

BRITISH PHARMACOPOEIA COMMISSION

Panel of Experts MIC: Microbiology

SUMMARY MINUTES

A meeting of the Panel of Experts was held at 151 Buckingham Palace Road, London, SW1W 9SZ on the 2nd December 2014.

Present: Mr V Fenton-May (Chair), Dr B Matthews, Mr P Hargreaves.

Mr A Hopkins (MHRA Inspectorate) and Mr S Jones (MHRA Licensing Division) both attended the meeting as non-members with relevant specialisms and were invited to contribute.

In attendance: Mr M Whaley.

An apology for absence was received from Prof S Denyer.

Dr P Newby was not in attendance.

1 Introductory Remarks

Welcome The Chair welcomed all present. Due to the infrequency of Panel MIC meetings he invited the attendees to briefly introduce themselves.

Background to the Meeting The Chair explained that the majority of pharmacopoeial microbiology responsibilities of the British Pharmacopoeia Commission had been devolved to the European Pharmacopoeia. This particular meeting had been convened due to the significance of the draft revisions to the chapters on Biological Indicators of Sterilisation (*Ph. Eur. 5.1.2*) and Methods of Preparation of Sterile Products (*Ph. Eur. 5.1.1*).

It was reported that both the current published chapters were perceived to be outdated and not fit for purpose. Both chapters had been undergoing revision since 2009. During this period Group 1, the European Pharmacopoeia group responsible for microbiological methods, had changed Chairs and Mr Fenton-May was currently also the Chair of Group 1.

Chapter 5.1.2 was due to be published in a future edition of *Pharmeuropa* for public consultation. Chapter 5.1.1 was already published in *Pharmeuropa* and public comments were being sought.

The Chair was of the opinion that both the chapters might still be radically changed following consultation but he had convened the meeting so the Panel could discuss and agree on the fundamental aspects of the proposed revisions.

Membership of Group 1 The Panel were informed that the European Pharmacopoeia Working Party on Modern Microbiological Methods (WP MMM) had been merged with Group 1. The UK members of WP MMM (Prof S Denyer and Mr G Marco) had both resigned following the merger of the groups. A new member, Ms Ioana Venet from the Licensing Division of the agency had been successfully nominated by the British Pharmacopoeia Commission as an MMM specialist to Group 1.

Modern Microbiological Methods A member asked whether the comments received during the consultation on the, as yet unpublished, draft revision to the Chapter on Modern Microbiological Methods would overlap with the consultation regarding chapters *5.1.1* and *5.1.2*. The Chair said that whilst the MMM chapter was not directly related to chapters *5.1.1* and *5.1.2* all three chapters were the responsibility of Group 1.

2 **Methods of Preparation of Sterile Products (*Ph. Eur. 5.1.1*)**

A revision to the European Pharmacopoeia Chapter on Methods of Preparation of Sterile Products (5.1.1.) had been published in *Pharmeuropa* 26.4. The views of Panel MIC and EAG PCY experts on the draft text had been sought. The draft chapter had also been circulated to the UK based Pharmaceutical Microbiology Interest Group (Pharmig) for comment.

The consultation period would close on the 31st December 2014 at which point the comments received by the UK would be collated and reviewed for submission to the EDQM. The Panel members were invited to discuss the draft revision and consider the comments received so far.

The Secretariat had circulated comments from a member in advance of the meeting which were used as a basis for the discussions about this draft chapter.

The pre-submitted comments considered that the introduction of a greater emphasis on the application of lethality kinetics into the chapter could lead to a situation where there was a shift from the application of good standards of sterilisation to mathematical modelling and validation, to the detriment of patient safety. It was commented that the new concepts being introduced as models might not be considered as being sufficient and had been applied poorly in some regulatory examples.

A member considered that it was the role of the pharmacopoeia to lay down principles and minimum standards. The pre-submitted comments were talked through by the Panel. The Panel agreed that in addition to the comments received, the BP Panel MIC should also submit comments on the draft chapter.

General Point It was agreed that a comment should be submitted which made it explicit that the choice of sterilisation process conditions should be those that achieve the highest level of sterility assurance compatible with the drug product.

Good Manufacturing Practice It was agreed that the chapter should make reference to good manufacturing practices.

Minimum Standards It was agreed that a comment should be made proposing the inclusion of minimum standards for moist heat terminal sterilisation. The group agreed to submit a comment proposing that cycles below a hold temperature of 110°C with a $F_0 < 8$ minutes should not be considered as sterilising cycles but may be suitable heat treatments to supplement an aseptic process. The F_0 value of a saturated steam sterilisation process is defined by the Pharmacopoeia as the lethality expressed in terms of the equivalent time in minutes at a temperature of 121 °C delivered by the process to the product in its final container with reference to micro-organisms possessing a theoretical Z-value of 10.

As a result of this decision it was agreed that Group 1 should be subsequently asked to revise the definition of F_0 in chapter 5.1.5.

It was also proposed that Group 1 should be asked that the chapter include similar minimum standards for dry heat and ionising radiation methods of terminal sterilisation.

Ionising radiation It was agreed that a comment should be submitted advising that well established standards such as ISO 11137 should be considered when setting minimum standards for terminal sterilisation. A member noted the expertise of the ISO committee responsible for this standard.

Pre-sterilisation Bioburden The Panel endorsed the pre-submitted comment that pre-sterilisation bioburden should be fully included in the chapter.

Steam Sterilisation – Section on Sterilisation Cycle It was noted that not all the relevant steam sterilisation techniques were covered by the draft chapter as written. It was therefore agreed that Group 1 should be asked to expand this chapter to incorporate all relevant technology.

Membrane Filtration The Panel discussed the proposed section on membrane filtration and agreed that a comment should be submitted to suggest the sentence “*Where redundant filters are used to increase the efficacy of the filtration process, the filter closest to the filling point in the final container is characterised as the sterilising filter*” should be amended to read “*Where multiple ~~redundant~~ filters are used to increase the efficacy of the filtration process, the filter closest to the filling point in the final container is characterised as the sterilising filter*”.

Use of Biological Indicators (BIs) The Panel discussed whether BIs should be necessary for validating the use of the reference steam sterilisation cycle (heating at a minimum of 121 °C for 15 min). Whilst it was agreed that the approach of using BIs for every validation could be justified for reference cycles, the Panel agreed that a comment should be submitted to the effect that Group 1 should be asked to amend the draft to indicate that reference cycles for standard products need not be validated with BIs.

3 **Biological Indicators**

MIC(14)01

of Sterilisation (Ph. Eur. 5.1.2)

The Chair introduced the latest draft revision to the European Pharmacopoeia chapter on Biological Indicators of Sterilisation (5.1.2).

Background The Secretariat outlined that an extensive revision to the European Pharmacopoeia chapter on the Biological Indicators of Sterilisation (5.1.2) had been ongoing. The initial reasons given by the EDQM for the revision were that: (1) users believed the chapter provided insufficient guidance; (2) international developments were either not addressed or insufficiently addressed; (3) the chapter showed numerous shortcoming and inconsistencies with Ph. Eur. policy.

A revised chapter had been published for consultation in Pharmeuropa 24.1 just after the publication of a position paper on behalf of Group 1 which set out the principles of the proposed revision.

A large number of comments had been received on the proposed revision in Pharmeuropa 24.1. The EDQM Secretariat had classified the four major concerns raised as: (1) the revision was not suitable for smaller companies; (2) it would be difficult to implement; (3) it was not suitable for all situations; (4) the proposals were impractical.

Following the close of the Pharmeuropa 24.1 consultation period, the matter had been referred to the European Pharmacopoeia Commission. The Commission had agreed that further input should be sought from national competent authorities.

A further survey on the need for the revision of the chapter had been circulated to the member states and the information collected had been considered by Group 1.

Latest Draft The panel discussed the latest draft of the chapter and gave the Chair, in his capacity as Chair to EDQM's Group 1, their comments. The Panel were generally satisfied that the draft was appropriate to be included in a future Pharmeuropa consultation publication.

4. **Test for the Determination of Bactericidal and Yeastidal activity (Ph. Eur. 5.1.11)** MIC(14)03

The Panel were asked to comment on the latest draft of a new general chapter being elaborated by Group 1 of the European Pharmacopoeia dealing with a test for antimicrobial activity of antiseptic products.

A member proposed that Group 1 should be made aware of currently existing tests and standards such as those developed by CEN Technical Committee 216. It was his opinion that developing tests and standards of this nature might be better dealt with by groups with pre-existing experience. The member agreed to provide some further details regarding the work of CEN Technical Committee 216. The Chair confirmed that this work was within the scope of the European Pharmacopoeia.

5. **Efficacy of Antimicrobial Preservation (Ph. Eur. 5.1.3)** MIC(14)04

A question had arisen surrounding the interpretation of the results of the efficacy of antimicrobial preservation test. The question was whether rounding rules could be applied in the interpretation of antimicrobial efficacy log reduction results. A theoretical example, of whether a result which was a log reduction of 1.51 would meet a limit in the preservation efficacy test to demonstrate a log reduction of 2, was used.

Several members were familiar with differences in the interpretation of results of this nature and it was noted that the rounding rules in the General Notices could allow users to interpret results, of the nature used in the example, in ways which were not intended.

The Chair suggested that a request for revision of the General Notices Part III might be appropriate in order to clarify the situation regarding the application of rounding rules to microbiological test results.

6. **European Reports** MIC(14)05

The reports of the most recent meetings of Ph. Eur. Group 1, Working Party BET, Working Party LBP and Group WAT were presented to the Panel.

Water for Injections The Panel discussed the revision of the Water for Injections monograph. The Secretariat informed the Panel that a draft monograph was due to be published in a future edition of Pharmeuropa for consultation and encouraged members to submit their comments.

ACTIONS The Secretariat to circulate the draft revision to the Water for Injections monograph to the Panel for comment as soon as possible.

7. **Next Meeting:**

No further meetings are currently scheduled