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Analytical advances in pharmaceutical impurity profiling

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ABSTRACT

Impurities will be present in all drug substances and drug products, i.e. nothing is 100% pure if one looks in enough depth. The current regulatory guidance on impurities accepts this, and for drug products with a dose of less than 2 g/day identification of impurities is set at 0.1% levels and above (ICH Q3B(R2), 2006). For some impurities, this is a simple undertaking as generally available analytical techniques can address the prevailing analytical challenges; whereas, for others this may be much more challenging requiring more sophisticated analytical approaches. The present review provides an insight into current development of analytical techniques to investigate and quantify impurities in drug substances and drug products providing discussion of progress particular within the field of chromatography to ensure separation of and quantification of those related impurities. Further, a section is devoted to the identification of classical impurities, but in addition, inorganic (metal residues) and solid state impurities are also discussed. Risk control strategies for pharmaceutical impurities aligned with several of the ICH guidelines, are also discussed.

Contents

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1. Introduction

Impurities within pharmaceutical products provide no benefits to the patient, and for many years regulators have wrestled with different strategies to address this problem (Jacobson-Kram and McGovern, 2007). These have included avoidance, as low as reasonably practicable (ALARP), safety-based limits, i.e. threshold of toxicological concern (TTC) or sometimes a combination of these approaches, for example, a combination of the ALARP and safety based limits.

However, it is equally true that the synthesis of multi-stage, complex active pharmaceutical ingredients (API) cannot be economically undertaken without the acceptance that there will be low, but controlled levels of residual impurities arising from the synthesis. Equally, the same considerations apply to drug product. Whilst, meaningful measures are implemented to optimise excipient selection, formulation design, the manufacturing process and the appropriate pack selection; degradation within a drug substance and drug product is still likely to be encountered because of the ubiquitous presence of moisture and oxygen in the environment leading to the two most common degradation pathways of hydrolysis and oxidation, respectively.

Therefore, there needs to be risk/benefit assessment undertaken to ensure that there is a ready supply of affordable medicines available to society and that risk to the patient from these concomitant impurities is minimised, i.e. 'tolerability of risk' (Boulder, 2015). This review will focus on the recent advances in analytical science that facilitate risk control strategies for pharmaceutical impurities aligned with the ICH quality guidance documents.

2. Regulatory Framework for Controlling Impurities

Impurities are controlled within the framework of the International Conference of Harmonisation (ICH) quality guidelines (ICH Q3A, Q3B, Q3C, Q3D, Q6A, Q6B) and the multi-disciplinary guidance (ICH M3 and M7). The latter will not be discussed here as it is the focus of a separate review in this issue.

ICH Q3A provides guidance on the content, identification and qualification of impurities in new APIs produced by chemical syntheses. Organic impurities can arise during API manufacturing process or subsequent storage. They can be classified as either identified or unidentified, and include starting materials, reagents, by-products, intermediates, filter aids, and degradation products. The guidance describes classification and identification of API impurities, the listing of impurities in specifications (see also ICH Q6A, ICH Q6B), and relevant analytical procedures. In addition, the guidance includes suitable advice for qualifying impurities using appropriate safety studies, in batches of a new API used in safety and clinical studies. Controlling the stereochemical or enantiomeric purity of an API should also be performed in a similar manner to the control of other achiral impurities (De Camp, 1989; Argentine et al., 2007).

Similarly, ICH Q3B provides guidance on the content, identification and qualification of impurities in new drug products. ICH Q3B has a comparable scope to ICH Q3A. Impurities in new drug products (or degradation products) arise as a result of manufacture or storage. They are typically degradants of the API or reaction products of the API with a processing aid or with an excipient (or an impurity within an excipient) or with the immediate primary packing materials.

ICH Q3C recommends the acceptable amounts of residual solvents that are allowable in APIs and drug products. The optimal selection of the solvent for the synthesis of an API may improve the yield, or define important physicochemical characteristics of API such as crystal form, purity, and solubility. Therefore, the solvent may sometimes be a critical process parameter (CPP) within the synthetic process. The guideline describes those levels considered to be toxicologically acceptable for some residual solvents, which are based on permitted daily exposure (PDE) limits and recommends the use of less toxic alternatives, i.e. avoidance of class 1 toxic solvents such as benzene. ALARP considerations based on process capability are required for class 3 solvents, but are specifically excluded for class 2 solvents. However, the reality is that regulators will expect process capability considerations to be applied to all classes of solvent.

ICH Q3D recommends the acceptable amounts of residual elemental impurities that are allowable in drug products. Elemental impurities may arise from several sources. The principal source is residual catalysts arising from the use of catalysed coupling reactions (often late stage) during API synthesis. These approaches are environmentally friendly in nature and typically decrease the cost of goods (CoGs) by making the process more efficient and increasing yields. Alternatively, elemental impurities may arise as API or drug product impurities; for example, drug product impurities in excipients, leachables from primary or secondary processing equipment or from packing materials. The guidance