



26 February 2015  
EMA/CHMP/QWP/109127/2015  
Committee for Medicinal Products for Human use (CHMP)

## Elemental impurities in marketed products. Recommendations for implementation

Products should comply with the ICH/CHMP Guideline for Elemental Impurities under the following timeframe:

Product	Should comply with Guideline from:
New Marketing authorisation for new product (containing new active substance)	June 2016
New Marketing authorisation for product containing an established active substance	June 2016
Marketed products including new mutual recognition applications of already approved products	December 2017

### Reminder

#### 1. Classification

Following classes of elemental impurities are defined:

- Class 1: elements with high toxicity by all routes of administration; possible from different sources
- Class 2: elements with route dependent toxicity:
  - A: possible from different sources; and
  - B: less likely unless intentionally added to the manufacturing process.
- Class 3: elements with low toxic potential by the oral route



2. The guideline covers elemental impurities from all possible sources (including equipment), since toxicity is independent of the source of an impurity. To ensure control for elements likely to be present at a safe level the guideline describes the principles of a risk-based approach to be followed.

## Implementation for existing marketed products

In order to have a common approach among National Competent Authorities and to avoid an unnecessary workload due to a lot of variations, the following proposals below are made.

1. Each national authority should notify to the MAH in its own country about this new guideline according to its national information procedure.
2. During the transition period the MAH should perform a risk assessment of the manufacture of the medicinal product covering all potential sources such as active substance starting materials, reagents, catalysts, process water, excipients, equipment, container closure materials etc. It is envisaged that parts of this risk analysis may be common for several products while others may be product specific. The risk assessment should form the basis for a control strategy that is able to ensure compliance with the Permitted Daily Exposures (PDE:s) given in the guideline for each element. In the guideline it is indicated by the classification which elements should be included in the risk assessment based on the circumstances. Whether additional controls or actions will be necessary is dependent on the outcome of the risk assessment.
  - 2.1. In all cases a thorough risk assessment should be performed and documented. It should be available for inspection.
  - 2.2. No variation is necessary if the outcome of the risk assessment is that, in order to comply:
    - 2.2.1 No further controls on elemental impurities to materials such as the designated active substance starting material, synthesis intermediates, active substance, excipients or the finished product are needed.
    - 2.2.2 No replacement or change of quality of materials such as the designated active substance starting material, synthesis intermediates, active substance, excipients or of the manufacturing equipment is needed.
    - 2.2.3 No change of the manufacturing process is needed.
  - 2.3. In other cases a variation is needed. It should be categorised according the Variation Guidelines (Official Journal 2013/C 223/01) and accompanied with the documentation required there. In addition, the variation should contain a short summary of the risk assessment and the conclusions drawn.
3. Where a control of an elemental impurity is warranted, an elemental specific method is requested by the guideline. Therefore, a non-specific compendial test for heavy metals will not be accepted.