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 Monday 15th October 2018.

Present: Mr V Fenton-May (*Vice-Chair*), Mr W Goddard, Ms S Hartley, Dr S Ho, Mr M Santillo, Dr J Smith and Mr P Weir.

In attendance: Dr F J Swanson, Mr S Young, Ms K Busuttil and Ms M Nanasi.

Dr K Bracht (MHRA Licensing Division) also attended the meeting as an observer.

Apologies for absence were received from Dr M G Lee (*Chair*), Mr D Caulfield and Mr A Sully. Dr S Branch and Mr J Rickard did not attend the meeting.

534 **Introductory Remarks**

Welcome; Secretariat The Chair welcomed Dr Bracht to the meeting and also Ms Busuttil and Ms Nanasi, from the BP Laboratory, who were attending their first meeting of EAG ULM.

Brexit The MHRA had launched a public consultation, which closed on 1st November, on how its legislation and regulatory processes would have to be modified in the event that the UK did not secure a deal after exiting the EU, (https://www.gov.uk/government/news/mhra-to-consult-on-eu-exit-no-deal-legislative-proposals).

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

535 The minutes of the meeting held on 23rd April 2018 were confirmed.

II MATTERS ARISING FROM THE MINUTES

536 The following matters arising from the meeting held on 23rd April 2018 were noted.

Minute 510 – Lorazepam Oral Suspension Work was being undertaken with a view to providing a Related substances test for inclusion in the monograph in due course.

Minute 512 – Extemporaneous Preparations The British Pharmacopoeia Commission had endorsed the final proposals relating to the review of monographs containing extemporaneous preparation information.

Minute 514 – Dispensing and Supply Statements The suggestion from this EAG to retain the information included in these statements in some format had been drawn to the attention of the Expert Advisory Group on Pharmacy.

Minute 519 – Naltrexone Capsules The item would be retained on the work programme for the time being, but it was unlikely that it would be progressed in the near future.

Minute 527 – Chloral Hydrate Oral Solution The Secretariat had written to the BNF requesting amendment of the entry relating to Chloral Mixture as agreed.

III REPORTS AND CORRESPONDENCE

537 Membership Review: Update ULM(18)22

The term of office for all members of BP Expert Advisory Groups, Panels of Experts and Working Parties would expire on 31st December 2018. Several expressions of interest relating to membership of EAG ULM had been received as a result of the recent posting on the BP website.

538 Issues Arising Through the BP Commission ULM(18)23

Members noted the following issues, which had recently been discussed by the British Pharmacopoeia Commission.

Dissolution A public response to the consultation would be issued in due course and members would be kept informed of any developments that affected the monographs of EAG ULM.

Oral Liquid Monographs The current policy regarding monographs for Oral Liquids that were presented as dry powders for re-constitution, rather than as ready-to-use solutions or suspensions, had been confirmed. For such formulations the monograph tests were carried out on the reconstituted solution or suspension and assay limits relating to the freshly constituted formulation, and to the formulation at the end of its period of use, were included.

Parenteral Preparations; Definition Monographs for injections or infusions presented as dry powders were defined as "*a sterile material consisting of [XXXX] with or without excipients*". This approach was intended to ensure that a monograph did not place any restrictions on formulation and had been in place for many years. The Commission had confirmed that the current approach was appropriate and should be maintained as it was the responsibility of a manufacturer to ensure that new formulations complied with the requirements of a published monograph.

539 Reconstituted Intravenous Infusions ULM(18)24

At the last meeting it had been agreed to explore the feasibility of (i) including a section on the preparation and stability of IV Additives in the Supplementary Chapter on Aseptic Preparation of Unlicensed Medicines and (ii) including additional non-mandatory information on individual preparations within the BP. Whilst members had been supportive of including general information, concerns had been raised about the huge amount of resources required to generate the more product-specific information and the difficulty of keeping it up-to-date. The consensus remained that it would still be useful to provide such additional information but that the BP might not be the most appropriate publication medium.

540 Sterility of Extemporaneous Preparations ULM(18)25

As extemporaneously prepared sterile products would be unable to demonstrate that they were sterile, due to the restricted availability of the product and the lack of batch production, it had been agreed to include a statement within the BP recognising that there might be instances where sterility testing could not be carried out. The General Monograph on Unlicensed Medicines already included the following proviso under Sterility: "*While it is expected that the formulated preparation will demonstrate compliance when tested, it is recognised that it might not be practicable to carry out the pharmacopoeial test routinely*.".

The European Pharmacopoeia General Monograph on Pharmaceutical Preparations also acknowledged that "*Where it is not practical, for unlicensed pharmaceutical preparations, to carry out the tests (e.g. batch size, time restraints), other suitable methods are implemented to ensure that the appropriate quality is achieved…*". Members were of the opinion that it would be almost impossible to carry out sterility testing on extemporaneous preparations.

A revised form of words was proposed for inclusion in the General Monograph.

541 **Intraocular Injections** ULM(18)26

The agreed texts on Intraocular Injections had been included within the General Monograph for Unlicensed Medicines and in Supplementary Chapter V F: Aseptic Preparation of Unlicensed Medicines in the British Pharmacopoeia 2019.

A number of minor changes would be incorporated within the BP 2020.

542 **Monographs for Omission or Transfer to EAG ULM** ULM(18)27

Members were reminded that a policy had been agreed in 2016 whereby any monograph for a previously licensed product should be reviewed and updated by the relevant Medicinal Chemicals EAG before being transferred to EAG ULM. During a review of their monographs the EAG MC1 Secretariat had identified a number of monographs for which licensed products were no longer available in the UK. This EAG had been asked to review the items on the list and to advise if any were used as unlicensed medicines.

The Secretariat had examined the items in the list against information in the Pro-file database, the British National Formulary and the list of the top 500 Special Order Products (December 2017) and none of the items were included. Members confirmed that to the best of their knowledge none of the identified items were currently used as unlicensed medicines. EAG MC1 would be informed accordingly and it was likely that the monographs would be omitted from a future edition of the British Pharmacopoeia.

543 **Adrenaline Preparations** ULM(18)28

There were no longer any UK licences for Adrenaline Eye Drops and Adrenaline Solution. Both formulations were listed in the Pro-file database and, as usage was indicated, it was agreed that the responsibility for these monographs should be transferred to EAG ULM. The monographs would be updated to include reference to the General Monograph for Unlicensed Medicines in the BP 2020 and would also reflect any agreed changes to the format of EAG ULM monographs (minute 552 refers).

IV NEW MONOGRAPHS

544 **Work Programme** ULM(18)29

The work programme had been reviewed since the last meeting to include prescription and hospital usage data and to identify those members who had previously offered to provide information to assist in monograph development. The review had highlighted a number of items for which licensed products were available and also a number of items that did not appear to be used. It was agreed that further comprehensive reviews should be undertaken at regular intervals to ensure that the work programme remained appropriate and realistic.

Licensed Products The following items had been identified as licensed products: Colecalciferol Oral Solution, Glycopyrronium Tablets, Mebeverine Oral Suspension, Sodium

Nitrite Injection. It was agreed that the responsibility for these monographs should be transferred to the relevant Expert Advisory Groups.

Hospital Usage and Prescription Data A number of items had been shown to have no usage from the available prescription and Special Order data. Members agreed that the identified items should be removed from the work programme.

Revised Monographs Steps had been taken to ensure that when family monographs were examined by the Laboratory any corresponding monographs for unlicensed formulations were included in the review.

545 **Calcium Carbonate Oral Suspension** ULM(18)30

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

546 **University Collaboration; Validation of Analytical Procedures** ULM(18)31

University reports At the last meeting members had been informed that interim reports had been received from Aston University relating to Carvedilol and Clomipramine Oral Suspensions. It had been noted that further work would be required before any methods could be published in BP monographs, but the reports had provided an indication of the type and level of work that could realistically be undertaken by students in a limited time-frame. The Secretariat had provided some feedback on these reports in order to provide guidance should further university projects be undertaken in the future.

It was intended to repeat the work on Carvedilol and Clomipramine at Aston.

Validation guidelines Following on from this work, a member had prepared a document entitled “Validation of Analytical Procedures” which was intended to provide guidance to students undertaking practical work to support BP monograph development. Feedback had been provided from the Secretariat and Laboratory side.

V MONOGRAPHS IN PROGRESS

547 **Carvedilol Oral Suspension** ULM(18)32

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

548 **Clomipramine Oral Suspension** ULM(18)33

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

549 **Metoprolol Oral Suspension** ULM(18)34

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

550 **Nadolol Oral Suspension; Nifedipine Oral Suspension** ULM(18)35

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

551 **Parenteral Nutrition Solutions** ULM(18)36

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

VI REVISION OF MONOGRAPHS

552 **Format of EAG ULM Monographs** ULM(18)37

At the last meeting it had been agreed that minor changes to the italic opening statement and the reference to General Monographs should be made to all monographs for unlicensed medicines.

It was intended to include the updated wording in all new monographs going forward and to update all current monographs in the BP 2020, if feasible. It would be preferable to update the texts at the same time, but it was noted that this would involve changes to about 80 published monographs.

Captopril Oral Solution The current monograph had been developed to cover formulations that were available as either a ready-to-use solution or a dry powder for reconstitution. Licensed forms of the ready-to-use solution were now available and the monograph would be updated to the new format in the BP 2020.

553 **Ciprofloxacin Eye Drops** ULM(18)38

The current monograph for Ciprofloxacin Eye Drops described a “sterile solution of ciprofloxacin lactate, prepared by the interaction of Ciprofloxacin and Lactic Acid”. A licensed formulation containing Ciprofloxacin Hydrochloride was available, which was on the work programme of the Expert Advisory Group on Antibiotics.

Members were strongly of the opinion that separate monographs should be included for these items.

554 **Ketamine Nasal Spray** ULM(18)39

Related substances; Assay During testing of the BPCRS required to support the BP 2019 monograph for Ketamine Nasal Spray, the Laboratory had noted that ketamine impurity A was insoluble in water. It had been noted from the original data that the impurity should be dissolved in methanol rather than in water and a note to this effect had been included in the BPCRS leaflet and on the BP website. This had necessitated a change to the monograph and a draft amendment had been prepared and was accepted for inclusion in the BP 2020.

555 **Silver Nitrate Preparations** ULM(18)40

Sterile Silver Nitrate Solution At the last meeting it had been agreed that the current monograph, which covered solutions that could be administered for ophthalmic use, for cutaneous use or for use as an irrigation solution, should be split into separate monographs depending on the availability and use of such products.

A number of Silver Nitrate preparations were listed in Pro-file, including non-sterile topical solutions, eye drops and sterile lotions. There did not appear to be any indication of material being used as an irrigation solution.

It was agreed that the monograph for Sterile Silver Nitrate Solution should be restricted to cover sterile topical formulations. A draft revised monograph had been prepared and was accepted. Non-sterile topical formulations were covered by the current monograph for Silver Nitrate Solution, to which no changes were required.

Silver Nitrate Eye Drops A draft monograph for Silver Nitrate Eye Drops had been prepared, based on the monograph for Sterile Silver Nitrate Solution, and was accepted.

VII INTERNATIONAL

556 **Paediatric Formulary Working Party** ULM(18)41

The reports of the 9th, 10th and 11th meetings of the Paediatric Formulary Working Party were provided for information.

Dr Bracht gave a brief overview of her experiences to date with the Working Party.

VIII ANY OTHER BUSINESS

557 **NHS Formulary** It was noted that the NHS were developing a formulary for a number of products and that, where possible, BP monographs for these items should be prepared. A number of TB products for which monographs already existed were included.

558 **MHRA Representation** Dr Ho said this would be her last attendance at EAG ULM meetings as Dr Marion Westwood would shortly be returning from maternity leave and would resume her role. Mr Fenton-May thanked Dr Ho for her contributions during her time with the EAG.

559 **Date of next meeting**

To be confirmed.