490.2 [redacted]

[redacted]

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491 **Alkyl Sulfonate Ester Impurities** COM(21)39

491.1 **Background** Members were provided with a summary of the activities leading to the introduction of Production statements in Ph Eur monographs for mesilate, besilate and tosilate salts and in BP monographs for mesilate substances and products regarding the need for risk assessment to be undertaken to evaluate the potential for alkyl sulfonate ester formation.

A manufacturing failure had occurred in 2008 during which an active substance had been contaminated with ethanol, which had led to the formation of toxic alkyl sulfonate ester impurities. The EP Commission had subsequently established a Working Party on Mesilates which had resulted in the addition of Production statements in relevant Ph Eur monographs. Throughout the development and implementation of the proposals considerable feedback had been received from several interested parties whose position was that such statements were unnecessary, were not supported by evidence and imposed a regulatory burden on the pharmaceutical industry. The UK delegation had carefully reviewed their position but had supported the consensus across the EP Commission and the European Medicines Agency (EMA) that the Production statements were a proportionate means of controlling these impurities and, since this approach did not introduce the need for mandatory testing, did not add to the regulatory burden for manufacturers.

491.2 **Recent correspondence** The Secretariat had received further correspondence and several freedom of information requests relating to the Production statements from Dr David Snodin (consultant) who had provided much of the original feedback and criticism of this subject. His main concerns related to (i) the wording of the Production statements, (ii) whether the statements were justified and (iii) the current lack of guidance from the BP, Ph Eur and EMA on risk assessments. Members were invited to discuss the issues raised and also to review their previous decisions in order to decide whether the BPC position should be maintained or if any changes should be made.

491.3 **Production statement wording** Dr Snodin had stated that use of the term “genotoxic” in the current BP and Ph Eur statements was imprecise and should be replaced by “mutagenic” which was more appropriate and would be in line with ICH guideline M7 (R1) on the “*Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk*”. The Secretariat had received confirmation from an assessor within the Licensing Division that “mutagenic” was a more precise term for alkylating agents and this information had been forwarded to the EDQM for information. Members agreed that the statements in BP monographs should be updated to refer to “mutagenic”. However, in order to avoid the possibility of confusion due to the use of different terminology in the BP and Ph Eur it was agreed that the Secretariat should request that the EPC consider changing the wording in their monographs before any changes were made to BP monographs.

491.4 **Continued use of Production statements** Dr Snodin had restated his original view that the statements were unnecessary since the risk of the impurities forming was extremely low. He had provided mechanistic and kinetic arguments to support his view that there was no need to control a specific alkyl methanesulfonate ester impurity listed in a draft monograph included in the current issue of Pharmeuropa. [redacted]

[redacted] said that the BP had not received any comments from any other individuals or from the pharmaceutical industry on this matter and Licensing colleagues had not reported any issues. [redacted] supported the Production statement approach, since although the risk of the impurities being present was very low, they had been detected in some instances. He said that the statements made it clear that testing was only required if a potential risk of their formation had been identified.

[redacted] was of the opinion was that the BPC should review the continued inclusion of Production statements. He said that if there were data available showing that the impurities were present, he could support the inclusion of a statement but that where there were no data, the statement was not justified. The historical information indicated that alklysulfonate esters might be present in drug substances, but the data were not publicly available and there was no evidence that such impurities were present in drug products. The original incident had been due to Good Manufacturing Practice (GMP) failure and the inclusion of Production statements in BP/EP monographs would not prevent future GMP failures.

[redacted] said that it had always been acknowledged that the risk of alkyl sulfonate ester formation was very low but, since there was a known risk, it had been considered appropriate to address this in a balanced way. As far as he was aware there had been no issues raised by industry and he suggested that the comments around increased regulatory burden could be due to a lack of understanding of the purpose of the Production statements. He said that it might be timely to seek a current view from industry but that no changes were required at the present time.

[redacted] highlighted the importance of data and noted that whilst regulators may not always have full data, they should have sufficient to ensure that appropriate decisions can be made. She noted that Dr Snodin had not provided any new information and that therefore the current risk-based approach remained the best option available. [redacted] said that as a member of an organisation preparing unlicensed medicines the presence of Production statements in active substance monographs had helped to inform the approach for manufacture and testing of the finished products.

[redacted] stressed the importance of maintaining consistency between active substance monographs and product monographs. He said that risk assessments were evaluated during the authorisation process and that the inclusion of Production statements in relevant monographs served a useful purpose. In response to a suggestion that such statements could be moved to the General Monograph on Substances for Pharmaceutical Use, he recommended that they should remain in relevant monographs for greater visibility.

After a wide-ranging discussion it was agreed that other than the proposed change to the wording noted under minute 491.3, no changes to the current approach were required. As it had now been some time since these statements had been introduced it was also agreed that it would be useful to seek a view from industry at a suitable opportunity.

491.5 **Guidance on risk assessment** Dr Snodin had criticised the lack of specific guidance from the BP, the Ph Eur and the EMA regarding what constituted an acceptable risk assessment. It was noted that a letter had been sent to all Marketing Authorisation Holders in 2008 which provided guidance to manufacturers (Letter for MA Holders) and no further action was required at this time.

ACTION (a) The Secretariat to inform Dr Snodin of the Commission's decisions.
(b) The Secretariat to request a revision of the Ph Eur Production statement wording as agreed and, pending a decision at EPC level, amend the wording in affected BP monographs accordingly.

492 [redacted]