EDQM Makes Ph. Eur. Chapter, Method, and Monograph Revisions, CEP Clarifications, as ICH Q3D Implementation Deadline Nears

The July 2017 publishing by the European Pharmacopeia (Ph. Eur.) of revisions to its general chapter, method, and monograph sections is the latest development in the effort by the pharmacopeia to align its coverage of elemental impurities (EI) with the implementation of the International Conference on Harmonization (ICH) Q3D guideline.

The ICH Q3D implementation effort by the European Directorate for the Quality of Medicines (EDQM), which overseas Ph. Eur., has also included clarifying the impact on the expectations for the Certificates of Suitability (CEPs) it issues. CEPs are used by drug substance manufacturers as evidence that their substances are suitably controlled in accord with the relevant Ph. Eur. monographs, and the certificates are included in a marketing authorization application (MAA) by drug manufacturers in lieu of detailed substance CMC descriptions.

In January 2017, the EDQM explained that the control of EIs was undergoing a shift in paradigm – moving away from pure substance-based testing towards a holistic control strategy for finished products. The change triggered the revision of numerous texts in the Ph. Eur.

The publication in July of elemental impurity updates in the third supplement of the ninth edition of the Ph. Eur. (9.3) is seen as one of the final steps in the evolution from no guidelines for safety limits of elemental impurities prior to 2008, through EMA’s 2013 guideline on specification limits for residues of metal catalysts or metal reagents, to the development and final full implementation of ICH Q3D on January 1, 2018.

EDQM issued a “policy guidance” in August 2016 to help companies understand and implement ICH Q3D EI reporting requirements in CEP submissions. The policy guidance, in turn, was reflected in the July 2017 Ph. Eur. changes.

EDQM Webinar Helps to Explain Changes

To help explain the impact of ICH Q3D implementation on the European Pharmacopeia and CEP assessments, EDQM held a webinar in late January 2017 hosted by two key EDQM scientific officers, Bruno Spieldenner from Ph. Eur. and Lennart Seidler from EDQM’s substance certification division.

Spieldenner led off the webinar with an overview of the evolution of EIs in Ph. Eur.

He explained that in 2008, a non-specific heavy metals test method with limits of 10 to 20 ppm lead was replaced with method 2.4.20 for the determination of EIs. Although 2.4.20 provided a more flexible method and included validation parameters to be used in testing for EIs, it was further revised in July 2017 to include a risk management approach for EI testing and control more closely aligned with ICH Q3D.

Spieldenner pointed out that Ph. Eur. communicated early on that the pharmacopeia would align with the EMA timelines for implementing Q3D of June 2016 for new product marketing authorizations or established active substances, and December 2017 for all European marketed products.

Spieldenner then provided an overview of historical Ph. Eur. ICH Q3D announcements, including: ● a July 2014 Ph. Eur. strategy for EIs and implementation of ICH Q3D ● an April 2015 Ph. Eur. policy on EIs and timelines
for revision of general and individual texts ● an August 2015 clarification for products outside of the scope of ICH Q3D and ● the January 2017 update on the Ph. Eur. implementation strategy.

The hierarchy of the European Pharmacopeia, he explained, consists of general notices, general chapters containing both general methods and general text, general monographs, which are specific to dosage forms or groups of products, and individual monographs.

### July Ph. Eur. Changes Regarding Elemental Impurities

| Following is a summary of the EI changes provided for in Ph. Eur. Supplement 9.3, published in July 2017. The changes are effective January 1, 2018. The summary is based on Spieldenner’s preview of the changes at the January webinar. |

**General chapter 5.20 on elemental impurities:** Revisions to general chapter 5.20 to replace reference to the EMA guideline on specification limits for residues of metal catalysts and metal reagents with the basic principles of the ICH Q3D Guideline.

**General method 2.4.20 on determination of elemental impurities:** ● Step 1) Alignment of the terminology with the ICH Q3D Guideline – from “metal catalyst and metal reagent residues” to “elemental impurities” ● Step 2) Ongoing harmonization of general methods in the Ph. Eur., USP and JP.

**General monograph 2034 on substances for pharmaceutical use:** ● Step 1) Control of elements intentionally added as defined by the statement ‘the identity of the elemental impurities derived from intentionally added catalysts and reagents is known and strategies for controlling them should be established by using the principles of risk management’ ● Step 2) Deletion of references to the heavy metals test (2.4.8) inclusion of an explanation for the absence of the test.

**General monographs 2619 on pharmaceutical preparations:** Inclusion of a cross reference to general text in chapter 5.20, thus rendering the principles of the ICH Q3D guideline legally binding for pharmaceutical preparations falling within its scope.

### Strategy for Individual Monographs in Focus

Spieldenner stressed that “for pharmaceutical preparations outside the scope of general chapter 5.20, manufacturers of these products remain responsible for controlling the levels of EIs using the principles of risk management.”

He commented on the concern expressed by some stakeholders in products out of scope of 5.20 that the EI revisions in monographs 2034 and 2619, which address pharmaceutical substances and preparations, respectively, would introduce additional requirements for them. He pointed out that ICH Q3D is not all inclusive – not covering, for example, vaccines and veterinary products. He added that a risk management strategy, in line with GMPs, should be in place for substances not covered by Q3D.

**The final layer of Q3D implementation is:** ● the removal of heavy metal tests 2.4.8 from individual monographs, except those for veterinary use only, and ● the development of a strategy for how to address specific metal tests found in individual monographs.

According to Spieldenner, heavy metal requirements were found in, and will be removed from, 43% of individual monographs (754). However, the absence of the heavy metal test from an individual monograph does not preclude substance manufacturers from controlling the levels of EIs in their products.

Spieldenner concluded by noting that about 300 monographs currently include more than 450 specific metals tests. To address how to handle these individual tests, four classes of testing were identified followed by development of a strategy for each class that justified whether to keep or remove specific tests from the individual monographs.

The next step will be to determine what specific metal tests can be eliminated. Then, for specific tests that remain, work will be done to acquire data to support the tests and specification limits.
EDQM Clarifies CEP Impact

Lennart Seidler then led the audience through the impact of ICH Q3D implementation on the certification process. After commenting on the new CEP policy published in August of 2016, Seidler discussed the two different EI reporting options for applicants and CEP holders:

- Option 1 – the “preferred option” – is for the applicant or CEP holder to provide an EI risk management summary (RMS) performed at the drug substance or excipient level.
- Option 2 is not to include an EI RMS in the CEP, but instead for a pharmaceutical company to provide EI data at the stage of the drug product.

A major benefit of including the risk assessment at the component level is that EDQM only has to perform a component’s EI assessment once, Seidler pointed out.

EIs Among Top 4 Ph. Eur. Priorities

At an international stakeholder conference held by EDQM in Tallinn, Estonia in the latter part of 2016, Director Susanne Keitel highlighted the control of elemental impurities as among the top four current EDQM priorities.

The other three priorities are:

- pharmacopeial standards for biotherapeutic products
- new technologies and their potential impact on monographs
- excipients, other components and international harmonization.

The conference brought together experts from EDQM and other pharmacopeias, regulatory agencies, industry and academia to discuss the pressing regulatory and standards-setting challenges for the quality of medicines globally and the role of the pharmacopoeia in helping solve them.

The plenary session included presentations by:
- EMA Executive Director Guido Rasi on the most prominent issues and developments that EMA is engaged with
- Paul-Erlich-Institute President Klaus Cichutek on the role played by the European Heads of Medicines Agencies (HMA), the concerns it is now engaged with, and how that role and those concerns intersect with EDQM – Cichutek chairs HMA’s Management Group
- Swissmedic’s Petra Dorr on the progress that has made in advancing international cooperation and harmonization, and the organizations driving it, and
- Keitel, who provided an update on the top challenges facing the European Pharmacopoeia in its efforts to advance medicinal quality.

Breakout workshops followed at the conference to explore the pharmacopeial challenges highlighted by Keitel. They brought together an impressive array of top experts from the international regulatory community to address.

The workshop on the control of elemental impurities included presentations by the former chair of the Q3D Expert Working Group, Mark Schweitzer (Novartis), and two presentations on the impact on users – by GSK’s Mike James, who represented the European Federation of Pharmaceutical Industries and Associations (EFPIA) in providing the perspective of the finished dosage product manufacturer, and by Colorcon’s Dave Schoneker, who presented the perspective of an excipient manufacturer and addressed EI issues that IPEC has been actively engaged with on the international level.

[A full review of the insights offered by Spieldenner and Seidler during the webinar and by Keitel at the Tallinn conference will be provided in IPQ’s upcoming Monthly Update. By special arrangement with IPEC, excipient suppliers who are members can receive a company-wide license for the normal price of the subscription for an individual user. The license allows everyone in a company to access all of IPQ’s coverage of the key drug/biotech CMC and GMP issues globally and the full searchable archives. Contact Wayne Rhodes (rhodes@IPQPubs.com, (202) 841-9720) for more information. IPQ will be providing in-depth coverage of a key excipient regulatory issue in each of its Monthly Updates, with an excerpt included in IPEC’s Insider.]
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