Antwoorden EDQM op vragen van Zembla en NRC:

Verzonden: woensdag 8 juli 2020 10:56

Question 1: What is the maximum level of 4-chloroaniline (PCA) in paracetamol approved for the European market?

Answer: We assume that your question pertains to the maximum level of PCA in the active pharmaceutical ingredient (API) paracetamol that would be considered acceptable for its use in the production of a medicinal product for the European market. Please note the EDQM doesn't approve medicinal products, this is the responsibility of the European Medicines Agency or EU national licensing authorities, depending on the marketing authorisation procedure.

If present in the API, levels of 4-chloroaniline should be within acceptable thresholds, calculated based on toxicological information available for this compound (according to the European Chemicals Agency (ECHA), PCA is officially recognised as carcinogenic in the EU. According to the annex to the ICH Guideline on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk (ICH M7(R1), the International Agency for Research on Cancer (IARC) has classified PCA as "possibly carcinogenic to humans with adequate evidence of carcinogenicity in animals and inadequate evidence in humans". ICH M7(R1) defines the Acceptable Intake of PCA for pharmaceuticals to be 34 µg/day). Information on the exact levels present in sources of the API paracetamol covered by CEPs is confidential and cannot be disclosed by EDQM, however they should not exceed the above limit.

Question 2: Does the European Pharmacopoeia (Ph. Eur.) provide mandatory safety and quality control for impurities of 4-chloroaniline (PCA) in paracetamol? If this is the case, please explain the safety and quality control procedures required. If this is not the case, please explain why this is not necessary.

Answer:

The European Pharmacopoeia defines mandatory controls for impurities in paracetamol and in general in substances for pharmaceutical use according to applicable European and international standards set for quality and safety. The General Monograph "Substances for Pharmaceutical Use" is applicable to all APIs, regardless of whether they are covered by an individual monograph or not. For those API covered by an individual Ph. Eur. monograph, e.g. paracetamol, the requirements of the General Monograph apply in addition. For example, 4-chloroaniline is not included in the list of impurities in the specific monograph for paracetamol. However, the General Monograph "Substances for pharmaceutical use" describes how controls for the quality and safety of pharmaceutical substances have to be defined, including specific reference to the requirements of ICH M7(R1). The presence of PCA in paracetamol depends on the synthetic process used. If PCA is likely to be present as an impurity in a source of paracetamol, it has to be eliminated or suitably controlled by virtue of the General Monograph "Substances for

Pharmaceutical Use", even if it is not described in the specific monograph for paracetamol.

Question 3: For granting Certificates of suitability (CEP) for paracetamol, which safety and quality control procedures are required for the risk of impurities of 4-chloroaniline (PCA)? In case there are no requirements, please state why this is not necessary.

Answer:

The risk of presence of 4-chloroaniline, like for any possible impurity, in the API is evaluated against applicable requirements for pharmaceutical substances (described in International and European guidelines on quality, e.g. ICH guidelines), based on the synthetic route applied for the production of the active substance. In order to obtain a CEP the active substance has to be in compliance with all current applicable quality standards, including the requirements of the individual monographs and all general monographs into the scope of which the API falls. Therefore if 4-chloroaniline is a potential impurity in a source of paracetamol due to the route of synthesis used, it has to be eliminated or suitably controlled and the manufacturer has to submit this information in the application for a CEP, for assessment.

Question 4: Do the official standards (Ph. Eur. and CEP) require safety and quality control of 4-Chloroaniline (PCA) during all critical stages of the chemical synthesis of paracetamol?

Answer:

As outlined above, the need to control PCA in the API depends on the route of synthesis used. Implementation of routine control of 4-chloroaniline during all critical stages of the synthesis is not a requirement and as mentioned above, 4-chloroaniline is not currently listed in the transparency statement of the Ph. Eur. monograph for paracetamol. However, if 4-chloroaniline is a potential impurity in a source of paracetamol due to the route of synthesis used, specific controls have to be implemented at a suitable stage of the chemical synthesis as needed to ensure that paracetamol does not contain PCA above the level defined in ICH M7(R1).

Question 5: Since when is the synthesis of paracetamol, where chlorobenzene is used at the start of the process instead of phenol, approved by EDQM (or other European authorities)?

Answer:

There are several well-known chemical synthetic routes for the manufacture of paracetamol, not all of them lead to the possible presence of 4-chloroaniline. These routes are readily available in the literature. Information on the manufacturing processes used by individual manufacturers in their CEP applications is confidential and cannot be disclosed by EDQM.