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 20th November 2014.

Present: Dr G Cook (*Chairman*), Mr C Goddard (*Vice-Chairman*), Mr P Murray, Dr J Lim, Mrs M Turgoose and Dr A Ruggiero. Mr S Jones was present for item MC2(14)37 only.

In attendance: Mr J Pound, Mr P Crowley, Ms E Sanderson (BP Lab) and Mr A Akhtar (BP Lab).

Apologies: Mr M Cole, Mr A Gibson, Prof J Miller, Dr J Qui, Ms J Francomb.

183 **Introductory Remarks**

Welcome The Chairman welcomed members to the meeting of Expert Advisory Group MC2: Medicinal Chemicals. A special welcome was extended to Ms Sanderson and Mr Akhtar from the BP Laboratory.

Members' News Members were informed that membership letters were due to be sent out before the end of the month.

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.

I MINUTES

184 The summary minutes of the meeting held on 22nd May 2014 were confirmed.

II MATTERS ARISING FROM THE MINUTES

185 The following matters arising from the meeting held on 22nd May 2014 were noted.

Enalapril Tablets (Minute 161) A laboratory report was pending for the assessment of the Related substances procedure and Assay.

Chlorpromazine Preparations (Minute 161) A laboratory report was pending for the examination of the current BP infrared identification method.

Bumetanide Injection, Bumetanide Oral Solution and Bumetanide Tablets (Minute 161) The Secretariat were assessing the need for any additional laboratory evaluation of the proposed methods.

Furosemide (Minute 161) This project was currently in progress.

Prolonged-release Co-careldopa Tablets (Minute 161) A laboratory report was pending for the assessment of the TLC identification, LC Related substances and LC Assay procedures.

Letrozole Tablets (Minute 161) 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 161) A laboratory report was pending for the development of Related substances and Assay procedures.

Neomycin and Chlorhexidine Nasal Cream (Minute 161) Further work on this monograph had been deferred pending further consultation with the sole UK MAH.

Quinapril Tablets (Minute 161) A laboratory report was pending for the assessment of the LC Related substances procedure.

Carprofen Injection and Tablets (Minute 161) A laboratory report was pending for the assessment of the infrared identification, LC Related substances and Assay procedures. The monographs had been circulated to the VMD and stakeholders for comments; no comments had been received at the time of the meeting.

Propranolol Oral Solution (Minute 161) The Secretariat was awaiting the response of the sole UK MAH for this product.

Sulfasalazine Oral Suspension (Minute 161) The Secretariat had requested the cooperation of the UK MAH for this product.

Verapamil Oral Solution (Minute 161) The Secretariat had requested the cooperation of the UK MAH for this product.

Prolonged-release Tamsulosin Tablets (Minute 161) A laboratory report was pending for the assessment of the LC Related substances procedure.

Benazepril Tablets (Minute 161) 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 161) A laboratory report was pending for the identification, Related substances and Assay procedures.

Ibuprofen and Codeine Tablets (Minute 161) A laboratory report was pending for the identification, Related substances and Assay procedures.

Ketoprofen Injection and Tablets (Minute 161) The monograph had been amended and circulated to MAHs, no comments had been received at the time of the meeting. 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 161) A laboratory report was pending for the identification, Related substances and Assay procedures.

Telmisartan Tablets (Minute 161) A laboratory report was pending for the identification, Related substances and Assay procedures.

Diclofenac Gel (Minute 161) A laboratory report was pending for the identification procedure.

Naftidrofuryl Capsules (Minute 161) A laboratory report was pending for the Assay procedure.

Tranexamic Acid Injection, Tranexamic Acid Tablets, Tranexamic Acid Mouthwash (Minute 161) A laboratory report was pending for the Assay procedure.

Candesartan Tablets (Minute 161) A laboratory report was pending for the identification, related substances and Assay procedures.

Fenofibrate Tablets, Fenofibrate Capsules, Prolonged-release Fenofibrate Capsules (Minute 161) 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 161) A laboratory report was pending for the identification, related substances and Assay procedures. The Secretariat was to circulate the revised monographs to manufacturers for comment.

Risendronate Tablets (Minute 161) A laboratory report was pending for the identification, related substances and Assay procedures.

Terbutaline Injection, Terbutaline Oral Suspension, Terbutaline Tablets (Minute 161) A laboratory report was pending for the identification, related substances and Assay procedures. The monograph had been revised and circulated to MAHs, no comments had been received.

Ciprofibrate Tablets (Minute 161) A laboratory report was pending for the identification, related substances and Assay procedures.

Salmeterol Inhalation Powder, Pre-dispensed (Minute 161) Responses regarding the draft monograph were pending.

Salmeterol Pressurised Inhalation (Minute 161) Responses regarding the draft monograph were pending.

Prolonged-release Diclofenac Tablets, Gastro-resistant Diclofenac Tablets, Sertraline Tablets, Phenoxybenzamine Hydrochloride, Phenoxybenzamine Capsules These revised monographs had been published in the BP 2015.

Fosinopril Tablets, Phenoxybenamine Injection (Sterile Phenoxybenzamine Concentrate), Valsartan Tablets, Valsartan Capsules, Montelukast Granules, Montelukast Tablets, Chewable Montelukast Tablets These new monographs had been published in the BP 2015.

Melphalan Injection (Minute 168) A laboratory report was pending for the Ph. Eur. parent Related substances procedure.

Sitagliptin Tablets (Minute 176) The monograph had been amended and circulated to the MAH and USP for comment.

Liothyronine Tablets, Liothyronine Injection (Minute 179) The monograph had been amended and will be circulated to MAHs for comment.

Nicorandil, Nicorandil Tablets (Minute 180) These monographs had been amended and were expected to be published in BP 2016.

Phenelzine Sulfate (Minute 181) A revised monograph was published in the BP 2015. The Secretariat had not received a request for revision for the Tablets monograph from the MAH.

Carbocisteine Capsules, Carbocisteine Oral Solution (Minute 129) A laboratory report was pending for the identification and Assay procedures. The monograph was to be circulated to MAHs for comment.

III REPORTS AND CORRESPONDENCE

186 **Emergency Evacuation Procedure** **MC2(14)22**

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

187 **BP 2015** **MC2(14)23**

Members were informed that the BP 2015 had been published in August 2014 and would come into effect on 1st January 2015.

188 **Membership** **MC2(14)24**

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

189 **BP Laboratory** **MC2(14)25**

A list of several reference materials relating to monographs within the remit of EAG MC2, which had been adopted since the meeting of 22nd May 2014, was provided for information.

190 **Current Work Programme** **MC2(14)26**

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

191 **Gliclazide Tablets** **MC2(14)27**

The monograph for Gliclazide Tablets had been amended to cross refer the name of the specified impurity in the Related substances to the relevant EP impurity code (EP impurity F), the BPCRS and relevant information leaflet had also been updated accordingly. The revised monograph would be published in the BP 2016.

192 **Ramipril Impurity K** **MC2(14)28**

The Secretariat reported that the BP Laboratory had encountered difficulties in establishing a replacement Ramipril Impurity K BPCRS. This BPCRS was required by the Related substances procedure in the Capsules and Tablets product monographs.

IV NEW MONOGRAPHS

193 **Rivastigmine Preparations** **MC2(14)29**

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

V MONOGRAPHS IN PROGRESS

194 **Anastrozole Tablets** **MC2(14)30**

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

195 **Aprepitant Capsules** **MC2(14)31**

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

196 **Carvedilol Tablets** **MC2(14)32**

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

197 **EzetimibeTablets** **MC2(14)33**

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

198 **Olmesartan Tablets** **MC2(14)34**

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

199 **Risedronate Tablets** **MC2(14)35**

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

200 **Temozolomide Capsules** **MC2(14)36**
Temozolomide Injection

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

VI REVISION OF MONOGRAPHS

201 **Adrenaline/Noradrenaline Preparations** **MC2(14)37**

Mr Sean Jones from the Licensing Division attended the meeting for this paper.

It had been previously reported at the May 2014 meeting of EAG: MC2 that the Adrenaline and Noradrenaline family of drug product monographs had been under review by this EAG for several years and that the Licensing Division had since requested that the determination of content for adrenaline products was also reviewed.

The MHRA Laboratory had developed a protocol to investigate ratios of the inactive D-adrenaline and active L-adrenaline isomers. Several pharmaceutical forms would be assessed using a chiral HPLC method drafted by the Secretariat, published Assay methods and methods proposed by manufacturers.

The outcomes of this protocol should lead to a better understanding of the content and impurity profiles. The intention would be to share the conclusions of this work with other pharmacopoeias and regulators, if appropriate.

202 **Aminophylline** **MC2(14)38**

The Secretariat had received a query from a manufacturer regarding the content limits for theophylline in the Aminophylline Injection monograph. A similar query regarding the content limits for ethylenediamine in the Aminophylline Tablets monograph had been raised and it was proposed that both content statements for the Aminophylline family of monographs were reviewed at the same time.

Aminophylline is a complex of 2 molecules of theophylline and 1 molecule of ethylenediamine with a variable proportion of water. The Ph. Eur. parent monographs (Aminophylline and Aminophylline Hydrate) as well as the Aminophylline Tablet and Prolonged-release Aminophylline Tablet monographs are written in terms of Anhydrous Aminophylline, “Aminophylline”.

Theophylline content The theophylline content limits of 73.25 to 88.25% of the stated amount of Aminophylline in the Aminophylline Injection monograph had remained unchanged since at least the BP 1963. At that time, “Aminophylline” referred to the hydrated form (mono or di) and would have been equivalent to a limit of 80.75 +/- 10% which was assumed to have allowed for use of both the monohydrate (82.18) and dihydrate (78.94).

Ethylenediamine content Members agreed with the Secretariat proposal to revise the content limits in line with the parent monographs, with the exception of the Injection monograph for which an excess of ethylenediamine is present in the Injection formula for solubility purposes.

203 **Alendronic Acid Tablets** **MC2(14)39**

The Secretariat had previously reported at the November 2012 meeting of EAG: MC2 that a number of laboratories and manufacturers had reported difficulties with the current Related substances and Assay procedures. The BP Laboratory was asked to perform an investigation of the Phosphate/Phosphite and Assay method specified in the Ph Eur parent monograph and that work had now been successfully completed and the monograph amended accordingly.

204 **Levothyroxine** **MC2(14)40**

Dr Ruggerio provided a brief oral update on current discussions in the Licensing Division on Levothyroxine products.

205 **Perindopril Erbumine Tablets** **MC2(14)41**

The Secretariat had previously received a request for revision of the limits for impurity B and F from a manufacturer. The revised monograph had been circulated to manufacturers and responses had been received from two additional MAHs. Members agreed that the revision should not proceed until a response was received from the manufacturer who raised the request for revision.

206 **Simvastatin Oral Suspension** **MC2(14)42**

The monograph for Simvastatin Oral Suspension had been published in the BP 2015. Members had agreed at the November 2013 meeting that manufacturer should be asked to submit long-term stability data to support their request for amended pH limits; this data had now been supplied.

Members agreed that the pH specification was not required and should be deleted from the draft monograph. This was based on data which demonstrated that pH did not have a significant effect on the product stability.

VII EUROPEAN PHARMACOPOEIA

207 **Comments on draft monographs of the Ph Eur.** **MC2(14)43**

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 26.2
Atorvastatin calcium
Deferoxamine mesilate
Mebeverine hydrochloride
Nicorandil
Rivastigmine hydrogen tartrate
Solifenacin succinate
5.21. Chemometric methods applied to analytical data
2.5.41. Methyl, ethyl and isopropyl benzenesulfonate in active substances

Pharmeuropa 26.3
Salbutamol
Salbutamol sulfate
Sitagliptin phosphate monohydrate tablets
Gefitinib
Rivastigmine hydrogen tartrate

Solifenacin succinate
5.21. Chemometric methods applied to analytical data
2.5.41. Methyl, ethyl and isopropyl benzenesulfonate in active substances
2.2.48. Raman spectroscopy
2.2.3. Potentiometric determination of pH
Introduction of the Production section in the monographs for besilate salts

VIII ANY OTHER BUSINESS

208 The Secretariat verbally noted that a Public Assessment Report had been published stating that licences for Orciprenaline Sulphate preparations had been withdrawn by September 2010 due an increased risk of adverse effects compared to other products. In light of this and as no products were currently marketed, members agreed that the monographs for Orciprenaline Oral Solution and Orciprenaline Tablets should be omitted from the BP 2016.

IX DATE OF NEXT MEETING

The next meeting is due to be held on TBC