**EFPIA responses to EDQM proposed texts published in Pharmeuropa 32.2 for plastics**

1. 2.4.35. EXTRACTABLE ELEMENTS IN PLASTIC MATERIALS FOR PHARMACEUTICAL USE

Reference PA/PH/Exp. 16/T (19) 22 ANP

1. 3.1.16. CYCLO-OLEFIN POLYMERS

Reference PA/PH/Exp. 16/T (16) 15 ANP

1. 3.1.17. CYCLO-OLEFIN COPOLYMERS

Reference PA/PH/Exp. 16/T (19) 17 ANP

**** Date:26/06/2020 **** Version:Final

# General Comments

EFPIA would like to submit the following comments on the proposed new general chapters Ph.Eur. 2.4.35, 3.1.16 and 3.1.17 for consideration by EDQM.

EFPIA is concerned that the new general chapter 2.4.35 is not aligned with the ICH Q3D Guideline. The risk- based approach and consideration of applicable limits in ICH Q3D should be applied in the development of this chapter.

Packaging materials were considered during the development of ICH Q3D and we understand the Expert Working Group considered these to be of very low risk with respect to the potential for elemental contamination to products and risk to the health of patients. This new chapter implies there is a significant risk and uses inappropriate methodology to evaluate the risk of leachable elemental impurities. A water extraction approach would be more appropriate to evaluate the potential for leachable elemental impurities than the aggressive extraction procedure described in the proposed new chapter.

EFPIA believes chapter 2.4.35 requires significant revision before inclusion in the Ph.Eur. EFPIA recognises the scientific work underpinning development of this chapter but suggests it would be better presented as a Scientific Note rather as a chapter in the Ph.Eur.

EFPIA would support the development of chapter 2.4.35 as a suitable analytical procedure to assess elemental impurities that might leach from plastic materials using a realistic aqueous medium and protocol, but without limits for such impurities. EFPIA believes that such an approach could be helpful to the users of the pharmacopoeia and consistent with ICH Q3D.

With respect to the new texts on Cyclo-olefin polymers and copolymers EFPIA appreciates the need for these two chapters but believes the sections on extractable elemental impurities should be removed because they are not consistent with ICH Q3D. EFPIA believes a simple cross reference to Ph.Eur. chapter 2.4.20 and ICH Q3D (or a revised 2.4.35 as described above) would be sufficient in these texts.

# Detailed Comments

The origin of the limits set for the elemental impurities in both these polymer specific chapters and the general chapter 2.4.35 is unclear and appear to be set based on data gathered rather through testing of unspecified materials as opposed to being established based on safety data. It is unclear as to the rationale for taking such an approach; it appears to be inconsistent with the principles defined within ICH Q3D which defines limits based on safety. Furthermore, the limits described within ICH Q3D relate to the final drug product and Q3D expressly states that limits are not required for individual components unless critical to control of the quality of the final product. An extensive review performed by Jenke et al. (Ref.1) found no evidence to support the assertion that polymers represent a significant risk

Even taking the lowest assigned ICH Q3D Option 1 limits for each element, based on a daily dose of 10 g of material, the limits in these chapters vary from a factor of 8 to a factor of 50 below the ICH Q3D limits. The need for such low limits is unclear.

It is unclear how to correlate the proposed limits to drug product risk. Even if present at the levels defined there is no evidence this would correlate with a risk in the final product.

There are also concerns over the method of extraction. The conditions applied are very aggressive and thus highly unlikely to represent the exposure in actual use of these materials in finished medicinal products. Furthermore, the conditions do not correlate with any defined accepted extraction protocol.

Limits for elemental impurities in ICH Q3D are differentiated based on the route of administration of the medicinal product. Introducing these limits for plastic materials does not seem to take this consideration into account, in particular as elements requiring evaluation vary depending on the route of administration. The approach with these chapters fails to take this into account.

The very low limits that have been assigned in the text appear to be based on data gathered on samples of plastic materials typically used in Europe.  These may not be representative of material from other global suppliers, and since Ph.Eur. is used by many regulators outside of Europe as reference for compliance there could be unforeseen consequences affecting the availability of products outside of Europe.

ICH Q3D allows use of both ICP-MS and ICP-OES techniques; ICP-OES is potentially a less expensive technique that could be more acceptable to some users of the pharmacopoeia and achieve the same goal.

# Specific comments for the proposed new chapter 2.4.35

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| **Section** | **Current text** | **Suggested text** | **Rationale for Comments** |
| Table 2.4.35.-2 | Limit (mg/L) | Concentration (mg/kg) | The concentration (limits) is the chapter are unclear. We suggest the procedure is revised as a test for leachables and, if necessary, guidance provided to relate the results to the the potential for elemental impurities to be present in the finished medicinal product. |
| Table 2.4.35.-3 | Acceptance criteria for precision: Repeatability 20% RSD  Intermediate precision 32% RSD | Acceptance criteria for  Intermediate precision 25% RSD | EFPIA notes that the suggested acceptance criteria for Intermediate precision is not aligned with Ph.Eur. 2.4.20. |

**Reference**

1. Materials in Manufacturing and Packaging Systems as Sources of Elemental Impurities in Packaged Drug Products: A literature review. Dennis R. Jenke, Cheryl L. M. Stults, Diane M. Paskiet, et al. PDA J Pharm Sci and Tech 2015, 69 1-48