Elemental analysis and Heavy metals



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ABSTRACT

"Heavy metal residues in pharmaceutical products

In accordance with the monographs of the European and US Pharmacopoeias (Ph. Eur.; USP), for reasons of patient safety, the heavy metals in pharmaceutical finished products and raw materials must not exceed the specified limit values and must be tested for that. Heavy metals can be introduced into the product by catalysts, synthesis reagents and even by the manufacturing process itself.

In the manufacturing of pharmaceutical products, catalysts containing heavy metals are often involved in the synthesis. Heavy metals can also transfer into the process by abrasion or by leaching (e.g. Fe, Ti, Cu, Cr and so on.) If they are not removed efficiently, then the tainted products could get into the market.

Legal regulations

For many years, it has been known that certain heavy metals exhibit toxic effects even at low concentrations. As a result, limit values for the protection of the patients have been defined in the legislation and in the various pharmacopoeias (e.g. Ph. Eur., USP, JP, BP).

Detection methods

If testing is not performed for a specific heavy metal, the most common source of evidence nowadays come from a limit test being carried out. After treatment, the heavy metal is complexed with thioacetamide or precipitated as a sulphide. Then, one compares the resulting colouring of the sample solution against that from a reference lead solution.

These limit tests still form the majority of testing for heavy metals in the current national and international Pharmacopoeias (e.g. Ph. Eur. 2.4.8 or USP <231>). Thereby, it is possible however to make only a semi-quantitative statement about the total contents of heavy metals in the sample, and in addition - and additionally, only for those heavy metals that actually form dark coloured complexes or sulphides.

Spectroscopic tests are to be found only in individual monographs and methods (e.g. nickel in polyols and oils, lead in sugar) to date. There is no sign of any changes in the near future with regard to the methods in the Ph. Eur. and JP. This is in contrast to the US Pharmacopoeia.

New testing standards in the US Pharmacopoeia (USP)

From May 2014, chapters <232> <<Elemental Impurities – Limits>> and <233> <<Elemental Impurities – Procedures>> completely replace the old heavy metals test and are valid for all monographed drugs. Chapter <232> serves the purpose of defining the allowable limit values for 15 individual heavy metals in all pharmaceutical products. For excipients and active ingredients, these limit values are only valid when they are referred to explicitly in a monograph.

Which elemental impurities are to be analysed

The USP lists limit values for 15 heavy metals. It should be observed that it is not always necessary to investigate all of these. After a risk-based estimation, determination is restricted to those elements which could unintentionally end up in the end product either through natural methods, or by being added (e.g. catalysts). Excluded from this are the so-called “bad 4”, arsenic, lead, cadmium and mercury which must always be integrated into the risk evaluation.

Standard limits for all formulations have been defined for excipients and active ingredients in pharmaceutical products whose daily dose exceeds 10g per day.

Important: To comply with GMP, all methods must be validated in a product-specific manner.

Biography

Muhammad Jehangir has 14 years diversified experience of Quality Control, Quality Assurance, Registration Affairs, Product development and Pharmaceutical manufacturing, Process Planning, Method development, Method validation, Statistical Methodology, Process & Cleaning Validation, and Equipment Validation etc. Certificate Courses on cGMP, cGLP, Process Validation, CTD Documents, ISO 17025:2017, ISO 9001:2008, 13485-2003, and 14001-2004 have strong scientific, analytical, statistical, managerial and training skills.

Currently he is working as a Senior Manager Quality Control and validation for Novamed Pharmaceuticals. It is toll manufacturing oriented company, manufacturing of companies like Getz Pharma, ICI, SEARLE, Macter, Ray, and for Sanofi-Aventis. He is also looking after the Quality of Novamed Healthcare, the nutraceutical and cosmeceutical manufacturing plant.