PHARMACY AND POISONS BOARD OF HONG KONG

Requirement of Elemental Impurities Levels/Limits in Registered Pharmaceutical Products

Background

Under the Pharmacy and Poisons Ordinance (Cap. 138) and its Regulations (Cap. 138A), pharmaceutical products should meet the criteria of safety, efficacy and quality, and be registered with the Pharmacy and Poisons Board before they can be sold in Hong Kong.

2. Elemental impurities may present in drug products and arise from several sources; they may be residual catalysts that were added intentionally in synthesis or may be present as impurities in raw materials, etc. As elemental impurities may pose toxicological concerns and do not provide any therapeutic benefit to the patient, their levels in the drug product should not exceed designated safety level.

3. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) updated the Guideline for Elemental Impurities (ICH Q3D) stipulating qualitative and quantitative limits on different classes (i.e., 1, 2A, 2B and 3 depending on the harmfulness to human and likelihood of occurrence) of elemental impurities in drug products. Among them, the Class 1 elemental impurities (i.e., arsenic, cadmium, mercury and lead) are considered as the most high risk human toxicants that have limited or no use in the manufacture of pharmaceuticals. The ICH Q3D established the permitted daily exposure (PDE) of individual elemental impurity which is determined according to the toxicity of the elements and the route of exposure.

Level of Elemental Impurities in Registered Pharmaceutical Products

4. To ensure the safety and quality of registered pharmaceutical products in terms of the level of elemental impurities, the Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances : Certification of Clinical Trial / Medicinal Test) Committee (the Committee) decided that, **with effect from 1 October 2019**, if a registered pharmaceutical product is found to contain and exceed the PDE level of any of the four high risk Class 1 elemental impurities (i.e., arsenic, cadmium, mercury or lead) as specified by the ICH Q3D (**Table 1**), the registration certificate holder is required to provide remedial measures[1] or justifications[2] (if any) to the Drug Office for assessment. If the

[1] Remedial measures should include, but not limited to, recall the product from market, and subsequently the product manufacturer should conduct risk assessment in accordance to ICH Q3D, include the control of relevant elemental impurity in the specification, take appropriate manufacturing changes to effectively address the potential safety concerns, etc.

[2] According to ICH Q3D, levels of elemental impurity higher than the established PDE may be acceptable in certain cases. These cases could include, but not limited to, the following situations: (i) intermittent dosing; (ii) short term dosing (i.e. 30 days or less); or (iii) specific indications (e.g. life-threatening diseases, unmet medical needs, etc.).

remedial measures or justifications are found to be unsatisfactory, the case would be brought up to the Committee for consideration; and the concerned pharmaceutical product may subject to deregistration, suspension of registration for a specified period of time, or a warning letter will be issued to the registration certificate holder in accordance with Regulation 36(8) of the Pharmacy and Poisons Regulations (Cap. 138A) if the Committee considers it to be in the public interest to do so.

Table 1: Permitted Daily Exposure (PDE) for High Risk Class 1 Elemental Impurities

Element	Oral PDE μg/day	Parenteral PDE μg/day	Inhalation PDE μg/day
Cadmium (Cd)	5	2	3
Lead (Pb)	5	5	5
Arsenic (As)	15	15	2
Mercury (Hg)	30	3	1

Reference: ICH Q3D (R1)

5. The Committee required new applications for registration of pharmaceutical products containing new chemical or biological entities (NCE) received **on and after 1 January 2020** shall submit the manufacturer's risk assessment and evidence to demonstrate the compliance with ICH Q3D requirements on the 24 elemental impurities, or unless otherwise justified. For other registered pharmaceutical products, manufacturers are advised to conduct risk assessment of elemental impurities on their own if they consider there is substantial risk of introducing elemental impurities in the manufacturing process. For new applications of non-NCE products (i.e. generics), if any substance is known to contain Class 1 elemental impurity which may be intentionally-added during the manufacturing process, applicants shall provide the details together with a testing report of Class 1 elemental impurities[3] or manufacturer's risk assessment[4] to demonstrate the risk has been mitigated.

6. The PDE levels referenced from ICH Q3D are subject to revision and updates. In case any discrepancies or inconsistencies of PDE levels between Table 1 and ICH Q3D, the latest version of ICH Q3D shall prevail.

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[3] The method of detection should be precise and based on recommendations in reputable pharmacopeias stated in paragraph 6.2.9 of < Guidance Notes on Registration of Pharmaceutical Products/Substances>.

[4] The risk assessment report should be reviewed by a drug regulatory authority of reference country stated in paragraph 3.1.1 of < Guidance Notes on Registration of Pharmaceutical Products Containing a New Chemical or Biological Entity>.