



The development of cutaneous limits for elemental impurities

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The skin is the largest organ in the human body. As with all organs, it is a complex multilayered structure with many roles and functions, such as entry prevention of exogenous substances and limiting loss of internal water. Normal skin, with a good level of hydration, is relatively permeable to lipid-soluble substances. This permeability has been used for the delivery of medicinal products since 3000 BC in ancient Egypt, China, and Babylon ⁽¹⁾. This approach was further advanced in ~150 AD by the Greek physician Galen, known as the 'Father of Pharmacy', who developed some of the first plasters which contained multiple herbal drugs and were applied to the local area for absorption through the skin ⁽²⁾.

Advancement in skin science and more recently transdermal drug delivery (TDD) - a method of delivering drugs systematically by applying a drug formulation onto intact and healthy skin - means we are still improving and modernising these ancient technologies. TDD offers a number of advantages over more conventional oral drug delivery, including ease of use on vulnerable age groups, convenient handling, and self-administration. Oral administration of drug compounds has its own drawbacks including metabolic reductions in the bioavailability of the active pharmaceutical ingredient (API) and the harsh repercussions these drug products can cause on the digestive system of the patient. Parenteral drug delivery is hailed as the most effective route of administration, bypassing the physical and biological barriers, however,

this route requires skilled personnel, specific equipment and is accompanied by high risks if administered incorrectly or if not performed in a sterile environment. These pitfalls have encouraged extensive interest in TDD with a sharp increase in patents being filed using this route of administration.

As with all drug products, the raw materials used in the manufacture of the drug substance and the drug product itself must be rigorously tested prior to selling in different global markets. The International Council for Harmonisation of Technical requirements for Pharmaceuticals for Human use (ICH), has recently established cutaneous Permitted Daily Exposure levels (PDEs) for 24 elements which are based on current safety considerations for Elemental Impurities (ICH section Q3D). Revised requirements from the ICH Q3D for control of elemental impurities in new drug products came into effect on 24 September 2022. Prior to the revision of the ICH Q3D, limits were provided for oral, parenteral, and inhalation routes of administration and guidance was provided on developing limits for impurities administered by alternative routes. During the revision of the ICH Q3D, industry requested that products for dermal absorption (skin, hair and nails) have PDE's for elemental impurities considered.

Dermal adsorption is different to any other route of administration due to the varying properties of the skin, the area on the body, the nature of the material, exposure time and the method of application. The amount

of material absorbed may also vary between components within a drug product. The lack of quantitative data in this area has led to a generic approach being adopted to establish limits rather than the element-by-element basis used in the other routes of administration.

In order to establish limits, an Expert Working Group began with the parenteral PDE's and developed limits based on the principles that the elements are 100% bioavailable but that absorption through the skin is very poor (approximately 1% for intact skin). It also assumes that enhancers are available in the product that can increase absorption by up to 10%. These principles were used to determine a Cutaneous Modifying Factor that was applied to the parenteral limits. Therefore, for all elements, excluding Arsenic and Thallium, the cutaneous limits were set at 10 times the parenteral limits. Arsenic was found to have a 5% adsorption thereby the limit was set at 2 times the parenteral limits. Thallium is the only element that shows systematic toxicity by the dermal route, known to have a high adsorption rate but there is no quantitative data to support this, therefore for safety of the patients, the cutaneous limit was set as per the parenteral limits.

The limits for elemental impurities in cutaneous products are not considered to be sufficient to elicit a sensitising response, with the exception of Nickel and Cobalt, according to the ICH. Additional cutaneous and transcutaneous concentration limits were developed for both Nickel and Cobalt to reduce the likelihood of causing skin reactions in sensitised individuals, as described in Appendix 5 of the ICH guideline Q3D on elemental impurities.

The Q3D limits for cutaneous administration are not applicable to drug products intended for treating the skin wherein the basal cell layer is compromised and could give rise to increased absorption. For cases where the material is applied to burns, ulcers or

otherwise disrupted skin, the parenteral limits are a more appropriate starting point.

With these new guidelines in place, it is in the interest of harmonisation that manufacturers of both prescription and over-the-counter products determine the levels of elemental impurities to provide a full and detailed risk assessment to regulators. Industries in both ICH and non-ICH regions are beginning to express interest in the risk associated with new drug products that use a dermal adsorption delivery system.

Analytical testing of topical creams and serums comes with its own challenges. Most are non-miscible with aqueous solutions and adhere to surfaces that may cause damage to analytical instrumentation and therefore require expertise and experience to successfully analyse.

At Almac, we have the experience and instrumental capacity to provide fully digested samples, using state-of-the-art microwave digesters, ensuring the solubility and stability of elements, and top of the range GMP qualified ICP-MS instruments to provide robust analytical testing methods. We have the knowledge and capability to fully develop and validate methods in accordance with current regulatory guidance.

- (1) Geller M.J. Ancient Babylonian medicine. Malden: Wiley-Blackwell; 2010
- (2) Bender GA, Thom RA, Great moments in Medicine and Pharmacy: a history of medicine and Pharmacy in Pictures, Northwood Institute Press; 1966

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