Zembla en NRC hebben voor onze publicatie op 9 juli 2020 over de aangetroffen vervuiling in paractamol het Chinese grondstofproducent Anqiu Lu'an herhaaldelijk om wederhoor verzocht. Het bedrijf heeft gekozen om geen inhoudelijk antwoord te gegeven. Voor de uitzending van 10 september 2020 hebben we opnieuw om wederhoor verzocht. Het bedrijf liet toen weten dat hun producten aan de norm voldoen. Het volledige wederhoor staat hieronder.

Verzoek wederhoor 7 juli 2020

Dear Sir/Madam,

We have been trying to get in touch with you on our journalistic investigation we are carrying out at the moment. We are happy that our colleague, NRC-correspondent Garrie van Pinxteren, could talk to one of your employees on the phone earlier today. Good to know that the matter has your attention now and that you will look into our e-mails we sent on the 2nd and 5th of July. Please also consider this present e-mail before getting back to us.

In this e-mail we provide you with the findings of our investigation and would like to request a statement from your company.

In collaboration with the Dutch newspaper NRC we are working on a story about impurities in active pharmaceutical ingredients (API's) used in the manufacturing of paracetamol. For our investigation, a certified lab analysed samples of paracetamol API produced by two Chinees API manufacturers, one being your company Anqiu Lu'an Pharmaceutical Co., LTD.
The lab results show contamination of 4-chloroaniline (PCA) in samples of three different batches manufactured at Anqiu Lu'an. The analysis detected PCA levels of 6mg/kg in two samples and 5mg/kg in one samples. The sample from the other Chinees company contained PCA levels of less than 1mg/kg.

According to the ICH Guideline M7, the levels of impurities found in the batches of your company are just below the approved daily intake limits of PCA for paracetamol API intended for the European market.
According to conclusions of the European Food Safety Authority (EFSA) and their used methodology of risk assessment of PCA, this concentration of PCA impurities present in the three samples from your company exceed the acceptable levels with a factor of 20. (Please find more information on the conclusions the following report: EFSA, 2015 Peer review on the review of the approval of the active substance diflubenzuron regarding the metabolite PCA)
Leading toxicologists qualify the results of the analysis of these three batches sourced from Anqiu Lu'an as concerning for the risks PCA poses to the health of patients.
They state that the API of these three batches should not have been used in the manufacturing of paracetamol.

To obtain your statement, we would like to ask you to respond to the following questions:

1. What is your reaction on the findings from the analysis?
2. Does your company test every batch of paracetamol API on possible impurities of PCA? If this is the case, please explain to us in detail what tests and safety procedures are in place to detect impurities of PCA in your paracetamol API products?
3. Has your company provided paracetamol API to the Dutch facility called Apotex based in the city of Leiden and owned by the Indian company Aurobindo?

4. Is it correct that the total volume of three batches of paracetamol API from your company can sum up to a maximum of 18.000 kilogramm? If this is not the case, what is the maximum volume for a batch that you manufacture at a Anqiu Lu'an facility?

Please provide us also with your comment on the following statements:

5. Toxicologist state that API with the contamination of 6mg/kg should not be getting on the market considering the risks of the genotoxic and carcinogenic effects of PCA for human patients.
6. Toxicologists state that there is too little controle of PCA impurities by manufacturers and European inspectorates and the EDQM.
7. When asked about the underlying explanation of such contaminations a toxicologist responded: " The underlying cause is that it is economic gain that counts. There is little controle and inspections, including from Europe."

We are happy to provide you with the results of the lab-analysis together with the Certificate of Analysis from you companiy that accompanied the API from these three specific batches.
Please let us know if you are interested in this information.

Our report on the matter is planned at the end of this week. The article will be published in the newspaper NRC and our online platforms.

In order to process your statement accurately and diligently, please send us your statement within 24 hours, at the latest tomorrow, Tuesday July 7th, before 4 p.m. Central European Time.

Kind regards,

Joep Dohmen NRC
Annette Schaetzle/ Jos van Dongen ZEMBLA

Reactie Anqui Lu'an op 14 juli 2020

Dear Jos,

Thank you very much for your email and sorry for late, unfortunately your emails were spamed by our email system and just today we located your emails.
We noticed your report from market and received EDQM's letter regarding PCA and we are working on investigation and could you provide us the results of the lab-analysis together with Certificate of Analysis from our company that accompanied that API from these three specific batches?

Appreciate your help and Best regards

Anqiu Lu'an Pharmaceutical Co., Ltd.

Verzoek wederhoor 3-09-2020

Dear X,

We have been in contact on an investigation we carried out together with our colleages from the Dutch newspaper NRC. (see e-mails below)

We would like to inform Anqiu Lu'an Pharmaceutical about our upcoming publication. On september 10th, Zembla and NRC will publish further investigations. The story will be on different medicines and APIs in which carcinogenic impurities have been found. We investigate why these impurities have not been detected earlier by the responsible manufacturers and European and national authorities. Experts will state that more testing, structural testing and more independent testing of on market products are necessary to guaranty safe medicines.

In the new publication we will include our earlier findings of our analysis that found PCA impurities in samples of Anqiu Lu'an's paracetamol API. Anqiu Lu'an chose not to respond to our earlier questions and several reminders. What concerns Anqiu Lu'an, no new alligations will be made in the publication.

Please send us an e-mail before tomorrow, 4 september 2020, 5 p.m. (CEST) in case you have additional comments on our ealier questions.

With kind regards,

Annette Schätzle
Journalist | Zembla

Reactie Anqiu Lu'an, 4-09-2020

Dear Annette,

Thank you for email. Upon receipt of PCA claim, we ever emailed to your colleague Jose to ask for the results of the lab-analysis together with Certificate of Analysis from our company that accompanied that API from these three specific batches, and, your colleague Joep reverted to us that since EDQM and the Dutch Medicines Evaluation Board were both looking into the issue, you can not provide us with information that might interfer with their investigation, you handed over the relevant information to the authorities and asked us to contact the authorities sothat they can consider which information can be shared with us. Then we spoke to EDQM to ask for the same, however, EDQM finally come back to us that in order to allow us to confirm further the root cause analysis and the statements made in the media, EDQM requested permission to share the batch number of the samples tested by the investigators with us, however the permission has been denied. Then we had to talk to Apotex to ask for the same, however Apotex confirmed they never provided any samples to any media. And as API manufacturer, we are very clear that there is certain requirement of sampling operation and only samples taken by sampling operation in compliance of the certain requirement can be regarded as representative and meaningful and effective for scientific investigation. Considering all of the above, we did not answer 7 questions mentioned in Jos's email dated 6 July 2020.

Even we failed to get all neccessary information of "our" Paracetamol API claimed by you from you, EDQM and Apotex, we investigated all batches of our Paracetamol supplied to

Apotex in Spring of the year of 2019 according to EDQM's requirement and we passed all analysis/investigation results to EDQM and Dutch Health Inspectorate and Medicines Evaluation Board, nowday, those authorities has finished their investigations and published their investigation results already, trust you must notice those already.

Please note: Pharmaceutical industry sampling should strictly follow drug sampling norms and should be conducted in accordance of EU GMP guidelines to ensure no contamination risk during sampling process, while, analysis methods must be properly validated before using. We would be highly appreciated if you can provide us where and how you took the 3 different batches samples in your claim, the relevant analysis method your dominated lab used and the relevant raw test data before 5:00 pm (Beijing Time) on 7 Sep 2020. Those information is the basis of test result, without which the results are of no reference value.

Look forward to your revert in due course.

Thank you and best regards

Anqiu Lu'an Pharmaceutical Co., Ltd.