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 Wednesday 2nd March 2016.

Present: Dr G Cook (*Chairman)*, Mr C Goddard (*Vice-Chairman*), Prof J Miller, Mr N Wynne, Mr P Murray, Dr J Lim and Dr A Ruggiero.

In attendance: Ms H Corns, Mr P Crowley, Ms S Gomersal, Mr S Wilson (BP Lab) and Mr D Holcombe (BP Lab). Ms C Pitt was present for items MC2(16)18 and MC2(16)19.

Apologies: Mr J Cowie, Dr D Edwards and Mrs M Turgoose.

Dr Cook, Mr Murray and Mr Goddard declared interests in one or more agenda items and appropriate action was taken.

271 Introductory Remarks

Welcome The Chairman welcomed Stuart Wilson and Dave Holcombe from the BP Lab and also the new Assistant Secretary for the EAG, Sarah Gomersal. Members were also informed that Andy Gibson had recently handed in his resignation from the EAG due to relocation.

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

272 Emergency evacuation procedure

The emergency evacuation procedure for the building was provided.

I MINUTES

273 The minutes and summary minutes of the meeting held on 11 November 2015 were confirmed with no amendments.

II MATTERS ARISING FROM THE MINUTES

274 The following matters arising from the meeting held on 11 November 2015 were noted.

Enalapril Tablets (Minute 241) A laboratory report was pending for the assessment of the Related substances and Assay procedures.

Chlorpromazine Preparations (Minute 241) A laboratory report was pending for the examination of the infrared identification method.

Bumetanide Injection, Bumetanide Oral Solution and Bumetanide Tablets (Minute 241) This projects was in progress.

Furosemide (Minute 241) This project was in progress.

Prolonged-release Co-careldopa Tablets (Minute 241) A laboratory report was pending for the assessment of the TLC identification, LC Related substances and LC Assay procedures.

Letrozole Tablets (Minute 241) 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 241) A laboratory report was pending for the development of Related substances and Assay procedures.

Carprofen Injection and Tablets (Minute 241) A laboratory report was pending for the assessment of the Infrared Identification, LC Related substances and LC Assay procedures.

Prolonged-release Tamsulosin Tablets (Minute 241) A laboratory report was pending for the assessment of the LC Related substances procedure.

Benazepril Tablets (Minute 241) A laboratory report was pending for the assessment of the drafted identification, Related substances and Assay procedures.

Ibuprofen and Codeine Tablets (Minute 241) A laboratory report was pending for the identification, Related substances and Assay procedures.

Ketoprofen Injection and Tablets (Minute 241) A laboratory report was pending for the identification, Related substances and Assay procedures. This work was in progress at the laboratory and a report expected in due course.

Methylphenidate Tablets, Prolonged-release Methylphenidate Capsules and Prolonged-release Methylphenidate Tablets (Minute 241) A laboratory report was pending for the identification, Related substances and Assay procedures.

Telmisartan Tablets (Minute 241) A laboratory report was pending for the identification, Related substances and Assay procedures.

Diclofenac Gel (Minute 241) A laboratory report was pending for the identification procedure.

Naftidrofuryl Capsules (Minute 241) A laboratory report was pending for the Assay procedure.

Tranexamic Acid Injection, Tranexamic Acid Tablets, Tranexamic Acid Mouthwash (Minute 241) A laboratory report was pending for the Assay procedure.

Fenofibrate Tablets, Fenofibrate Capsules, Prolonged-release Fenofibrate Capsules (Minute 241) 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 241) A laboratory report was pending for the identification, related substances and Assay procedures.

Terbutaline Injection, Terbutaline Oral Suspension, Terbutaline Tablets (Minute 241) A laboratory report was pending for the identification, related substances and Assay procedures.

Carbocisteine Capsules, Carbocisteine Oral Solution (Minute 241) A laboratory report was pending for the identification and Assay procedures.

Rivastigmine Preparations (Minute 241) A laboratory report was pending for the Identification, Related substances and Assay procedure.

Anastrozole Tablets (Minute 241) A laboratory report was pending for the Identification, Related substances and Assay procedures.

Ezetimibe Tablets (Minute 241) A laboratory report was pending for the identification, Related substances and Assay procedures.

Inhaled Products (Minute 241) These were to be presented at a future meeting.

Candesartan Tablets (Minute 241) A laboratory report was pending for the identification, Related substances and Assay procedures.

Risedronate Tablets (Minute 241) A laboratory report was pending for the identification, Related substances and Assay procedures.

Levothyroxine (Minute 248) A revision request was to be submitted to EDQM at the earliest opportunity.

Metformin and Sitagliptin Tablets (Minute 253) Comments from EAG MC2 were provided to EAG MC1, who were responsible for the development of this monograph.

Sitagliptin and Prolonged-release Metformin Tablets (Minute 254) Comments from EAG MC2 were provided to EAG MC1, who were responsible for the development of this monograph.

Ciprofibrate Tablets (Minute 255) A laboratory report was pending for the Identification procedure.

Aminophylline Injection, Aminophylline Tablets and Prolonged-release Aminophylline Tablets (Minute 261) The monographs were amended as agreed and circulated to stakeholders.

Nicorandil Tablets (Minute 267) The revised Related substances test was to be published in the BP 2017, as agreed.

Phenindione Tablets (Minute 268) The monograph was amended as agreed and circulated to stakeholders.

Correspondence Items
8 items were circulated following the previous meeting as time constraints had not allowed for discussion of these topics.

Minutes The minutes of the correspondence items were confirmed with no amendments.

Montelukast Tablets and Chewable Montelukast Tablets Members agreed a revision to the limit for impurity G from 0.15% to 0.5% which would be published by means of the BP 2017.

Montelukast Granules, Montelukast Tablets and Chewable Montelukast Tablets The correction of a typographical error in the Montelukast monographs Related substances test guard column (4 mm x 3.0 mm to replace 4 cm x 3.0 mm) would be made by means of the BP 2017.

III MONOGRAPHS

276 Fluvastatin Preparations:
Fluvastatin Capsules
Prolonged-release Fluvastatin Tablets

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

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

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

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

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

281 Liothyronine Preparations:
Liothyronine Injection
The draft monograph would be included in a future BP publication, subject to comments.

Liothyronine Tablets
Dissolution A laboratory report indicated that 0.1M HCl was the most discriminatory medium and limits of Q=75% in 45 minutes were considered acceptable. Members recommended that the LC quantification should be harmonised with the Uniformity of Content/ Assay for analytical convenience.

Related Substances Members agreed the inclusion of a UHPLC procedure in the absence of suitable methodology using conventional HPLC.

Members agreed that the impurity limits should be assessed based on the procedures improved capability compared to TLC base specifications.

282 Adrenaline Preparations:
Adrenaline Injection
Dilute Adrenaline Injection
The draft revised monographs were amended in-line with the actions agreed at the November 2015 meeting, and were posted on the BP website for stakeholders comment during the period 1 January – 31 March 2016.

Subsidiary titles (Injection only) The definition had been amended to account for products prepared from either the tartrate or the base.

D-Adrenaline Comments received by the Secretariat indicated that a limit of 5% for D-adrenaline in the draft revised monograph would be too restrictive. Members requested that further information was obtained to inform the decision on an appropriate limit.

Related substances Comments received by the Secretariat indicated that a limit of 5% for adrenaline sulfonate in the draft revised monograph would be too restrictive. Members requested that further information was obtained to inform the decision on an appropriate limit.

283 Chlorhexidine Irrigation Solution

The Secretariat reported that revision of the Ph Eur Chlorhexidine Acetate monograph resulted in the withdrawal of the Chlorhexidine for performance test CRS, used in the BP monograph for Chlorhexidine Irrigation Solution.

4-Chloroaniline The Secretariat agreed to investigate a replacement of the packed GC column for future revision.

Related substances Members agreed that the Related substances test and limits should be harmonised with the Ph Eur Chlorhexidine Gluconate Solution monograph, subject to comments from stakeholders.

284 Aprepitant Capsules

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

285 Temozolomide Preparations:
Temozolomide Capsules
Temozolomide for Injection

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

286 Mesalazine Preparations:

Mesalazine Enema
Mesalazine Foam Enema
Prolonged-release Mesalazine Granules
Mesalazine Suppositories
Gastro-resistant Mesalazine Tablets
Prolonged-release Mesalazine Tablets

Dissolution (Enema and Foam Enema only) Members discussed dissolution requirements for rectal suspensions. The Secretariat agreed to investigate whether a test should be included in a future revision.

Related substances The update to use mesalazine for system suitability for EPCRS, which contained impurities F, J and P to replace the withdrawn mesalazine for peak identification EPCRS and a separate solution for impurity F, was agreed.

Assay (Enema and Foam Enema only) The determination content was amended to be in terms of weight per mL.

287 Prolonged-release Tamsulosin Tablets

Related substances Members agreed that the unspecified impurity should be revised to NMT 1.0%, in-line with ICH Q3B (R2) and published by means of the BP 2017.

288 Phenelzine Sulfate

Content Members agreed a revision of the content limits to 98.0 – 102.0%, as a HPLC method had replaced a titration.

289 Labetalol Injection

BPCRS The Secretariat reported that the bulk material for the 5-[1-hydroxy-2-(1-methyl-3-phenylpropylamino)ethyl]salicylic acid hydrochloride BPCRS had been exhausted and that the previous donor of this material was unable to provide an additional bulk.

Members agreed that Labetalol Impurity A EPCRS could be used; however as the EPCRS was the base rather than the hydrochloride salt used in the BPCRS, the solution concentration in the monograph would require adjustment.

Post meeting note: A source of bulk material for this BPCRS has been procured by the Laboratory. No revision to the monograph will therefore be progressed.

290 Salmeterol Inhalation Powder, pre-dispensed

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

291 Salmeterol Pressurised Inhalation, suspension

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

292 Melphalan Injection/ Melphalan for Injection

Title As there were no ready-made solutions for injection or infusion on the UK market, the monograph was updated to be a standalone Melphalan for Injection monograph. Members accepted this proposal.

Identification A Data had been provided to demonostrate that the less well-defined maximum was seen at 301 nm instead of 310 nm. A review of the data provided to support the establishment of the monograph indicated the less well-defined maximum was seen at 303 nm. Members agreed the amendment to a less well defined maximum at 302 nm.

293 Indapamide Preparations:
Indapamide Tablets
Prolonged-release Indapamide Tablets

Members agreed at the November 2015 meeting to specifically control genotoxic impurity C, a hydrolysis product of indapamide, in the indapamide preparation monographs. The draft revised monographs had been posted on the BP website for public comment during the period 1 January – 31 March 2016.

Impurity C limit (Prolonged-release Tablets only) A manufacturer requested that the proposed limit for impurity C was increased from 600 ppm to 1000 ppm, based on the maximum available strength of 1.5 mg for the prolonged-release tablets rather than the maximum daily dose of 2.5 mg for the API. Licensing representatives had advised that an expert non-clinical toxicological assessment should be requested to support the requested increase. Members agreed an assessment should be provided before an increase in the limit could be accepted.

Impurity C method If the drafted method was found to be unsuitable; it was accepted by members that impurity C should be controlled using a production statement in the BP 2017 until a suitable method was found.

294 Cyclophosphamide for Injection

Members had previously reviewed the Cyclophosphamide for Injection monograph at the November 2015 meeting following a request to revise the pH limits. As agreed, the Secretariat had amended the monograph title in line with the revised parenteral preparations policy. The revised monograph had been made available for public consultation on the BP website between 1 January to 31 March 2016.

Identification A As the IR identification procedure used chloroform as an extraction solvent, manufacturers had been contacted with a request for a suitable alternative solvent. No alternative had been suggested, however an MAH indicated that the TLC method from the parent monograph or the Oral Solution monograph may be suitable. They did not however have experience of using either and members agreed to retain the test as published in the absence of supporting data.

Identification B It had been identified that this test was specific for identifying cyclophosphamide and not a counter-ion test as was suggested at the previous meeting. Members confirmed that this test should be replaced with a cross reference to the Related substance TLC.

Acidity The pH limit had been revised from "4.0 to 6.0" to "3.0 to 6.0" as agreed at the last meeting and in line with data received from another MAH. No comments had been received on the revised limits.

Uniformity of content An MAH had queried if the Uniformity of Content test was required. Members agreed that as the Uniformity of dosage units and Uniformity of mass tests from the Parenteral Preparations general monograph applied, there was no compelling reason to retain this test. .

Assay MAHs had been contacted to determine if the LC method from the Oral Solution monograph would be a suitable replacement for the published titrimetric procedure. One MAH confirmed that they used an in-house method based on the LC Assay from the USP and were asked to provide details of their method. Members agreed that in the absence of a response from this MAH, a method based on the Assay in the USP Cyclophosphamide for Injection monograph should be drafted and circulated to MAHs for comment.

IV FOR INFORMATION

295 Ph. Eur. Monograph Titles – Degree of Hydration

EAG: MC2 monographs affected by the Ph. Eur. monograph title changes were presented for information.

296 Heavy Metals Test

A list of EAG: MC2 monographs which would have the heavy metals test removed in-line with Ph. Eur. implementation of ICH Q3D was presented for information.

297 Fees and Expenses

The revised Fees and Expenses policy was provided to members.

298 BP Laboratory

A table detailing the status EAG: MC2 laboratory requisitions was provided for information.

299 MC2 Work Programme

A list of new additions to the EAG: MC2 work programme, endorsed by BPC in November 2015, was provided.

V EUROPEAN PHARMACOPOEIA

300 Pharmeuropa 28.1

A list of Pharmeuropa 28.1 documents for comments was presented. Members were invited to submit comments to the Secretariat by 31 March 2016.

VI ANY OTHER BUSINESS

No items were raised.

VII DATE OF NEXT MEETING

The next meeting was scheduled for 1 November 2016