BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group MC1: Medicinal Chemicals

SUMMARY MINUTES

A meeting of Expert Advisory Group (EAG): Medicinal Chemicals 1 (MC1) was held via videoconference on Tuesday 30 June 2020.

Present: Professor A G Davidson *(Chair),* Professor D Cairns *(Vice-Chair),* Dr S Bale, Dr J C Berridge, Dr E Bush, Mr A J Caws, Mr D Deutsch, Dr E Gray, Dr J Lough and Mr D Malpas.

In attendance: Ms H Corns, Mr L Elanganathan, Ms K Busuttil (BP Lab) and Ms M Nanasi (BP Lab).

Apologies: Dr H Batchelor, Mr P Fleming and Mr S Nolan.

Mr A J Caws and Mr D Malpas declared an interest in one or more agenda items and appropriate action was taken.

INTRODUCTORY REMARKS

595 **Welcome** The Chair welcomed members, Ms K Busuttil and Ms M Nanasi from the BP Laboratory to the meeting.

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 thanked for providing their interests prior to the meeting. Members were reminded to inform the Secretariat of any changes to their interests throughout the year.

596 BP Update

Members were provided with an update on recent BP activities and personnel changes.

597 MINUTES

The minutes and summary minutes of the meeting held on 03 December 2019 were confirmed.

598 Matters Arising from the Minutes

Matters arising from the 03 December 2019 meeting were noted and members had no additional comments.

MONOGRAPHS

599 Co-codamol preparations (Revisions):
Co-codamol Capsules
Co-codamol Effervescent Tablets
Co-codamol Tablets

The Secretariat presented draft monographs following completion of the required laboratory assessments.

Content The Secretariat confirmed that the licensed products only contain the Hemihydrate form of Codeine, and therefore retained the existing Content statement.

Identification (Co-codamol Effervescent Tablets only) The Laboratory reported that the drafted infrared method for Paracetamol identification was found to be suitable. Members agreed with the inclusion of this test.

Dissolution (Co-codamol Capsules, Co-codamol Tablets, and Co-dydramol Tablets) Members agreed that revised draft limits of 75% (Q) in 45 minutes for paracetamol should be included in the monographs for publication consultation in the next available window.

Related substances Members previously agreed to revise the TLC Related substances tests in the aforementioned monographs with a HPLC method. Laboratory reports confirmed that the drafted method was suitable for all Co-codamol products tested.

Paracetamol impurities Members agreed that a limit of 0.001% for impurity J should be included in the revised monographs.

Members agreed that a draft limit of 0.01% for impurity K should be included for publication consultation.

Members agreed with a limit of 0.1% for unspecified impurities due to Paracetamol (RRT < 2.7), in line with ICH guidelines.

Codeine impurities Members agreed that a draft limit of 1% for Impurity A should be included.

Members agreed that a draft limit of 0.2% for Impurity B and C should be included.

Members agreed for the inclusion of Impurity I and Codeine Sulfonic Acid under the limit of 0.2% for unspecified impurities (RRT > 2.7).

Unknown impurities (Co-codamol Tablets, Co-codamol Effervescent Tablets, Co-codamol Capsules) Members agreed that advice should be sought from manufacturers regarding unidentified peaks detected in some of the products tested.

Total unspecified impurities Members agreed with the inclusion of a draft limit of 0.75%, with a change to the wording to read “The total impurity content, excluding codeine impurity A, is not greater than 0.75%”.

Disregard limit Members agreed that impurities were most likely to arise from paracetamol, and therefore a single disregard limit of 0.05% was considered appropriate.

Labelling (Co-codamol Capsules, Co-codamol Effervescent Tablets, Co-codamol Tablets) The Secretariat were awaiting input from EAG PCY regarding the need to retain the dispensing and supply Labelling statements with. It was agreed that the labelling statements should be retained until then.

600 Caffeine-containing Paracetamol Preparations
Paracetamol and Caffeine Soluble Tablets
Paracetamol and Caffeine Tablets
Paracetamol, Codeine Phosphate, and Caffeine Capsules
Paracetamol, Codeine Phosphate, and Caffeine Tablets

The Secretariat presented draft monographs following completion of the required laboratory assessments.

Content The Secretariat confirmed that the licensed products only contain the Hemihydrate form of Codeine Phosphate, and therefore retained the existing Content statement.

Identification The Laboratory found that the drafted TLC method for Caffeine identification, based on an MAH's validated method, was found to be suitable for all of the products with modifications.

Dissolution Members agreed for the inclusion of a draft limit of 75% (Q) in 45 minutes for paracetamol only, subject to comment from stakeholders.

Disintegration (Paracetamol and Caffeine Soluble Tablets) Members agreed that the test should be removed, as it was a requirement of the general monograph.

Related Substances (Paracetamol, Codeine Phosphate, Caffeine Capsules & Tablets) Members previously agreed to revise the TLC Related substances tests in the aforementioned monographs with a HPLC method based. Laboratory reports were presented that showed that the method drafted was suitable for the products tested.

Related Substances (Paracetamol and Caffeine Soluble Tablets & Tablets) Members agreed to the Secretariat's proposal to investigate whether the Related substances test found suitable for the Paracetamol, Codeine, and Caffeine product monographs could be applied to these monographs.

Paracetamol impurities Limits were agreed as per minute 599, subject to comments from stakeholders.

Codeine impurities Limits were agreed as per minute 599, subject to comments from stakeholders.

Caffeine impurities (Paracetamol, Codeine, and Caffeine Capsules, and Tablets) Members agreed that a draft limit of 0.1% for secondary peaks (with an of RRT < 2.7) would be suitable for inclusion.

Caffeine impurities (Paracetamol and Caffeine Tablets, and Soluble Tablets) Members agreed that a limit of 0.1% for secondary peaks, and a 0.5% total impurities limit should be posted for public consultation.

Total impurities A limit was agreed as per minute 599.

Disregard limit A limit was agreed as per minute 599.

601 Co-dydramol Tablets (Revision)

The Secretariat presented draft monographs following completion of the required laboratory assessments.

Related substances The drafted method did not adequately resolve the peaks due to dihydrocodeine and codeine. The laboratory confirmed that all impurities were detected using an alternative HPLC method.

Paracetamol impurities Limits were agreed as per minute 599, subject to comments from stakeholders.

Dihydrocodeine Tartrate Related substances Members agreed that a draft limit for 0.5% for Impurity A, and a limit of 0.3% for unspecified impurities would be suitable, subject to stakeholder comments.

Unknown impurities Four unknown impurities were detected above the drafted limit for unspecified impurities during the laboratory evaluation. The Secretariat agreed to contact the MAHs to aid in identification.

Total impurities It was previously agreed that the suitability of a limit of 0.75% for all of the combination products was investigated. Without confirmation of the identity of the unknowns, it was not clear if it would be suitable. A limit of 0.75%, excluding the specified impurities, had been drafted in line with the other family of monographs. Members agreed, subject to stakeholder comments.

Disregard limit A limit was agreed as per minute 599.

Assay (Dihydrocodeine) An instruction to use the average results of the Uniformity of content test had been added as per BP policy for tablets containing less than 2% w/w of dihydrocodeine.

Labelling See minute 599.

602 Digoxin preparations (revised):
Digoxin Tablets
Paediatric Digoxin Oral Solution
Digoxin Injection

Following the agreement to revise the Digoxin Tablets and Digoxin Injection monographs, dissolution method and data had been received from a Digoxin Tablets manufacturer.

Content Members requested that the content limits for the Tablets and Oral Solution monographs were tightened to 95.0 – 105.0%, if possible, as digoxin had a narrow therapeutic range. It was noted, however, that the Ph Eur monograph allowed up to 6% of related substances to be present, which could make meeting tighter limits too challenging.

Dissolution (Tablets only) The method proposed by the manufacturer allowed the test to be carried out on one tablet per vessel, instead of 6 as per the published method, and used UPLC chromatographic conditions. Members recommended that the method's suitability was assessed by the laboratory, as well as an investigation into a suitable limit.

Identification (Oral Solution only) The colour change test in the published monograph had been deleted and replaced with a TLC procedure and a peak comparison in the revised Assay test. The revised tests were accepted, subject to laboratory evaluation.

Related substances (Oral Solution only) A new HPLC test had been drafted based on the Ph. Eur. method for Digoxin and accepted by members. Limits for impurities A, B, C, E, F, G, K and L at the same level as the parent substance had been included. It was agreed that manufacturers would be asked to comment on the limits.

It was acknowledged that due to the low product strength, low detection wavelength and potential for interfering excipients, this method may not be suitable for controlling related substances in the oral solution.

Assay (Oral Solution only) An updated assay method, harmonised with the related substances test was accepted by members, as the method separated impurities and digoxin eluted in the initial isocratic step.

Impurities (Oral Solution only) An impurities section had been added to the draft revised monograph and would be confirmed on completion of the laboratory assessment.

603 Nitrofurantoin preparations (Revision)
Nitrofurantoin Capsules
Nitrofurantoin Prolonged-release Capsules
Nitrofurantoin Oral Suspension
Nitrofurantoin Tablets

This item was deferred to a future meeting due to changes following subsequent correspondence.

604 Pregabalin preparations (new):
Pregabalin Capsules
Pregabalin Oral Solution

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

605 Mebendazole Oral Suspension (Revision)

Revisions to the previously agreed draft revised monograph were proposed.

Related substances A test capable of identifying impurity G had been included, but members agreed that the need for a correction factor should be evaluated by the laboratory.

A resolution requirement between methylparaben and impurity A had been drafted as per the method, and the previously agreed limits were retained.

Assay A test had been drafted to harmonise with the Related substances test. Members agreed for the monograph to be posted for public consultation.

606 Haloperidol preparations (revisions):
Haloperidol Capsules
Haloperidol Injection
Haloperidol Oral Solution
Haloperidol Tablets

The draft revised monographs had been posted on the BP website for stakeholder comments between 1 January and 31 March 2020.

Content (Injection only) A request to retain the published content limits of 90.0 – 110.0% was received during the comment window. Members concluded that the data provided by the manufacturer was not sufficient to support the retention of the published limits, and agreed that the draft revised limits of 95.0 – 105.0% should be adopted.

Related substances (Injection only) A request to increase the limits for impurity B, from 0.3% to 0.5%, and total impurities from 1.0% to 1.5%, was received during the comment window. It was highlighted that impurity B was not likely to be a degradation product and therefore, a limit higher than the Ph Eur Haloperidol monograph (0.3%) was difficult to justify. Members also agreed that the data provided to support the request to increase the drafted total impurity limit did not indicate that an increased limit was necessary.

607 Ondansetron preparations (revisions):
Ondansetron Injection
Ondansetron Tablets

Following the receipt of user queries surrounding the Related substances test and the Bacterial Endotoxins test, the Secretariat presented proposals for revision.

Definition (Tablets) Members agreed that the requirement for the tablets to be coated in the Definition statement should be removed if it was not a functional coating.

Dissolution (Tablets) The inclusion of a limit of 75% (Q) in 30 minutes was agreed by members, subject to stakeholder comments.

Related substances A user had highlighted that correction factors may be needed for impurities E and F, and members agreed that this should be evaluated by the laboratory or addressed by using an external standard.

Bacterial endotoxins (Injection) Members agreed that the test should be removed as it would be covered by the general monograph.

608 Hydroxychloroquine Tablets

A request for a dissolution test to be included in the monograph had been received by the Secretariat. A review of the whole monograph had also been carried out.

Definition Members agreed that 'They are coated' should be deleted from the definition.

Content Members agreed the proposal to tighten the content limits to 95.0 to 105.0%, subject to manufacturers' comments.

Identification A Members agreed that an alternative extraction procedure that removed the use of chloroform from the monograph should be investigated.

Identification B Members agreed that the test for sulfates was omitted from the monograph, subject to stakeholder comments.

Disintegration Members agreed that the disintegration test should be deleted, as it was no longer required due to the currently marketed product formulations.

Dissolution A user had proposed a dissolution procedure, aligned with the USP Hydroxychloroquine Sulfate Tablets monograph, for inclusion in the monograph. Members accepted the proposed change, and recommended that release limit of NLT 75% (Q) in 45 minutes was applied, subject to comments by manufacturers.

Related substances Members agreed that the limits applied to the related substances test were aligned with the current regulatory expectations of ICH Q3B (R2), and that a resolution requirement of 1.5 was reinstated in the test, subject to stakeholder comments.

Assay Members agreed that the revised system suitability requirement for related substances should also be applied to the assay.

Impurities A transparency section had been added to the monograph.

609 Supplementary papers: Mycophenolate Mofetil preparations (New) Fentanyl Injection (Revision)

Decisions made by members via correspondence on monographs published in the BP 2021 were reported for official record.

Mycophenolate Mofetil preparations – Content The drafted content limits had been retained as the data received did not support wider content limits for the Mycophenolate Mofetil Capsules, Tablets and for Infusion monographs.

Fentanyl Injection – Related substances Fentanyl Impurity A BPCRS was replaced with a solution producing in-situ generation of impurity A.

610 MC1 Work status and updates

The MC1 work programme was presented to members for information.

611 MC1 Out of stock BPCRS review

The Secretariat outlined BPCRS that have been out of stock long term, and provided an update of the plans and options that were in place to re-establish these.

612 Pharmeuropa Update

The Secretariat presented BP monographs that would require revision in the next publication or addition to the work programme following adoption of the revised monographs presented in Pharmeuropa 32.1 and 32.2