International Harmonization for Quality Control - Impurity

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The control of pharmaceutical impurities is currently a critical issue to the pharmaceutical industry. The International Conference on Harmonization (ICH) has formulated a workable guideline regarding the control of impurities. In this review, a description of impurities in relation to ICH guidelines and impurity profiles in quality control are presented.

The topic of impurity on the harmonization for quality control was first issued in the ICH1 conference in 1991. It was necessary to adjust the difference of impurity requisite for drug approval in three countries; EU, Japan, USA. The ICH Expert Working Group meeting was held in 1992 and make out a draft of "Q3A : Impurities in New Drug Substances". The guidance had been subject to consultation by the regulatory parties, in accordance with the ICH process and endorsed by the ICH Steering Committee at *Step 4* of the ICH process on February 6, 2002. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States. ICH Q3A provides recommendations for (1) inclusion of information regarding specified impurities in certain new drug applications (NDAs) (identified and unidentified impurities in new drug substance specifications) and (2) qualification of impurities (the process of acquiring and evaluating data that establishes the biological safety of individual impurities or a given impurity profile at the levels specified). Generic drugs are not covered by ICH Q3A; however, many of the recommendations in ICH Q3A are applicable to drug substances used in generic drug products.

The USP defines an impurity profile as "a description of the impurities present in a typical lot of drug substance produced by a given manufacturing process." Each commercial lot should be comparable in purity to this standard release profile which is developed early on and maintained for each pharmaceutical chemical. We can also call this profile a "Reference Profile" because the quality control unit refers to it (1) when assessing the purity of each batch of active pharmaceutical ingredient (API), and (2) when evaluating the viability of proposed process changes. To illustrate, one of the more critical process changes in the life of a pharmaceutical chemical (both API and key intermediate) is justification of scale-up from smaller development size lots to full-scale production batches. In the absence of a full impurity profile, there would be little support for claims of equivalency of the two process scales. When reviewing an API impurity profile, the

following basic information should be available for impurities present at or above the 0.1% level (or lower based on toxicity of the compound): (1) Identity or some identifier (e.g., HPLC retention time), (2) Ranges normally (historically) found. Note that some impurities may only be detected sporadically. However, for an impurity profile to be considered complete, it's important to include these as well, (3) Limits, (4) Description or type of impurity (e.g., organic solvent, in-process decomposition product, unreacted intermediate, etc.). Many companies use at least two test methods (e.g., HPLC, GC) for routine purity testing of their pharmaceutical chemicals. It is vital that these methods are of appropriate sensitivity and capable of detecting and quantifying actual and potential impurities. We expect manufacturers to have fully characterized the purity of their pharmaceutical chemicals and consider the failure to perform sufficient impurity profile studies inconsistent with KFDA provision for drug substances and products.