

## **1 Purpose**

The intent of this procedure is to provide the Active Pharmaceutical Ingredient (API) Manufacturing Sites with the principles of a stability program.

## **2 Scope and Applicability**

This procedure is applicable to all sites manufacturing active pharmaceutical ingredients.

This procedure applies to all active pharmaceutical ingredients. The protocols cover the following categories:

- (1) New commercial active pharmaceutical ingredient - first three, or early, full-scale batches manufactured at the commercial manufacturing site.
- (2) Annual Maintenance Stability testing
- (3) Stability testing associated with process modifications
- (4) Stability testing associated with process validation and process deviations

Stability studies conducted as described in the procedure will conform to worldwide registration and QA/GMP/ICH/WHO requirements.

## **3 Definitions**

### **3.1 Lead Team/Site**

Is the Team/ site that is accountable for conducting specified QA activities, notably QC analysis, release and Stability studies, as recorded in the QA agreement between the Lead Site and the Receiving Site.

### **3.2 Commercial Stability Team/Site**

Refers to the site that either conducts the stability studies on a product(s) or Active Pharmaceutical Ingredient (API) or is responsible for managing studies at a specified contractor. When a Commercial Stability Team/Site allocates all or part of a stability study to another site or contractor the work will be managed by the Commercial Stability Site. The Lead Site and Commercial Stability Site may be the same.

### **3.3 Primary Package**

Any material employed in the packaging of a pharmaceutical product or active pharmaceutical ingredient. Primary packaging material(s) form the container/closure system for the product and therefore may be in direct contact with the product. Examples include HDPE bottles/caps, blister strip packs, tubes/caps for ointments, syringes or plastic bag.

For the purposes of commercial stability studies, the primary package, i.e. the container closure system, shall be considered to be independent of any differences in labeling and/or printing attached to, or on, the primary package,

### **3.10 Trend Analysis**

A non-statistical approach to evaluate stability data tendencies over time utilizing techniques such as scatter plots, visual examination, etc. It is intended to detect stability trends that may be indicative of changes in process, methodology or any other parameters that might affect the chemical/physical parameters of the active pharmaceutical ingredient.

### **3.11 Statistical Analysis**

Analysis using formal statistical techniques, e.g. regression analysis, to objectively analyse and compare data.

### **3.12 Re-test Date**

The date when samples of the active pharmaceutical ingredient shall be re-examined to ensure that the drug is still suitable for use.

### **3.13 Re-test Period**

The period of time during which the active pharmaceutical ingredient can be considered to remain within specifications and therefore acceptable for use in the manufacture of a given drug product, provided that it has been stored under the defined conditions; after this period, the batch shall be re-tested for compliance with specifications and then used within a previously defined time period.

## **4 Responsibilities**

**4.1** It is the responsibility of each Operation Site to establish stability testing procedures that are consistent with the requirements of this Q&C Procedure and to follow these procedures when conducting stability studies assigned to the site in the Stability Master Plan (SMP).

**4.2** It is the responsibility of each Commercial Stability Site to conduct individual stability studies according to the relevant `Integrated Stability Protocols` or local protocols if no `Integrated Stability Protocol` has been issued.

## **5 Procedure**

In case of discrepancies, the regulatory filing/commitments supersede the clauses contained in this Q&C Procedure.

### **5.1 Introduction**

Ongoing surveillance of the stability profiles of commercially available active pharmaceutical ingredients is an integral part of the Company's quality assurance program. It is essential that stability studies are conducted at Stability Sites as detailed in the SMP issued by the Dossier Management Group (DMG). It is recognized that minor variations may be required as a result of special

reduction where this is carried out) of the batch manufacture and stability set down is 60 calendar days.

### **5.2.5 Data Generation and Analysis**

**5.2.5.1** All analytical and microbiological tests shall be fully validated in accordance with ICH requirements (ICH Q2) and the assay for active pharmaceutical ingredient purity must be stability indicating.

**5.2.5.2** Testing shall be performed in singlicate where method precision allows and where not prohibited by local regulatory authorities.

**5.2.5.3** Documented procedures shall be used to investigate adverse trends and/or 'out-of-specification' results and report any confirmed out-of-specification results to local senior QA management.

**5.2.5.4** The Commercial Stability Site shall provide data to DMG in the agreed format and to an agreed time schedule.

**5.2.5.5** Record all valid results. This will normally be only one, but if more than one determination is carried out, record each result, and compare each result with the specification. Act on any individual, confirmed 'out-of-specification' result.

**5.2.5.6** The use of 'trend analysis' is required annually. Statistical analysis is not a routine requirement, but may be useful in situations where the data is not conforming to expectations, e.g. comparison with historical data.

**5.2.5.7** When required, transfer of test methods to a site shall be subject of an analytical and/or microbiological technology transfer from R&D, (new products) or from another commercial manufacturing site (established/mature API:s).

## **5.3 Active Pharmaceutical Ingredient - Annual Maintenance Stability Protocols**

### **5.3.1 Selection of Batches/Packs**

One batch of each active pharmaceutical ingredient manufactured at each site shall be placed on stability annually, together with any additional studies detailed in the SMP.

Each batch shall be set down in a miniaturized replica of the actual packaging used for storage and distribution, including the closure system and any desiccants e.g. solid drug substance in polyethylene liners and liquid drug substance in glass.

### **5.3.2 Testing Schedule**

The schedule below prescribes a varied pull schedule for annual maintenance stability testing dependent on the retest period of the active pharmaceutical

The general requirements for studies on new APIs (see Section 5.2.5) shall apply to annual maintenance studies.

#### **5.4 Post-Marketing Approval Changes**

Where a process has been modified, additional samples shall be retained and placed into the commercial stability program. The test protocol and number of batches shall be dependent upon the magnitude of the change and local regulatory requirements. During the MCM process, Regulatory, Operations QA, and possibly R&D, will determine what stability studies are mandated to support the change. Additionally, locally managed changes could require the initiation of stability studies.

The following modifications are typical of situations, which will require additional stability studies:

- Change in manufacturing process of the active pharmaceutical ingredient
- Change in manufacturing site and/or manufacturer of the active pharmaceutical ingredient
- Change in the batch size of the active pharmaceutical ingredient

Note: Changes to an active pharmaceutical ingredient may require additional stability studies on formulated products incorporating the active pharmaceutical ingredient.

#### **5.5 Validation Studies and Process Deviations**

The need for studies to be conducted in support of manufacturing process validation studies or to support the release of batches that have been subject to a 'deviation' during processing shall be decided by the QA Management of the processing site, in consultation with the QA Management of downstream manufacturing (formulation) sites who may receive the batches for processing. The study conditions and testing schedules given in Sections 5.2.2 and Section 5.3.2 shall be used by the QA Management as a reference point when deciding on the protocols for these studies.