A.1 Assessment of need for the establishment of chemical reference substances

The production, validation, maintenance and distribution of chemical reference substances is a costly and time-consuming undertaking. It is, therefore, crucial to determine for certain whether a need for a given substance exists. Requests for new chemical reference substances usually arise when a particular approach to developing a specification for a new substance or product has been adopted. Methods may have been proposed in a specification that require the establishment of a chemical reference substance for use as a comparative standard. Therefore, the first matter that should be assessed is whether an alternative, equally satisfactory, procedure could be adopted that does not require a comparative standard.

Analytical procedures currently used in specifications for pharmaceutical substances and products that may require a chemical reference substance are:

– infrared (IR) spectrophotometry, whether for identification or quantitative purposes;
– quantitative methods based on ultraviolet (UV) absorption spectrophotometry;
– quantitative methods based on the development of a colour and the measurement of its intensity, whether by instrumental or visual comparison;
– methods based on chromatographic separation for identification or quantitative purposes;
– quantitative methods (including automated methods) based on other separation techniques that depend on partition of the substance to be determined between solvent phases, where the precise efficiency of the extraction procedure might depend upon ambient conditions that occasionally vary and from laboratory to laboratory;
– quantitative methods, often titrimetric but sometimes gravimetric, that are based on non-stoichiometric relationships;
– assay methods based on measurement of optical rotation; and
– methods that might require a chemical reference substance consisting of a fixed ratio of known components (for example, *cis/trans* isomers, spiked samples).