

## Qualification of Impurities in Drug Substances and Drug Products

*Karl A. Traul, K.A. Traul Pharmaceutical Consulting*

U.S. and international guidance, especially International Conference on Harmonization (ICH) Q3A(R2), ICH Q2B(R2), Q3C(R4) and VICH GL10R<sup>1</sup> require that drug manufacturers identify, quantify and qualify real or potential impurities in drug substances and drug products. These regulations apply to both human and veterinary drugs and are further delineated in terms of organic or inorganic materials and solvents. Identification and quantification are, generally, achieved with analytical methods.

Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual degradation product, impurity or metabolite at the level(s) specified. The rationale for establishing impurity acceptance criteria must include safety considerations. The interpretation of this section of the regulations is very important for defining a course of action that will meet the intent of the regulations with regard to “qualification” i.e. *Does this impurity pose a health hazard for the consumer?* An impurity, present in a new drug product that has been adequately tested in nonclinical safety and/or clinical studies, could be considered qualified. The most important step in the process is to quantify impurities that were in the batches used for the nonclinical safety studies. Impurities that are also significant human metabolites present in animal studies are generally considered qualified. Impurities could be considered qualified at levels higher than those administered in safety studies based on a comparison of actual doses given in the safety studies and the proposed clinical dose.

Often, nonclinical safety studies are conducted at dosage levels far in excess of the proposed clinical dose and, as a result, the impurity (as well as the active ingredient) has been tested at elevated doses. Comparing the nonclinical doses versus the proposed clinical dose may yield a margin of safety that would be sufficient to assure safety. Depending on the proposed clinical regimen, longer term repeated dose safety studies and specialized studies such as genetic toxicity and reproductive toxicity are the preferred types of studies. Impurities are, usually, at low relative concentrations, and there is less concern for single dose toxic effects.

If there are no prior toxicity data, the regulators would expect to see, at a minimum, genotoxicity studies (gene mutation and chromosomal damage tests) and a toxicity study in one species of 14-90 days duration (depending on the proposed clinical dosage regimen).

The guidelines encourage the use of computer programs, such as DEREK to assess whether an impurity is similar to a known class of toxic materials; however these programs provide little information on the degree of toxicity a material possesses and are limited to classes of compounds with similar structures for which there is a significant body of toxicology data.

The ICH documents provide guidance for thresholds at which impurities in new drug substances and products must be reported and identified and thresholds for qualification of the impurities. The guidances each provide a decision tree that allows one to determine the necessary course of action. This includes simply reducing the level of the contaminant(s) and avoiding unnecessary testing. The thresholds are based on the estimated clinical dose of the drug product.

For Example, the ICH Q3A(R2) guidance on new drug substances provides the following thresholds:

| Thresholds Maximum Daily Dose | Reporting Threshold | Identification Threshold                            | Qualification Threshold                             |
|-------------------------------|---------------------|---|---|
| ≤ 2g/day                      | 0.05%               | 0.10% or 1.0 mg per day intake (whichever is lower) | 0.15% or 1.0 mg per day intake (whichever is lower) |
| > 2g/day                      | 0.03%               | 0.05%   | 0.05%   |

The Guidance in ICH Q3B(R2), for drug products, is a bit more detailed because it is based on a finer differentiation of the total daily intake of the active pharmaceutical ingredient (api).

| Thresholds Maximum Daily Dose of Drug Substance | Reporting Threshold | Identification Threshold               | Qualification Threshold                 |
|---|---------------------|--|---|
| ≤ 1g/day  | 0.1%                | -                                      | -                                       |
| > 1g/day  | 0.05%               | -                                      | -                                       |
| < 1mg/day                                       | -                   | 1% or 5 µg TDI (whichever is lower)    | -                                       |
| 1 – 10 mg/day                                   | -                   | 0.5% or 20 µg TDI (whichever is lower) | -                                       |
| >10mg – 2 g/day                                 | -                   | 0.2% or 2 mg TDI (whichever is lower)  | -                                       |
| > 2 g/day                                       | -                   | 0.1%                                   | -                                       |
| < 10mg/day                                      | -                   | -                                      | 1% or 50 µg TDI (whichever is lower)    |
| 10 – 100 mg/day                                 | -                   | -                                      | 0.5% or 200 µg TDI (whichever is lower) |
| >100mg – 2 g/day                                | -                   | -                                      | 0.2% or 3mg TDI (whichever is lower)    |
| > 2 g/day                                       | -                   | -                                      | 0.15%                                   |

TDI – Total daily Intake

Similar guidance is provided for residual solvents in ICH Q3C(R2), Solvents are grouped by toxicologic potential into three categories (Solvents to be Avoided, Solvents to be Limited and Solvents of Low Toxicologic Potential) and then limits are identified for each.

VICH GL 10, for veterinary products, has its own thresholds:

| <b>Use</b>                              | <b>Reporting Threshold</b> | <b>Identification Threshold</b> | <b>Qualification Threshold</b> |
|---|----------------------------|---------------------------------|--------------------------------|
| New Vet Drug used in Human Medicine     | As per ICH                 | As per ICH                      | 0.50%                          |
| New Vet Drug not used in Human Medicine | 0.01%                      | 0.20%                           | 0.50%                          |

1. - The ICH Documents can be found on the FDA website at:

<http://www.fda.gov/RegulatoryInformation/Guidances/ucm122049.htm>

(Human Drugs)

<http://www.fda.gov/RegulatoryInformation/Guidances/ucm122050.htm>

(Veterinary Drugs)

The ICH website also provides access to these documents, for human drugs:

<http://www.ich.org/cache/compo/276-254-1.html>

Karl A. Traul, Ph.D.

K.A. Traul Pharmaceutical Consulting

16 Marvin Ct.

Lawrenceville, NJ 08648

[katraul@aol.com](mailto:katraul@aol.com)