BRITISH PHARMACOPOEIA COMMISSION

EXPERT ADVISORY GROUP: MEDICINAL CHEMICALS 3

SUMMARY MINUTES

A meeting of Expert Advisory Group (EAG): Medicinal Chemicals 3 (MC3) was held at 151 Buckingham Palace Road, London SW1W 9SZ on Tuesday 21st February 2017.

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

In attendance: Ms V Chapman, Mr A Evans, Mr L Elanganathan, Dr G Kemp, Ms C Galdino, Ms M-L Wall, Mr D Walker.

Apologies: Dr K Pugh, Dr J Beaman, M Tubby.

Introductory remarks

The Chairman welcomed Mr Elanganathan and Ms Wall, from the Secretariat; Ms Chapman, an MSc Student; and Mr Walker, from the MHRA/BP Laboratory who were attending the meeting for the first time.

The Chairman noted that this was Professor Almond's first meeting as Vice Chair.

Declaration of interests

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

Emergency evacuation procedure **MC3(17)01**

The emergency evacuation procedure for Buckingham Palace Road was noted.

I MINUTES

The minutes and summary minutes of the meeting held on 28th September 2016 were confirmed.

II MATTERS ARISING FROM THE MINUTES

The following matters arising from the meeting held on 28th September 2016 were noted.

Acarbose Tablets

The draft monograph would be published in a future edition of the BP.

Clobazam Oral Suspension

Identification A The Laboratory had investigated the mobile phase and confirmed that 40 volumes acetone and 60 volumes hexane should be used, this would be included in

the BP 2018.

Colecalciferol Tablets

The review regarding identification was ongoing.

Dutasteride Capsules

Revision of the monograph was in progress and the Secretariat were awaiting further information from the manufacturer.

Phytomenadione Preparations

The Secretariat were awaiting further information from the manufacturer.

Midazolam Oromucosal Solution

The Secretariat were awaiting further information from the manufacturer.

Rotigotine Transdermal Patches

It was noted that the monograph could only be published once the Ph Eur had published the API monograph.

III MONOGRAPHS

516 QUETIAPINE TABLETS — MC3(17)03; QUETIAPINE PROLONGED-RELEASE TABLETS

The draft monographs would be published in a future edition of the BP.

517 DIHYDROCODEINE PREPARATIONS — MC3(17)04; DIHYDROCODEINE TABLETS; DIHYDROCODEINE INJECTION; DIHYDROCODEINE ORAL SOLUTION; DIHYDROCODEINE PROLONGED-RELEASE TABLETS

Content The content limits of the Injection monograph had been tightened to 95-105% (from 90-110%), in line with all other preparations and BP policy.

Identification

Oral Solution The IR method in the draft Oral Solution monograph had been found suitable.

Tablets, Injection, Prolonged-release Tablets The original method in the laboratory requisition was not suitable. The laboratory had successfully developed a new IR method which had been included in the draft monograph. Members agreed that the method was suitable and should go to public consultation.

Dissolution (tablets only) The laboratory had successfully demonstrated that the chromatographic conditions in the Related substances method could be used for quantification purposes in the test for Dissolution. Members noted that the Q limit had not been used in the test; the Secretariat explained that this was because the monograph had been published in the BP 2007 or before and therefore the old limits of not less than 70% in 45 minutes applied. The Secretariat invited members to participate

in the dissolution consultation (BP website) should they wish to comment on the current policy.

Related substances The Ph. Eur. HPLC method had been shown to be suitable to control the related substances requirement.

Tablets, Prolonged-release Tablets All samples complied with the limits in the draft monograph, which were in line with ICH requirements.

Injection The results obtained failed the limits in the draft monograph, however, it was noted that there were excipients in the product and these could be interfering with the test. Members agreed that the method should be retained as is in the draft monograph as manufacturers would have the chance to comment on them.

Oral Solution The HPLC method had to be modified for the Oral Solution due to significant interference from excipients. Further to the known excipients, the Laboratory reported unknown peaks that were failing the draft specification. Members again recommended that the monograph was put on the website for public consultation where manufacturers would have the chance to comment on the limits.

Assay The chromatographic conditions described in the Related substances test had been successfully used, with the following modifications:

- the injection volume had been reduced
- the mobile phase had been used as the diluent, rather than water, to harmonise the Assay and Related substances methods
- the sample solution concentrations of dihydrocodeine tartrate had been reduced from 0.04 % w/v to 0.01 % w/v to prevent the interference with the peak due to codeine phosphate
- the system suitability solution and criteria from the Relating substances test had been included in the draft monograph

518 MORPHINE SULFATE INJECTION MC3(17)05; Annexes 1-4

Comments were received on the draft Morphine Sulphate Injection monograph during the public consultation window (July-September 2016). The comments stated that after analysing the proposed Related substances method in the draft monograph (which was based on the Ph. Eur. method), a peak was observed that failed the limit for any secondary peak which is currently set at 0.2%. The impurity was thought to be due to “morphine sulphonates”, produced from a reaction between morphine and sodium metabisulfite (excipient).

The Secretariat had requested supporting characterisation data for the impurity peaks, however no data had been received. Members agreed that in the absence of data to justify the impurities, the BP should publish the monograph with the current limits as they are in line with ICH guidelines.

519 MOMETASONE PREPARATIONS: MC3(17)06
MOMETASONE POWDER FOR INHALATION

The draft monograph for Mometasone Powder for Inhalation would be published in a future edition of the BP.

MOMETASONE AQUESOUS NASAL SPRAY
MOMETASONE CREAM
MOMETASONE OINTMENT
MOMETASONE SCALP APPLICATION

Related substances The draft monograph included LC procedure to control impurities. Members recommended a review of the limits, since there was range for each impurity across the preparations. Members recommended including the run time in the chromatographic conditions. It was agreed by all members that the new methods should be assessed in the laboratory prior to publication.

520 FLUTICASONE AND SALMETEROL PRESSURISED INHALATION, SUSPENSION **MC3(17)07**

Related substances The concentration of fluticasone in the sample solution had been increased to 0.02%. The concentration of salmeterol in the sample solution had been increased to 0.01%.

The Secretariat had included more impurities and their retention times relative to the principal peaks to allow analysts to better identify which impurity was a degradant to which active substance.

Following the review of data, the impurity limits had been increased with the registered specification of UK licenced products.

Assay The Secretariat noted that further questions have arisen from the Assay due to discrepancies in procedures used by different manufacturers (i.e. sampling the formulation from a whole pMDI as opposed to using the mean delivered dose). The issue required further consultation with manufacturers and EAG PCY in order to control all available products.

Members agreed that the changes in the Related substances monograph should be published in the BP 2018. Furthermore, members agreed that the Secretariat should review the monograph and recommend any further changes.

521 CALCIPOTRIOL OINTMENT **MC3(17)08; Annexes 1-3**

521.1 **Assay** The chromatographic conditions in the BP was the same as those in the API Ph. Eur. monograph. The draft monograph had been amended to indicate the same sentence as used in the Ph. Eur. “A reversible isomerisation to pre-calcipotriol takes place in solution, depending on temperature and time. The activity is due to both compounds” and the specific indication to sum the peaks due to calcipotriol and pre-calcipotriol had been removed.

522 FLUPENTIXOL TABLETS **MC3(17)09**

Dissolution A statement to “Carry out the following procedure protected from light and prepare solutions immediately before use” had been included in the draft monograph. It had been reported that flupentixol was not stable in the dissolution medium and

degraded over time.

Under the Determination of Content section, a statement had been included to "Calculate the total content of flupentixol *(both E and Z isomers)* in the medium…", as flupentixol consisted of approximately 50:50 mixture of isomers.

Members agreed to the amendment but were concerned that a more specific method was being used for the Dissolution quantification compared to the Assay.

523 FLUORESCEIN PREPARATIONS MC3(17)10;
FLUORESCEIN INJECTION
FLUORESCEIN EYE DROPS

A user had highlighted an issue with the fluorescein preparation monographs. Both monographs contained a requirement to carry out a test for dimethylformamide (DMF) by GC – a solvent that was used in the manufacture of the API. However, according to the user, the use of DMF in fluorescein production ceased in 1993 and therefore could be removed from the fluorescein preparation monographs.

After reviewing the current licence specifications of the UK approved products, DMF was not mentioned in any of the API specifications. As DMF was no longer used, members agreed to remove the test for DMF.

524 NORGESTIMATE & ETHINYLESTRADIOL TABLETS MC3(17)11
NORETHISTERONE ACETATE & ETHINYLESTRADIOL TABLETS

The draft monograph would be published in a future edition of the BP

525 VARDENAFIL TABLETS MC3(17)12;

The draft monograph would be published in a future edition of the BP

ACITRETIN CAPSULES MC3(17)13

Identification test A A user highlighted an issue with the wavelength of the UV maxima in the test. The Secretariat had amended the test to compare the UV spectra to an equivalent concentration of acitretin BPCRS as the wavelength variability observed between laboratories and equipment was too large to indicate a target wavelength.

IV FOR INFORMATION

Members Details MC3(17)14

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

MC3 Work Programme **MC3(17)15**

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.

V EUROPEAN PHARMACOPOEIA **MC3(17)16**

Members were directed to go to the BP website to view the latest text from the Ph. Eur.

VI ANY OTHER BUSINESS **MC3(17)17**

No further items were raised for discussion.

VII NEXT MEETING **MC3(17)18**

TBC