

A.6 Handling and distribution of chemical reference substances

The handling, distribution and use of established chemical reference substances must ensure that their integrity is safeguarded and maintained throughout their period of use.

A.6.1 Packaging operations Appropriate GMP requirements (6) should be observed. The various stages in packaging chemical reference substances should be clearly defined and controlled, to avoid contamination of the sample, mislabelling of containers, or any other event which might result in mishandling or mismanagement.

Containers for chemical reference substances should protect their contents from moisture, light and oxygen and must be tested for permeability to moisture. Additional measures may be necessary to ensure long-term integrity and stability. Most chemical reference substances, however, are conveniently supplied in moisture-proof containers which should be uniform in type and size to facilitate distribution. The lack of permeability to moisture and the compatibility of the material of which the closure is made with the chemical reference substance are important factors in determining the suitability of container closure systems. The best containers for chemical reference substances from the point of view of stability are sealed glass ampoules, but these have certain disadvantages. There is a risk of contaminating the substance with glass particles when the ampoules are opened.

It is preferable to restrict the quantity of reference substance held in each container to that required to perform the test(s). The use of multidose containers is not excluded, but is not recommended.

Before undertaking any packaging operations, the health hazards of the item to be packaged should be assessed using suitable information sources, e.g. the material safety data sheet. Appropriate precautions should be taken to protect the person(s) handling the chemical reference substance.

The packaging of a batch of a chemical reference substance into containers is a small-scale operation for which suitable equipment is not always available to the manufacturer of the material. Therefore, the packaging of chemical reference substances is usually undertaken by the responsible issuing body. Screw-type feeders have been constructed, but generally the packaging of chemical reference substances is carried out manually. Substances which are expensive or available only in very small quantities may have to be divided between containers in solution and then lyophilized, or evaporated to dryness.

Some chemical reference substances must be packaged under an inert gas or in conditions of controlled humidity. Therefore, the use of a glovebox or an air-tight cabinet is necessary. Single-use vials can be used for hygroscopic materials.

A.6.2 Storage Information about suitable storage conditions can often be obtained from the manufacturer of the source material and should be requested routinely when a new chemical reference substance is established. Theoretically, the stability of the substances should be enhanced by keeping them at low temperatures but, for substances that contain water, storage below 0 °C may impair the stability. It should also be remembered that the relative humidity in normal refrigerators or cold rooms may be high and, unless ampoules or other tightly closed containers are used, the improvement in stability may be more than offset by degradation due to the absorption of moisture. Storage at about 5 °C, with precautions to prevent such absorption, has proved satisfactory for most chemical reference substances. Vials should, however, not be opened until they have attained room temperature to prevent ingress of moisture by condensation.

A.6.3 Stability A chemical reference substance is an integral part of the drug specification. Thus, if the reference substance deteriorates, this will change the specification of the drug. It is, therefore, of the utmost importance that the stability of chemical reference substances is monitored by regular re-examination and that they should be replaced as soon as a significant change in a property is noted.

The definition of a "significant change" differs according to the intended use of the chemical reference substance. Several per cent of degradation products found in a substance may not impair the usefulness of the material in identification tests. For chemical reference substances that are used in chromatographic assays, however, even small amounts of impurities may be unacceptable. When establishing a chemical reference substance, consideration must be given to its intended use and to the performance characteristics of the analytical methods in which it will be used. The tolerable degree of degradation will differ from case to case but should be predefined.

Laboratories in charge of collections of chemical reference substances should have a system for regular re-examination of the materials in stock. The frequency of re-testing may be modified according to need. It must be borne in mind that the stability of a specially prepared chemical reference substance may not always be the same as that of commercial samples of the same material.

The selection of suitable analytical methods for monitoring the stability of chemical reference substances depends on the nature and intended use of the substance. A substance used solely for identification purposes will normally only require demonstration that it is still suitable for this use, e.g. that the IR spectrum is identical to that obtained during establishment. If substances are employed for other purposes, the testing must be more extensive, but should use methods which are rapid and sensitive so as not to consume too much of the existing stock. In many cases it is important to check that there has been no significant uptake of moisture, which could result in degradation by hydrolysis and/or a decrease in the assigned content of the substance. Chromatography is employed extensively, as are absolute methods such as differential scanning calorimetry where applicable.

Changes in the impurity profile or purity determination usually mean that the batch must be replaced. Changes which compromise the integrity of the batch indicate that it should immediately be withdrawn from use. Sometimes a batch of a chemical reference substance will discolour or otherwise change in appearance. Steps should be taken to replace this substance whether or not the results of subsequent analyses indicate significant degradation. Such changes in physical appearance reduce the confidence of the user in the suitability of the chemical reference substance. Appropriate testing of active bulk substance should be carried out before further dispensing into vials or ampoules.

A.6.4 Information to be supplied with chemical reference substances The labels on chemical reference substances should give the following information:

- the appropriate name of the substance: the international nonproprietary name (INN) should be used wherever possible;
- the name of the issuing body;
- the approximate quantity of material in the container; and
- the batch or control number.

Where associated documents are provided they should incorporate relevant items from the list above. The following information should be given, as necessary, on the labels and/or in associated documents:

- the name and address of the issuing body;
- the recommended storage conditions (if special conditions apply);
- the intended use of the chemical reference substance;
- directions for use (e.g. storage and handling);
- information about the assigned analytical value of the chemical reference substance (needed for calculation of the results of tests in which the substance will be used);
- a disclaimer of responsibility in cases where chemical reference substances are misused, or stored under inappropriate conditions, or used for purposes other than those intended by the issuing body; and
- health hazard information or warnings in conformity with national and regional regulations or international agreements.

If analytical data are to be supplied with the chemical reference substances, it is recommended that the data provided be limited to what is necessary for the proper use of the substances in the tests and assays.

A.6.5 Distribution and supply Distribution of chemical reference substances within the same country usually does not present problems. However, when samples are to be sent to other countries, both the sender and the receiver of the goods may encounter difficulties because of the vagaries of postal and customs regulations, e.g. the application of special procedural requirements applicable to substances under international control. Distributors of chemical reference substances waste considerable resources in seeking information on different international import regulations, and in completing the required forms. A way of reducing such difficulties and barriers to effective distribution of chemical reference substances should be sought. There should be a minimum of delay in providing the chemical reference substances to the users, and the most speedy means of transport should be chosen.

A.6.6 Period of use Chemical reference substances do not carry an "expiry date" in the conventional sense. To avoid the unnecessary discarding of satisfactory substances, a mechanism for general control of the batch of a chemical reference substance may be used by the issuing body. If the issuing body applies stability considerations and a monitoring procedure to its collection based on its experience, this should be a guarantee to the user of the acceptability of the chemical reference substance for its intended use.

Whenever a batch of primary reference standards needs to be replaced, the issuing body should, wherever practical, allow for a transition period.

If, exceptionally, it is considered necessary to specify an expiry or re-test date, this should be stated on the label and/or in a document accompanying the chemical reference substances. Adequate shipping records should be kept to enable contact to be made with the purchaser of a batch for recall or other notification.

The storage and maintenance of unopened containers of the chemical reference substance in accordance with the information provided are integral to its suitability for use. To avoid potential doubts concerning the integrity of opened containers, it is suggested that potential users obtain only the quantities of substances necessary to meet their short-term needs and to obtain fresh stocks (held under controlled and known conditions) when required. Long-term storage of substances in opened containers should be avoided. Similarly, efforts should be made to avoid possible degradation, contamination and/or introduction of moisture during the repeated use of portions of a substance from the same container.