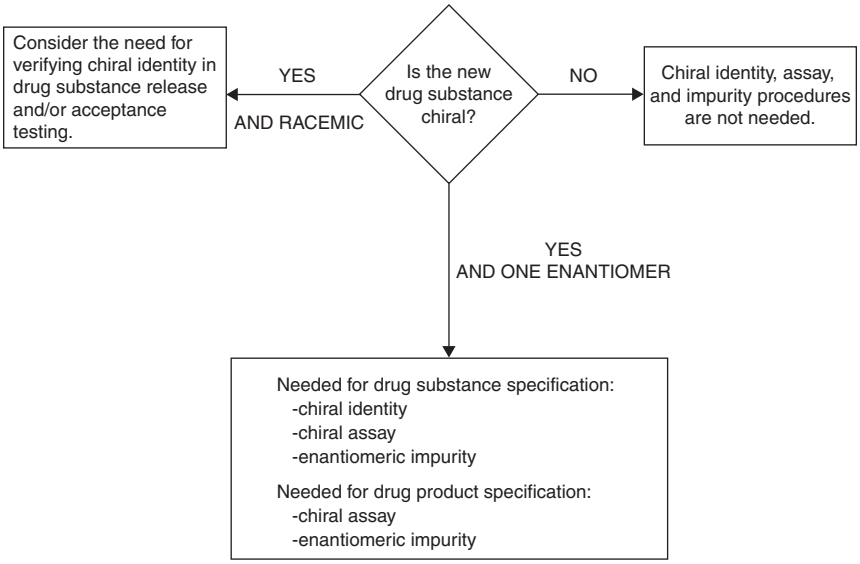

SCHEME 8.2 Decision tree for chiral compound resolution. (Courtesy of Pharmquest Corporation, Mountain View, CA.)

same limits of quantification or qualification from being applied. Assurance of control could also be given by appropriate testing of a starting material or intermediate, with suitable justification. An enantioselective determination of the drug substance should be part of the specification. It is considered acceptable in order to achieve this, either through the use of a chiral assay procedure or by the combination of an achiral assay and appropriate methods for controlling the enantiomeric impurity. For a drug substance developed as a single enantiomer, the identity test(s) should be capable of distinguishing both enantiomers and the racemic mixture. For a racemic drug substance, there are generally two situations where a stereospecific identity test is appropriate for the release/acceptance testing: one, where there is a significant possibility that the enantiomer might be substituted for the racemate, and second, when there is evidence that preferential crystallization may lead to unintentional production of a nonracemic mixture. Scheme 8.2 shows a decision-making tree on the studies that are needed when a chiral substance is suspected.

8.2.2 Assay

A specific, stability-indicating procedure should be developed to determine the content of the new drug substance. In many cases, it is possible to employ the same procedure (e.g., HPLC) for both the assay of the new drug substance and the quantification of the impurities. In cases where use of a nonspecific assay is justified, other supporting analytical procedures should be used to achieve the overall specificity. For example, where titration is adopted to assay the drug substance, the combination of the assay and a suitable test for impurities should be used. Assay methods clearly