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Metal Residue: How Much is Too Much?

To comply with evolving guidelines, drug makers will need analytical and regulatory support

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Contamination of medicinal products with heavy metals may arise from metals deliberately added as catalysts or reagents. Natural occurrence in source materials or processing equipment including vessels, pipes or metal connections to tubes or hoses may be further causes for metal residues. The presence of heavy metals may exert toxicological effects and therefore should be excluded or limited to an acceptable threshold. For many existing substances, approved specifications are provided by the pharmacopoeias in various regions of the world. The following compares current requirements for pharmaceutical substances (APIs, excipients and process chemicals) and describe new guidelines such as those from USP that will take effect in 2014.

Metals in medicinal products or human nutrition can be beneficial or problematic: On one hand, they are used directly as active substances in drug products to exert a beneficial effect, or they are necessary as minerals or trace elements. Many products on the market used as dietary supplements contain trace elements like iron, copper, zinc, selenium, manganese, chromium, molybdenum or other. Many of these metals are essential as parts of enzymes, vitamins or cofactors. Supplementation of minerals or trace elements is needed when dietary intake is deficient and may be beneficial for compensation of deficiencies.

Metals used in drug substances still have importance in modern drug therapy. For example platin compounds (cisplatin, carboplatin) are administered as highly potent anticancer drugs. Aluminum is widely used in antacids; iron is used for treatment or prevention of iron deficiency and anemia; zinc is part of insulin zinc suspensions; cobalt is part of vitamin B12; gold compounds were shown to be efficacious as anti-rheumatoid drugs.

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On the other hand, metals in medicinal products may also be present as impurities. Contamination may arise from metals deliberately added as catalysts or reagents. Natural occurrence in source materials (e.g., in minerals or herbals) or processing equipment like vessels, pipes or metal connections to tubes or hoses may be further causes for metal residues. As contaminants, these metals may exert toxicological effects and therefore they should be excluded or limited to an acceptable threshold.

NO THERAPEUTIC BENEFIT

Since there is no therapeutic benefit from metal residues in pharmaceutical products unless administered therapeutically, they should be removed to the extent possible to meet product specifications, good manufacturing practices or other quality-based criteria.

For many existing substances, approved specifications are provided by the pharmacopoeias in each region, such as the European Pharmacopoeia, United States Pharmacopeia and the Japanese Pharmacopoeia. Further, the International Conference on Harmonization (ICH) has published a concept paper (Q3D: Impurities: Guideline for Metal Impurities) on the development of a guideline which would harmonize the limits of metal impurities in the three large economic areas Europe, United States and Japan.

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Impurities typically arise from the manufacturing process or from degradation of the substance (Figure 1). An impurity in a drug substance as defined by the guideline ICH Q3A(R2) is any component of the drug substance that is not the chemical entity defined as the drug substance. Quite similar is the definition for an impurity in a drug product. It is any component of the new drug product that is not the drug substance or an excipient in the drug product (ICH Q3B). The impurities which are already controlled in the drug substance need not be monitored or specified in the drug product again, unless they are also degradation products (ICH Q6A).

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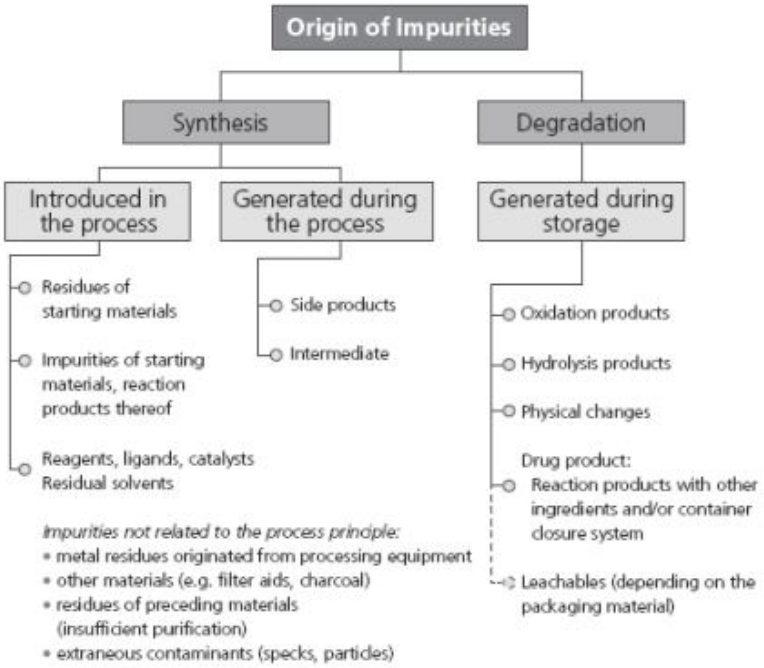

Figure 1. Origins of impurities in chemical substances.

EMA GUIDELINES

EMA guidelines on specification limits for residues of metal catalysts and reagents were put into place in 2008. The guidelines define maximum acceptable concentrations limits for metal residues arising from the use of metal catalysts or metal reagents in the synthesis of pharmaceutical substances. The objective of the guidelines is to control residues from metals added intentionally.

For products that were already on the market when the new guidelines were enacted, the drug product manufacturer had five years to address. This transition period will end September 1, 2013.

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According to the guideline, limits should be provided for metals which are likely to be present due to introduction into the manufacturing process as metal catalyst or metal reagent. What is not in the scope of the EMA guidelines are metals introduced through raw materials, metals arising from interaction with processing equipment, metals added inadvertently or by the environment and packaging materials. The guidelines indicate that these so-called “extraneous metal contaminants” are more appropriately addressed by GMP, GDP or other relevant quality provision.

Thus, only process-related metal residues are in the scope of the guideline to control the sufficient removal of the pharmaceutical substance. Pharmaceutical companies do not need to perform extensive tests on metal residue findings of unknown sources to comply with the guideline. In these cases, companies typically rely on general information from trusted suppliers.

There are four conditions for a metal to be in the scope of this guideline:

1) The metal has to be used in the manufacturing process as catalyst or reagent (regardless of the speciation or form of the element
2) It is likely to be present in the pharmaceutical substance
3) It is not a deliberate component of the pharmaceutical substance
4) It is among the metals of the guideline (see below)

The term “pharmaceutical substances” is defined as a substance that is either an active pharmaceutical ingredient or an excipient. The guideline refers also to metals used in the synthesis of any of the pharmaceutical excipients used during the manufacture of the drug product, but no longer present in the drug product itself and includes 14 metals which are divided in three classes:

Class 1 metals are considered to be metals of significant safety concern. This group includes metals that are known or suspect human carcinogens, or possible causative agents of other significant toxicity. Class 1 is further divided into three subclasses 1A, 1B, and 1C. The subclasses 1A and 1B cover highly toxic or carcinogenic metals. For subclass 1B a group limit is applied, the total amount of listed metals should not exceed the indicated limit.

Class 2 metals are metals of low safety concern. This group includes metals with lower toxic potential to man. They are generally well tolerated up to exposures that are typically encountered with administration of medicinal products. They may be trace metals required for nutritional purposes or they are often present in food stuffs or readily available nutritional supplements.

Class 3 metals represent a minimal safety concern. This group includes metals with no significant toxicity. Their safety profile is well established. They are generally well tolerated up to doses that are well beyond doses typically encountered with the administration of medicinal products. Typically they are ubiquitous in the environment.

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