification – infrared spectrum** Members agreed that infrared was a selective method and that the BP Laboratory would be asked to establish a reference infrared spectrum.

**Related substances test – specified impurities** The manufacturer's method had been drafted. The method limited the specified impurities diethylene glycol butyl ether at NMT 2.0%, dipiperonyl methane at NMT 2.0%, dipiperonyl ether at NMT 1.5% and dihydrosafrole at not more than 50 ppm.

**Related substances – unspecified and total impurities** Any unspecified impurity had been limited at NMT 0.5%. The limit for all impurities had been drafted at NMT 2.0%.

**Limit of disregard** A limit of disregard of less than 0.1% had been drafted except for dihydrosafrole.

## Expert Advisory Group Medicinal Chemicals 1

15<sup>th</sup> December 2014

**Signal-to-noise ratio** It was agreed that a system suitability requirement of a signal-to-noise ratio of at least 10 for the principal peak in a 50 ppm solution of dihydrosafrole would be included in the test to ensure that the impurity peak was detected by the method.

**Assay** The draft method was accepted.

**Circulation to manufacturers** The draft revised test would be circulated to manufacturers for comment.

**Use as a synergist** The Secretariat would find out more information from the Veterinary Medicines Directorate (VMD) on the use of Piperonyl Butoxide as a synergist.

\*Please see post meeting note

**Reference materials** The manufacturer would be asked to supply an assay standard and the named impurities in order to establish BPCRSs for the active and an impurity standard.

### 313 **Abacavir Tablets** MC1 (14) 46

The Secretariat was informed that a manufacturer was unable to achieve reliable results when carrying out the infrared test in the monograph for Abacavir Tablets. They had experienced problems with interference from the excipients and coatings. Members agreed that the monograph would be revised for BP 2016 to include a thin layer chromatography test and a cross reference to the principal peaks in the Assay.

**Further review of the monograph** It was agreed that it was unnecessary to include a limit for impurity C of NMT 0.2% in the Related substances test as this was the limit for any other impurity.

### 314 **Baclofen Lactam BPCRS** MC1 (14) 47

Members were informed that the BP Laboratory was unable to source baclofen lactam, (4*RS*)-4-(4-chlorophenyl)pyrrolidin-2-one, to establish a replacement BPCRS needed to support the monographs for Baclofen Oral Solution and Baclofen Tablets. The two monographs had been revised for BP 2016 to include baclofen lactam EPCRS.

**Baclofen Oral Solution – identification test A** Members noted that the method of detection in Identification test A was incorrect. The detection solution was named mobile phase 2. The Secretariat would amend the text.

### 315 **Aspirin Preparations:** MC1 (14) 48

**Aspirin and Caffeine Tablets**  
**Aspirin Tablets**  
**Co-codaprin Tablets**  
**Dispersible Aspirin Tablets**  
**Dispersible Co-codaprin Tablets**  
**Effervescent Soluble Aspirin Tablets**  
**Gastro-resistant Aspirin Tablets**

The BP Laboratory had found that the Ph. Eur. Related substances test for Acetylsalicylic Acid (Aspirin) was suitable for use in the BP monographs for Aspirin containing products and that the test could be adapted for use for Assay for most of the monographs.

**Aspirin and Caffeine Tablets, Co-codaprin Tablets – Content** Members recommended that the content requirements were reviewed for these products with a view to bringing them in line with the standard 95.0 – 105.0%.

**Identification** Members proposed that IR identification was assessed for suitability for controlling the identification requirement of these monographs. The Secretariat would submit a requisition to the BP Laboratory.

## Expert Advisory Group Medicinal Chemicals 1

15<sup>th</sup> December 2014

**Dispersible Co-codaprin – Identification A** It was noted that Identification test A for Dispersible Co-codaprin Tablets was ‘Effervesce on the addition of water’. Members queried whether the correct standard term had been used for the monograph as the basis for dispersible tablets and effervescent tablets was different. The Secretariat agreed to investigate.

**Effervescent Soluble Aspirin Tablets – Disintegration** Members queried whether the disintegration requirement in the monograph was covered by the general monograph. Including a direction to comply with the requirement under Effervescent Tablets in the finished product monograph was simply re-stating a requirement and therefore not necessary.

**Aspirin and Caffeine Tablets, Aspirin Tablets, Co-codaprin Tablets, Gastro Aspirin Tablets – Dissolution** It was noted that target concentrations had not been given for solutions (1) and (2) in the Dissolution procedure. The Secretariat agreed to amend the monographs, as appropriate.

**Co-codaprin Tablets – Foreign Alkaloids** A manufacturer had carried out work in-house to produce an improved Foreign alkaloids test and would look into the possibility of sharing the methods with the BP.

**Related substances – sample concentration** The BP Lab had found that the original sample concentration of 0.6% w/v had overloaded the column and had recommended that a concentration of 0.1% w/v was used. Members accepted the recommendation.

**Related substances – unknown peak at 6 minutes** Members agreed that further work to investigate the nature of an unknown peak and/or the trial of alternative columns was needed before the revision to the Related substances test could be accepted.

**Assay** The method assessed by the BP Laboratory was accepted.

**Co-codaprin Tablets, Dispersible Co-codaprin Tablets– Assay for codeine** Members noted that the assay procedure for codeine in the monographs was outdated and recommended that revision of the tests was investigated.

### 316 Sumatriptan Tablets MC1 (14) 49

A dissolution procedure had been identified for Sumatriptan Tablets in the data that had been provided during monograph development. The pre-2007 dissolution format and release limit had been applied. It was noted that a sampling time of 15 minutes, rather than 45 minutes, had been included due to the fast release required for migraine products and this was consistent with licensed specifications. Members agreed that the draft revised monograph should be circulated to stakeholders for comment and the revised monograph published in the BP 2016, subject to comments.

### 317 Gastro-resistant Sodium Valproate Tablets MC1 (14) 50

The BP Commission had agreed that GC packed-columns would be removed from tests in BP monographs where possible to be replaced by GC capillary columns.

**Opening statement** Following the decision at a BPC meeting on category 2 anti-epileptics the statement was included: *Gastro-resistant Sodium Valproate Tablets from different manufacturers, whilst complying with the requirements of the monograph, may not be interchangeable.*

**Identification test** Members agreed that a test for sodium would be added as an identification test as the infrared test identified valproic acid.

**Dissolution** The monograph had been amended to include a 2-stage dissolution test for

## Expert Advisory Group Medicinal Chemicals 1

15<sup>th</sup> December 2014

gastro-resistance. The first stage was carried out in 0.1M hydrochloric acid for 2 hours with an instruction that NMT 5% of the active was released after this time. The final stage was carried out in phosphate buffer pH 6.8 with more than not less than 70% active released after 1 hour. As the monograph had been published pre-2007 a Q-value was not included.

**Related substances test** The test had been based on the Ph. Eur. Related substances test using gas chromatography. A new impurity standard reference material would be established containing Sodium Valproate and (2RS)-2-ethyl-2-methylpentanoic acid (Impurity K). Impurity K was limited at not more than 0.2% and any other impurity at not more than 0.1%. Total impurities had been limited at NMT 0.4%.

**Assay** The draft test, based on the Related substances test, was agreed.

**Circulation to manufacturers** The revised monograph would be circulated to manufacturers and, if no adverse comments were received, the revised monograph would be published in BP 2016.

### 318 Sodium Valproate Oral Solution MC1 (14) 51

The BP Commission had agreed that GC packed-columns would be removed from tests in BP monographs, where possible, to be replaced by GC capillary columns.

**Opening statement** Following the decision at a BPC meeting on category 2 anti-epileptics the statement was included: *Sodium Valproate Oral Solution from different manufacturers, whilst complying with the requirements of the monograph, may not be interchangeable.*

**Related substances test** see 317.4.

**Circulation to manufacturers** The revised monograph would be circulated to manufacturers and, if no adverse comments were received, the revised monograph would be published in BP 2016.

### 319 Sodium Valproate Tablets MC1 (14) 52

The BP Commission had agreed that GC packed-columns would be removed from tests in BP monographs, where possible, to be replaced by GC capillary columns.

**Opening statement** Following the decision at a BPC meeting on category 2 anti-epileptics the statement was included: *Sodium Valproate Tablets from different manufacturers, whilst complying with the requirements of the monograph, may not be interchangeable.*

**Related substances test** see 317.4.

**Assay** The draft test, based on the Related substances test, was agreed.

**Circulation to manufacturers** The revised monograph would be circulated to manufacturers and, if no adverse comments were received, the revised monograph would be published in BP 2016.

## VI REPORTS AND CORRESPONDENCE

### 320 Gastro-resistant Bisacodyl Tablets MC1 (14) 53

A manufacturer had experienced difficulties meeting the dissolution requirements of the Gastro-resistant Bisacodyl Tablets monograph and had requested that the sampling times were increased. Members stated that extending the dissolution time could result in the test being no longer discriminatory and therefore they agreed that without justification, the sampling times should not be increased. It was noted that at the time that the published test had been adopted a manufacturer had submitted an alternative dissolution test procedure.

## Expert Advisory Group Medicinal Chemicals 1

15<sup>th</sup> December 2014

Members agreed that the alternate test should be investigated for suitability, with a view to replacing the published method.

**321 Aciclovir Cream** MC1 (14) 54

**Related substances and Assay** A manufacturer had encountered difficulties when attempting to filter solutions of Aciclovir Cream containing 25 mg Aciclovir in 10 mL of dimethylsulfoxide as directed in the Related substances test and Assay. Members agreed to the request from the manufacturer to amend the tests to dilute the 10 mL solution to 25 mL with the specified solvent mixture before filtering. The revised tests would be published in BP 2016.

### VII ANY OTHER BUSINESS

**322 Aide memoire** MC1 (14) 55

Members were provided with a copy of the revised BP *aide memoire* and were advised that an electronic version was also available.

**323 European Pharmacopoeia matters** MC1 (14) 56

Members were provided with an update on Pharmeuropa and a recent session of the European Pharmacopoeia Commission. They also received feedback on the conference held to celebrate 50 Years of the European Pharmacopoeia.

**324 Data Security** MC1 (14) 57

Members were provided with an update on procedures for handling data provided by the Secretariat, included a trial of electronic-only meeting papers during 2015.

**325 Dates of next meetings** MC1 (14) 57

2015:  
Monday 8<sup>th</sup> June  
Tuesday 15<sup>th</sup> December

2016:  
Monday 6<sup>th</sup> June  
Tuesday 13<sup>th</sup> December



## Expert Advisory Group Medicinal Chemicals 1

15<sup>th</sup> December 2014

### Annex 1. Matters arising from previous meetings other than those mentioned on the agenda

<b>Loperamide Preparations</b>	The BP Laboratory would begin the laboratory work in the new year.
<b>Fenthion</b>	The Fenthion BP monograph was presented for omission from the publication at the September 2014 BPC meeting. The proposal was agreed by BPC members.
<b>Itraconazole Capsules</b>	A laboratory requisition had been submitted and the draft new monograph had been posted on the BP website for initial comments.
<b>Cinnarizine Tablets</b>	A laboratory requisition had been submitted.
<b>Pantoprazole Injection and Gastro-resistant Pantoprazole Tablets</b>	A laboratory requisition had been submitted and the draft new monograph had been posted on the BP website for initial comments.
<b>Rizatriptan Tablets and Orodispersible Rizatriptan Tablets</b>	No further comments had been received on the draft monographs and these would be published in the BP 2016.
<b>Terbinafine Tablets</b>	No further comments had been received on the draft monograph and this would be published in the BP 2016.
<b>Clonidine Injection and Clonidine Tablets</b>	Data had been received from a manufacturer to assist in the revision of these monographs. Revised monographs would be presented to the EAG at a future meeting.
<b>Metformin Preparations</b>	Laboratory work had been carried out and the findings would be reported to the EAG at a future meeting. Data had been received from a manufacturer for the development of a monograph for Prolonged-release Metformin Tablets. Members agreed to a continuation of the BP Laboratory work to extend to this monograph and assess the suitability of the received methods for the published monographs.
<b>Phenytoin Preparations</b>	The MHRA Laboratory was in the process of carrying out a product survey and had been asked by the Secretariat to assess the Ph. Eur. method for Related substances for use in the BP monographs to control Related substances and Assay in all formulations. Dissolution tests will also be included in the Capsules and Tablets monographs following the completion of the lab work.
<b>Warfarin Tablets</b>	A requisition had been submitted to the BP Laboratory.
<b>Repaglinide Tablets</b>	Data had been received from a manufacturer to assist in the development of this monograph. A draft new monograph would be presented to the

## Expert Advisory Group Medicinal Chemicals 1

15<sup>th</sup> December 2014

	EAG at a future meeting.
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### POST MEETING NOTES:

*Minutes 300, 301 refer Anti-epileptics-Prolonged-release products Opening statement vs Production statement:*

Following the December meeting and when reviewing the monographs for Prolonged-release Sodium Valproate Capsules and Prolonged-release Sodium Valproate Tablets, it was noted that there was a conflict in the wording of the Opening statement and the statement for Prolonged-release preparations. The wording in the Opening statement was *may be interchangeable* and in the Production statement was *are not interchangeable unless otherwise justified and authorised*. It was agreed that the Opening statements would be removed from both monographs.

*Minute 312 refers Use of Piperonyl Butoxide as a synergist.* Following the December meeting it was found that Piperonyl Butoxide is mixed with insecticides in ratios of between 3:1 and 20:1, Piperonyl Butoxide: Insecticide.