BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group MC2: Medicinal Chemicals

SUMMARY MINUTES

A meeting of this Expert Advisory Group was held at 151 Buckingham Palace Road, London SW1W 9SZ on Thursday 21 May 2015.

Present: Dr G Cook (*Chairman*), Mr C Goddard (*Vice-Chairman*), Mr J Cowie, Dr D Edwards, Mr A Gibson, Dr J Lim, Prof J Miller (not present for items MC2(15)09,10, 26, 27), Mr P Murray, Dr A Ruggiero and Mr N Wynne.

In attendance: Mr J Pound, Mr P Crowley, Ms J Francomb (not present for item MC2(15)10) and Ms E Sanderson (BP Lab). Ms C Pitt was present for items MC2(15)03, 04, 05, 06, 07, 15, 16 and 20 only.

Apologies: Mrs M Turgoose.

209 **Introductory Remarks**

Welcome The Chairman welcomed members to the meeting of Expert Advisory Group MC2: Medicinal Chemicals. A special welcome was extended to the new members (Mr J Cowie, Dr D Edwards, and Mr N Wynne) and Ms Sanderson from the BP Laboratory.

Staff News Mr J Pound had recently been promoted to Editor-in-Chief of the British Pharmacopoeia following the announcement of Mrs M Vallender's retirement.

Expense Claims Members were invited to contact Mr W Jeffries (BP Secretariat) for enquires concerning expenses claims.

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

Declaration of Interests Members were reminded of the need to inform the Secretariat of any changes to their interests throughout the year and of the need to declare any specific interests at the start of relevant discussions during the meeting. Mr Goddard, Mr Murray and Mr Wynne declared intetests in one or more agenda items and appropriate action was taken.

I MINUTES

210 The summary minutes of the meeting held on 20 November 2014 were confirmed.

II MATTERS ARISING FROM THE MINUTES

211 The following matters arising from the meeting held on 20 November 2014 were noted.

Enalapril Tablets (Minute 185) A laboratory report was pending for the assessment of the Ph. Eur. parent Related substances procedure and manufacturers Assay.

Chlorpromazine Preparations (Minute 185) A laboratory report was pending for the examination of the current BP infrared identification method.

Bumetanide Injection, Bumetanide Oral Solution and Bumetanide Tablets (Minute 185) This project was in progress.

Furosemide (Minute 185) This project was in progress.

Prolonged-release Co-careldopa Tablets (Minute 185) A laboratory report was pending for the assessment of the TLC identification, LC Related substances and LC Assay procedures.

Letrozole Tablets (Minute 185) A laboratory report was pending for the development of an IR identification test and for the assessment of the LC Related substances and Assay procedure.

Prolonged-release Galantamine Capsules, Galantamine Oral Solution and Galantamine Tablets (Minute 185) A laboratory report was pending for the development of Related substances and Assay procedures.

Quinapril Tablets (Minute 185) A laboratory report was pending for the assessment of the LC Related substances procedure.

Carprofen Injection and Tablets (Minute 185) A laboratory report was pending for the assessment of the infrared identification, LC Related substances and Assay procedures.

Prolonged-release Tamsulosin Tablets (Minute 185) A laboratory report was pending for the assessment of the LC Related substances procedure.

Benazepril Tablets (Minute 185) A laboratory report was pending for the assessment of the drafted identification, Related substances and Assay procedures.

Fluvastatin Sodium Capsules and Prolonged-release Tablets (Minute 185) A laboratory report was pending for the identification, Related substances and Assay procedures.

Ibuprofen and Codeine Tablets (Minute 185) A laboratory report was pending for the identification, Related substances and Assay procedures.

Ketoprofen Injection and Tablets (Minute 185) A laboratory report was pending for the identification, Related substances and Assay procedures.

Methylphenidate Tablets, Prolonged-release Methylphenidate Capsules and Prolonged-release Methylphenidate Tablets (Minute 185) A laboratory report was pending for the identification, Related substances and Assay procedures.

Telmisartan Tablets (Minute 185) A laboratory report was pending for the identification, Related substances and Assay procedures.

Diclofenac Gel (Minute 185) A laboratory report was pending for the identification procedure.

Naftidrofuryl Capsules (Minute 185) A laboratory report was pending for the Assay procedure.

Tranexamic Acid Injection, Tranexamic Acid Tablets, Tranexamic Acid Mouthwash (Minute 185) A laboratory report was pending for the Assay procedure.

Fenofibrate Tablets, Fenofibrate Capsules, Prolonged-release Fenofibrate Capsules (Minute 185) A laboratory report was pending for the identification, related substances and Assay procedures.

Prolonged-release Ibuprofen Capsules, Ibuprofen Capsules, Ibuprofen Cream, Ibuprofen Gel, Ibuprofen Granules, Ibuprofen Injection, Ibuprofen Oral Suspension, Effervescent Ibuprofen Tablets, Prolonged-release Ibuprofen Tablets, Ibuprofen Tablets (Minute 185) A laboratory report was pending for the identification, related substances and Assay procedures.

Terbutaline Injection, Terbutaline Oral Suspension, Terbutaline Tablets (Minute 185) A laboratory report was pending for the identification, related substances and Assay procedures.

Ciprofibrate Tablets (Minute 185) A laboratory report was pending for the identification, related substances and Assay procedures.

Sitagliptin Tablets (Minute 185) Further work on this monograph would not be progressed following publication of the Ph. Eur. Sitagliptin phosphate monohydrate tablets monograph in Supplement 8.7.

Liothyronine Tablets (Minute 185) This project was in progress

Carbocisteine Capsules, Carbocisteine Oral Solution (Minute 185) A laboratory report was pending for the identification and Assay procedures.

Rivastigmine Preparations (Minute 193) A laboratory report was pending for the identification, Related substances and Assay procedure.

Anastrozole Tablets (Minute 194) A laboratory report was pending for the identification, Related substances and Assay procedures.

Ezetimibe Tablets (Minute 197) This project was in progress.

Adrenaline/Noradrenaline Preparations (Minute 201) A laboratory report would be presented at the next meeting.

Levothyroxine (Minute 204) A paper, considering matters raised by EAG: MC2, would be presented at the next meeting of the Chemistry, Pharmacy and Standards EAG.

III REPORTS AND CORRESPONDENCE

212 **Emergency Evacuation Procedure** **MC2(15)02**

Members were presented with a paper on the emergency evacuation procedure.

213 **BP 2016** **MC2(15)03**

Members were presented with a list of new and revised monographs that would be published in the BP 2016.

214 **Membership** **MC2(15)04**

Members were asked to confirm that their contact details were correct and inform the Secretariat of any amendments required.

215 **BP Laboratory** **MC2(15)05**

A list of several reference materials relating to monographs within the remit of EAG MC2, which had been adopted since the meeting of 20 November 2014, was provided for information.

216 **Current Work Programme** **MC2(15)06**

A list of initiated monographs for EAG MC2 was provided for information.

217 **Inhaled Products** **MC2(15)07**

British Pharmacopoeia Monographs for Inhaled Products The revised "British Pharmacopoeia Monographs for Inhaled Products" policy document had recently been approved by the BP Commission. New monographs would be written as per the policy document which included monograph templates.

Revision of currently published monographs could now commence.

218 **Propranolol Tablets** **MC2(15)08**

The Secretariat had received correspondence from a manufacturer querying the system suitability criteria in the related substances test of the Propranolol Tablets monograph which stated

The test is not valid unless the chromatogram for solution (1) resembles that supplied with *propranolol hydrochloride for performance test EPCRS*.

The chromatogram supplied with *propranolol hydrochloride for performance test EPCRS* was obtained using the chromatographic conditions from the Ph. Eur. Propranolol Hydrochloride monograph which differed from those in the BP Propranolol Tablets monograph.

The Secretariat noted that the chromatographic conditions were originally harmonised with the Ph Eur parent monograph, but had diverged following a subsequent revision proposed by the EDQM Laboratory in 1999. The Prolonged-release Tablets and Injection monographs were both harmonised with the Tablets, although they specified a BPCRS impurity standard which was never established.

Members considered a number of approaches but agreed that the system suitability in the Tablets should be replaced with suitable resolution criteria and that manufacturers should be provided with a letter of intent detailing this errata to enable use of the current monograph.

Additionally, it was agreed that the Related substances chromatographic conditions in the three product monographs should be harmonised with the parent monograph and that a disregard limit should be included.

IV NEW MONOGRAPHS

219 **Fosaprepitant for Injection** **MC2(15)09**

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

220 **Liothyronine for Injection** **MC2(15)10**

Mr Goddard declared an interest in this item. He participated in the discussion.

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

V MONOGRAPHS IN PROGRESS

221 **Aprepitant Capsules** **MC2(15)11**

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

222 **Candesartan Tablets** **MC2(15)12**

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

223 **Propranolol Oral Solution** **MC2(15)13**

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

224 **Risedronate Tablets** **MC2(15)14**

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

225 **Salmeterol Inhalation Powder, pre-dispensed** **MC2(15)15**

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

226 **Salmeterol Pressurised Inhalation Suspension** **MC2(15)16**

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

227 **Sulfasalazine Oral Suspension** **MC2(15)17**

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

228 **Temozolomide Capsules** **MC2(15)18**
Temozolomide for Injection

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

229 **Verapamil Oral Solution** **MC2(15)19**

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

VI REVISION OF MONOGRAPHS

230 **Aminophylline Injection** **MC2(15)20**
Aminophylline Tablets
Prolonged-release Aminophylline Tablets

Following a technical revision to the content statements in the Aminophylline Injection, Aminophylline Tablets and Prolonged-release Aminophylline Tablets monographs for the BP 2016, further revisions to the monographs had been proposed by the Secretariat and BP Commission.

Aminophylline Tablets It was noted that there were no UK Product Licences for Aminophylline Tablets and generally this would make the monograph a candidate for omission. The Secretariat had received a number of queries on the monograph from international stakeholders over the years and therefore there would be value in retaining the monograph in the BP. Members agreed that the monograph should not be nominated for omission.

Labelling Both the Aminophylline Tablets and Aminophylline Prolonged-release Tablets monographs definition statements allow for the use of Aminophylline or Aminophylline Hydrate, but the content should be stated in terms of aminophylline. The two licenced products for Aminophylline Prolonged-release Tablets stated their content in terms of aminophylline hydrate. Members considered whether the MAHs should be asked to revise their product labelling, or whether the monograph should be revised so that it is written in terms of Aminophylline Hydrate. Members agreed that as this would have an impact on prescribing, the item should be referred to EAG Pharmacy for advice.

Additionally, members agreed that the Aminophylline family of monographs should be revised to include Related substances tests in a future edition. It was noted that the method from the Aminophylline parent monograph may be appropriate. It was also agreed that the melting point Identification test should be removed from the monographs and that a storage statement should be added to the Aminophylline Injection monograph.

231 **Fluvoxamine Tablets** **MC2(15)21**

Related substances During the editorial revision of the monograph for the BP 2016, it was noted that a limit for the total impurities and a transparency statement should be included in the monograph to clarify which impurities were controlled by the monograph. The review of a BP Laboratory report indicated which impurities were detected by the method and the relative retention times were included in the draft revised monograph. Members approved the new limits of 0.5% for Impurity B, 0.2% for Impurity A, 0.15% for Impurity D, and 1.0% for total (excluding Impurity C) proposed by the Secretariat, based on the Ph. Eur. parent monograph as well as revised limits of 0.2% for unspecified and 0.1% for disregard, based on ICH Q3B (R2). No revision to the limit of 3% for Impurity C was required as long as it was supported by current batch data.

Impurities The proposed statement "The impurities limited by the requirements of this monograph include Impurity A, B, C, D and F listed under Fluvoxamine Maleate" was accepted.

Members proposed that a different TLC plate should be used in the Identification B test as silica gel HF_{254} plates could be difficult for analysts to use. Members also recommended that the advice regarding mobile phase adjustment should be removed from the Related substances test and that the resolution factor system suitability criterion should be revised from "at least 1.0" to "at least 1.5".

232 **Fosinopril Tablets** **MC2(15)22**

The naming of the Fosinopril impurity 1 BPCRS was discussed by members following concerns raised by the Chair and Vice-chair during the QA check of the laboratory report. It was noted that although the structure of the impurity was known, it was not included in the BP monograph and that the name of the BPCRS was misleading as it was identified as an impurity.

The Secretariat noted that it was a manufacturing intermediate used solely as a measure of system suitability in the dissolution test. No data had been provided by the manufacturer to suggest that this intermediate could be controlled by the related substances test. For clarity, members therefore agreed to change its name to 2-[hydroxyl(4-phenylbutyl)phosphinyl]-acetic acid BPCRS.

233 **Methylthioninium Injection** **MC2(15)23**

Consequential revisions to the Methythioninium Injection monograph were discussed following revision to the Ph. Eur. parent monograph.

Identification The absorption maxima were corrected (from 675-685 nm to 670-680 nm) in Identification A in line with the parent monograph.

Assay Members agreed that an HPLC Assay and the introduction of a Related substances test should be included in a future edition when possible. It was noted that the parent monograph definition was being revised from "95.0 per cent to 101.0 per cent (dried substance)" to "93.0 per cent to 102.0 per cent (dried substance). It contains a variable quantity of water." and that the Methylthioninium Injection Assay is written in terms of the trihydrate. The Secretariat will confirm the declaration of content with the MAH and determine which consequential changes to the monograph will be required.

234 **Montelukast Tablets** **MC2(15)24**
Chewable Montelukast Tablets

The Secretariat received a request for revision to the impurity limits in the monographs for Montelukast Tablets and Chewable Montelukast Tablets. It was proposed that the limit for Impurity G, the cis-isomer of Montelukast, was increased from 0.15% to 0.50% in both monographs.

The MAH provided batch data to support their request which indicated that their products could comply with a limit of 0.25% for Impurity G. Members agreed that the MAH should be asked for further rationale to support a revision of the limit to 0.50%.

Prior to the meeting, the MAH had submitted a further request for revision to the Related substances and Dissolution methods. They proposed the use of their in-house HPLC method for Related substances, but did not provide the details, and that Impurities D, E and F should be disregarded from the total impurity limit. They also proposed the use of their in-house HPLC method for Dissolution, but did not provide the details, and that the limits should be revised from Q=80% in 20 minutes to Q=75% in 30 minutes. Members agreed that as a wide range of marketed products from multiple MAHs were tested at the time of monograph development, no additional revisions to the Related substances or Dissolution tests would be considered at this time.

235 **Nicorandil** **MC2(15)25**
Nicorandil Tablets

The Secretariat had received several comments from stakeholders on the Nicorandil and Nicorandil Tablets monographs prior to their publication in the BP 2016. The Chair and Vice Chair agreed to a technical change to the water content limit for the Nicorandil monograph and to only publish the editorial revisions to the Nicorandil Tablets monograph in the BP 2016. Members discussed the following technical revisions further.

Identification (Parent only) Members agreed that Identification test B (melting point determination) should be removed from the monograph as the infrared method was a suitable standalone test.

Related substances (Tablets only) Several MAHs had proposed revisions to the draft monograph. Members agreed that a method which used a single HPLC method with two detection wavelengths to replace the Related substances and Polymeric Impurities tests should be investigated and that oxazaolyl pyridine should be excluded from the Related substances test.

236 **Simvastatin Tablets** **MC2(15)26**

The Secretariat had received correspondence from a manufacturer detailing that they had encountered resolution and detection issues for a number of impurities when using the Related substances procedure of the Simvastatin Tablets monograph.

Members considered the suitability of the procedure included in the monograph which is harmonised with the Ph Eur parent monograph. It was noted by the Licensing Division that there did not appear to be a significant concern with the co-eluting peaks and although desirable, resolved peaks are not critical. Therefore, the method was considered fit for its intended purpose.

It was noted that the Ph Eur parent monograph was currently under revision to include an improved Related substance procedure which provided resolution of all named impurities. Members agreed that harmonisation with this method should be reviewed by the EAG following the finalisation of the parent monograph.

VII EUROPEAN PHARMACOPOEIA

237 **Comments on Draft Monographs of the Ph. Eur.** **MC2(15)27**

It was noted that the following European Pharmacopoeia monographs for which Expert Advisory Group MC2 has responsibility had been published in Pharmeuropa for comments:

Pharmeuropa 26.4
Fenoterol hydrobromide
Irbesartan
Permethrin (40:60) for veterinary use
Enalapril maleate

Pharmeuropa 27.1
Dobutamine hydrochloride
Clopidogrel besilate
Clopidogrel hydrochloride
Tablets
2.2.14. Melting point – capillary method

EDQM News It was noted that the Sitagliptin phosphate monohydrate tablets monograph had been adopted at the 151st Session of the Commission and would be published in Ph. Eur. Supplement 8.7 (effective on 01 April 2016).

VIII ANY OTHER BUSINESS

238 The Secretariat highlighted the Tetracaine Eye Drops and Etidronate Tablets monographs for omission from the BP 2017. Members requested that overseas health authorities were consulted prior to providing their approval.

IX DATE OF NEXT MEETING

The next meeting is due to be held on 11 November 2015.