28 April 2015, Strasbourg, France

Ph.Eur. POLICY ON ELEMENTAL IMPURITIES

Background. In preparation for implementation of the ICH Q3D guideline on elemental impurities, the European Pharmacopoeia (Ph. Eur.) Commission endorsed a preliminary implementation strategy at its 149th Session (June 2014) and information on this strategy was communicated in a press release issued on 18 July 2014.

The ICH Q3D guideline on elemental impurities was finally signed-off at the end of 2014 and it was published on the ICH website on 16 December 2014. In the following weeks, the Committee for Medicinal Products for Human use (CHMP) set implementation dates of June 2016 for new marketing authorisation applications and of December 2017 for all existing products on the EU market.

The Ph. Eur. Commission then went on to approve a refined strategy for the different texts impacted by the ICH Q3D guideline at its 151st session (March 2015):

Heavy metals test (chapter 2.4.8). The process of deleting the *Heavy metals* test from individual Ph. Eur. monographs is currently ongoing. A list of the monographs concerned was published for public consultation in Pharmeuropa 27.2 (deadline for comments: 30 June 2015). Given the large number of monographs requiring revision, the final date for deletion of this test from all monographs on substances for pharmaceutical use (except monographs for veterinary use only) will be aligned with the publication of the 9th edition of the Ph. Eur. (i.e. implementation date of 1 January 2017). It should be noted that the absence of the heavy metals test from an individual monograph does not preclude substance manufacturers from controlling the levels of elemental impurities in their products. Control of heavy metals according to method 2.4.8 is still acceptable until ICH Q3D comes into force for a given finished product.

Individual metal tests. The Ph. Eur. individual metal tests for individual synonym class 1, 2A, 2B and 3 elemental impurities (according to the ICH Q3D guideline) will be assessed individually by the responsible Group of Experts. The Ph. Eur. Commission has recommended that, unless otherwise justified, these tests be deleted from monographs once the ICH Q3D guideline comes into force. Conversely, the Ph. Eur. Commission also recommended keeping the different tests for elements with no established Permitted Daily Exposure (PDE) limits, i.e. those identified as "other elements" in the ICH Q3D guideline (e.g. Al and Fe), in individual monographs. Any changes will be made in alignment with the date the ICH Q3D guideline becomes applicable for all products on the market (December 2017).

Chapter 5.20. The *"Metal catalyst or metal reagent residues"* chapter, which is currently a verbatim reproduction of the EMA *Guideline on the specification limits for residues of metal catalysts or metal reagents* , will be replaced by a verbatim copy of the ICH Q3D guideline. This will be done in time for the implementation date applicable for existing products on the EU market (December 2017) and the revised chapter will be published in Supplement 9.3 of the Ph. Eur. (implementation date 1 January 2018).

Additionally, in Supplement 9.3, the Ph. Eur. intends to introduce a cross-reference to revised chapter *5.20.* in the general monograph *Pharmaceutical preparations (2619)* thus making application of the ICH Q3D guideline mandatory for all the medicinal products the latter covers. The revised monograph *Pharmaceutical preparations* (2619) will be published in Pharmeuropa for public enquiry in due time.

Chapter 2.4.20. Currently entitled "*Determination of metal catalyst and metal reagent residues*", this chapter provides additional guidance for aspects of method development such as sample preparation and method validation. At its meeting in June 2014, the Pharmacopoeial Discussion Group (PDG) decided to harmonise their respective general chapters on elemental impurities. Harmonisation of chapter 2.4.20 is currently being discussed and the Ph. Eur. Commission may need to revise chapter 2.4.20 to align its title and content with the ICH guideline Q3D, if the harmonised PDG chapter has not yet been published.

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Note for the Editor: Further information is available on the internet site **www.edqm.eu**
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[1]There are now thirty-eight members of the European Pharmacopoeia Commission: *Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, the former Yugoslav Republic of Macedonia, Turkey, Ukraine, United Kingdom and the European Union.* There are twenty-seven observers: *Albania, Algeria, Argentina, Armenia, Australia, Azerbaijan, Brazil, Canada, China, Georgia, Israel, Madagascar, Malaysia, Moldova, Morocco, Republic of Belarus, Republic of Guinea, Republic of Kazakhstan, Republic of Singapore, the Russian Federation, Senegal, South Africa, Syria, Tunisia, United States of America, the Taiwan Food and Drug Administration (TFDA) and the World Health Organization (WHO)*.

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