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UPDATE ON THE PH. EUR. POLICY ON ELEMENTAL IMPURITIES

With the implementation of the ICH Q3D guideline on elemental impurities, the control of elemental impurities is undergoing a shift in paradigm, moving away from pure substance-based testing towards a holistic control strategy in the finished product. While these approaches are not contradictory, this change has triggered the revision of numerous texts in the European Pharmacopoeia (Ph. Eur.).

The Ph. Eur. Commission has already communicated its plan for the implementation of this important guideline via a number of press releases (see hyperlinks below). The implementation schedule in the Ph. Eur. has been aligned as closely as possible with the application timelines decided by the Committee for Medicinal Products for Human use (CHMP), i.e. June 2016 for new marketing authorisation applications and December 2017 for all authorised products on the market of the European Economic Area.

Therefore, at its 156th Session in last November, the Ph. Eur. Commission adopted several general texts integrating the new approaches and requirements of the ICH Q3D guideline for elemental impurities into the Ph. Eur. and, in broader terms, into the global regulatory framework. These texts are to be published in Supplement 9.3 with an implementation date of 1st January 2018. The revision plan for general texts was broken down as follows:

- General chapter *5.20 Elemental impurities*: reproduces parts of the Scope and the Introduction sections of the ICH Q3D guideline and refers to the guideline which can be found in full on the ICH website;
- General monograph on *Pharmaceutical preparations (2619)*: refers to chapter *5.20*, rendering it—and by extension the ICH Q3D guideline—legally binding;
- General monograph on *Substances for pharmaceutical use (2034)*: introduces requirements for the control of elemental impurities intentionally added during production and explains the absence of a test for elemental impurities from individual monographs except for special cases (see paragraph on specific tests below);
- General method *2.4.20 Determination of elemental impurities*: provides guidance for aspects of method development such as sample preparation and method validation for the determination of elemental impurities. In addition to this recent revision, this text remains a priority on the work program of the Pharmacopoeial Discussion Group (PDG), the aim being to harmonise the respective general chapters on elemental impurities in the different regions.

The Ph. Eur. Commission has also discussed the fate of specific elemental impurities (individual metal) tests (about 500 of these tests for various elemental impurities are described). Feedback gathered from stakeholders during workshops and conferences held over the past year has been used to help define the best approach to these tests. Consequently, the Ph. Eur. Commission has decided to keep the published specific elemental impurities tests in monographs on substances of natural origin only. Given the intrinsic nature of elemental impurities in these substances, they are amongst the major potential sources of elemental contamination in medicinal products. The Ph. Eur. Commission has also recommended keeping in particular the different tests for elements for which no Permitted Daily Exposure limits have been established, i.e. those identified as “other elements” in the ICH Q3D guideline (such as aluminium and iron), in individual monographs.

Conversely, specific elemental impurities tests will be deleted from monographs on other substances (i.e. not from natural origin), unless otherwise justified. In particular, the Ph. Eur. Commission decided that, unless otherwise justified, specific tests for elemental contaminants originating from the production process will be deleted. As these elemental impurities are specific to the production process, they will remain the responsibility of the substance manufacturer; this is reflected in the new sentence added to the Production section of the general monograph on *Substances for Pharmaceutical Use (2034)*.

The Ph. Eur. Commission and the corresponding groups of experts will continue their work on clearly defining on a case by case basis which monographs are concerned and to what extent they are



impacted by the rationale developed above. The list of concerned monographs will be published in Pharmeuropa for public consultation in due time.

As new data become available, the groups of experts intend to examine opportunities for revision of the set of individual metal tests in monographs in order to align them with newer standards and/or to reflect more closely the actual quality of substances available on the European market. Support from stakeholders will be crucial for the success of this initiative.

For your convenience, previous communications on the Ph. Eur. implementation strategy of the ICH Q3D guideline on elemental impurities can be accessed by clicking on the following links:

Press release from [April 2015](#)

Press release from [August 2015](#)

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Note for the Editor: Further information is available on the internet site 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 world-wide. The European Pharmacopoeia is legally-binding in Member States¹. Similarly, the EDQM develops guidance and standards in the areas of blood transfusion, organ transplantation and consumer health issues.

¹There are thirty-eight 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, 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.*

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