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

SUMMARY MINUTES

A meeting of Expert Advisory Group (EAG): Medicinal Chemicals 1 (MC1) was held at 151 Buckingham Palace Road, London SW1W 9SZ on Monday, 8th June 2015.

Present: Professor A G Davidson *(Chairman),* Professor D Cairns *(Vice-chairman),* Dr. M Ahmed, Mr. M Broughton, Mr. A J Caws, Mr. P Fleming, Mr. A James, Dr. J Lough and Mr. D Malpas.

Apologies: Dr. J C Berridge, Dr. V Loh.

In attendance: Mrs. M Barrett, Ms. H Corns, Ms. S Gomersal, Ms. E Sanderson and Ms. A Vasilaki.

Also present for part of the meeting: Ms. H Bowden, Ms. C Pitt.

326 Welcome

The Chairman welcomed everyone to the meeting especially a new expert, Mr. A. James, Ms. S Gomersal from the British Pharmacopoeia Secretariat, and Ms. E Sanderson and Ms. A Vasilaki from the BP Laboratory.
Ms. H Bowden from Reading University and Ms. C. Pitt from the Secretariat were also welcomed.

I GENERAL MATTERS

327 Minutes

The minutes and summary minutes of the meeting held on 15th December 2014 were confirmed.

328 Emergency evacuation procedure MC1 (15) 1

The emergency evacuation procedure for Buckingham Palace Road was noted.

329 Declaration of interests MC1 (15) 2

Mr. M Broughton, Mr. A Caws, Professor D Cairns, Mr. P Fleming and Mr. D Malpas declared interests in one or more agenda items and appropriate action was taken.

330 Issues arising from the BP Commission MC1 (15) 3

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

Assessment of manufacturers' data The extent of laboratory evaluation required for a new or revised analytical method was considered during the elaboration or revision of a monograph by the relevant Expert Advisory Group. This could result in laboratory evaluation of methods or inclusion of a manufacturer's validated method without laboratory checking (*arm-chairing* monographs).
BPC members had agreed to a formalised approach and that this would be trialled for the autumn round of meetings.
European Pharmacopoeia Commission (EPC) Issues A summary of the EAG: MC1 related decisions, taken at the 151st EPC Session of the (March 2015), were provided for information.

II MATTERS ARISING FROM THE MINUTES

331 Matters arising MC1 (15) 4

A list of 'Matters Arising' from the minutes of the meeting of EAG: MC1 held in June 2014 and those outstanding from previous meetings has been appended (Annex 1).

332 MC1 status update MC1 (15) 5

A document outlining the EAG: MC1 work schedule was presented for information.

333 New and Revised Monographs for BP 2016 MC1 (15) 6

It was noted that 15 new and 38 revised British Pharmacopoeia monographs, which were the responsibility of EAG: MC1, would be published in BP 2016.

334 Extemporaneous Preparations MC1 (15) 7

Members were informed that the Pharmacy Expert Advisory Group (EAG: PCY) and the Unlicensed Medicines Group (EAG: ULM) had been carrying out a review of BP monographs, containing information on extemporaneous preparations, to identify areas for omission from the BP in view of the lack of usage in clinical practice. The relevant EAG: MC1 monographs were reviewed in full by members and the following comments were made.

Digoxin Injection

Definition It was agreed that the extemporaneous formula would be removed and replaced with a fixed strength, of 0.025% w/v of Digoxin, for BP 2017.

Content It was agreed that the Secretariat would review manufacturers' data and determine whether the content limits could be tightened as the preparation had a narrow therapeutic range.

Identification, Assay Members agreed that the monograph should be reviewed for a future publication to include a more robust Identification test and to avoid the use of chloroform as a solvent in the Assay.

Related substances The current monograph had no Related substances test. Manufacturers had been asked to provide suitable data to develop a test.

Revised monograph A revised monograph would be presented to members at the earliest opportunity.

Paediatric Digoxin Injection

Members agreed that responsibility for the monograph for Paediatric Digoxin Injection would be transferred to EAG: ULM as there were no UK licences for the product. The preparation was currently used as an unlicensed medicine. It was agreed that EAG: ULM and EAG: MC1 would collaborate in any revision of the monograph.

Dimercaprol Injection

Definition Members agreed that the extemporaneous formula in the monograph for

Dimercaprol Injection would be removed and replaced with a fixed strength of 5% w/v of Dimercaprol for BP 2017.

Content It was agreed that the current figures of 95.0% to 105.0% would be retained.

Identification; Related substances; Assay There were currently no Identification or Related substances tests in the monograph and the Assay was non-specific. Manufacturers had been contacted to obtain methods. It was agreed the Secretariat would investigate the extent of usage of the injection and review the methods as necessary for a future publication.

Dithranol Ointment

As there were no UK licences and the preparation was currently used as an unlicensed medicine members agreed that responsibility for the monograph would be transferred to EAG: ULM.

Methyl Salicylate Ointment

Definition Members agreed that the extemporaneous formula for Methyl Salicylate Ointment would be removed for BP 2017.

Further revision of the monograph The monograph would be revised, where necessary, at a future date.

335 Inhaled Products MC1 (15) 8

Members noted the revised BP Commission policy on the content and format of BP monographs for inhaled products. The relevant EAG: MC1 monographs were reviewed by members and the following comments were made.

Sodium Cromoglicate Inhalation Powder, Hard Capsule

It was noted that the product was not available in the UK but it was marketed in other European countries. As there were no UK licences for this product members agreed that the monograph would be omitted in BP 2017 subject to comments from overseas authorities.

Ribavirin Powder for Nebuliser Solution

Definition The Definition, in line with the revised policy for Inhaled products, had been revised to include the statement *and it is reconstituted with an appropriate liquid in accordance with the manufacturer's instructions to obtain a nebuliser solution intended to be converted into aerosols by a nebuliser.* Members approved the change to the definition and the revised monograph would be published in BP 2017.

III NEW MONOGRAPHS

336 Carbamazepine Oral Suspension MC1 (15) 9

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

337 Chewable Carbamazepine Tablets MC1 (15) 10

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

338 Valaciclovir Tablets MC1 (15) 11

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

339 Mebendazole Oral Suspension MC1 (15)12

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

340 Leflunomide Tablets MC1 (15) 13

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

341 Prolonged-release Metformin Tablets MC1 (15) 14

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

342 Moxonidine Tablets MC1 (15) 15

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

IV MONOGRAPHS IN PROGRESS

343 Itraconazole Capsules MC1 (15) 16, Annexes 1-3

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

344 Zidovudine Impurity G and Impurity 1 MC1 (15) 17

Following the December 2014 meeting a manufacturer had sent a sample of Zidovudine impurity G (impurity dimer) to enable the BP laboratory to determine the relative response times and relative retention times in relation to Zidovudine.
The BP Laboratory had assessed the tests for Zidovudine preparations using the HPLC systems outlined in the related substances tests.

Zidovudine Capsules, Zidovudine Injection and Zidovudine Tablets The BP Laboratory ran the isocratic system used for the Related substances tests and determined that the relative retention time of impurity G with respect to Zidovudine at 265 nm was 2.8. The relative response of the impurity was similar to Zidovudine.

Abacavir, Zidovudine and Lamivudine Tablets, Zidovudine and Lamivudine Tablets The BP Laboratory ran the gradient system used in the Related substances tests and determined that the relative retention time of impurity G with respect to Zidovudine at 270 nm was 1.4. The relative response of the impurity was similar to

Zidovudine. The gradient system, as published in BP 2015, had not been capable of detecting impurity G and the gradient had been amended after the elution of abacavir to detect impurity G.

Impurity 1 in the monograph for Abacavir, Zidovudine and Lamivudine Tablets A manufacturer had requested that impurity 1 was limited at NMT 0.4% in the tablets' monograph. A sample of impurity 1 was sent to the BP Laboratory after the assessment of impurity G had been completed. Members agreed that the wording of the test would be revised to include *the area of any peak corresponding to zidovudine impurity 1 (eluting between lamivudine impurity G and zidovudine impurity C) is not greater than 0.4 times the area of the peak due to zidovudine in the chromatogram obtained with solution (2) (0.4%).* The relative retention time for this impurity would be determined when Zidovudine or Zidovudine Impurity Standard was next assessed in the laboratory.

Publication The new and revised Zidovudine-containing monographs would be published in BP 2016.

V REVISION OF MONOGRAPHS

345 Metformin Tablets MC1 (15) 18

Related substances test. A test in BP 2015 determined the content of 1-cyanoguanindine (impurity A) only by HPLC. The BP Laboratory had assessed the Ph. Eur. Related substances test for the tablets which limits 5 impurities, A to E. All of the named impurities eluted before metformin but the principal peak due to metformin was very broad and any impurities that eluted after the main peak might not have been detected. The Secretariat had re-drafted the revised monograph for Metformin Tablets to contain a manufacturer's method for Prolonged-release Metformin Tablets. Members reviewed the revised draft and the following comments were made.

Impurity limits Impurity A had been limited at NMT 0.02 as per the current monograph. All other impurities were limited at NMT 0.1% and a disregard limit of 0.05 had been applied.

System suitability A resolution of at least 2.0 between impurity E and Metformin was agreed. A signal-to-noise limit of not less than 25 for impurity A would also be included to ensure that the impurity was detected. (See post meeting note).

Circulation to manufacturers Manufacturers would be asked if the draft Related substances test was suitable for their product.

POST MEETING COMMENT: Following the meeting the Chairman and Secretariat discussed the signal-to-noise ratio for solution (3) and agreed that it would be amended to not less than 10.

346 Clomethiazole MC1 (15) 19
Clomethiazole Edisilate
Clomethiazole Capsules
Clomethiazole Infusion
Clomethiazole Oral Solution

Analysts had found the wording used to determine the level of impurities in the Related substances tests for Clomethiazole, Clomethiazole Edisilate and Clomethiazole preparations confusing. The analyst was instructed to convert edisilate solutions to base and for 2 of the monographs 2 conversion factors were required. The Secretariat had

revised the wording in the monographs and had also reviewed the content of the monographs.
Members reviewed the draft revised texts and the following comments were made.

Clomethiazole

Identification test A Members agreed that the ultraviolet absorption test in the current test would be omitted in BP 2017.

Identification test C Members agreed that the colour test to distinguish between Clomethiazole and Clomethiazole base was not necessary as the infrared tests for both compounds were discriminatory.

Identification BP 2017 A stand alone infrared identification test would be published in BP 2017.

Related substances The impurity 4-methyl-5-vinylthiazole edisilate was renamed impurity A, 5-(2-chloroethyl)-4-methyl-3-[2-(4-methylthiazol-5-yl)ethyl]-thiazolium chloride was renamed impurity B and 4-methyl-5-(2-hydroxyethyl)thiazole was renamed impurity C. The systematic names had been placed in a transparency statement. The order of the solvents in the mobile phase had been revised to include the lowest volume first as per BP current policy.

System suitability Members discussed the current system suitability test - that baseline separation should be achieved between each of the 3 impurities, and agreed that the resolution factors were too high to be meaningful. The suitability test would be revised to refer to a reference chromatogram to be supplied with the 3 impurities.

Unknown impurities The current monograph limited impurities A, B and C. A limit of NMT 0.2% for each unknown impurity had been drafted with a total of unknown impurities of NMT 0.5%.

Circulation to manufacturers Manufacturers would be asked to comment on the draft revised monograph. The revised text would be published in BP 2017 subject comment.

Clomethiazole Edisilate

Identification tests A, B and C Members agreed that an infrared test would be published as a ‘stand-alone’ test in BP 2017 and that tests A, B and D would be omitted.

Related substances The current monograph instructs the user to calculate the content of each impurity with reference to clomethiazole base. The test has been revised to reference the substance being examined as being equivalent to the base.

Related substances-names of impurities *see item under Clomethiazole*

System suitability, unknown impurities, circulation to manufacturers *see items under Clomethiazole*

Clomethiazole Capsules

Identification tests A and C Members agreed that an infrared test would be published as a ‘stand-alone’ test in BP 2017 and that tests A and C would be omitted.

Related substances, system suitability, names of impurities, circulation to manufacturers – *see items under Clomethiazole.*

Clomethiazole Infusion

Members were informed that Clomethiazole Infusion was no longer licensed within the UK. It was agreed that if no unlicensed preparations were available then the monograph would be omitted in BP 2017.

Clomethiazole Oral Solution

Identification test B The current monograph cross refers to identification test B for Clotrimazole Edisilate in the intravenous infusion. The full test had been drafted as per BP policy. Two identification tests were necessary as test A identified Clomethiazole base rather than Clomethiazole Edisiliate.

Related substances and Assay The current tests cross-reference the capsules and intravenous infusion monographs. The monograph was revised to reproduce the tests in full.

347 Alfuzosin Tablets
Prolonged-release Alfuzosin Tablets MC1 (15) 20

Limit of disregard (LOD) The Related substances methods in the BP 2015 monographs for Alfuzosin Tablets and Prolonged-release Alfuzosin Tablets had a LOD of 0.05. Members agreed that the LOD would be widened to 0.1 following a request from a manufacturer and taking into account the ICH guidelines for preparations with a maximum daily dose of less than 2 g.

Infrared test A manufacturer had requested a review of the method used for the infrared identification tests in both monographs as they were having difficulty extracting the active from the tablet matrices using the low volume of solvent. The Secretariat suggested adding a larger volume of water to extract the active before adjusting the pH to 13 with ammonia. The manufacturer confirmed that the method worked well. The revised monographs would be published in BP 2106.

348 Cyclizine (Lactate) Injection MC1 (15) 21

The sole UK manufacturer of Cyclizine Injection had requested that the limits for impurities A (1-methylpiperazine) and B (diphenylmethanol) in the monograph were widened. Members reviewed the submitted data and agree that more batch data was required before a decision was made.

349 Clonidine Tablets MC1 (15) 22

Following the December 2014 meeting information to support the revision of the monograph for Clonidine Tablets had been received from a manufacturer. Members reviewed the draft prepared by the Secretariat and the following comments were made.

Identification test A The manufacturer had provided 2 thin layer chromatography tests for 2 different strengths to replace the current UV absorbance test. Members agreed that the BP Laboratory would assess the test using the conditions for the lower strength tablet to see if it was suitable for all available strengths.

Identification test B Members agreed that the current precipitation test would be replaced by a cross reference to the principal peaks in the Uniformity of Content test.

Dissolution Members agreed that the manufacturer's Dissolution test would be included in the monograph. The paddle speed had been reduced to 50 rpm as members stated that a speed of 100 rpm could not be justified.

Related substances The manufacturer's method had been drafted. The BP Laboratory would be asked to assess if Ph.Eur. impurities A, B or C would be suitable for use in a resolution solution.

Impurity limits Any unknown impurity was limited at NMT 0.5% with a total impurity limit of NMT 1.0%. A disregard limit of NMT 0.1% was agreed.

Uniformity of content The method was revised to include an LC procedure.

Assay The test was revised to include the average of 10 tablet test results from the Uniformity of Content test. All products available on the UK market contained less than 2 mg per tablet.

350 Clonidine Injection MC1 (15) 23

Following the December 2014 meeting information to support the revision of the monograph for Clonidine Injection had been received from a manufacturer. Members reviewed the draft prepared by the Secretariat and the following comments were made.

Content of Clonidine Revised content limits of 95.0% to 105.0% were agreed.

Identification test A The test provided by the manufacturer had been drafted. Members agreed that the BP Laboratory would assess the test for suitability as a pharmacopoeial test.

Identification test B Members agreed that the current precipitation test would be replaced by a cross reference to the principal peaks in the Assay.

Related substances (see 349.4) The manufacturer used the same Related substances test for the tablets and injection with the exception of the run time which was shorter for Clonidine Injection. Members agreed that the run time would be the same as the tablets' test so ensure that 2,6-dichloroaniline, Ph. Eur. impurity C, was detected by the test.

Impurity limits *(see item under Clonidine Tablets)*

Assay The Related substances test procedure was agreed.

VI REPORTS AND CORRESPONDENCE

351 Aciclovir Eye Ointment MC1 (15) 24

Following the December 2014 meeting the Related substances test and Assay methods for Aciclovir Cream were amended to include a larger volume of dimethylsulfoxide (DMSO) to extract the active before the solution was filtered. The amendments would be published in BP 2016.
A manufacturer had subsequently stated that isooctane was a better extraction solvent. The Secretariat had asked the manufacturer to carry out the amended tests for BP 2016

and to compare them with the results using isooctane before a decision was made on whether to further amend the monograph.

352 Meloxicam Injection MC1 (15) 25

The monograph for Meloxicam Injection was first published in BP 2012 based on manufacturers' data provided at the time. The pH range had been set at 8.0 to 9.0. A manufacturer in Pakistan requested that the pH range was adjusted to 12.0 to 13.0 as their product had crystallised out of solution after 3 months if the pH was 8.0 to 9.0. Members stated that more stability data was required before a decision was made. The Secretariat would ask the manufacturer to supply further data.

353 Nicotine Resinate Medicated Chewing Gum MC1 (15) 26

Dissolution A UK manufacturer had requested a revision to the published dissolution test method in the BP monograph for Nicotine Resinate Medicated Chewing Gum. The company manufactured mint and fruit flavoured gums in 2 mg and the 4 mg strengths. It had proposed modifying the published BP method to incorporate a dissolution medium containing the surfactant sodium dodecyl sulfate. At the meeting held in December 2012 members were of the opinion that the manufacturer would need to demonstrate the discriminatory nature of the proposed method before a decision to amend the monograph was made.
Members were informed that UK licences had now been granted for the products. A dissolution test containing sodium dodecyl sulfate had been included in the licence. Members agreed that the Dissolution test would be revised for BP 2017 to include the surfactant in the dissolution medium subject to comments for other manufacturers.

354 Co-Codamol Tablets MC1 (15) 27

Related substances: Test A A manufacturer in Greece stated that he was unable to detect the spots from the dilute solutions (2) and (3), by thin layer chromatography, in the monograph for Co-codamol Tablets when using potassium iodobismuthate as the detection agent. Investigation had shown that *dilute* potassium iodobismuthate reagent was suitable for detection of the spots at the limiting levels.
Members agreed that the wording of the test would be amended to include dilute potassium iodobismuthate as the detection agent subject to comments from manufacturers.

Co-codamol Capsules Related substances test A would also be amended in the monograph for Co-codamol Capsules as the test conditions were the same.

355 Gastro-resistant Bisacodyl Tablets MC1 (15) 28

At the December 2014 meeting members were informed that a manufacturer in Cyprus had experienced difficulties meeting the dissolution requirements for Gastro-resistant Bisacodyl Tablets. Members agreed that an alternative test supplied by another manufacturer would be investigated for suitability, with a view to replacing the published method.

Comparison of methods The manufacturer had subsequently compared the method with the current BP dissolution method and had found that all but one of the samples tested complied with the current BP limit of not less than 75% (Q) after 45 minutes. All samples complied when the dissolution time was increased to 60 minutes. Members agreed that the dissolution time would remain at 45 minutes.

First stage run time Members agreed that, based on the data submitted, the first stage run time would be reduced to 2 hours from 3 hours.

Publication It was agreed that the alternative dissolution test would be published in BP 2017 subject to comments from manufacturers.

VII ANY OTHER BUSINESS MC1 (15) 29

356 Alverine Capsules

Members were informed that the monograph for Alverine Tablets would be revised at the earliest opportunity to include the Related substances method included in the Ph. Eur. monograph for the parent substance.

357 Dates of next meetings MC1 (15) 30

2015:
Tuesday 15th December

2016:
Monday 6th June
Tuesday 13th December

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8th June 2015

Annex 1. Matters arising from previous meetings other than those mentioned on the agenda

Loperamide Preparations	The BP Laboratory has finished the analytical assessment. The results will be presented to members at the December 2015 meeting.
Itraconazole Capsules ***Minute 272 refers***	A requisition had been submitted to the BP Laboratory and the draft new monograph had been posted on the BP website for initial comments.
Cinnarizine Tablets ***Minute 273 refers***	A requisition had been submitted to the BP Laboratory.
Pantoprazole Injection, Gastro-resistant Tablets ***Minutes 274, 275 refer***	A laboratory requisition had been submitted and the draft new monograph had been posted on the BP website for initial comments.
Phenytoin Preparations ***Minute 284 refers***	The MHRA Laboratory was in the process of carrying out a product survey and had been asked by the Secretariat to assess the Ph. Eur. method for Related substances for use in the BP monographs to control Related substances and Assay in all formulations. Dissolution tests will also be included in the Capsules and Tablets monographs following the completion of the lab work.
Warfarin Tablets ***Minute 288 refers***	The BP Laboratory has started the assessment and the results will be presented at the December 2015 meeting.
Amlodipine Tablets ***Minute 307 refers***	The BP Laboratory to start the assessment at the earliest opportunity.
Aspirin Tablets ***Minute 315 refers***	The BP Laboratory to continue the assessment at the earliest opportunity.