## 8.3 Impurities

Impurities can be classified into the following categories:

- Organic impurities (process- and drug-related)
- Inorganic impurities
- Residual solvents

Organic impurities can arise during the manufacturing process and/or storage of the new drug substance. They can be identified or unidentified, volatile or nonvolatile, and include the following:

- Starting materials
- By-products
- Intermediates
- Degradation products
- Reagents, ligands, and catalysts

There is a need to summarize the actual and potential impurities most likely to arise during the synthesis, purification, and storage of a new drug substance. This summary should be based on sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials that could contribute to the impurity profile of the new drug substance, and the possible degradation products. This discussion can be limited to those impurities that might reasonably be expected based on the knowledge of the chemical reactions and the conditions involved.

In addition, the applicant should summarize the laboratory studies conducted to detect impurities in the new drug substance. This summary should include test results of batches manufactured during the development process and of batches from the proposed commercial process, as well as the results of stress testing (see ICH Q1A(R) on stability) used to identify potential impurities that arise during storage. The impurity profile of the drug substance batches intended for marketing should be compared with those used in development, and any differences should be discussed.

The studies conducted to characterize the structure of actual impurities present in a new drug substance at a level greater than the identification threshold calculated using the response factor of the drug substance are described separately. Note that any impurity at a level greater than the identification threshold in any batch manufactured by the proposed commercial process should be identified. In addition, any degradation product observed in stability studies at recommended storage conditions at a level greater than the identification threshold should be identified. When identification of an impurity is not feasible, a summary of the laboratory studies demonstrating the unsuccessful effort should be included in the application. Where attempts have been made to identify the impurities present at levels of not more than the identification thresholds, it is also useful to report the results of these studies.

Identification of impurities present at an apparent level of not more than the identification threshold is generally not considered necessary. However, analytical