European Medicines Agency
Inspections

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THE FOLLOWING LETTER IS INTENDED FOR ALL MARKETING AUTHORIZATION HOLDERS FOR MEDICINAL PRODUCTS CONTAINING ACTIVE SUBSTANCES IN THE FORM OF MESILATES, (DI)ISETIONATES, TOSILATES OR BESILATES.

REQUEST TO ASSESS THE RISK OF OCCURRENCE OF CONTAMINATION WITH MESILATE ESTERS AND RELATED COMPOUNDS IN PHARMACEUTICALS.

Dear Sirs,

Preclinical studies with certain mesilate esters have revealed that their DNA alkylation action can induce mutagenic, carcinogenic and teratogenic effects. This has been reported for methyl and ethyl mesilate and it is not unreasonable to suspect that similar toxic effects may exist in alkyl esters of other low molecular weight sulfonic acids, e.g. tosilates. Although there are no data showing the toxic effect of such esters in humans, there is nevertheless a potential risk that genotoxic substances as described above may be present as impurities in medicinal products containing active substances in the form of sulfonic acid esters.

For this reason and following the recent case of mesilate ester contamination of Viracept, Competent Authorities requests all Marketing authorization holders concerned to undertake a risk assessment on the occurrence of these impurities in their preparations and to inform Competent Authorities should any risk be detected that requires corrective measures in the manufacture and control of the medicinal product. This risk assessment should also include the procedure regarding the cleaning procedures and the used solvents etc.

Below you will find some information to help you in your risk assessment.

(1) In which preparations can mesilate esters (or alkyl mesilates) occur as impurities?

Alkyl mesilates, e.g. methanesulfonic acid methyl esters (MMS) and methanesulfonic acid ethyl esters (EMS), are esters of methanesulfonic acid with methanol, ethanol, or other lower alcohols. Alkyl mesilates can therefore be found as potential impurities, in particular in active substances that occur as salts of methanesulfonic acid or mesilates or in active substances for which methanesulfonic acid is used in the synthesis.

(2) Are there any other potentially dangerous sulfonic acid ester impurities that can occur in medicines?

The similar alkyl or aryl sulfonic ester contaminations could be found in active substances that are in the form of (di)isetionates, besilates (benzenesulfonic acid esters) and tosilates (toluene-p-sulfonic acid esters). The risk of them occurring should therefore be clarified.

(3) Is there a threshold value for these impurities, under which the risk is negligible? Which limits should be used?

In the absence of other toxicological data the TTC (threshold of toxicological concern) for genotoxic impurities (cf. EMEA guidelines 'Limits for Genotoxic Impurities' EMEA/CHMP/QWP/251334/2006) should be used to set limits.
(Calculating the limits to be applied: 1.5 micrograms divided by the maximum daily dose in grams gives the limit in ppm to be applied to the active substance).

(4) What legislative basis is there for restricting alkyl mesilates in pharmaceutical active substances?

In all monographs for active substances that are present in the form of mesilates and diisetionates the European Pharmacopoeia requires the following safety measures to be applied in the manufacturing process:
„The production method must be evaluated to determine the potential formation of alkyl mesilates (respectively alkyl diisetionates), *which is particularly likely to occur if the reaction medium contains lower alcohols. Where necessary, the production method is validated to demonstrate that alkyl mesilates (respectively alkyl diisetionates) are not detectable in the final product.“*

(5) How can these requirements be put into practice?

The production and storage of the active substances and preparations concerned should be subjected to a risk analysis taking account of the following points (not an exhaustive list) .
• Does the production of the active ingredient involve the use of lower aliphatic alcohols, such as methanol, ethanol, n-propanol, or isopropanol, in the presence of methanesulfonic acid (or isetionic acid, benzolsulfonic acid, paratoluolsulfonic acid) or the corresponding acid chlorides? If so, is the formation of alkyl mesilates or the analogous alkyl besilates and alkyl tosilates minimized and is followed by an efficient purification stage?
Does the cleaning procedures for equipments, particularly those in contact of sulfonic acid reagents involve the use of lower aliphatic alcohols?
• Are appropriate specifications and validated testing methods available to verify the alkyl- or arylsulfonic acid ester impurities in the active substance (at theTTC)?
• Is the quality of the starting materials methanesulfonic acid (benzolsulfonic acid, paratoluolsulfonic acid, isetionic acid) checked for alkyl- or arylsulfonic acid ester impurities (e.g. EMS and MMS in methanesulfonic acid) and the corresponding acid chlorides? Are appropriate specifications and validated testing methods available for this?
• Is it ensured that when using sulfonic acids contaminated with sulfonic acid esters or related compounds as the starting materials for producing the active ingredient the TTC for the potential genotoxic impurities in the active substance is not exceeded? The cumulative risk of various alkyl- or aryl-substituted sulfonic acid ester impurities should be taken into account.
• If a sulfonic acid derivative is used in one of the last stages of synthesis during production of the active substance, this should be included in the risk analysis.
• Is the quality of recycled solvents controlled for the enrichment and carry-over of sulfonic acid ester impurities (e.g. EMS in ethanol, MMS in methanol, IMS in isopropanol)?
• Can the formation of alkyl- or aryl-sulfonic acid esters be excluded during the storage of an active substance that exists in the form of a mesilate, besilate, tosilate or isetionate/diisetionate, or in the related preparation?
• Can the formation of alkyl- or aryl-sulfonic acid esters be excluded during the processing of mesilate, disetionate, besilate or tosilate active substances to make thefinished preparation, e.g. when using alcohols for granulation? Is a sufficiently sensitive method available to detect these impurities in the pharmaceutical dosage form (at the TTC)?

(6) In which cases should the results of the risk analysis carried out under (5) and the related investigations be reported to Competent Authorities **?**

The Marketing Authorization Holder for the finished product is responsible for carrying out the risk analysis.The information necessary for risk assessment should be made available to the Marketing Authorization Holder by the manufacturers involved in the galenic production and in particular by the manufacturers of the active substance.

If there is a related risk that must be controlled by making changes to the production process or by means of specifications, any changes to the marketing authorization that require amendment to the method of manufacture or control of the active substance and/or finished product must be submitted to Competent Authorities using the relevant procedure for assessment..

We hereby request that you provide us by 30 April 2008 a statement that the risk analysis has been carried out and specifying its outcome:

a. no safety risk identified
b. amendment to the manufacturing process/control of active substance and/or finished product has been provided to the Competent Authority by variation to the marketing authorisation.

In the latter case the Marketing Authorization Holder should provide a justified timetable for the submission of the variations(s) needed.
The statement should include a commitment to make the risk analysis available upon request from any Competent Authority.

Yours faithfully,