procedures should be developed for those potential impurities that are expected to be unusually potent, producing toxic or pharmacological effects at a level not more than the identification threshold. All impurities described as follows should be qualified:

- Each specified, unidentified impurity
- Any unspecified impurity with an acceptance criterion of not more than the identification threshold
- Total impurities

Inorganic impurities can result from the manufacturing process. They are normally known and identified and include the following:

- Reagents, ligands, and catalysts
- Heavy metals or other residual metals
- Inorganic salts
- Other materials (e.g., filter aids and charcoal)

Inorganic impurities are normally detected and quantified using pharmacopoeial or other appropriate procedures. Carryover of catalysts to a new drug substance should be evaluated during development. The need for the inclusion or exclusion of inorganic impurities in a new drug substance specification should be discussed. Acceptance criteria should be based on pharmacopoeial standards or known safety data.

Solvents are inorganic or organic liquids used as vehicles for the preparation of solutions or suspensions in the synthesis of a new drug substance. As these are generally of known toxicity, the selection of appropriate controls is easily accomplished (see ICH Q3C on Residual Solvents). The control of residues of the solvents used in the manufacturing process for a new drug substance should be discussed and presented according to ICH *Q3C Impurities: Residual Solvents*.

A registration application should include documented evidence that the analytical procedures are validated and suitable for the detection and quantification of impurities (see ICH Q2A and Q2B on Analytical Validation). Technical factors (e.g., manufacturing capability and control methodology) can be considered as part of the justification for the selection of alternative thresholds based on manufacturing experience with the proposed commercial process. The use of two decimal places for thresholds does not necessarily reflect the precision of the analytical procedure used for routine quality control (QC) purposes. Thus, the use of lower-precision techniques (e.g., thin-layer chromatography) can be appropriate where justified and appropriately validated. Differences in the analytical procedures used during development and those proposed for the commercial product should be discussed in the registration application. The quantification limit for the analytical procedure should be not more than the reporting threshold.

Organic impurity levels can be measured by a variety of techniques, including those that compare an analytical response of an impurity with that of an appropriate reference standard or with the response of the new drug substance itself.