1 Purpose

The purpose of this Procedure is to define the requirements for the retesting and assignment of storage periods for APIôs, excipients, intermediates and raw materials.

2 Scope and Applicability

This Procedure is applicable to all APIôs, excipients, intermediates and raw materials (herein after termed ñmaterialsò) used for manufacturing of formulated products and pure Active Pharmaceutical Ingredients.

3 Definitions

3.1 API (Active Pharmaceutical Ingredient)

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product that when used in the production of a drug becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body. Note: Also known as Bulk drug or Drug Substance.

3.2 Excipients

Any material that is used in the manufacture of a Formulated Product that excludes the active ingredient; an excipient may be used during processing but not be present in the final formulation, e.g. Water.

3.3 Intermediate

Material produced during manufacture that undergoes further change or purification. **Intermediate**s may or may not be isolated.

3.4 Retest Date

The date after which a material shall be re-examined to ensure that it is still suitable for use. The initial retest date is the date of manufacture plus the initial retest period. Additional retest dates are calculated from adding appropriate retest periods to the dates of retesting.

3.5 Initial Retest Period

The period of time following manufacture / release testing that a material can be used prior to retesting and the setting of a new retest date, providing the material has been stored under appropriate conditions. For an API, this initial retest period will be registered.

Retest dating and the use of retest periods is the standard method of controlling the use of APIs. APIs shall have initial retest periods based on available stability data assigned in accordance with the tightest international product registration requirements. QA & Supply chain Group has responsibility for ensuring this data is included in the relevant documentation. Typically, for new chemical entity APIs stability studies will support an initial retest period of 12-36 months. The retest period can be formally extended over time using data generated from mature stability study programs. This is preferable to the long term real-time retesting of material in stock.

The retest date shall be calculated from the date of manufacture of the API. Once an API has reached its retest date, the API shall not be used until it has been retested, or the retest period extended.

A maximum initial retest period of 5 years shall be given to an API providing supporting stability data is available.

5.1.2 Retesting

Once an API has reached its retest date, it may be retested and a new retest period assigned. Retesting is undertaken on a sample taken from the material stock. The new retest period shall be assigned on the basis of :-

1. Available stability data

2. Retest data meeting specification / results comparison with previous analysis
3. Available retest data from previous batches
4. Avoidance of ó1 batch testingô
5. To assure continued suitability, and not rely on 1 batch QC testing, build up of a stability profile for the API using extended stability studies. Where limited stability data is available, further supporting data can be obtained such as :-

   Analysis of samples from stock of several batches of similar age
   An evaluation comparing impurity levels and profiles with original results

6. Evaluation of the effect of ageing on the physical parameters of the material.

7. Consideration of the final usage form of the product.

8. Consideration of the conditions the API has been stored in.
9. Consideration of regulatory implications.

Consideration shall also be given to the use of stability indicating methodology. The rationale used to determine the retest period shall be documented. The new retest date shall be calculated from the retest period added to the date of completion of analysis.

It is recommended that retesting shall be conducted by the same laboratory that conducted the initial release testing.

the reprocessing operation.

5.1.6 Stability

Formal stability studies shall be conducted for APIôs. Data from ongoing studies can be used to extend initial retest periods. Stability studies may be undertaken by the company itself or at a contractor, or a vendor as appropriate / registered.

5.1.7 Changes to Initial Retest Periods

Permanent extensions to assigned initial retest periods may be made where satisfactory evidence is available to support the changes. For an API such evidence is typically data from stability programs but may also include real time testing of material in stock. Any change must be made via the change management system in order that it is subject to regulatory compliance and to ensure that all relevant documents and systems are updated.

5.2 Excipients, Intermediates and Raw Materials

5.2.1 Retest Dating and Initial Retest Periods

Retest dating and the use of retest periods is the standard method of controlling the use of these materials.

Excipients and Raw Materials shall be assigned an indicative initial retest period and retest date based upon available data on a case by case basis. The initial retest date shall be determined by :-

1. The retest date assigned by the vendor (either stamped on the container or indicated on the certificate of analysis), assuming storage conditions at the vendor are comparable with those at the receiving site, and that the company specification is comparable with the vendorôs specification.

2. Where available, stability determined by the company or stability data provided by the vendor (where a retest date is not provided by the vendor on the label or on the Certificate of Analysis).

3. Examination (e.g. analysis, user trials, etc) of samples from stock of several batches of similar age.

For intermediates a one-off stability study is typically used to determine the initial retest period.

The retest date shall be calculated from the date of manufacture of the material if available.

For raw materials and excipients where a date of manufacture is not available from the supplier, the date of testing or date of release on the Certificate of Analysis may be used. For non-certified materials, the date of receipt at the site may also be used.

Once any material has reached its retest date, the material shall not be used until

