BRITISH PHARMACOPOEIA COMMISSION
EXPERT ADVISORY GROUP (EAG): MEDICINAL CHEMICALS 1 (MC1)

SUMMARY MINUTES

A meeting of Expert Advisory Group (EAG): Medicinal Chemicals (MC1) was held at 151 Buckingham Palace Road, London SW1W 9SZ on Wednesday, 11th June 2014.

Present: Professor A G Davidson *(Chairman)*, Dr J C Berridge, Dr V Loh, Dr J Lough and Mr D Malpas.

Apologies: Professor D Cairns *(Vice-chairman)*, Dr M Ahmed, Mr M Broughton, Mr A J Caws and Mr P Fleming.

In attendance: Mrs M Barrett, Ms H Corns, Mr M Coxon and Ms C Galdino.

INTRODUCTORY REMARKS

263 Welcome

The Chairman welcomed everyone especially Mr M Coxon and Ms C Galdino from the BP Laboratory who were attending their first MC1 meeting.

Members were informed that the meeting was quorate as 50% of the expert group were present.

The Secretariat would canvass members in the next month to ask if they would consider being re-appointed to Expert Advisory Group MC1.

I GENERAL MATTERS

264 Minutes

The minutes of the meeting held on 17th December 2013 were confirmed with a minor editorial change.

265 Emergency evacuation procedure MC1 (14) 01

The emergency evacuation procedure for Buckingham Palace Road was noted.

266 Declaration of interests MC1 (14) 02

Members had declared their interests prior to the meeting.

267 Issues arising from the BP Commission MC1 (14) 03

Members were provided with an update on matters recently discussed by the BP Commission.

Chloroform-containing Preparations

The Committee on Human Medicines (CHM) had advised that the Acceptable Daily Intake (ADI) for chloroform, as an excipient in medicines, should be restricted to 10µg/kg/day. On the advice of CHM the same limit would be applied to oral preparations included in the BP which might be prepared extemporaneously for oral use in a future BP publication. No monographs for which EAG: MC1 had

responsibility were affected by this issue.

Anti-epileptics – interchangeability

Members were informed that guidance had been circulated by the MHRA to prescribers, pharmacists and patients on the interchangeability of anti-epileptic drugs (AEDs). The Committee on Human Medicines (CHM) had reviewed evidence on patients switching between different manufacturers' products and had concluded that, although there was no clear evidence of harm associated with switching products, an effect on some patients could not be ruled out. CHM had classified the various AEDs into three categories.

Category 1 Practitioners were advised to ensure that the patient was maintained on a specific product.

Category 2 The need to maintain a specific product would be based on clinical judgement and consultation with the patient or carer and taking into account seizure frequency and treatment history.

Category 3 It was unnecessary to maintain a single manufacturer's product.

MC1 members had sought guidance from the BP Commission on the inclusion of a statement on non-interchangeability in the monographs for the 3 categories classified by CHM. The BPC had recommended that statements should be included in a future BP publication for both category 1 and category 2 monographs for anti-epileptics.

II MATTERS ARISING FROM THE MINUTES

268 Matters arising MC1 (14) 04

A list of 'Matters Arising' from the minutes of the meeting of EAG: MC1 held in December 2013 and those outstanding from previous meetings was circulated with the papers for the meeting. A copy is appended (Annex 1).

269 Laboratory Work update MC1 (14) 05

A document outlining the BP Laboratory work schedule for BP 2016 was presented for information.

270 New and Revised monographs for BP 2015 MC1 (14) 06

It was noted that 5 new and 19 revised British Pharmacopoeia monographs, that were the responsibility of EAG: MC1, would be published in the BP 2015.

271 Fenthion BP (Vet) MC1 (14) 07

Following a review of the Fenthion BP (Vet) monograph the Secretariat had sought advice from the Veterinary Medicines Directorate (VMD) on the use of Fenthion within the UK. The VMD had stated that Fenthion was no longer used in veterinary medicines and that there were severe restrictions on its use as a pesticide within the European Union. Members would recommend that the BP Commission omit Fenthion from a future edition of the BP (Vet).

III NEW MONOGRAPHS

272 **Itraconazole Capsules** MC1 (14) 08

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

273 **Cinnarizine Tablets** MC1 (14) 09

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

274 **Gastro-resistant Pantoprazole Tablets** MC1 (14) 10

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

275 **Pantoprazole Injection** MC1 (14) 11

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

276 **Ketoconazole Cream** MC1 (14) 12

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

277 **Ketoconazole Shampoo** MC1 (14) 13

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

IV MONOGRAPHS IN PROGRESS

278 **Rizatriptan (Benzoate) Tablets** MC1 (14) 14

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

279 **Rizatriptan (Benzoate) Orodispersible Tablets** MC1 (14) 15

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

280 **Terbinafine Tablets** MC1 (14) 16

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

V REVISION OF MONOGRAPHS

281 **Clonidine Tablets** MC1 (14) 17

Assay A user had noted an inconsistency in the amount of powdered tablet used for Assay in the monograph for Clonidine Tablets. Members agreed that the amendment should be adopted for consistency.

Major revision It was highlighted that the monograph was in need of revision as it had a non-specific Assay, did not contain a Dissolution or Related substances test, had wide content limits and used chloroform as a solvent in the tests. New methods would be investigated and sent to the Laboratory for assessment.

282 Clotrimazole Pessaries MC1 (14) 18

A query had been received regarding the Definition in the monograph for Clotrimazole Pessaries – *Clotrimazole Pessaries are* vaginal tablets *containing Clotrimazole.* Vaginal Pessaries and Vaginal Tablets were defined by different EDQM Standard Terms. Members were of the opinion that separate monographs should be published for vaginal tablets and pessaries given that there were distinct Standard Terms for each but that the decision should lie with the Pharmacy Expert Group as the monographs were the responsibility of more than one BP expert advisory group.

Isoconazole Pessaries During the review the Secretariat had found that there were no active UK licences for Isoconazole Pessaries. Members would recommend to the BPC that the monograph should be omitted from a future edition of the BP.

283 Clotrimazole Cream MC1 (14) 19

Identification test A - UV absorbance Identification test A for Clotrimazole Cream had previously been amended to replace the extraction solvent, carbon tetrachloride, with dichloromethane following no adverse comments on the change from manufacturers. Subsequently it had been found that dichloromethane did not extract Clotrimazole from the Cream. Members agreed that the test would be deleted from the monograph and that a cross reference to the LC assay would be used as a second identification test while keeping the current TLC test.

Further review of TLC test The TLC identification test had no system suitability test mixture. The BP Laboratory would be asked to find a suitable system suitability mixture for the TLC test when next assessing the reference material for Clotrimazole.

284 Phenytoin Tablets MC1 (14) 20
(also concerns Phenytoin Capsules, Phenytoin Injection and Phenytoin Oral Suspension)

Related substances test A BP user had informed the Secretariat that they had encountered problems with the Related substances test in the monograph for Phenytoin Tablets. The method had been validated by the company 15 years ago but in the last 2 years they had not been able to detect the spots applied at lower concentrations. They were of the opinion that changes may have been made to the fluorescent coating on the plates. As pre-washing the plates with methanol before carrying out the test enabled the spots to be detected the monograph would be revised to include a statement to pre-wash the plates.

Further review of monographs Members reviewed the monographs for the 4 published Phenytoin preparations and agreed that the BP Laboratory would assess whether the Related substances and Assay could be updated and a Dissolution requirement added to the Phenytoin Capsules and Phenytoin Tablets monographs.

285 Carbimazole Tablets MC1 (14) 21

Following the revision to the Thiamazole and other related substances test the manufacturer who requested the revision had made further comments on the revised method.

Thiamazole and other related substances - solution (2) The manufacturer had requested that the limiting solution was prepared from carbimazole BPCRS instead of a dilution of the test solution. It was standard practice in BP monographs to prepare a limiting solution by dilution of the test solution and members agreed that the preparation 'Dilute 1 volume of solution (1) to 200 volumes with 5% of acetonitrile' should be retained.

Thiamazole and other related substances - solution (4) The manufacturer had highlighted an error in solution (4). The Secretariat agreed to correct the error.

286 Sumatriptan Preparations MC1 (14) 22

Content A user had queried why the content in the Sumatriptan Tablets monograph was in terms of the succinate and not in terms of the base, to be in-line with the licensed products. This was also true of the Sumatriptan Injection monograph. Members agreed that the content should be in terms of the active moiety.

Impurity standard solutions A user had been experiencing poor chromatography when running solution (3) in the Related substances test and had queried why the solution was prepared in 0.1M hydrochloric acid instead of mobile phase. Upon investigation it was found that the preparation in 0.1M hydrochloric acid had been carried over from the Tablets monograph into the Injection and Nasal Spray monographs and that the original data indicated mobile phase should be used. Members agreed that the monographs should be amended accordingly.

Dissolution Members noted that there was no specified Dissolution requirement in the Sumatriptan Tablets monograph and requested that the Secretariat investigated a suitable test.

Labelling statement The Secretariat agreed to include a labelling statement in the Tablets and Injection monographs to state that the quantity of the active ingredient was stated in terms of the equivalent amount of sumatriptan.

287 Piperonyl Butoxide BP(Vet) MC1 (14) 23

A draft revised monograph for Piperonyl Butoxide BP (Vet) had been reviewed by members to include a Related substances test. The Secretariat circulated the draft to a known manufacturer and they had responded that a more robust Related substances test was available. The Secretariat would review the new data and a revised monograph would be presented to members for discussion.

VI REPORTS AND CORRESPONDENCE

288 Warfarin Tablets MC1 (14) 24

A Laboratory had experienced difficulties when performing the TLC Related substances test in the BP monograph for Warfarin Tablets. The Laboratory had suggested that the HPLC method in the Ph. Eur. API monograph could be adapted for use with the tablets. Members agreed that the Ph. Eur. method should be

assessed for suitability for the tablets monograph.

VII ANY OTHER BUSINESS

289 Any other business MC1 (14) 25

Members approved of the rearrangement of items in the agenda which allowed for minor revisions to be deferred to acceptance by correspondence should the meeting over-run.

It was noted that the BP Laboratory had commenced work on the Metformin Tablets revision.

290 Date of next meeting MC1 (14) 26

Monday, 15th December 2014

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2.1. MATTERS ARISING FROM PREVIOUS MEETINGS OTHER THAN THOSE MENTIONED ON THE AGENDA

Dipyridamole Impurities	The BP Laboratory is currently carrying out work to establish the impurity standards.
Aspirin Preparations	The BP Laboratory will assess the Related substances tests with a view to harmonising with the Ph. Eur. monograph for the active at the earliest opportunity.
Cetirizine Impurities	The Secretariat will review the data at the earliest opportunity.
4-Aminophenol Limit for Paracetamol Preparations	The Secretariat are awaiting a response from EDQM and Ph. Eur. regarding data to support tighter limits for 4-aminophenol.
Mianserin Tablets	The Secretariat to review and revise before sending a requisition to the BP Laboratory.
Procyclidine Hydrochloride	The Secretariat to review and revise before sending a requisition to the BP Laboratory.
Abacavir, Zidovudine and Lamivudine Tablets, Abacavir and Lamivudine Tablets, Zidovudine Injection	The Secretariat will prepare a laboratory requisition at the earliest opportunity.
Loperamide Preparations	The Secretariat will prepare a laboratory requisition at the earliest opportunity.
Dihydrocodeine Injection Dihydrocodeine Tablets	The BP Laboratory was asked to assess the suitability of the revised draft method for Related substances and Assay in order to advise on suitability for purpose. The results of the analysis will be presented to this EAG at the earliest opportunity.
Propofol Injection – test for Lysolecithin	The BP Laboratory will reassess the robustness of the lysolecithin test method at the earliest opportunity.
Brompheniramine Tablets	The BP Laboratory will assess the suitability of the draft revised Related substances test method.