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 11 November 2015.

Present: Mr C Goddard (*Acting Chairman*), Prof J Miller (*Acting Vice-Chairman*), Mr J Cowie, Dr D Edwards, Mr A Gibson, Dr J Lim, Mr P Murray, Dr A Ruggiero, Mrs M Turgoose and Mr N Wynne.

In attendance: Ms H Corns, Mr P Crowley, Ms J Francomb, Ms A Gardiner, Mr N Vadukul and Mr A Handley. Ms C Pitt was present for items MC2(15)35, MC2(15)47 and MC2(15)48. Mrs M Barrett was present for items MC2(15)39 and MC2(15)40. Mr S Jones was present for item MC2(15)46. Mr D Deutsch was present for item MC2(15)54.

Apologies: Dr G Cook

Mr J Cowie, Mr C Goddard, Mr A Gibson and Mr N Wynne declared interests in one or more agenda items and appropriate action was taken.

239 **Introductory Remarks**

Welcome Mr C Goddard informed members that as the Chairman was unable to attend the meeting, he would act as Chairman and Prof J Miller would act as Vice-Chairman. The Chairman welcomed members to the meeting of Expert Advisory Group MC2: Medicinal Chemicals. A special welcome was extended to Ms A Gardiner, a new member of the BP Secretariat, Mr N Vadukul from the BP Laboratory and Mr A Handley from LGC.

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 reminded of the need to inform the Secretariat of any changes to their interests throughout the year and of the need to declare any specific interests at the start of relevant discussions during the meeting.

I MINUTES

240 The summary minutes of the meeting held on 21 May 2015 were confirmed subject to the following amendment:

Present: Dr A Ruggiero was not present for the meeting and his name should have appeared under Apologies.

II MATTERS ARISING FROM THE MINUTES

241 The following matters arising from the meeting held on 21 May 2015 were noted.

Enalapril Tablets (Minute 211) A laboratory report was pending for the assessment of the Related substances and Assay procedures.

Chlorpromazine Preparations (Minute 211) A laboratory report was pending for the examination of the infrared identification method.

Bumetanide Injection, Bumetanide Oral Solution and Bumetanide Tablets (Minute 211) This project was in progress.

Furosemide (Minute 211) This project was in progress.

Prolonged-release Co-careldopa Tablets (Minute 211) A laboratory report was pending for the assessment of the TLC identification, LC Related substances and LC Assay procedures.

Letrozole Tablets (Minute 211) 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 211) A laboratory report was pending for the development of Related substances and Assay procedures.

Quinapril Tablets (Minute 211) A laboratory report was pending for the assessment of the LC Related substances procedure.

Carprofen Injection and Tablets (Minute 211) A laboratory report was pending for the assessment of the Infrared Identification, LC Related substances and LC Assay procedures.

Prolonged-release Tamsulosin Tablets (Minute 211) A laboratory report was pending for the assessment of the LC Related substances procedure.

Benazepril Tablets (Minute 211) A laboratory report was pending for the assessment of the drafted identification, Related substances and Assay procedures.

Fluvastatin Sodium Capsules and Prolonged-release Tablets (Minute 211) A laboratory report was pending for the identification, Related substances and Assay procedures.

Ibuprofen and Codeine Tablets (Minute 211) A laboratory report was pending for the identification, Related substances and Assay procedures.

Ketoprofen Injection and Tablets (Minute 211) The monograph has been amended and circulated to MAHs, no comments had been received to date. A laboratory report was pending for the identification, Related substances and Assay procedures.

Methylphenidate Tablets, Prolonged-release Methylphenidate Capsules and Prolonged-release Methylphenidate Tablets (Minute 211) A laboratory report was pending for the identification, Related substances and Assay procedures.

Telmisartan Tablets (Minute 211) A laboratory report was pending for the identification, Related substances and Assay procedures.

Diclofenac Gel (Minute 211) A laboratory report was pending for the identification procedure.

Naftidrofuryl Capsules (Minute 211) A laboratory report was pending for the Assay procedure.

Tranexamic Acid Injection, Tranexamic Acid Tablets, Tranexamic Acid Mouthwash (Minute 211) A laboratory report was pending for the Assay procedure.

Fenofibrate Tablets, Fenofibrate Capsules, Prolonged-release Fenofibrate Capsules (Minute 211) A laboratory report was pending for the identification, related substances and Assay procedures. These monographs had been circulated to MAHs, and comments had been received.

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 211) A laboratory report was pending for the identification, related substances and Assay procedures. The Secretariat would circulate the revised monographs to manufacturers for comment.

Terbutaline Injection, Terbutaline Oral Suspension, Terbutaline Tablets (Minute 211) A laboratory report was pending for the identification, related substances and Assay procedures. The monographs had been revised and circulated to MAHs, no comments had been received to date.

Liothyronine Tablets & Injection (Minute 211 & 220) The monograph would be amended and presented to a future meeting of the EAG. A laboratory report was pending from the MHRA lab for a second survey of marketed products, focussing on Dissolution.

Carbocisteine Capsules, Carbocisteine Oral Solution (Minute 211) A laboratory report was pending for the identification and Assay procedures. The monograph would be circulated to MAHs for comment.

Rivastigmine Preparations (Minute 211) A laboratory report was pending for the identification, Related substances and Assay procedure. The monographs would be circulated to MAHs for comment.

Anastrozole Tablets (Minute 211) A laboratory report was pending for the identification, Related substances and Assay procedures.

Ezetimibe Tablets (Minute 211) The draft monograph had been circulated to stakeholders for comment and publication of the Ph. Eur. monograph was awaited.

Inhaled Products (Minute 217) Data had been received from manufacturers to support revision of monographs in-line with new BP policy for inhaled product monographs. These would be presented at a future meeting.

Propranolol Tablets (Minute 218) A letter of intent instructing the user that the system suitability would be revised to baseline separation will be posted on the BP website. The monographs had been updated as agreed and would be circulated to MAHs for comment.

Fosaprepitant Dimeglumine for Injection (Minute 219) EDQM have confirmed that this monograph is on their finished product monograph work programme, therefore this would no longer be taken forward by the BP unless the situation changed.

Candesartan Tablets (Minute 222) A laboratory report was pending for the identification, Related substances and Assay procedures. The monograph had been updated as agreed and circulated to MAHs for comment.

Risedronate Tablets (Minute 224) A laboratory report was pending for the identification, Related substances and Assay procedures.

Salmeterol Inhalation Powder, pre-dispensed & Pressurised Inhalation, Suspension (Minute 225 & 226) Comments had been received from manufacturers to support revision of monographs in-line with new BP policy for inhaled product monographs. These would be presented at a future meeting.

Temozolomide Capsules & Injection (Minute 228) The Secretariat had amended the monographs and circulated to USP as agreed. The Secretariat is awaiting USP drafts and comments.

Fosinopril Tablets (Minute 232) This monograph had been updated as agreed at the previous meeting and would be published in the BP 2017.

Simvastatin Tablets (Minute 236) The MAH had been contacted regarding the decision taken by EAG MC2.

III REPORTS AND CORRESPONDENCE

242 **Emergency Evacuation Procedure** **MC2(15)28**

Members were presented with a paper on the emergency evacuation procedure.

243 **New website** **MC2(15)29**

The Secretariat informed members that the new BP website had gone live in August 2016 and confirmed that all members were able to access the Forum.

The Secretariat informed members that draft new and revised monographs would be posted to the BP website at regular intervals for comment beginning in 2016. The four intervals would be 1 January – 31 March, 1 April – 30 June, 1 July – 30 September and 1 October – 31 December.

244 **BP 2016** **MC2(15)30**

Members were presented with a list of new and revised monographs that had been published in the BP 2016.

245 **BP Laboratory** **MC2(15)31**

A list of reference materials relating to monographs within the remit of EAG MC2, which had been adopted since the meeting of 21 May 2015, was tabled for information.

246 **Current Work Programme** **MC2(15)32**

A list of initiated monographs for EAG MC2 was provided for information.

Members asked whether the BP had a policy about accepting requests for revision to monographs. The Secretariat generally pursued all requests for revision and technical revisions were brought to the attention of the EAG.

247 **Metoclopramide Oral Solution** **MC2(15)33**

Members agreed to progress the item by correspondence in advance of the next meeting, due to time constraints.

248 **Levothyroxine** **MC2(15)34**

It was reported that the stability of Levothyroxine had been discussed at the Pharmacy and Standards (CPS) meeting held on 14 July 2015. CPS also concluded that Levothyroxine is most stable as the pentahydrate form and recommended that this be raised with the Ph. Eur. Members agreed that the Secretariat should submit a request for revision to the monograph definition statement and water content test to reference the pentahydrate.

Members agreed that the production statement in the Levothyroxine Tablets monograph was suitable and that no further revision to the monograph was required at this time.

249 **Ph Eur Monograph Titles – Degree of Hydration** **MC2(15)35**

The Secretariat informed members of how the Ph. Eur. monograph title changes would impact BP monographs. Members noted that some revisions would need to be handled carefully.

IV NEW MONOGRAPHS

250 **Clenbuterol Granules (BP Vet)** **MC2(15)36**

Members agreed to progress the item by correspondence in advance of the next meeting, due to time constraints.

251 **Pimobendan Capsules (BP Vet)** **MC2(15)37**

Members agreed to progress the item by correspondence in advance of the next meeting, due to time constraints.

252 **Chewable Pimobendan Tablets (BP Vet)** **MC2(15)38**

Members agreed to progress the item by correspondence in advance of the next meeting, due to time constraints.

253 **Metformin and Sitagliptin Tablets** **MC2(15)39**

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

254 **Prolonged-release Metformin and Sitagliptin Tablets Or Sitagliptin and Prolonged-release Metformin Tablets** **MC2(15)40**

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

V MONOGRAPHS IN PROGRESS

255 **Ciprofibrate Tablets** **MC2(15)41**

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

256 **Aprepitant Capsules** **MC2(15)42**

Members agreed to progress the item by correspondence in advance of the next meeting, due to time constraints.

257 **Propranolol Oral Solution** **MC2(15)43**

Members agreed to progress the item by correspondence in advance of the next meeting, due to time constraints.

258 **Sulfasalazine Oral Suspension** **MC2(15)44**

Members agreed to progress the item by correspondence in advance of the next meeting, due to time constraints.

259 **Verapamil Oral Solution** **MC2(15)45**

Members agreed to progress the item by correspondence in advance of the next meeting, due to time constraints.

VI REVISION OF MONOGRAPHS

260 **Adrenaline Preparations:** **MC2(15)46**
Adrenaline Injection/Epinephrine Injection
Dilute Adrenaline Injection 1 In 10,000/Dilute Epinephrine Injection 1 In 10,000
Adrenaline Eye Drops/Epinephrine Eye Drops
Adrenaline Solution/Epinephrine Solution

The Adrenaline and Noradrenaline family of drug product monographs had been under review by EAG MC2 for a number of years. The outcomes of a MHRA Medicines Testing Scheme (MTS) market survey had been reported and draft revised monographs prepared in light of the report, taking into account Licensing Division advice, as had been agreed at the May 2014 meeting. Draft revised monographs for Noradrenaline and Adrenaline combination products would be presented at a future meeting.

Definition (Injection and Dilute Injection)
It was noted that the definition differed between the Injection and Dilute Injection; the Dilute Injection could be prepared from both Adrenaline Acid Tartrate or adrenaline hydrochloride but the Injection, only from Adrenaline Acid Tartrate. This may have been due to the available products at the time the monograph was written.

Members queried whether the definition for the Dilute Injection was correct, as '0.01% w/v of adrenaline hydrochloride' in the current monograph did not account for the hydrochloride, when the concentration of the product was 0.01% w/v of adrenaline.

The Secretariat agreed to review the definitions and to amend the monographs as necessary, to ensure suitability for all available products.

Content (Injection and Dilute Injection)
It was highlighted that both monographs as written would allow an assay result of 85% - 114% due to permitted rounding. Members recommended that the content of adrenaline should be given as 0.0900 to 0.1100% w/v for Adrenaline Injection and 0.00900 to 0.01100% w/v for Dilute Adrenaline Injection.

Members questioned whether the fixed strength of the monographs was required, as it was standard practice not to have strength specific monographs. The Secretariat agreed to look into this although noted that whilst open strength monographs were preferred, there may be justifiable reasons why fixed strength monographs have been published which would need to be taken into consideration.

Characteristics (Injection and Dilute Injection)
The statements under characteristics in the current monographs were slightly different and members recommended that both sections were harmonised to read 'a colourless solution' unless justification for additionally including 'or almost colourless solution' for the dilute injection was found.

Identification (Injection only)
Members questioned the need for an additional identification control in the Injection monograph compared to the Dilute Injection. The Secretariat agreed to investigate whether three identification tests were required for the Injection monograph.

Acidity (Injection and Dilute Injection)
pH control had been shown to be a critical parameter for adrenaline injection products, and members agreed this justified retaining the tight pH limits of 2.8 to 3.6 for the Injection monograph.

For the Dilute Injection, it was considered that the definition may explain the much wider limits of 2.2 to 5.0. Split limits per salt form were considered; however, as all of the dilute

injection products tested in the MTS survey, which covered both salt forms, were within the pH range 2.5 to 3.6, members recommended tightening the limit from pH 2.2 to 5.0 to pH 2.5 to 3.6 in the Dilute Injection monograph.

D-Adrenaline (Injection and Dilute Injection)
Members agreed that as it appeared from the information available racemisation occurred upon storage, that control of D-Adrenaline would be appropriate in the Adrenaline Injection and Dilute Adrenaline Injection monographs.

Members supported a proposal to submit a request to EDQM asking for an enantiomeric impurity test to be included in these monographs, based on the procedure used in the MTS survey.

Members agreed the inclusion of the 5% limit for D-Adrenaline recommended by Licensing and which was not exceeded by any within shelf-life product tested in the MTS survey. The Secretariat agreed to circulate the draft revised monographs to MAH for comments and to request data to justify an increase to this limit, if asked for.

Members noted that the reagent '*(±) epinephrine hydrochloride'* specified in solution (3) should be named '*(±) adrenaline hydrochloride'.* The Secretariat agreed to check against the Ph. Eur. reagent naming convention and, if necessary, amend the draft monographs in accordance with this. Members recommended that should '*(±) epinephrine hydrochloride'* need to be retained that the text should read: '*(±) epinephrine hydrochloride ((±) adrenaline hydrochloride)*'.

A column temperature of 10°C was considered potentially difficult for some laboratories to meet. It was noted that this had been specified in the original method and different temperatures had not been tested. Members agreed that if a 10°C column temperature was justified, that an autosampler temperature of 4°C should also be included in the chromatographic conditions for this test as had been used in the MTS survey.

Related substances (Injection and Dilute Injection)
Related substances tests based on the Ph Eur parent monographs had been included in the draft revised monographs.

Limits of impurity B at NMT 1%, impurity F at NMT 5%, any other secondary peak at NMT 0.5% and total impurities, excluding F, at NMT 3% with a disregard limit at 0.1% were agreed by members. Adrenaline sulfonate (Ph Eur impurity F) formed in reaction with sodium metabisulfite, an antioxidant added to prevent degradation to adrenochrome and may need a higher limit than 5%.

It was noted that there was no isocratic hold at the beginning of the gradient in the method. Members agreed that, whilst not ideal, in order to remain harmonised with Ph Eur, the gradient could be retained as written, as this test would not require testing by the BP Laboratory.

The Secretariat noted that correction factors for impurities D and E had not been applied in the drafts presented to the group. This omission would be corrected in the revised monographs, along with the inclusion a solution to identify peaks due to impurities D and E following the meeting.

Noradrenaline (Injection and Dilute Injection)
Members agreed that the Noradrenaline test could be deleted from both monographs as this impurity was controlled under the proposed new Related substances.

Assay (Injection and Dilute Injection)
Anomalous results between the current assay in the monographs and the chiral assay were highlighted to the group. It was noted that these results had been obtained with expired samples and that no further investigation had been carried out at time, nor was there an

obvious explanation from the chromatograms obtained by the MHRA lab. On the basis that the BP assay was a well-established method, with no major reported issues since publication and that the chiral assay had not been assessed for suitability for the monographs, members agreed the proposal to retain the current assay procedure.

It was noted that BP Commission had agreed that the assay for all liquid products should be determined in terms of weight per mL. The Secretariat agreed to make the required amendments in-line with this policy.

Adrenaline Eye Drops and Adrenaline (Cutaneous) Solution
EAG ULM had been asked whether there was significant unlicensed use of adrenaline eye drops and adrenaline solution as there were no licensed UK products. As unlicensed usage had been identified, EAG ULM had agreed to accept responsibility for these monographs.

Members agreed that the monographs were to be transferred to EAG: ULM without revision; however information regarding the monographs remaining under the responsibility of EAG MC2 revisions would be provided to allow EAG ULM to evaluate revision to the transferred monographs.

261 **Aminophylline Injection** **MC2(15)47**
Aminophylline Tablets
Prolonged-release Aminophylline Tablets

Draft revised monographs for Aminophylline Injection, Aminophylline Tablets and Prolonged-release Aminophylline Tablets had been prepared based on decisions taken at the previous meeting. The monographs had been sent to stakeholders and made available on the BP website for comment with a deadline of 31 December 2015.

Identification (Tablets and Prolonged-release Tablets only)
The melting point tests (Identification tests A and C) had been removed from the Aminophylline Tablets and Prolonged-release Tablets monographs as agreed at the previous meeting.

Related substances
A HPLC method based on the analytical method in the Ph. Eur. monograph for Aminophylline had been included in all monographs. Limits of 0.2% for unspecified impurities, 0.2% for total impurities and 0.1% for disregard were approved by members. In the absence of any negative comments from stakeholders, it was agreed that the method would be added to the monographs in the BP 2017.

Storage (Injection only)
The statement “Aminophylline Injection should be protected from light.” had been added to the Aminophylline Injection monograph as agreed at the previous meeting.

Labelling (Prolonged-release Tablets only)
Members of EAG Pharmacy agreed that no revision to the labelling statement in the monograph was necessary. The Secretariat would notify the relevant MAH that their declaration of content did not comply with that in the monograph. The Secretariat would also confirm that the change to Ph. Eur. monograph titles would not affect the family of monographs.

Impurities
A standard impurities statement referring to the parent monograph had been included.

It was also suggested that the Aminophylline Tablets should be revised to include an Action and Use statement and that the Dissolution test should be revised to clarify that the established BP criteria (not less than 70% of label claim in 45 min) applied.

262 **Cyclophosphamide Injection** **MC2(15)48**

The Secretariat had received a request to revise the pH limits in the 'Cyclophosphamide Powder for Injection' sub-monograph within the Cyclophosphamide Injection monograph. Additional revisions to the monograph were recommended by the Secretariat.

Monograph Title (Injection)
Members noted that there were no licensed products available for a ready to use Cyclophosphamide Injection and agreed that the monograph should be written in terms of the powder for injection only, as per BPC minute 569.

Definition (Injection)
Members agreed that this section should be removed.

Monograph Title (for Injection)
As there were two licensed products available "Cyclophosphamide Powder for Solution for Injection or Infusion" and "Cyclophosphamide Powder for Solution for Injection" it was agreed that the title Cyclophosphamide for Injection was appropriate as it would apply to both products.

Definition (for Injection)
The Definition statement would be amended in line with Ph. Eur. degree of hydration changes, as required.

Acidity (for Injection)
The limit of 3.0 to 6.0 proposed by the Secretariat would require further input from the Licensing Division. MAHs would also be asked to comment on the revised limit.

It was also noted that reference to "anhydrous" cyclophosphamide would be removed from the content statement, Identification tests, Uniformity of content test, Related substances test, Assay and Labelling statements in line with the provisional Ph. Eur. degree of hydration changes go ahead.

Identification A
Members recommended that Identification test A should be revised to use dichloromethane, or preferably ether, as the extraction solvent in order to remove the use of chloroform. It was noted that the BPCRS reference spectrum would need to be updated depending on which extraction solvent was used. Additionally, the value of retaining Identification test B was questioned. It was thought that it may be a counter-ion test as previous products may have been formulated with sodium chloride to render the solution for injection isotonic. The Secretariat would confirm this at the next meeting. If Identification test A was not sufficient as a standalone test, members agreed that a concordant retention time from the Related substances method could be used as Identification test B.

Uniformity of content & Assay
Members recommended that the Uniformity of content test could be removed from the monograph unless there was a valid reason for retaining it. The Secretariat would look into the monograph history to determine why it was included in the monograph. It was agreed that the Assay should be updated so that the contents of the sealed container for all pack sizes were dissolved in diluent. Further dilutions could be made as necessary to prepare the test solution. It was noted that it would be preferable to replace the TLC Related substances method and Assay titration method with HPLC methods if possible. The Secretariat would request updated test methods from MAHs when circulating the draft monograph for comment.

263 **Fluvoxamine Tablets** **MC2(15)49**

Members agreed to progress the item by correspondence in advance of the next meeting, due to time constraints.

264 **Indapamide Tablets** **MC2(15)50**
Prolonged-release Indapamide Tablets

The Secretariat had noted that the draft revised monograph for Indapamide published in Pharmeuropa 27.2 included a limit and test method for the control of the genotoxic impurity (2*RS*)-1-amino-2-methyl-2,3-dihydro-1*H*-indole (Impurity C). It was confirmed that this could be both a synthetic impurity (starting material) as well as a degradation impurity (hydrolysis product) and therefore should be controlled in the finished product monograph. As MAHs were likely to view the impurity as synthetic only, members agreed that the test method and limits of 'maximum 600 ppm' should be included in the draft revised monograph. As this was a genotoxic impurity and therefore could be a public health concern, it was agreed that this revision should be progressed as high priority.

265 **Methylthioninium Injection** **MC2(15)51**

Members agreed to progress the item by correspondence in advance of the next meeting, due to time constraints.

266 **Montelukast Tablets** **MC2(15)52**
Chewable Montelukast Tablets

Members agreed to progress the item by correspondence in advance of the next meeting, due to time constraints.

267 **Nicorandil Tablets** **MC2(15)53**

A draft revised monograph for Nicorandil Tablets had been prepared based on decisions taken at the previous meeting and circulated to stakeholders for comments. Comments from multiple MAHs were received.

Polymeric Impurities
Due to the various ways that polymeric impurities were quantitated by MAHs, it was agreed that a test would not be included in the monograph for the BP 2017 and that the production statement would be retained to control polymeric impurities in the interim. At the next meeting, further consideration would be given to using nitrate quantitation as a measure of polymeric impurities, but a better understanding of how the two were linked was required.

Related substances
The revised test method would be published in the BP 2017 as it had been assessed by MAHs and was determined to be suitable.

268 **Phenindione Tablets** **MC2(15)54**

A draft revised monograph for Phenindione Tablets was presented to the EAG for consideration. This monograph had been revised based on the submission of validated LC Assay, Uniformity of Content and Related substance procedures from a manufacturer.

The Secretariat highlighted that the Phenindione Tablets monograph had been published prior to 1963 and although it had been revised in line with the development of technology, that the monograph was in need of modernisation.

Content
The monograph included limits of 92.5 – 107.5% and members queried the justification for deviating from standard BP policy. The Secretariat noted that the monograph originally had content limits of 95.0 – 105.0% but that this was widened in the 1981 Addendum of the BP 1980. It was highlighted that there were stability problems with this product, but it was noted that a minimum of 95.0% was still achievable given the impurity limits. Members concluded that the content limits in the draft monograph should be revised to 95.0 – 105.0% and the manufacturer requested to provide justification should the limit need to be wider.

Identification
Members noted that chloroform was used as an extraction solvent in the infrared identification test and should be replaced with dichloromethane. Members concluded that a laboratory assessment was not necessary for this change as the IR spectra was produced from the dried residue.

Dissolution
Members requested that a dissolution test be added to the monograph and that the manufacturer be asked to provide an analytical procedure. Members additionally requested that the limit was drafted with the harmonised "Q" value. The Secretariat noted that as this monograph had been published prior to the BP 2008, the historic criteria (not less than 70% of label claim in 45 min) as set out in Supplementary chapter I E. Dissolution of Solid Oral Dosage Forms would have to be applied.

The Secretariat informed members the BP Commission had recently discussed the retrospective application of the harmonised "Q" value and that stakeholders would be consulted on this change to policy.

Related substances
The Secretariat had replaced the existing thin-layer chromatography procedure with a LC procedure based on the manufacturer's data. This applied gradient conditions and quantification at 220 nm. The limits for impurity 1 (1.5%), total impurities (2.0%) and unspecified impurities (0.5%) had been drafted in line with information from the manufacturer and existing limits from the current monograph. Impurity 1 had been identified by the manufacturer as the major degradation product.

As Impurity 1 had a response factor of 0.72, a limiting solution had been included in the draft procedure which would require the establishment of a BPCRS. A peak identification solution containing impurities 1, 2 and 3 was also proposed for which system suitability criteria could be set. It was agreed however that impurities 2 and 3 were available from commercial sources and so would be specified as reagents.

Uniformity of Content
The Secretariat highlighted that the Uniformity of Content test had been included at the request of the BP Commission to provide additional control of product quality when the content limit was widened in 1981. Given the modernisation of the analytical procedures in the monograph, the Secretariat questioned the necessity of including a specific Uniformity of Content procedure. Members agreed that the test could be deleted from the draft monograph provided that a dissolution test was added.

Assay
In the interests of modernisation, members agreed to replace the current titrimetric procedure with the drafted LC based Assay.

VII EUROPEAN PHARMACOPOEIA

269 **Comments on Draft Monographs of the Ph. Eur.** **MC2(15)55**

Members agreed to progress the item by correspondence in advance of the next meeting, due to time constraints.

VIII ANY OTHER BUSINESS

270 None

IX DATE OF NEXT MEETING

The next meeting is scheduled for 11 April 2016. The Secretariat proposed that the meeting should be moved to the end of February 2016 to facilitate publication of monographs in the BP 2017. The date would be confirmed shortly.

Post meeting note: The date of the next meeting is 2 March 2016.