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, 22 May 2014.

Present: Dr G D Cook (Chair), Mr C T Goddard (Vice-Chair), Mr A Gibson, Dr J Lim, Prof J Miller, Mr P Murray and Dr A Ruggiero.

In attendance: Mr J Pound, Ms J Francomb, Mr P Crowley, Dr K Courtney (BP Lab) and Dr Anita Ciesluk (BP Lab), Mr S Jones (items MC2(14)16, MC2(14)17 and MC2(14)18 only).

Apologies: Mr M Cole, Dr J Qiu and Mrs M Turgoose.

159 **Introductory Remarks**

BP 150th Anniversary The BP celebrated its 150th Anniversary in April. The Chairman congratulated the Secretariat for organising successful events. The week's activities included hosting an NPA meeting (EDQM), a Technical Conference, the 3rd International Meeting of the World Pharmacopoeias (WHO) and an evening reception at the House of Lords. Feedback from stakeholders had been very positive and the MHRA would be releasing a press release summarising the events shortly.

Staff News Ms J Francomb had returned to the Secretariat following her maternity leave. She would resume secretarial responsibilities for the EAG and Peter Crowley would be responsible for coordinating the laboratory work for the EAG as well as QbD projects.

Dr A Ruggiero was congratulated on the arrival of his first child, Pietro, born on 6 May.

Welcome The Chairman welcomed members to the meeting of Expert Advisory Group MC2: Medicinal Chemicals. A special welcome was extended to Dr K Courtney and Dr A Ciesluk from the BP Laboratory. Dr Ciesluk had joined the BP Laboratory in February 2014 and had previously worked at LGC in the Foods and Consumer Safety section.

Prof Kevin Taylor, the new BPC Chairman, was interested in the work of the EAG and would like to attend a future meeting.

Expense Claims Members were invited to contact Miss J Paine (BP Secretariat) for enquires concerning expenses claims. Members were reminded that they were not eligible to claim £5 subsistence if they had the buffet lunch provided by the Secretariat.

Members' News The next EAG/Panel membership review was scheduled for the end of 2014. Members were invited to suggest suitable individuals for EAG/Panel membership.

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.

I MINUTES

160 The minutes of the meeting held on 19 November 2013 were confirmed.

Mr A Gibson arrived at this point in the meeting.

II MATTERS ARISING FROM THE MINUTES

161 The following matters arising from the meeting held on 19 November 2013 were noted.

Enalapril Tablets (Minute 129) A laboratory report was pending for the assessment of the Ph. Eur. parent Related substances procedure and a manufacturers Assay method.

Chlorpromazine Preparations (Minute 129) A laboratory report was pending for the examination of the current BP infrared identification method.

Aminophylline Preparations (Minute 129) Revision of the Aminophylline preparation monographs was in progress.

Bumetanide Injection, Bumetanide Oral Solution and Bumetanide Tablets (Minute 129) This project was in progress.

Furosemide (Minute 129) This project was in progress.

Prolonged-release Methyldopa Tablets (Minute 129) A laboratory report was pending for the assessment of the TLC identification, LC Related substances and LC Assay procedures.

Letrozole Tablets (Minute 129) 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.

Carvedilol Tablets (Minute 129) A laboratory report was pending for the development of an IR identification test and for the assessment of the LC Related substances and Assay procedures.

Prolonged-release Galantamine Capsules, Galantamine Oral Solution and Galantamine Tablets (Minute 129) A laboratory report was pending for the development of Related substances and Assay procedures.

Neomycin and Chlorhexidine Nasal Cream (Minute 129) Further work on this monograph had been deferred pending further consultation.

Quinapril Tablets (Minute 129) A laboratory report was pending for the assessment of the LC Related substances procedure.

Alendronic Acid Tablets (Minute 129) A laboratory report was pending for the assessment of the Ph. Eur. procedure for Related substances.

Carprofen Injection and Tablets (Minute 129) Comments were being sought on the draft monographs.

Propranolol Oral Solution (Minute 129) The Secretariat had requested further information from stakeholders for this monograph.

Sulfasalazine Oral Suspension (Minute 129) The Secretariat had requested further information from stakeholders for this monograph.

Verapamil Oral Solution (Minute 129) The Secretariat had requested further information from stakeholders for this monograph.

Rampiril Capsules and Tablets (Minute 129) The qualification of the BPCRS was in progress.

Prolonged-release Tamsulosin Tablets (Minute 129) The laboratory was awaiting receipt of further samples to assist in the assessment of the Related substances test.

Benazepril Tablets (Minute 129) 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 129) A laboratory report was pending for the Identification, Related substances and Assay procedures.

Ibuprofen and Codeine Tablets (Minute 129) A laboratory report was pending for the Identification, Related substances and Assay procedures.

Ketoprofen Injection and Tablets (Minute 129) 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 129) A laboratory report was pending for the Identification, Related substances and Assay procedures.

Telmisartan Tablets (Minute 129) A laboratory report was pending for the Identification, Related substances and Assay procedures.

Diclofenac Gel (Minute 137) A laboratory report was pending for the Identification procedure.

Prolonged-release Diclofenac Tablets, Gastro-resistant Diclofenac Tablets (Minute 138) These revised monographs would be published in the BP 2015.

Naftidrofuryl Capsules (Minute 139) A laboratory report was pending for the Assay procedure.

Sertraline Tablets (Minute 140) A revised monograph would be published in the BP 2015.

Tranexamic Acid Injection, Tranexamic Acid Tablets, Tranexamic Acid Mouthwash (Minute 141) A laboratory report was pending for the Assay procedure.

Candesartan Tablets (Minute 142) A laboratory report was pending for the Identification, Related substances and Assay procedures.

Fenofibrate Tablets, Fenofibrate Capsules, Prolonged-release Fenofibrate Capsules (Minute 143) 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 144) A laboratory report was pending for the Identification, Related substances and Assay procedures.

Risendronate Tablets (Minute 145) A laboratory report was pending for the Identification, Related substances and Assay procedures.

Terbutaline Injection, Terbutaline Oral Suspension, Terbutaline Tablets (Minute 146) A laboratory report was pending for the Identification, Related substances and Assay procedures.

Ciprofibrate Tablets (Minute 147) A laboratory report was pending for the Identification, Related substances and Assay procedure.

Fosinopril Tablets (Minute 148) This new monograph would be published in the BP 2015.

Phenoxybenzamine Injection (Sterile Phenoxybenzamine Concentrate) (Minute 149) This new monograph would be published in the BP 2015.

Salmeterol Inhalation Powder, Pre-dispensed (Minute 151) Further comments on the monograph were pending.

Salmeterol Pressurised Inhalation (Minute 152) Further comments on the monograph were pending.

Simvastatin Oral Suspension (Minute 153) This new monograph would be published in the BP 2015.

Valsartan Tablets, Valsartan Capsules (Minute 154) These new monographs would be published in the BP 2015.

Phenoxybenzamine Hydrochloride, Phenoxybenzamine Capsules (Minute 157) These revised monographs would be published in the BP 2015.

III REPORTS AND CORRESPONDENCE

162 **Emergency Evacuation Procedure** **MC2(14)01**

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

163 **BP 2014** **MC2(14)02**

Members noted that the BP 2014 had been published in August 2013 and came into effect on 01 January 2014.

164 **Membership** **MC2(14)03**

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

165 **BP Laboratory** **MC2(14)04**

A list of several reference materials relating to monographs within the remit of EAG MC2, which had been adopted since the meeting of 19 November 2013, was provided for information.

166 **Current Work Programme** **MC2(14)05**

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

167 **Pharmacy Update** **MC2(14)06**

Advice on Inhaled Products and Effervescent Tablets was still pending from EAG Pharmacy.

168 **Melphalan Injection** **MC2(14)07**

The Secretariat had received a request from a manufacturer to increase the limit for melphalan dimer (Impurity G) in the Related substance test B from 0.75% to 1.0%. The manufacturers' product had exceeded the 0.75% dimer impurity limit in samples stored at 30°C/75% RH. The Related substances test had been added to the monograph in the BP 2006. The limits had been based on batch data available at that time. The Ph. Eur. parent monograph was first published in 2012 with a gradient LC method for the control of a number of impurities including the dimer which had a limit of 1.0%. The Secretariat noted that the limit for total impurities was 5.5% which indicated that the Ph. Eur. Related substances procedure was capable of detecting impurities not currently controlled by the existing BP Injection monograph.

Members agreed with the Secretariat's proposal to increase the limit for the dimer impurity to 1.0% in-line with the parent monograph for publication in the BP 2016. Additionally, it would be referred to as Impurity G in the BP monograph in-line with the parent monograph. The BP Laboratory would assess the Related substances procedure detailed in the Ph. Eur. parent monograph for its suitability to the range of marketed injection formulations.

169 **Perindopril Erbumine Tablets** **MC2(14)08**

The Secretariat had received a request from a manufacturer for revision to the impurity limits in the monograph for Perindopril Erbumine Tablets first published in the BP 2012. They had proposed that the limits for the active metabolite, Impurity B (perindoprilat), and the metabolite Impurity F be widened from 1.5% to 5.0% and 1.5% to 3.0% respectively. Their rationale for the request was that as they were metabolites, they were considered qualified and therefore not subject to ICH threshold limits.

Members reviewed the batch data supplied and agreed that the Impurity B limit should be widened to 3.0%, but that no revision to the Impurity F limit was required. The revised monograph would be circulated to all MAHs for comment prior to revision of the monograph in the BP 2016.

IV NEW MONOGRAPHS

170 **Anastrozole Tablets** **MC2(14)09**

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

171 **Ezetimibe Tablets** **MC2(14)10**

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

172 **Olmesartan Tablets** **MC2(14)11**

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

173 **Temozolomide Capsules** **MC2(14)12**
Temozolomide Injection

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

V MONOGRAPHS IN PROGRESS

174 **Aprepitant** **MC2(14)13**
Aprepitant Capsules

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

175 **Montelukast Granules** **MC2(14)14**
Montelukast Tablets
Chewable Montelukast Tablets

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

176 **Sitagliptin Tablets** **MC2(14)15**

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

VI REVISION OF MONOGRAPHS

177 **Adrenaline Eye Drops/Epinephrine Eye Drops** **MC2(14)16**
Adrenaline Injection/Epinephrine Injection
Dilute Adrenaline Injection 1 in 10,000/Dilute Epinephrine Injection 1 in 10,000
Adrenaline Solution/Epinephrine Solution
Adrenaline and Cocaine Intranasal Solution/Epinephrine and Cocaine Intranasal Solution
Bupivacaine and Adrenaline Injection/Bupivacaine and Epinephrine Injection
Noradrenaline Injection/Norepinephrine Injection

The Adrenaline and Noradrenaline family of drug product monographs had been under review with a view to introducing improved control of impurities for these products.

Current Position The single component monographs had been presented to the EAG in April 2012, and were revised to include the Ph. Eur. parent monograph Related substances test. These monographs had been circulated to manufacturers; however, no comments had been received. Further review of the impurities control would be required prior to publication of revised monographs to accommodate products that contained sodium metabisulfite which leads to the formation of adrenaline sulfonate. The adoption of the Ph. Eur. test for the combination products would require laboratory evaluation prior to revision.

Content/Assay/Related substances The Licensing Division of the MHRA recommended that the Assay should be revised to an achiral LC Assay in order to quantitate the active isomer, L-adrenaline. Additionally, the Related substances test should be reviewed to ensure that all degradation products were controlled. They would provide more detailed proposals at a future meeting.

178 **Levothyroxine Sodium** **MC2(14)17**

Mr Gibson and Mr Goddard declared an interest. They both participated in the discussion.

The request for revision to the Definition in the monograph to specify the pentahydrate state and to amend the Water content limits accordingly had been reviewed by Group 11 at EDQM. The request for revision was not supported as Group 11 concluded that particle size, not degree of hydration, impacted stability. It was agreed that the UK Expert on Group 11 should ask Group 11 to re-evaluate their decision and consider an appropriate revision to the monograph.

179 **Liothyronine Tablets** **MC2(14)18**
Liothyronine Injection

The MHRA Licensing Division had requested a review of the BP Liothyronine Tablets monograph with a view to introducing control of the dissolution performance of Liothyronine Tablets.

Content The content limits in the published monograph were 90.0 to 110.0% of the stated amount. Members agreed that the limits should be retained as published.

Identification Members agreed that it would be beneficial for the Secretariat to consider the inclusion of a second Identification test, in addition to the current test for concordant retention time in the Assay.

Dissolution The Licensing Division had been concerned about the absence of a dissolution performance test. Members agreed that a modified USP method using 0.1M hydrochloric acid, which was the most discriminating medium, should be further investigated for the suitability to the Liothyronine products.

Related substances Members acknowledged that the development of a Related substances test would be difficult due to the low dose strength of both the Tablets and Injection but agreed that the Ph. Eur. parent method should be investigated for application to the Tablets.

Uniformity of content and Assay The results from the MHRA Laboratory Pre-approval Report indicated that the current test procedures for both the Uniformity of content and Assay requirements were satisfactory. The Secretariat noted that the Ph. Eur. parent monograph instructed users to protect solutions from light. Members agreed that a similar statement should be included in the BP monograph.

180 **Nicorandil** **MC2(14)19**
Nicorandil Tablets

The draft revised monographs for Nicorandil and Nicorandil Tablets had previously been reviewed at the November 2013 meeting. The monographs had been amended following the meeting and circulated to manufacturers for comment.

A draft Ph. Eur. monograph for Nicorandil had been published for comment in Pharmeuropa 26.2. The Secretariat highlighted the differences between the Ph. Eur. and BP monographs and encouraged members to provide comments on the Ph. Eur. draft monograph.

Production (Tablets only) At the previous meeting, members requested that the Production statement in the Nicorandil Tablets monograph be revised for clarity as manufacturers may introduce heat into their production process that they may not deem to be excessive. Members noted that a minor change did not improve understanding of the statement and agreed to retain the original statement from the published monograph.

Characteristics (Parent only) The monograph had been revised to state "white to off-white crystalline powder" as agreed at the previous meeting following information received from a MAH.

Loss on drying/Water (Parent only) The Loss on drying test had been replaced with a Water content test as agreed at the last meeting because the material was decomposing before reaching the LOD temperature. No comments had been received from MAHs on the proposed limit of 0.1%.

Polymeric Impurities (Tablets only) No comments had been received from MAHs on the Polymeric Impurities test. The method would be published as drafted pending receipt of a report from the BP Laboratory.

181 **Phenelzine Sulfate** **MC2(14)20**

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

Identification The Secretariat previously reported that a manufacturer was unable to successfully perform reaction B characteristic of sulfates for Phenelzine Sulfate. The monograph had been revised to specify reaction A in Identification test C for the BP 2015.

Assay The Secretariat had received a request to revise the titrimetric Assay with a LC procedure based on the method in the USP monograph. The manufacturer had performed an evaluation of the method with a similar column which complied with the system suitability requirements. Members adopted the proposed procedure and agreed that the revised monograph should be circulated for comments with a view to publication in the BP 2016. It was noted that a quantitative BPCRS would be required to support the monograph.

VII **EUROPEAN PHARMACOPOEIA**

182 **Comments on Draft Monographs of the Ph. Eur.** **MC2(14)21**

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 26.1

Bromhexine hydrochloride
Methylthioninium chloride
Simvastatin
Sitagliptin phosphate monohydrate

VIII ANY OTHER BUSINESS

NA

IX DATE OF NEXT MEETING

The next meeting is due to be held on 20 November 2014.