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Recent advances in the determination of elemental impurities in pharmaceuticals – Status, challenges and moving frontiers

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ABSTRACT

Elemental impurities have been regulated in pharmaceutical products for many decades. Metal impurities such as As, Cd, Cu, Pb, Hg, V and Pt in pharmaceuticals and drugs are known to originate from sources like raw materials, catalysts, metal reagents and even manufacturing equipments. An account of the recent changes implemented by the European Pharmacopoeia (EP), the United States Pharmacopoeia (USP) and other International regulatory bodies for constraining inorganic impurities in pharmaceutical and drug products coupled with new strategies to be adopted for heavy metal analyses is presented. Rapid methods of screening during quality control operations, and a brief account of classical spectrophotometry and the role of instrumental techniques such as atomic absorption spectrometry (AAS), X-ray fluorescence spectrometry (XRF), instrumental neutron activation analysis (INAA), inductively coupled plasma atomic emission spectrometry (ICP-AES) and the inductively coupled plasma mass spectrometry (ICP-MS) for the accurate determination of inorganic impurities in pharmaceutical materials are presented.

Contents

1. Introduction

Toxic metals like As, Pb, Cd, Hg, Se, Cr, Al, Ni, Cu and U enter the human body via the food chain including medicines, ambient air and drinking water leading to health problems. Environmental scientists have worked on the ill-effects of the toxic trace elements such

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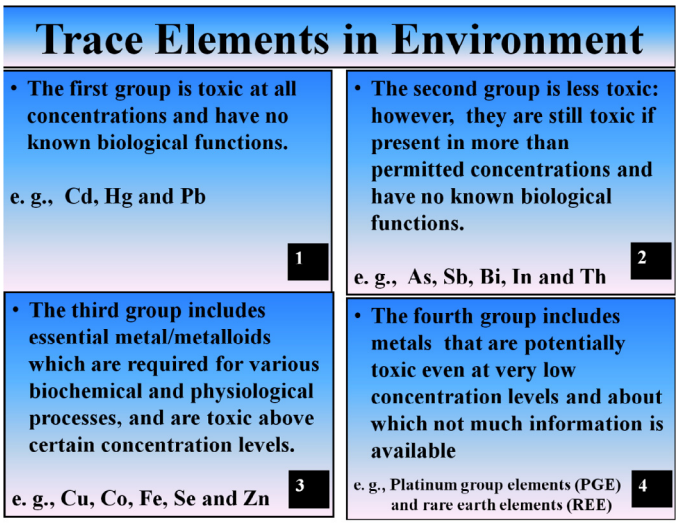

Fig. 1. Trace elements divided into four groups depending up on their function in the environment [9,10].

as Cr, Cu, Ni, Cd, As, Hg, Pb and U in the past [1–4]. However, many other elements, which were not commonly used in the past, e.g., the rare earth elements (REE) and platinum group of elements (PGE) are increasingly being used in modern industries for the production of numerous new materials, finished products including drugs and pharmaceuticals, and for several technological applications. The use of advanced analytical techniques such as inductively coupled plasma mass spectrometry (ICP-MS) and high resolution ICP-MS (HR-ICP-MS) are helping in improving our understanding of the reactivity and mobility of these metals in near-surface environment [5–7]. These elements which are also finding their way into different environmental pathways especially those related to the ground and surface waters; probably have their own contribution to the environmental pollution and human health [7,8]. As a consequence, a new group of elements viz., REE and PGE has been added to the already existing classification of elements (Fig. 1) depending up on their function in the environment and their toxicity in terms of human health [9,10]. Technological innovations in medical and pharmaceutical sciences and healthcare in addition to modern living conditions have enhanced intake of significant quantities of these toxic elements in to the human body leading to health problems.

Impurities such as As, Cd, Cu, Sn, Sb, Pb, Bi, Ag, Hg, Mo, In, Os, Pd, Pt, Rh, Ru, Cr, Ni and V in pharmaceutical-drug substances/products may originate from various sources like metal catalysts and metal reagents used during the synthesis of an active pharmaceutical substance (e.g., from naturally derived plant or mineral sources) and the excipients (e.g., stabilizers, fillers, binders, release agents, flavors, colors and coatings), impurities from manufacturing equipment (e.g., leaching from pipes), water and the container closure system (Fig. 2). Some of these metals can also be encountered as active drug ingredients rather than as contaminants to enhance the beneficial effects on human health. In fact, some active pharmaceutical ingredients (API's) incorporate metals and metalloids by design. These include antimicrobials containing iron, silver and gold; imaging agents using barium, gadolinium, iron, manganese and sodium, lithium drugs for psychotic illness, and platinum-based chemotherapy agents. For example, the platinum compounds; cisplatin, carboplatin and oxaliplatin are widely used in cancer therapy and the potential of ruthenium compounds is also being currently explored. Aluminum is used in antacids, zinc is a part of insulin suspensions and iron is used for treatment or prevention of anemia.

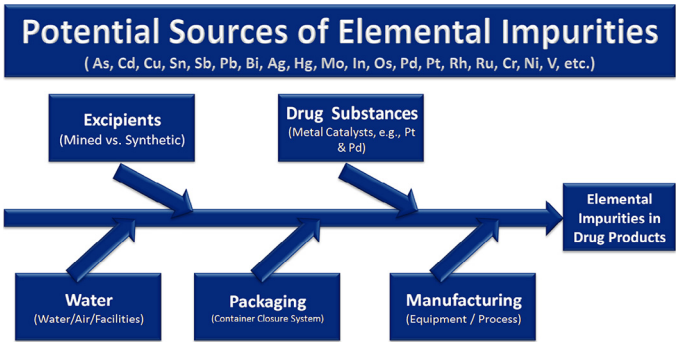

Fig. 2. Potential sources of metallic impurities during the production process of drugs and pharmaceuticals (modified after Toxikon Europe).

Currently, REE are beginning to find pharmaceutical applications. For example, Gd has been used in a chelated form as a contrast agent in magnetic resonance imaging (MRI) measurements [11], though new research finds direct evidence of gadolinium deposition in neuronal tissues which can be harmful to patients [12]. Metals such as Pt and Pd are excellent catalysts and hence widely used in drug synthesis and as such can be potentially present in the finished product as catalyst residues. In spite of exercising maximum care, pharmaceutical raw materials may be contaminated by factors such as environmental conditions, selective use, or as a consequence of natural processes. Moreover, any product or raw material can come into contact with a wide range of materials during manufacture and processing. Sometimes, storage conditions can impact leaching (heat, UV radiation and storage time). In addition, metal ions also can affect the stability and shelf life of the formulation, catalyze the degradation of the API's leading to the formation of unqualified degradates, or pose a toxicity threat on their own [13]. These impurities have to be monitored in pharmaceuticals for basically two reasons. Some metals are known to be toxic and have to be controlled during the entire manufacturing process starting from the testing of source material to the finished products. Some inorganic impurities are toxic even at low levels, and hence should be closely monitored to ensure safety of human health. Thus metals and metalloid impurities are gaining an increasing focus for pharmaceutical regulators anticipating high standards of QC/QA for pharmaceuticals with regard to efficacy and patient safety. The recent changes in the European Pharmacopoeia (EP), the United States Pharmacopoeia (USP) and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) regulations for inorganic impurities and new strategies require companies to adopt new strategies for heavy metal analyses [14]. Compared to the earlier existing heavy metal analytical procedures, the new strategies involve elimination of the specificity issue, extend the range of elements detected almost simultaneously and decrease detection levels. With the new standards, drug product/substance, manufacturers will have to ensure that all their products adhere stringently to the new requirements. Simultaneously, pharmaceutical companies also need to ascertain the quality of product components provided by their suppliers. Various guidelines and criteria of harmful elements in pharmaceutical products have been established. According to USP <232> of USP, pharmaceutical products are classified based on toxicity levels [15]. The European medicines agency (EMA) has set guidelines for the limits of residual metal elements [16]. Recently ICH has proposed safety standard guidelines for metal impurities (Q3D) for the purpose of quality assurance of pharmaceutical products [17] (Tables 1 and 2).The U.S. Food and Drug Administration (FDA) and the British Pharmacopeia (BP) and other regulating bodies such as the Japanese Pharmacopoeia (JP) and the Indian Pharmacopoeia (IP), strongly