

BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group ULM: Unlicensed Medicines

SUMMARY MINUTES

A meeting of the Expert Advisory Group on Unlicensed Medicines was held at 151 Buckingham Palace Road, London, SW1W 9SZ on Thursday 21 April 2016.

Present: Dr M G Lee (*Chair*), Mr V Fenton-May (*Vice-Chair*), Mr D Caulfield, Mr W Goddard, Dr N Hussain, Mr S Jones, Mr J Rickard, Mr M Santillo, Mr A Sully and Mr P Weir.

In attendance: Dr F J Swanson, Mr S Young, Mr D Holcombe, Ms A Hurpaul and Miss C Pitt.

Apologies for absence were received from Dr S Branch and Dr J Smith.

397 **Introductory Remarks**

Welcome The Chairman welcomed members to the meeting. A special welcome was extended to a new member of the EAG, Mr James Rickard, and to Mr David Holcombe who was attending on behalf of the Laboratory. Ms Ashvina Hurpaul, MHRA, also attended the meeting as an observer.

Declaration of Interests Members were reminded to declare specific interests as they arose during the meeting and to inform the Secretariat of any changes to their interests throughout the year.

I **MINUTES**

398 The minutes of the meeting held on 8 October 2015 were confirmed.

II **MATTERS ARISING FROM THE MINUTES**

399 The following matters arising from the meeting held on 8 October 2015 were noted.

Minute 367 – Phenylephrine Intracameral Injection The Laboratory had recently completed the work to develop a related substances test and a report would be presented at the next meeting.

Minute 367 – Bendroflumethiazide Oral Suspension The Laboratory had not yet carried out practical examination of Rosemont's methods and a report would be presented at a future meeting.

Minute 374 – Evaluation of Methods; Provision of information and feedback Members were reminded to provide the Secretariat with a list of named contacts to ensure that draft monographs were seen by the most appropriate people.

Minute 382 – Lorazepam Oral Suspension Information to enable the draft monograph to be progressed was awaited.

Minute 394.3 – Monographs Proposed for Transferral to EAG ULM: Adrenaline Eye Drops The preparation did not appear to be widely used and members agreed that the monograph should be omitted from a future edition of the BP rather than being transferred to EAG ULM.

III REPORTS AND CORRESPONDENCE

400 **Membership** ULM(16)1

Retirement Mr Rothwell had tendered his resignation from EAG ULM at the end of 2015, due to conflicting commitments. Mr Bennett had also resigned from the group, due to his retirement from the NHS.

New Member Mr James Rickard had recently been appointed to the group, following endorsement by the British Pharmacopoeia Commission. Mr Rickard was the Head of Technical Services and Deputy Chief Pharmacist at Barts Health NHS Trust (Royal London Hospital).

A copy of the current membership list had been included on the BP website forum and members were reminded to inform the Secretariat of any errors in the list. Members were invited to alert the Secretariat to any potential additional candidates for the group.

401 **British Pharmacopoeia Commission** ULM(16)2

A review of the membership of the British Pharmacopoeia Commission had been undertaken in 2015. Eight new members had been appointed with effect from 1st January 2016. A list of members had been provided and was available on the BP website.

402 **British Pharmacopoeia 2017** ULM(16)3

The Secretariat was currently heavily involved in the production of the British Pharmacopoeia 2017, which would be published at the end of August and would come into effect on 1st January 2017. The BP 2017 would contain all of the text from the eighth edition of the European Pharmacopoeia, together with that from Supplements 8.1 to 8.8. Updates to the online version of the BP 2017 would be made during the year, adding the text of the 9th edition of the European Pharmacopoeia and Supplements 9.1 and 9.2. A list of the 3 new texts and 15 revised texts that would be published in the BP 2017 that were the responsibility of this EAG had been provided for information.

Lisinopril Oral Solution The Laboratory had been asked to develop a system suitability test for inclusion in the Related substances test. Prior to the Laboratory starting their practical evaluation, however, the Secretariat had become aware that Lisinopril Oral Solution was now a licensed product. Consequently the responsibility for the monograph had been transferred to the Expert Advisory Group on Medicinal Chemicals (MC2) and the unlicensed medicines introductory statement would be deleted from the monograph in the BP 2017.

403 **Issues Arising through the BP Commission** ULM(16)4

Heavy metals The BP Commission had agreed that the heavy metals test should be removed from about 50 BP monographs and other texts in the BP 2017 to harmonise with the Ph Eur policy regarding implementation of the ICH Guideline on Elemental Impurities (Q3D). This change would affect two monographs that were the responsibility of this EAG: Dantrolene Sodium and Melatonin. No other changes to these monographs were required.

Monographs for Anhydrous and Hydrated Substances It had been confirmed that the changes to remove the term “anhydrous” from a number of monographs would be made in the 9th Edition of the European Pharmacopoeia, which would come into effect on 1st January 2017.

The BP Commission had recently endorsed inclusion of the necessary changes to affected BP and Ph Eur monographs in the British Pharmacopoeia 2017, which would come into effect on the same date as the Ph Eur 9th Edition (1st January 2017). The change affected the following monographs that were the responsibility of this EAG: Ceftriaxone Eye Drops; Compound Glucose, Sodium Chloride and Sodium Citrate Oral Solution.

Triennial Review Update; Public Consultation on Draft Monographs Following a recommendation from the Triennial Review, a timetable for including draft new and revised monographs for comment on the BP website at regular intervals had been agreed by the BP Commission. This allowed four review periods during the year, each of 3 months duration.

404 **Policy For Transferring Monographs to EAG ULM** ULM(16)5

As agreed at the last meeting the Secretariat had drafted proposals to ensure that a consistent policy was applied when EAG ULM were asked to take over the responsibility for monographs. It was noted that the Expert Advisory Group on Unlicensed Medicines had been established to develop publicly available standards for [widely used] medicines that were prepared in order to address patient requirements that were not met by current UK licensed medicines. The remit of the group was not to take over monographs for which licensed products were no longer available.

Proposals for future action Members were invited to discuss the proposals from the Secretariat, which were accepted.

It was agreed that the proposals should be presented to the BP Commission.

405 **Extemporaneous Preparations** ULM(16)6

Monograph revisions Definition; Extemporaneous Preparation Further to the discussions at the previous meeting, the Secretariat had completed a stakeholder consultation exercise and discussed initial proposals with EAG PCY (Pharmacy).

A number of options were discussed, including: retaining the current extemporaneous formulae within the individual finished product monographs; moving the extemporaneous formulae to a Supplementary Chapter; carrying out a case-by-case review of whether key information from the extemporaneous formulae could be moved to a Production statement.

Members agreed that it would not be appropriate to move the details to a Production statement since this section of a monograph provided mandatory instructions to manufacturers relating to aspects that cannot be controlled as part of a generic standard. The value of retaining extemporaneous preparation information in the BP had been highlighted at previous meetings and the preferred approach of EAG ULM was to include the relevant information in a Supplementary Chapter. This was in line with the responses to the stakeholder consultation. It was agreed that a paper presenting the various options, together with the recommendations from EAG PCY and EAG ULM should be presented to the BP Commission.

Aromatic Ammonia Solution; Aromatic Ammonia Spirit; Buffered Cream; Calamine Ointment; Compound Aluminium Paste; Compound Orange Spirit; Paediatric Ipecacuanha Emetic Mixture; Paediatric Opiate Squill Linctus It was agreed that the monographs should be omitted from a future edition of the BP.

Strong Ammonium Acetate Solution; Ammonium Chloride Mixture; Alcoholic Iodine Solution; Aromatic Cardamom Tincture; Cetrimide Emulsifying Ointment; Chloroxylenol Solution; Compound Magnesium Trisilicate Oral Powder; Compound

Podophyllum Paint; Lemon Spirit; Phosphates Enema; Quillaia Liquid Extract; Quillaia Tincture; Salicylic Acid Collodion; Squill Liquid Extract; Surgical Spirit; Tolu Syrup; Orange Syrup; Weak Ginger Tincture It was agreed that these monographs should be retained in the BP.

IV NEW MONOGRAPHS

406 **Ceftazidime Injection** ULM(16)7

The draft monograph would be included in a future publication, subject to resolution of any outstanding points.

407 **Diltiazem [Hydrochloride] Oral Suspension** ULM(16)8

The draft monograph would be included in a future publication, subject to resolution of any outstanding points.

408 **Metoprolol [Tartrate] Oral Suspension** ULM(16)9

The draft monograph would be included in a future publication, subject to resolution of any outstanding points.

409 **Tretinoin, Hydrocortisone and Hydroquinone Cream; Hydroquinone** ULM(16)10

The draft monographs would be included in a future publication, subject to resolution of any outstanding points.

V MONOGRAPHS IN PROGRESS

410 **Supplementary Chapter V F: Aseptic Preparation of Unlicensed Medicines** ULM(16)11

The draft Supplementary Chapter would be included in a future publication, subject to resolution of any outstanding points.

411 **Parenteral Nutrition Solutions** ULM(16)12

The draft General Monograph would be included in a future publication, subject to resolution of any outstanding points.

412 **Sterile Sodium Benzoate Concentrate** ULM(16)13

The draft monograph would be included in a future publication, subject to resolution of any outstanding points.

413 **Tobramycin Oral Solution; Tobramycin Sulfate** ULM(16)14

The draft monographs would be included in a future publication, subject to resolution of any outstanding points.

VI REVISION OF MONOGRAPHS

414 Format of Dissolution Tests ULM(16)15

Acceptance criteria The BP Commission had agreed that it would be more transparent if the limit was included in all dissolution tests instead of relying on information in the Supplementary Chapter I E: Dissolution Testing of Solid Oral Dosage Forms. It had been agreed that tests should be updated when monographs were undergoing revision.

Approach for Unlicensed Medicines It was agreed that the following wording should be included in relevant BP monographs for unlicensed Oral Suspensions when the monographs were undergoing revision:

“LIMIT The amount of [drug name] released is not less than 75% (Q) of the stated amount.”

415 Chlorhexidine Gluconate Eye Drops ULM(16)16

Related substances Members were informed that solution (2) and the system suitability test would be deleted for the BP 2017, as the Ph Eur had withdrawn *chlorhexidine for performance test EPCRS*.

Further to the discussions at the previous meeting, further information had been provided in relation to the request to relax the total impurity limits. The limit in the product monograph (3%) was the same as that for the active substance and it had been noted that the product might fail to comply with the test after manufacture if it was prepared from starting material with a high level of impurities. The data provided indicated that increasing the limit to 3.5% or 4% might be suitable.

4-Chloroaniline The other chlorhexidine gluconate BP monographs contained a test for 4-chloroaniline, which was a carcinogenic degradant. It was noted that this impurity was detected using the current Related substances test and it was agreed that it should be specified as a named impurity in the Eye Drops monograph.

416 Paediatric Digoxin Injection ULM(16)17

The monograph had been transferred to EAG ULM at the last meeting and the unlicensed medicine statement would be included in the BP 2017.

Assay The proposal to increase the standing time to 2 hours, in view of a request from a manufacturer which had been approved by EAG MC1 (Medicinal Chemicals), was accepted.

Extemporaneous preparation It was agreed that this section should be retained and reviewed as part of the wider review of extemporaneous preparations.

417 Folic Acid Injection ULM(16)18

Alkalinity It was agreed that the pH limits should be revised to 7.0 to 9.0 in a future publication, in line with Royal College of Nursing (RCN) Guidelines and the specifications of some available preparations, subject to the receipt of further information on the formulation.

418 Paediatric Phenobarbital Oral Solution ULM(16)19

Related substances A draft HPLC method had been prepared, based on work undertaken at the Robert Gordon University (RGU) to ascertain if the method from the parent monograph was suitable for application to the phenobarbital preparations. It was agreed that

the method was suitable for the Oral Solution, subject to checking the solution concentrations and comments from stakeholders.

Assay The new HPLC procedure was also suitable as an Assay method. It was agreed that views should be sought on whether the current method should be retained or replaced.

VII WORK PROGRAMME

419 Work Programme ULM(16)20

The work programme had been updated to reflect changes since the last meeting and a copy was provided for information. Members were encouraged to provide information to assist in the development of suitable monographs.

Unlicensed Oral Medicines for the treatment of tuberculosis No further information had been received.

Ethambutol Oral Liquid A member agreed to provide information to support the development of a monograph.

420 Standards for Intraocular Injections ULM(16)21

Proposals for future text A draft document being prepared by the UK Ophthalmic Pharmacists Group on Standards for Intraocular Injections had previously been provided to members for consideration. Members agreed that it would be valuable to include general information on these formulations in a future publication, possibly in the form of a Supplementary Chapter in the first instance.

Moxifloxacin Intracameral Injection The Secretariat had been provided with the list of former Moorfield's products, together with a list of the NHS Production Units that had taken over responsibility for preparing/supplying these items. There was no supplier listed for Moxifloxacin Intracameral Injection, meaning that the Laboratory were unable to obtain a sample for infrared testing. Further enquiries would be made before deciding whether the work should be abandoned.

421 Monograph Development Using Information from the Literature ULM(16)22

The Chairman had brought to the Secretariat's attention a number of published stability studies for unlicensed oral formulations. It had been suggested that these might provide a useful source of information for the development of new monographs.

Carvedilol Oral Suspension; Midazolam Oral Suspension; Nadolol Oral Solution/Suspension; Naltrexone Hydrochloride Oral Solution/Suspension It was agreed that the items should be added to the work programme, with a view to preparing monographs based on the published information.

Clomipramine Hydrochloride Oral Liquid; Hydrochlorothiazide Oral Liquid; Pentoxifylline Oral Liquid It was agreed that the items should be added to the work programme.

Loperamide Oral Suspension It was agreed that a monograph should be elaborated based on the information in the literature and the monograph for the Oral Solution. The product was used in preference to the oral solution for short bowel syndrome.

Nifedipine Oral Suspension The monograph was on the secondary work programme and a skeleton draft monograph had been prepared based on information from the literature.

422 **EAG ULM Data Template** ULM(16)23

Data Template A guidance template for the submission of information to support monograph development had been prepared and circulated in November 2015. The template included information on the types of tests that were expected to be included in monographs for unlicensed medicines and provided details of further supporting information (Supplementary Chapters, Aide Memoire, etc.). Members agreed that the template would be a useful guide and that information on the form of the active ingredient (base or salt), the maximum daily dose and therapeutic indications should also be included.

VIII INTERNATIONAL

423 **Pan-European Paediatric Formulary Project: Update** ULM(16)24

Members had been provided with documents presented at the 154th Session of the European Pharmacopoeia Commission, which had been approved by the European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH). These included items outlining the criteria for inclusion and evaluation of monographs, the maintenance of monographs and procedures for development of the European Paediatric Formulary.

The Paediatric Formulation Working Party would be holding its inaugural meeting later in April to select a work programme and develop the formulary. It was intended to publish draft monographs for comment in Pharmeuropa, the newsletter of the European Pharmacopoeia Commission, in due course.

IX ANY OTHER BUSINESS

424 **BP Laboratory** It was noted that, in the absence of suitable formulations for testing, the Laboratory had previously prepared solutions or suspensions using active ingredients and known excipients. Members were asked if they could provide any guidance on preparing preparations extemporaneously for Laboratory testing.

425 **Date of next meeting** Thursday, 20th October 2016.