Experts stellen in de uitzending dat de huidige controle op de kankerverwekkende stof PCA in de grondstof van paracetamol onvoldoende is. De Europese eisen aan de fabrikanten zouden strenger moeten zodat er ook de daadwerkelijke vervuiling met PCA vastgesteld kan worden, aldus de deskundigen. Volgens de Nederlandse toezichthouders volstaan de huidige voorschriften. Lees hieronder de reacties van de toezichthouders.

Verzoek wederhoor aan CBG, 27-08-2020

Hoi X,

Dank voor het rapport.

Ik heb nog een vraag over 2.4 'Controle van PCA bij de productie van paracetamol' in jullie rapport.

Jullie schrijven: "De combinatie van de limiet voor onzuiverheid K en de 10 ppm limiet voor onzuiverheid J zorgt er voor dat de ICH limiet voor PCA in paracetamol niet overschreden wordt."

Experts zeggen tegen ons dat deze indirecte controle onvoldoende is om de daadwerkelijk vervuiling met PCA te meten:

"The European pharmacopoeia requires indirect control of the residue of 4-chloroaniline through a stringent test of chloroacetanilide in paracetamol, but any control on 1-chloro-4-nitrobenzene depends on the manufacturer's performance of a test of *N*-(4-chlorophenyl) acetamide in 4-aminophenol. The pharmacopoeia does not require this second test."

Volgens de experts zou deze test in de monografie voor paracetamol moeten worden opgenomen.

Kun je me uiterlijk morgen laten weten wat jullie reactie hierop is?

Groet,
Annette

Reactie CBG, 27-08-2020

Dag Annette,

Ons antwoord hierop:

"Een indirecte controle van PCA in paracetamol door de hoeveelheid chloroacetanilide te bepalen volstaat omdat de laatste stap in elke paracetamol synthese een acetylering is en PCA hierdoor ook omgezet zal worden in chloroacetanilide.

Als extra zekerheid dat deze omzetting van PCA plaatsvindt wordt paracetamol ook nog eens op 4-aminophenol gecontroleerd met een limiet van 50 ppm. Een directe controle van PCA in paracetamol biedt hierdoor geen aanvullende zekerheid.

Groet, X

Verzoek en antwoorden EDQM, 9-7-2020

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.

Verzoek en antwoorden EDQM op 16-7-2020

Question 1: With "initial application dossier" do you refer to the dossier in relation to the CEP that Anqiu Lu'an Pharmaceutical has been granted in 2002 for the paracetamol API?
Yes by initial application we mean the application submitted in 2000 for which the initial CEP was granted in 2002. The data given in the initial application refers to PCA in 4-aminophenol. The levels in paracetamol were estimated based on PCA levels in amino phenol and levels of impurities J and K of the Ph. Eur. monograph.

Question 2: Do I understand correctly that "the levels identified at that time" refer to the levels that are included in the application dossier from the manufacturer? Could you let us know what these levels were?
The data included in the application are confidential and cannot be disclosed.

Question 3: What is the level from which a PCA impurity in paracetamol API is considered 'significantly' below the limits for the Acceptable Intake of 34 µg/day for PCA by EDQM?
In general terms, one would consider a value of up to 30% of the specified limit significantly below the limit.