

# BRITISH PHARMACOPOEIA COMMISSION

## Expert Advisory Group: Medicinal Chemicals 3

### SUMMARY MINUTES

A meeting of this Expert Advisory Group was held at 151 Buckingham Palace Road, London SW1W 9SZ on Thursday 25<sup>th</sup> February 2016.

**Present:** Mr V Fenton-May (*Chairman*), Professor E Williamson (*Vice Chair*), Dr J Beaman, Mr C T Goddard, Mr P Hampshire, Dr R Torano, Mr I R Williams, Mr B Rackstraw.

**In attendance:** Mr A Evans, Dr A Gardiner, Ms S Gomersal, Mr S Wilson, Mr N Vadukul, Mr D Holcombe. Ms C Pitt attended for part of the meeting.

**Apologies:** Professor M Almond, Mr J Beach and Mr M Tubby

Mr Torano, Mr Goddard, Mr Hampshire and Dr Beaman declared interests in one or more agenda items and appropriate action was taken.

### INTRODUCTORY REMARKS

The Chairman welcomed Ms Sarah Gomersal who was attending her first meeting of EAG MC3. Ms Gomersal had taken over from Dr Gardiner as the new assistant secretary to EAG MC3.

The Chairman informed members that Mr Wayne Jeffries was retiring, and he was thanked for his hard work over the years. Mr Brian Delahunty should be contacted if members experienced any difficulties with their travel bookings or expenses claims.

The Chairman reiterated to members the confidential nature of the papers presented at EAG meetings and that members should declare any interests at the start of each agenda item.

### I MINUTES

The minutes and summary minutes of the meeting held on 7<sup>th</sup> October 2015 were confirmed.

### II MATTERS ARISING FROM THE MINUTES

The following matters arising from the meeting held on 7<sup>th</sup> October 2015 were noted.

#### **Ergocalciferol Injection**

Members were informed that the MAH was experiencing problems with the development of the related substances test, however work was continuing on the project.

#### **Analytical Methods Evaluation Assessment**

Feedback from the four groups which trialled the process will be discussed at the upcoming BPC meeting.

#### **Capecitabine Tablets**

#### **Folic Acid Oral Solution**

#### **Imipramine Tablets**

#### **Tolterodine Preparations**

The draft monographs has been amended and the methods would be investigated by the Laboratory.

### **Finasteride Tablets**

The agreed change to the related substances method would be published in the BP2017

## **III REPORTS AND CORRESPONDENCE**

### **449 Emergency Procedure MC3(15)25**

The emergency procedure for 151 Buckingham Palace Road was provided.

### **450 Members' details MC3(15)26**

Members were asked to check the circulated contact details and to inform the Secretariat of any amendments required.

### **451 British Pharmacopoeia Chemical Reference Substances MC3(15)27**

The British Pharmacopoeia Chemical Reference Substances approved since the last meeting of the EAG were noted.

### **452 EAG Work Programme MC3(15)28**

A copy of the work programme for the EAG was provided to members for information. Members were asked to contribute data should they have an interest in any of the products.

The Secretariat informed members that the work programme had been prioritised by known problems, hospital/prescription data and products with multiple manufacturers.

## **IV MONOGRAPHS FOR THE BP2017**

### **471 Buprenorphine Transdermal Patches MC3(16)06**

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

### **472 Chlordiazepoxide Preparations MC3(16)07** **Chlordiazepoxide Tablets and Chlordiazepoxide Capsules**

**Dissolution** The method from the capsules had been included in the tablets monograph. Members questioned using the basket apparatus for a tablet, however agreed to retain the test as is unless there was a specific reason to amend it.

It was noted that for the tablets monograph, the A(1%, 1cm) value should be changed to 327 as the product was expressed in terms of chlordiazepoxide and not chlordiazepoxide hydrochloride.

Members agreed that the proposed methods could be published in the BP2017.

**Name change** Since there was only one salt available for the tablets, the correct name should be Chlordiazepoxide Tablets. The title of the BP monograph would be amended in the BP 2017.

### **473 Co-Cyprindiol Tablets MC3(16)08**

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

- 474 Dutasteride Capsules MC3(16)09**
- The draft monograph would be included in a future BP publication, subject to comments from manufacturers.
- 475 Ferrous Fumarate and Folic Acid Capsules (Ferrous Fumarate and Folic Acid Tablets) MC3(16)10**
- The draft monograph would be included in a future BP publication, subject to comments from manufacturers.
- 476 Gabapentin Preparations MC3(16)11**
- The draft monograph would be included in a future BP publication, subject to comments from manufacturers.
- 477 Hyoscine Butylbromide Preparations MC3(16)12**
- Content** Members had previously requested that the limits be tightened to 95.0 – 105.0%. The MAH had been asked to provide data to justify the wider limits if required.
- Identification** The manufacturer had been requested to provide an alternative test that did not use chloroform.
- Test for Hyoscine** The manufacturer indicated that hyoscine was a synthetic impurity and not a degradation product. Members agreed that it did not need to be controlled by a separate test and that the test should be removed.
- Related substances** The method from the MAH had been included in the draft monograph.
- Impurities** Members agreed that the method and control of impurities could be used as long as the validation data confirmed the ratio of the principal impurities and tropic acid upon degradation of the API.
- The limits provided in the MAH specification had been included in the draft monograph.
- Dissolution** Members had previously requested that efforts were made to include a dissolution test in the tablets monograph. The MAH had been asked to provide validated methodology to support the inclusion of a specific test.
- 478 Nitrazepam tablets MC3(16)13**
- Identification** The IR was deemed sufficient as a stand-alone test for identification purposes. The draft monograph had been updated to use acetone as the solvent which was suitable for all samples tested.
- Related substances** The LC procedure investigated by the Laboratory had been included in the draft monograph. The Laboratory report indicated that impurities A and B could be controlled to 0.5% and unknown peaks could be controlled to 0.2%. Members agreed to include these limits for publication in the BP 2017.
- 479 Nitrazepam Oral Solution MC3(16)14**
- Identification** The TLC method proposed in the report from the Laboratory had been included in the draft monograph. The Secretariat agreed to include a reference to centrifuging the final solution obtained in Solution (1).

**Related Substances** Members were asked to comment on the revision of impurity limits following concern from the laboratory that the draft method resulted in two unidentified peaks higher than the unknown impurity limit. It was agreed that the Secretariat should contact MAH to review and publish the method in BP 2017 subject to comments.

**Assay** The Laboratory investigated using the Assay procedure in the Nitrazepam Tablets draft monograph. It was intended that this would remove the requirement to use chloroform in the test as currently published. The Laboratory obtained inconsistent results and indicated that the method was not suitable for this pharmaceutical form. The Laboratory were not able to amend the non-chloroform method to obtain satisfactory results in the time allocated to the investigation.

480 **Phenobarbital Preparations: MC3(16)15**  
**Phenobarbital Tablets**

**Identification A and C** Members agreed that Identification A and C were unnecessary and should be removed from the draft monograph.

**Disintegration** The test for disintegration would be omitted since it was specified in the general Tablets monograph.

**Dissolution** Members noted that the monograph should include a dissolution test. It was agreed that this would be included on the work programme, but that it would not delay the publication of the current revisions.

**Related substances** Members agreed that the method in the draft monograph was acceptable. The ICH guideline of an identification limit of not more than 0.2% and a disregard limit of 0.1% were found to be suitable for all products tested and included in the draft monograph.

Members requested that a run time be included in the test.

**Assay** All products tested were found to be within 95.0 – 105.0%, and members endorsed tightening the limits to reflect this.

**Phenobarbital Elixir**

**Interchangeability statement** Members questioned the interchangeability statement in the draft monograph but were informed by the Secretariat that its inclusion was policy and could not be changed.

**Identification B** Members agreed that Identification B was unnecessary and should be removed from the draft monograph.

**Related substances** Members agreed the method was acceptable. The ICH guideline of an identification limit of not more than 0.2% and a disregard limit of 0.1% were found to be suitable for all products tested and included in the draft monograph.

Members suggested that a run time should be included in the test.

**Assay** Members agreed the method was acceptable. All products tested were found to be within 95.0 – 105.0%, and members endorsed tightening the limits to reflect this.

**Phenobarbital Injection**

**Definition** Members noted the reference to propylene glycol in the definition and questioned whether it was appropriate. The Secretariat agreed to investigate the purpose of propylene

glycol in the injection and amend the statement accordingly.

**Content** Members noted that the monograph was written in terms of a fixed strength, but that there were several strengths available on the market. The Secretariat agreed to amend the monograph to make it open-strength.

**Identification B and C** Members agreed that Identification B and C were unnecessary and should be removed from the draft monograph.

**Weight per mL** The Secretariat agreed to remove the test, as it was formulation specific.

**Related substances** Members agreed the method was suitable. The ICH guideline of an identification limit of not more than 0.2% and a disregard limit of 0.1% were found to be suitable for all products tested and included in the draft monograph.

Members suggested that a run time should be included in the test.

**Assay** Members agreed the method was acceptable. All products tested were found to be within 95.0 – 105.0%, and members endorsed tightening the limits to reflect this.

**Phenobarbital Paediatric Oral Solution** Members were informed that the methods discussed were also found to be suitable for Phenobarbital Paediatric Oral Solution, the monograph for which is the responsibility of the Expert Advisory group for unlicensed medicines. It was agreed that the paper and draft monograph will be passed to the EAG ULM for their next meeting.

**481 Colecalciferol Tablets MC3(16)16**

**Identification** Members agreed that a different method should be investigated to replace the current procedure which used chloroform and antimony trichloride. The Secretariat agreed to carry out the review.

**Uniformity of content** The draft monograph had been amended to control all available strengths and solution (1) had been simplified.

**Assay** The UV procedure in the published BP monograph had been replaced in the draft monograph with the LC procedure from the Uniformity of content test.

**Prescribing statement** The final statement regarding the prescribing of “calciferol” would be deleted as it was regarded as it was considered obsolete.

**482 Diamorphine for Injection MC3(16)17**

**Content** Members suggested that the limits of 95.0 – 105.0% were tight as the permitted amount of the impurity 6-O-Acetylmorphine was 5%. It was noted that the draft monograph would be circulated to stakeholders so they would have an opportunity to comment on the limits.

**Uniformity of Content** Members noted that the uniformity of content test was not required and should be removed. The Secretariat agreed to delete the test.

**6-O-Acetylmorphine** The Secretariat informed members that the test was harmonised with the related substances monograph in the Ph. Eur. API monograph. It was noted that the test could be amended to a general Related substances procedure. Members agreed to the principal of the Related substances requirement but would need to review data on impurities for limit setting requirements prior to publication. The Secretariat agreed to produce a draft monograph for circulation to MAH in order to prompt dialogue for the setting of impurity limits.

**Assay** The monograph had previously contained a titration assay. This had been replaced with the LC assay used in the Bupivacaine and Diamorphine Injection monograph.

## V MONOGRAPHS FOR THE BP2018 +

### 483 Alprostadil Injection MC3(16)18

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

### 484 Inhaled products MC3(16)19

Members were informed that the recommendations of the former Inhaled Products Working Party on the content and format of BP monographs for inhaled products had been revised to incorporate stakeholder feedback and the discussions of the Expert Advisory Group on Pharmacy and the BP Commission. Feedback on the policy was invited before June 1<sup>st</sup> 2016, and the group were encouraged to circulate the documents to any interested parties.

13 monographs that were the responsibility of EAG MC3 would be affected by the policy. The monographs would be amended and included in a future BP publication.

### 487 Methadone Oral Solutions MC3(16)22

Members were informed that, following request for advice from EAG MC3, the Expert Advisory Group on Pharmacy (EAG PCY) had discussed whether the current monograph Titles and Definitions should be revised and whether an additional standalone monograph should be prepared for the Oral Concentrate. It was noted that there were two separate published monographs: Methadone Linctus (with a fixed strength of 0.04% w/v of Methadone Hydrochloride) and Methadone Oral Solution (1mg per mL). Methadone Oral Concentrate is an open-strength sub-monograph within the Methadone Oral Solution (1mg per mL) monograph.

#### **Methadone Concentrate for Oral Solution**

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

### 488 Methadone Preparation Revisions MC3(16)23

The Secretariat noted that the methadone preparation monographs required significant revision as none contained tests for Related substances and the Injection and Tablets monographs contained a UV assay.

#### **Methadone Injection**

**Identification B** Members agreed that Identification B was unnecessary and should be removed.

**Related substances/Assay** The Laboratory would investigate suitable methods.

**Assay** The method published in the oral solution monographs was included in the draft and the existing limits of 92.5 – 107.5% retained.

### **Methadone Oral Solution (1mg/ml)**

**Identification/Related substances** The Laboratory would investigate suitable methods.

### **Methadone Oral Concentrate**

**Identification/Related substances** The Laboratory would investigate suitable methods.

**Labelling** The Secretariat agreed to remove the labelling statement as it was no longer applicable.

### **Methadone Tablets**

**Identification B and C** Members agreed that Identification B and C were unnecessary and should be removed.

**Dissolution/Related substances** The Laboratory would investigate suitable methods.

**Assay** The group questioned whether the limits of 92.5 – 107.5% were justified and the Secretariat agreed to investigate this.

### **489 Dydrogesterone Tablets MC3(16)24**

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

### **490 Fluticasone Nasal Spray MC3(16)25**

The group were informed that a report had been received from a user requesting a revision to solution (1) of the related substances method. The user had explained that the current concentration of 0.02% w/v resulted in the poor recovery, and provided chromatographic evidence that a concentration of 0.01% w/v with twice the injection volume resulted in significantly better recovery. The group noted that this was probably due to low solubility at the higher concentration and endorsed the change subject to comments from stakeholders.

### **491 Ergocalciferol Tablets MC3(16)26**

**Uniformity of content** The Secretariat informed the group that the colecalciferol for performance test EPCRS specified in Uniformity of Content test in solution (3) of the Ergocalciferol Tablets monograph had been discontinued. This solution had been used for the system suitability test. It was recommended that the colecalciferol for system suitability EPCRS, which contains the same impurities was included in the monograph instead; members endorsed this proposal.

**Assay/Identification B** Members noted that Identification B used antimony trichloride solution and suggested that a TLC test should be included instead. The Secretariat agreed to add the monograph to the revision programme.

**Dispensing statement** The Secretariat agreed to remove the dispensing statement from the monograph.

### **492 Progesterone Injection MC3(16)27**

**Related substances** The Secretariat had revised the method to include a retention time relative to Progesterone (retention time about 20 minutes) for Impurity C of 0.92.

Furthermore, Progesterone impurity C EPCRS, used in the monograph for system suitability had been discontinued. The group agreed that the progesterone for system suitability

EPCRS, which contains the required impurities, should be specified instead.

**493 Vinblastine Injection MC3(16)28**

**Definition** Members agreed that the statement should be amended to “Vinblastine Injection is a sterile solution of Vinblastine Sulfate in Water for Injections. It is supplied as ready-to-use solution or it is prepared by dissolving Vinblastine Sulfate for Injection in accordance with the manufacturer’s instructions”.

**Content** Members requested that the Secretariat investigate the expression of strength in available products to ensure that it was the same as that specified under Content in the monograph.

**494 Ph. Eur. Monograph Titles – Degree of Hydration MC3(16)29**

Members were updated on the Ph. Eur. revision to their degree of hydration proposal, which is likely to be agreed at the March 2016 meeting of the Ph. Eur. Commission.

**495 Heavy Metals MC3(16)30**

The group were informed that the European Pharmacopoeia would be implementing the requirement of ICH Q3D in the 9th Edition and thus the Heavy Metals test in raw materials monographs for human use would be deleted in the 9th Edition. In order to remain consistent with the Ph. Eur., BP monographs for like materials will also have the test for Heavy Metals deleted.

There were 8 monographs affected that are the responsibility of MC3.

**VII EUROPEAN PHARMACOPOEIA COMMISSION**

Members were directed to log-in to the BP website to view the latest text from the Ph. Eur.

**VIII ANY OTHER BUSINESS**

No further items were raised for discussion.

**Date of Next Meeting**

28<sup>th</sup> September 2016.