



**28 August 2018, Strasbourg, France**

## **Update on EDQM's actions following detection of impurity in valsartan**

The EDQM is continuing the investigations and actions which started in July 2018 to address the issue related to the detection of a nitrosamine (N-nitrosodimethylamine (NDMA)) in a source of active substance valsartan.

Following the complete review of the manufacturing information submitted in all Certificate of suitability (CEP) applications for valsartan and other structurally related active substances (e.g. losartan, olmesartan medoxomil, candesartan cilexetil), the EDQM has firstly contacted those CEP holders whose substances may present a contamination risk and has requested that they investigate and address the possible presence of NDMA. As a second step, all other holders of CEPs for these substances have been requested to evaluate their manufacturing process too and to confirm that their products do not present any risk of contamination.

The EDQM has been assessing the data received and is informing CEP holders by letter as soon as the evaluation of their data is completed. Based on the results, it seems that a limited number of sources of valsartan and other structurally related active substances may present a risk of contamination. Adequate measures and controls are being put in place to ensure the impurity is eliminated or reduced to an acceptable limit.

Following the suspension of the CEP on valsartan held by Zhejiang Huahai Pharmaceutical Co. Ltd, the EDQM ad-hoc committee in charge of taking measures on CEPs has also decided to suspend the following Certificates:

- CEP 2013-159/Valsartan held by Zhejiang Tianyu Pharmaceutical Co. Ltd.
- CEP 2016-069/Valsartan held by Hetero Labs Ltd.
- CEP 2014-162/Valsartan held by Zhejiang Changming Pharmaceutical Co. Ltd.

The decision was either triggered by the detection of some levels of NDMA in valsartan (albeit at much lower levels than those found in the active substance manufactured by the company Zhejiang Huahai), or as a precautionary measure in case insufficient information was received from the CEP holder or in case the CEP holder claimed that their product is not currently supplied to the market. The suspension of these CEPs is intended to reduce risks for the patients in all countries where the CEPs may be referred to, including beyond Europe. The EDQM's international partner authorities and institutions have been informed accordingly.

Since the issue was identified, Official Medicines Control Laboratories (OMCLs) of the General European OMCL Network, which is coordinated by the EDQM, have also been involved in the activities. In the meantime, this Network has developed methods for the specific testing of nitrosamines in sartans on the basis of 2 different analytical principles. It established risk-based sampling plans and provided the first independent test results of batches of valsartan and related medicinal products to European authorities. The Network has also supported European authorities in evaluating the methods used by concerned companies to test their active substances. Experts from the Network are involved in the different discussion groups established in Europe on this topic. Since mid-July 2018 they have been organising meetings with their own testing group via teleconference on a regular basis, in order to allow for scientific exchanges and coordination of sampling and testing activities.

As a way of ensuring that the necessary steps are taken to prevent similar incidents in the future, the EDQM continues to cooperate closely with the European Medicines Agency (EMA) and national and international competent authorities to elucidate the root cause of the contamination. The EDQM will



communicate further on the matter, as soon as more information becomes available. For more information, follow us on [www.edqm.eu](http://www.edqm.eu).

**Background:**

The so-called "Certificate of suitability" (CEP) procedure of the EDQM is one of three possible options that manufacturers can rely on to demonstrate that the quality of their active substance is suitably controlled by the respective monograph of the European Pharmacopoeia and is in compliance with current regulatory requirements. To obtain a certificate, the manufacturer may submit an application to the EDQM describing the manufacturing process and the methods applied for the quality control, including for the control of impurities. The data is assessed by experienced quality assessors nominated by National Competent Authorities and the EDQM. Following a positive conclusion of the assessors, the EDQM grants a CEP. A copy of the CEP can then be used in any Marketing Authorisation Application (MAA) for a medicinal product which includes the active substance from this specific source. Alternatively, the same data can be filed either in an Active Substance Master File (ASMF), to be submitted to each competent authority, or in the active substance part of the quality dossier of the MAA.

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**Note for the Editor:** Further information is available on the internet site <https://www.edqm.eu/>  
The EDQM is a leading organisation that protects public health by enabling development, supporting implementation, and monitoring the application of quality standards for safe medicines and their safe use. Our standards are recognised as a scientific benchmark worldwide. The European Pharmacopoeia is legally binding in member states<sup>1</sup>. Similarly, the EDQM develops guidance and standards in the areas of blood transfusion, organ transplantation and consumer health issues.

<sup>1</sup>There are thirty-nine 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, Republic of Moldova, 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.*

*A political organisation set up in 1949, the Council of Europe works to promote democracy and human rights continent-wide. It also develops common responses to social, cultural and legal challenges in its 47 member states.*