

**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, 6th June 2016.

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

Apologies: Mr. P Fleming.

In attendance: Mrs. M Barrett, Ms. H Corns, Mr. D Holcombe, Mr G Lay and Ms F Lee.

404 Welcome

The Chairman welcomed everyone to the meeting especially Dr Edward Bush who was attending his first meeting, also Ms Fiona Lee and Mr David Holcombe from the BP Laboratory and Mr G Lay from the MHRA.

I GENERAL MATTERS

405 Minutes

The minutes and summary minutes of the meeting held on 15th December 2015 were confirmed subject to an editorial change.

406 Emergency evacuation procedure MC1 (16) 1

The emergency evacuation procedure for Buckingham Palace Road was noted.

407 Declaration of interests MC1 (16) 2

Dr E Bush, Mr. A Caws, Professor D Cairns, Mr A James and Mr D Malpas declared interests in one or more agenda items and appropriate action was taken.

II MATTERS ARISING FROM THE MINUTES MC1 (16) 3

408 Matters arising MC1 (16) 4

A list of 'Matters Arising' from the minutes of the meeting of EAG: MC1, held in December 2015, and those outstanding from previous meetings has been appended (Annex 1).

409 December 2015 meeting items discussed by correspondence MC1 (16) 5

Members had reviewed the monographs for Meloxicam Injection, Cyclizine Injection (pH), Caffeine Citrate Injection (pH) and Dipyridamole Oral Suspension following the December 2015 meeting and amendments to the texts were agreed by correspondence. The changes had been recorded as post meeting notes in the December 2015 minutes.

410 Pyrimethamine Tablets MC1 (16) 6

The UK manufacturer had sent information to support the revision of the monograph. Members reviewed the draft revised monograph and the following comments were made.

Content of Pyrimethamine Members agreed that the limits would be tightened to 95.0% to 105.0% from the current limits of 92.5% to 107.5% based on the data supplied.

Dissolution A test had been drafted based on the manufacturer's licensed specification. As the monograph was published pre-1998 the BP standard limit of limit of 70% in 45 minutes was agreed.

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Related substances-limit for each impurity The manufacturer had provided a HPLC test to replace the current tlc test. Three impurities were specified and labelled as impurities 1, 2 and 3 as they were not listed in the Ph. Eur. monograph for the active substance. The specification provided had tighter impurity limits than the monograph for the active material but, as it is BP policy not to set tighter limits in a product than the active material, a limit of not more than (NMT) 0.25% was set for each impurity as per the monograph for the active.

Related substances-total impurities A limit of NMT 0.5% for total impurities was agreed.

Related substances-system suitability A resolution of 4.5 between impurities 1 and 2 had been drafted and the manufacturer would be asked if this was suitable for system suitability.

Related substances-description of HPLC column The Secretariat would check if the drafted description of the HPLC column was appropriate for the specified column.

Assay The Assay method based on the Related substances test had been drafted.

Reference standards The manufacturer would be asked to supply sufficient Pyrimethamine and impurities 1, 2 and 3 to establish an assay standard and an impurity standard respectively.

411 Alverine Capsules MC1 (16) 7

The monograph for the active substance, Alverine, had recently been revised by the Ph. Eur. to tighten the limits for some of the impurities. While reviewing the monograph for Alverine Capsules the Secretariat had noted that there was no limit for unspecified impurities, no limit of disregard or a total limit for impurities.

Unspecified impurities Members agreed a limit of NMT 0.2% for each unspecified impurity.

Total impurities – specified and unspecified Members agreed a total limit of NMT 1.4%

Limit of disregard Members agreed a limit of disregard of NMT 0.1% as the maximum daily dose was 360 mg.

Publication The revised text would be circulated to manufacturers and, in the absence of any adverse comments, would be published in BP 2017.

412 Halquinol MC1 (16) 8

A request had been made by an overseas manufacturer to reinstate the monograph for Halquinol which had been omitted from the BP (Vet) in 1988. The Secretariat had sought advice from the BP Veterinary Panel and they had stated that they were unaware of significant use of Halquinol in EU veterinary medicine. The Panel stated that they would not support the reinstatement of the former monograph. MC1 members agreed that the monograph would not be reinstated.

413 Papaveretum, Papaveretum Injection MC1 (16) 9

The BP Laboratory had been unable to source Codeine Hydrochloride to establish a replacement BP reference substance to support the identification tests and assays in the monographs for Papaveretum and Papaveretum Injection.

Members suggested that Codeine Phosphate, which was established as a BP reference material, could replace Codeine Hydrochloride in the monograph. The BP Laboratory would assess the tlc identification test using Codeine Phosphate in place of the hydrochloride salt and, if suitable, the revised monograph would be sent to the sole manufacturer for review. In the absence of any adverse comments the revised monograph would be published at the earliest opportunity.

414 MC1 status report MC1 (16) 10

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

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415 New and revised monographs 2017 MC1 (16) 11

It was noted that 8 new and 20 revised British Pharmacopoeia monographs, which were the responsibility of EAG: MC1, would be published in BP 2017 and 2 monographs would be omitted from the publication.

III NEW MONOGRAPHS

416 Ritonavir Oral Solution MC1 (16) 12

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

417 Ritonavir Tablets MC1 (16) 13

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

418 Celecoxib Capsules MC1 (16) 14

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

419 Amlodipine Oral Solution MC1 (16) 15

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

420 Repaglinide Tablets MC1 (16) 16

Members agreed to defer this item to the next meeting due to time constraints.

IV MONOGRAPHS IN PROGRESS

421 Metformin and Sitagliptin Tablets MC1 (16) 17

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

422 Sitagliptin and Prolonged-release Metformin Tablets MC1 (16) 18

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

423 Mebendazole Oral Suspension MC1 (16) 19

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

424 Chewable Mebendazole Tablets MC1 (16) 20

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

425 Moxonidine Tablets MC1 (16) 21

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

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V REVISION OF MONOGRAPHS AND REPORTS AND CORRESPONDENCE

426 Paracetamol Capsules (Soft Gel) MC1 (16) 22

At the December 2015 meeting members were informed that a European manufacturer had applied for a UK licence for 500 mg soft gel paracetamol capsules. There were no soft gel Paracetamol Capsules licensed within the UK and this product did not comply with the dissolution test in the current BP monograph for Paracetamol Capsules. It was suggested that that one of the licensing assessors, who had responsibility for this marketing authorisation, should be invited to the June 2016 MC1 meeting to discuss the issue further.

Members agreed that the BPC would be asked to decide on a way forward now that a licence had been granted.

427 Aspirin Tablets MC1 (16) 23

Identification – infrared The BP Laboratory had assessed the draft tests for Aspirin Tablets, Dispersible Aspirin Tablets and Gastro-resistant Aspirin Tablets. The extraction solvent used was absolute ethanol and the spectra were compared with Aspirin reference standard crystallised from absolute ethanol. All of the tablet samples assessed by the laboratory produced spectra that were concordant with the reference spectrum, after extraction of the active from the matrix. The 3 monographs would be revised to include the infrared test.

Related substances - unknown peak at 6 minutes The BP Laboratory had previously assessed a Related substances test for Aspirin preparations and an unknown peak at 6 minutes had been detected in all samples tested. Members had agreed that further work to investigate the nature of the unknown peak and/or the trial of alternative columns was needed before the revision to the Related substances test would be accepted. A MPharm student had re-assessed the related substances test.

The student had confirmed that peaks were found on the tail of the main aspirin peak and that they arose from trace aspirin related impurities. It was also confirmed that these peaks were over-estimated when using default integration parameters but could be integrated accurately when setting the parameters to carry out a tangential skim.

It had been show that the unknown peak at 6 minutes was due to trace impurities which had the same retention time as *m*- and *p*- acetylsalicylic acid and using tangential skim these impurities were present at less than 0.05%.

Related substances- system suitability Members endorsed the student's recommendation that resolution between aspirin and impurity C (salicylic acid) should be used as the system suitability requirement.

Circulation to manufacturers The revised draft monographs would be circulated to manufacturers and, in the absence of adverse comments, would be published in BP 2018.

428 Caffeine Citrate Injection MC1 (16) 24

Members were informed that the monograph for Caffeine Citrate Injection in BP 2016 had no Related substances test and the 2 identification tests were a cross-reference to the assay peaks and a test for Citrate. A manufacturer had provided information to revise these tests. Members reviewed the tests.

Definition It was agreed that reference to sodium citrate in certain formulations would be added.

Identification – thin layer chromatography Members reviewed the draft test and it was agreed that a suitable system suitability test would be found.

Related substances The manufacturer's method had been drafted. The methodology was the same as the Ph. Eur. related substances test for Caffeine. A system suitability solution containing Caffeine Impurity D, xanthine, Caffeine impurity A and Caffeine had been drafted. Members reviewed the Ph. Eur. Related substances test and suggested that a solution containing impurities C and D should be also be used as this was the critical pair.

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Related substances – limits A limit of NMT 0.2% for each impurity and NMT than 0.5% for total impurities was agreed subject to comments from manufacturers.

Assay A method based on the Related substances test was agreed.

429 Caffeine Citrate Oral Solution MC1 (16) 25

Members were informed that Caffeine Citrate Injection was also used as an oral solution. The minute 428 for the Injection also applied to the Oral Solution.

430 Cisplatin Injection MC1 (16) 26

Related substances The BP monograph for Cisplatin Injection in BP 2016 limited 2 impurities only – Transplatin (Ph. Eur. impurity A) at NMT 2.0% and trichloroammineplatinate (Ph. Eur. impurity B) at NMT 3.0%. The Secretariat had revised the monograph to include a general Related substances method. The limits for the 2 named impurities were drafted at the same level as the Ph. Eur. monograph (1.0%). Manufacturers would be asked to supply data to support the higher limits of 3.0% for trichloroammineplatinate and 2.0% for transplatin. Any other impurity had been limited at NMT 0.2% with a total for any other impurities of NMT 1.0%. Manufacturers would be asked to provide data to support these increased levels.

Cisplatin for Injection The same Related substances test had replaced the separate tests for Transplatin and Trichloroammineplatinate.

431 Propofol Injection MC1 (16) 27

The BP monograph for Propofol Injection was first published in BP 2007 based on information provided by a manufacturer. The Secretariat had received many queries since publication concerning problems for the tests for Lysolecithin and the determination of Globule Size. Members discussed whether the monograph could be revised to include more robust tests.

Lysolecithin Users had reported problems with the current BP HPLC method with UV detection and the BP Lab had not successfully obtained results using evaporative light scattering (ELSD) for detection, a method provided by a manufacturer. Members would decide at the next meeting if an alternative method could be drafted or if a Production statement would be suitable.

Globule size Members discussed whether alternative methods to the current Coulter Counter method should be included in the test. The USP, for example, also recommended dynamic light scattering and light obscuration methods. BP Appendix XIII A also listed alternative methods for determining particle size. A decision on alternative tests would be made at the December meeting.

432 Ranitidine Preparations MC1 (16) 28

A number of comments had been received from stakeholders on the proposed revision to the Related substances limits for the Injection and Oral Solution monographs. Members agreed that full discussion would be deferred to the next meeting.

433 Prolonged-release Diltiazem Tablets MC1 (16) 29

Impurity F limit The monograph for Prolonged-release Diltiazem Tablets was published in BP 2009. The limit for the degradant impurity F, desacetyldiltiazem, (2S,3S)-5-[2-(dimethylamino)ethyl]-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one, was limited at not more than 0.3% - the same limit as the parent monograph. Members reviewed specifications for Diltiazem Tablets and agreed that the limit for impurity F could be broadened to NMT 1.0% as the impurity was also one of the major human metabolites of Diltiazem.

Prolonged-release Diltiazem Capsules A new draft monograph for Prolonged-release Diltiazem Capsules would be presented to members at a future meeting.

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434 Trazodone Hydrochloride & preparations MC1 (16) 30

A new batch of Trazodone Hydrochloride Impurity Standard BPCRS, used in the Related substances A and B tests, had been analysed using a different make of column to the previous batch which had resulted significant differences in the reference chromatograms supplied with the impurity standards. The current system suitability requirement was a close resemblance to the reference chromatograms provided with the standard and the column change had caused problems for users who had continued to use the column listed as suitable in the monographs. The Secretariat proposal to include resolution requirements of:

“For Related substances A:

The test is not valid unless, in the chromatogram obtained with solution (4), the resolution between impurity C and trazodone is at least 2.5.” and

“For Related substances B:

The test is not valid unless, in the chromatogram obtained with solution (4), the resolution between trazodone and impurity E is at least 3.5.”
was accepted by members.

VI ANY OTHER BUSINESS

435 Revised Experts Claims' Policy MC1 (16) 31

Members received the revised Experts Claims' Policy for information. It was noted that electronic signatures were now acceptable when claims were made.

436 Doxepin Capsules and Amantadine Tablets

Members were informed that the monograph for Doxepin Capsules would be revised for the December 2016 meeting to include a capillary column in the Related substances test. The GC conditions in the monograph for Amantadine Tablets would also be reviewed.

437 Dates of next meeting

Tuesday 6th December, 2016

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

Itraconazole Capsules <i>Minute 272 refers</i>	A requisition has been submitted to the BP Laboratory.
Cinnarizine Tablets <i>Minute 273 refers</i>	A requisition has been submitted to the BP Laboratory.
Pantoprazole Injection, Gastro-resistant Tablets <i>Minutes 274, 275 refer</i>	The BP Laboratory had assessed the tests in the draft monograph
Phenytoin Preparations <i>Minute 284 refers</i>	The MHRA Laboratory is 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.
Amlodipine Tablets <i>Minute 307 refers</i>	The BP Laboratory to start the assessment at the earliest opportunity.
Leflunomide Tablets <i>Minute 340 refers</i>	The BP Laboratory to start the assessment at the earliest opportunity.