

Introduction

In 1975 the WHO Expert Committee on Specifications for Pharmaceutical Preparations recommended the “General guidelines for the establishment, maintenance and distribution of chemical reference substances” (1). At that time these general guidelines were aimed at fostering greater collaboration and harmonization among various national and regional authorities responsible for collections of chemical reference substances. This aim is still relevant. The guidelines were initially drawn up specifically for use by the WHO Collaborating Centre for Chemical Reference Substances in Sweden, which supplies International Chemical Reference Substances (ICRS). These substances are primarily intended for use with pharmacopoeial monographs included in *The International Pharmacopoeia* (2).

It became evident that to ensure ready availability and cost-effectiveness, and in order to meet particular national or regional pharmacopoeial requirements, it was necessary to establish chemical reference substances external to the WHO Collaborating Centre for Chemical Reference Substances. Since the meticulous work of the WHO Collaborating Centre establishing the international collection would have to be duplicated in local or regional laboratories, guidelines were necessary to ensure the integrity of national or regional collections. The 1975 guidelines were reviewed and modified in 1982 (3) and subsequently revised in 1999 (4).

In 2004, the WHO Expert Committee on Specifications for Pharmaceutical Preparations recommended the development of more detailed guidelines on the establishment of secondary chemical reference substances. This additional guidance forms part B of the present revision and is intended to apply to secondary reference substances supplied as “official”, e.g. regional/national standards, and not to the working standards of manufacturers or other laboratories. However, in principle, secondary reference standards prepared by manufacturers can be prepared as “working standards” using the same procedures.

The purpose of establishing chemical reference substances is to achieve accuracy and reproducibility of the analytical results required by pharmacopoeial testing and pharmaceutical control in general. These substances are normally prepared and issued by the regional or national pharmacopoeia commission or the regional or national quality control laboratory on behalf of the drug regulatory authority. In the context of these guidelines, the general use of a chemical reference substance should be considered an integral part of a compliance-oriented monograph or test procedure used to demonstrate the identity, purity and content of pharmaceutical substances and preparations.

The purpose of establishing secondary reference substances is for use in routine analysis to determine the identity, purity and, in particular, the content of pharmaceutical substances in pharmaceutical preparations. The extent of characterization and testing of a secondary reference substance is less than that for a primary reference substance. It is essential that a secondary reference substance is traceable to a primary reference substance, such as a pharmacopoeial or other officially recognized reference substance. In the cases of doubtful results or dispute when using secondary chemical reference substances, the test should be repeated using the primary standard.

The establishment of a chemical reference substance is based on the evaluation of the results of analytical testing. The report should subsequently be approved and adopted by a certifying body, normally the relevant pharmacopoeial committee or drug regulatory authority. The establishment of the reference substance can be on an international, national or regional basis. Each substance is generally established for a specific analytical purpose, defined by the issuing body. Its use for any other purpose becomes the responsibility of the user and a suitable caution is included in the accompanying information sheet. The present guidelines are concerned with both primary and secondary chemical reference substances as defined below.

The preparation of a chemical reference substance should comply with the requirements for quality assurance systems, including applicable principles of good manufacturing practices (GMP) and good control laboratory practices (5–10).

Adequate training programmes are also required. Both the WHO Collaborating Centre and other laboratories concerned with the evaluation and establishment of chemical reference substances give assistance in training, subject to the availability of resources.