Reference standards used in the analytical procedures for control of impurities should be evaluated and characterized according to their intended uses. The drug substance can be used as a standard to estimate the levels of impurities. In cases where the response factors of a drug substance and the relevant impurity are not close, this practice can still be appropriate, provided a correction factor is applied or the impurities are, in fact, being overestimated. Acceptance criteria and analytical procedures used to estimate the identified or unidentified impurities can be based on analytical assumptions (e.g., equivalent detector response). These assumptions should be discussed in registration applications.

The specification for a new drug substance should include a list of impurities. Stability studies, chemical development studies, and routine batch analyses can be used to predict those impurities that are likely to occur in the commercial product. The selection of impurities in a new drug substance specification should be based on the impurities found in batches manufactured by the proposed commercial process. Those individual impurities with specific acceptance criteria included in the specification for a new drug substance are referred to as *specified impurities* in this guidance. Specified impurities can be identified or unidentified.

A rationale for the inclusion or exclusion of impurities in a specification should be presented. The rationale should include a discussion of the impurity profiles observed in the safety and clinical development batches, together with a consideration of the impurity profile of batches manufactured by the proposed commercial process. Specified, identified impurities should be included, along with the specified, unidentified impurities estimated to be present at a level greater than the identification threshold given. For the impurities known to be unusually potent or that produce toxic or unexpected pharmacological effects, the quantification/detection limit of the analytical procedures should be commensurate with the level at which the impurities should be controlled. For the unidentified impurities, the procedure used and the assumptions made in establishing the level of the impurity should be stated clearly. Specified, unidentified impurities should be referred to by an appropriate qualitative analytical descriptive label (e.g., "unidentified A" and "unidentified with relative retention of 0.9"). A general acceptance criterion of not more than the identification threshold for any unspecified impurity and an acceptance criterion for total impurities should be included.

Acceptance criteria should be set no higher than the level that can be justified by the safety data and should be consistent with the level achievable by the manufacturing process and the analytical capability. Where there is no safety concern, impurity acceptance criteria should be based on the data generated on batches of a new drug substance manufactured by the proposed commercial process, allowing sufficient latitude to deal with normal manufacturing and analytical variations and the stability characteristics of the new drug substance. Although normal manufacturing variations are expected, significant variation in batch-to-batch impurity levels can indicate that the manufacturing process of the new drug substance is not adequately controlled and validated (see ICH Q6A guidance on specifications, decision tree #1, for establishing an acceptance criterion for a specified impurity in a new drug substance). The use of two decimal places for thresholds does not necessarily indicate the precision of the acceptance criteria for the specified impurities and total impurities.