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Potential presence of mutagenic alkyl sulfonates in active substances

With the coming into force of the European Pharmacopoeia Supplement 8.7 on 1 April 2016, the last of the five general methods elaborated by the Mesilate Working Party will be implemented in the European Pharmacopoeia (Ph. Eur.):

- 2.5.37 Methyl, ethyl and isopropyl methanesulfonate in methanesulfonic acid
- 2.5.38 Methyl, ethyl and isopropyl methanesulfonate in active substances
- 2.5.39 Methanesulfonyl chloride in methanesulfonic acid
- 2.5.40 Methyl, ethyl and isopropyl toluenesulfonate in active substances
- 2.5.41 Methyl, ethyl and isopropyl benzenesulfonate in active substances [*Suppl. 8.7.]*

Publication of chapter 2.5.41 terminated the work of the Mesilate Working Party. This working party had been appointed by the Ph. Eur. Commission in 2008 to assist users in determining mutagenic impurities potentially present in mesilate-, besilate- or tosilate salts of active substances.

In addition to the elaboration of these methods, the Ph. Eur. Commission had also decided to revise the Production section of monographs on those active substances to further assist users: "*It is considered that [XXX esters] are genotoxic and are potential impurities in [name of the API]. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general method [2.5.XX] is available to assist manufacturers*."

As stated in the General Notices of the Ph. Eur., general chapters (including general methods) are not mandatory *per se*: "*General chapters become mandatory when referred to in a monograph, unless such reference is made in a way that indicates that it is not the intention to make the text referred to mandatory but rather to cite it for information*."

This is the case of these five methods. The purpose of these Production sections is to alert users of the risk related to the potential presence of such mutagenic impurities in mesilate-, besilate- or tosilate salts of active substances. Marketing Authorisation Applicants are not obliged to perform the testing when they can justify via risk assessment that alkyl sulfonates are not expected to be present in their product.

The final decision on the evaluation of the Marketing Authorisation Application and especially whether "*the manufacturing process [has been] developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation*" lies with the Competent Authorities.

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Note for the Editor: Further information is available on the internet site **www.edqm.eu**
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[1]There are thirty-eight members of the European Pharmacopoeia Commission: *Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, the Former Yugoslav Republic of Macedonia, Turkey, Ukraine, United Kingdom and the European Union.*

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