BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group: Medicinal Chemicals 3

SUMMARY MINUTES

A meeting of this Expert Advisory Group was held at 151 Buckingham Palace Road, London SW1W 9SZ on Wednesday 7th October 2015.

Present: Mr V Fenton-May (*Chairman*), Professor M Almond, Mr J Beach, Mr C T Goddard, Mr P Hampshire, Dr R Torano and Mr I R Williams.

In attendance: Mr A Evans, Ms A Gardiner.

Apologies: Professor E Williamson, Dr J Beaman, Mr M Tubby and Dr K Pugh.

INTRODUCTORY REMARKS

The Chairman welcomed Ms Alice Gardiner attending her first meeting as the new assistant secretary to EAG MC3, replacing Ms Helen Corns who had been promoted to secretary of MC2.

The Chairman reminded members that the BP Secretariat should be contacted if members experienced any difficulties with their travel bookings or expenses claims.

The Chairman reiterated to members the confidential nature of the papers presented at EAG meetings and that members should declare any interests at the start of each agenda item.

Mr Goddard, Mr Hampshire and Dr Torano declared interests in one or more agenda items and appropriate action was taken.

I MINUTES

The summary minutes of the meeting held on 25th February 2015 were confirmed.

II MATTERS ARISING FROM THE MINUTES

The following matters arising from the meeting held on 25th February 2014 were noted.

Ergocalciferol /Colecalciferol Preparations Information would be provided when the company's investigation was complete.

Free Prednisolone Further information was required regarding the limit in this monograph.

III REPORTS AND CORRESPONDENCE

449 Emergency Procedure MC3(15)25

The emergency procedure for 151 Buckingham Palace Road was provided.

450 Members' details MC3(15)26

Members were asked to check the circulated contact details and to inform the Secretariat of any amendments required.

451 British Pharmacopoeia Chemical Reference Substances MC3(15)27

The British Pharmacopoeia Chemical Reference Substances approved since the last meeting of the EAG were noted.

452 EAG Work Programme MC3(15)28

A copy of the work programme for the EAG was provided to members for information. Members were asked to contribute data should they have an interest in any of the products.

The Secretariat informed members that the work programme had been prioritised by known problems, hospital/prescription data and products with multiple manufacturers.

453 BP Updates MC3(15)29

The Secretariat provided members with an update on changes within the MHRA and the BP.

Publications The BP2016 had been published

Website The new BP website had gone live and members should be able to access the correct areas. Members were advised to contact the Secretariat if they were experiencing difficulties.

EAG MC3 Members were congratulated as MC3 had published 40 monographs over the past three years. It was noted that a considerable portion of the papers were for new monographs in order to progress the work program for the next three years.

454 Analytical Methods Evaluation Assessment MC3(15)30

Members were asked to review and comment on the proposal from the Secretariat regarding the paper on a risk based approach to deciding when and what the Laboratory should investigate. Members indicated that the proposal was suitable but requested further information be included on where Laboratory Evaluation was not required:

- What partial validation will be performed
- Any related substances procedures used for liquid preparations identified and controlled the hydrolysis products for the given API
- The formulation review would be sufficient to ensure that the methods would be suitable for all available products

IV NEW MONOGRAPHS

455 Capecitabine Tablets MC3(15)31

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

456 Dutasteride Capsules MC3(15)32

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

457 Ferrous Fumarate and Folic Acid Capsules MC3(15)33

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

458 Folic Acid Oral Solution **MC3(15)34**

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

The published Folic Acid Injection and Folic Acid Tablets monographs would also be updated during the development of this monograph.

459 Quetiapine Preparations **MC3(15)35**

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

460 Tolterodine Preparations **MC3(15)36**

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

V MONOGRAPHS IN PROGRESS

461 Gabapentin Preparations **MC3(15)37**

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

VI REVISIONS

462 Chlordiazepoxide Preparations **MC(15)38**

The Secretariat explained that the monographs required updating. The current monographs for Chlordiazepoxide Hydrochloride Tablets and Chlordiazepoxide Caspules contained a TLC related substances test and UV Assay. Furthermore, there was no Dissolution procedure in the tablets monograph.

There were 3 MAH for the tablets and 7 MAH for the capsules.

Identification Members noted that the capsules draft monograph contained two identification tests, while the tablets contained three. Identification B in the tablets draft monograph was considered unnecessary and the Secretariat agreed to remove the test.

Capsules Identification A the method had been replicated from the tablets monograph, the Secretariat agreed to investigate if the hydrochloride salt would interfere with this test.

Dissolution Members questioned whether the dissolution test introduced to the tablets monograph should be in terms of Q, in line with new monographs. The Secretariat noted the general monograph states that 70% in 45 minutes should be applied to old monographs and therefore the dissolution test should not be updated to use Q at this time.
Members requested that the target concentration be included in the dissolution test. However, they were informed by the Secretariat that it was not BP policy to do so in the case of UV quantification.

Members noted that in the tablets draft method, as the base was being measured, the determination of content should read ‘Calculate the total content of chlordiazepoxide, $C_{16}H_{14}ClN_3O$, in the medium taking 327 as the value of A(1%, 1 cm) at the maximum at 308 nm.’

Related substances It was noted that impurity A was limited at 3% in both monographs, but only 0.2% in the Ph. Eur. parent monograph. The Secretariat agreed to investigate the origin of this large limit to determine whether it could be tightened.

Assay Members suggested that the wide content limits may no longer be required (90% - 110% in the tablets and 92.5% -107.5% in the capsules) and requested justification from the manufacturer to support these limits. The Secretariat agreed to request batch/stability data to retain the limits or the usual BP limits (95.0 to 105.0%) would be applied.

The expression of strength in the tablets/capsules draft monographs and the declared content of *chlordiazepoxide hydrochloride BPCRS* would be updated following the review of the base/salt investigation for the expression of strength in the products.

463 Finasteride Tablets MC(15)39

Related substances/EPCRS The Secretariat informed the group that the Ph. Eur. had amended the calculation of impurity A in the related substances method of the parent monograph. A correction factor was now used in the monograph and the finasteride for peak identification EPCRS no longer contains a declared content for impurity A. The BP Finasteride Tablets monograph used the declared content for impurity A (and the EPCRS); therefore the draft monograph had been revised to reflect the change implemented by the Ph. Eur. Members agreed with this amendment.

It was questioned why the identification and disregard limits were tighter than ICH guidelines. The Secretariat explained that the limits were in line with the registered specifications of the product. Members felt that that if the licenced limits were achievable that they should be retained in the draft monograph.

464 Hysocine Buylbromide Preparations MC3(15)40

The two BP monographs for Hyoscine Butylbromide preparations (Tablets and Injection) used a TLC related substances test. The Related substances test in the draft monographs used a LC procedure adapted from the Ph. Eur. parent monograph.

Identification It was noted that two of the three identification methods for both preparations contained chloroform. Members requested that these were amended using one or more of the 6 tests in the Ph. Eur. parent monograph.

Dissolution Members noted that the revised tablets monograph did not contain a dissolution test and felt that during the revision process one should be introduced. The Secretariat agreed to investigate a suitable dissolution procedure.

Test for Hyoscine Members noted that as the revised related substances test controlled hyoscine. The current BP monograph included a specific test for hyoscine which would be unnecessary. The Secretariat agreed to remove the test for hyoscine from the draft monograph.

Related substances The limits from the parent monograph were adopted in the draft monograph and stakeholders would be given the chance to comment on these limits.

Members suggested that the run time be increased from 3.5 to 4 times that of hyoscine butylbromide to ensure impurity G eluted. Members also suggested that the system suitability statement should read ‘the symmetry of the peak due to butylhyoscine is between 0.8 and 2.5.’.

It was noted that the draft method informed the analyst to disregard the peak relating to the bromide ion; however instructions for identifying this peak were not included. Members suggested that a suitable identification solution was incorporated into the monograph.

Assay The Secretariat agreed to transfer the chromatographic conditions from the current hyoscine test to the Assay.

Members requested that the usual content limits were applied (95.0 – 105.0%). Stakeholders would be asked to submit batch/stability data to maintain the current limits.

465 Imipramine Tablets MC3(15)41

The Secretariat informed members that the current Imipramine BP monograph contained outdated Related substances/Assay methods and no Dissolution procedure. The monograph had been updated based on methodology in the Ph. Eur. Imipramine Hydrochloride parent monograph.

Identification Members noted that all three of the identification tests contained preparation in chloroform and requested that this should be investigated during the monograph review.

Dissolution Members noted that the limit statement should read 'The amount of imipramine hydrochloride released is not less than 70% of the stated amount'.

Related substances Members noted that solution (2) should be 10 times more dilute and solution (3) should be deleted. The Secretariat agreed to address these points.

Assay Members requested that the usual content limits were applied (95.0 – 105.0%). Stakeholders would be asked to submit batch/stability data to maintain the current limits.

VII EUROPEAN PHARMACOPOEIA COMMISSION

Members were directed to log-in to the BP website to view the latest text from the Ph. Eur.

VIII ANY OTHER BUSINESS

No further items were raised for discussion.

Date of Next Meeting
Thursday 25nd February 2016.