1 Purpose

The purpose of this document is to describe the procedure for the preparation and management of Stability Protocols and Stability Master Plans for marketed products and Drug Substances.

2 Scope and Applicability

This Procedure is applicable to all plans and protocols for stability studies on commercial products and Drug Substances.

3 Definitions

3.1 Commercial Stability Site

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

3.2 Commercial Packaging Site

Refers to the Site at which manufactured product is packaged in the primary marketed sales package.

3.3 Stability Master Plan (SMP)

A plan that details the stability studies required to maintain compliance with regulatory and GMP obligations and commitments and assigns each study to a specific Commercial Stability Site.

3.4 Stability Protocols

A Stability Protocol is a detailed plan used to generate and analyze stability data in support of the shelf (expiry) life of a Drug Product or retest period of a Drug Substance in a single specified market. It should include time points and conditions employed, and methodology used to generate stability data.

3.5 Integrated Stability Protocols

A detailed plan used to generate and analyze stability data in support of the retest period of a Drug Substance or the shelf (expiry) life of a Drug Product. It should whenever possible incorporate the stability requirements of more than one Drug Product containing the same Drug Substanceand/or the requirements of more than one market in a single plan/document.

3.6 Manufacturing Formulation Number (MF) or Article Number (Art. No.)

on the extremes are tested, e.g. to evaluate a range of primary package sizes. (See ICH Q1D Bracketing and matrixing designs for stability testing of drug substance and drug products.)

4 Responsibilities

4.1 Registration Officers ROs

The Registration Officer in the Dossier Management Group is responsible for creating and maintaining Stability Protocols and Stability Master Plans for the marketed products and Drug Substances in consultation with the Stability Manager.

4.2 Commercial Site Stability Manager

The Commercial Site Stability Manager or person nominated by the Stability Manager is responsible for

- creating and maintaining protocols that are required for studies that are a result of process validation or process deviations.
- approving Stability Protocols created by DMG ROs
- assuring adequate facilities and resources to execute studies according to the SMP at their site
- acting as the primary contact for the flow of samples and information between international sourcing sites
- ensuring stability set downs according to plans and protocols

4.3 Pack Evaluation Team

The DMG ROs responsible for coordinating Pack Codes and Pack Equivalency Reports (PER) within the Pack Evaluation Team are responsible for supplying other DMG ROs with the relevant information for their Drug Products or Drug Substances.

5 Procedure

5.1 Introduction

The DMG RO in consultation with the Stability Manager or person nominated by the Stability Manager from the Commercial Stability Site shall create the Stability Protocol and Stability Master Plan.

The protocol shall be based upon the ICH Stability Guidelines for new products, WHO Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms and other local guidelines that may be relevant to specific studies.

The Stability Protocol shall include the first or early commercial batches and/or the Annual Maintenance stability protocols. These protocols may be used for special studies when they exactly match the special study requirements. For new

A stability schedule shall be available for

- new formulated products that include a schedule for the three early commercial batches and for Annual Maintenance stability.
- mature formulated products that contain only an Annual Maintenance stability schedule
- Drug Substances

A stability schedule shall contain the initial and all test points in months for each condition that is applicable for the various Climatic Zones (I-IV), which the studies support. A table with the time points and required tests (as identified in the Registered Tests section) shall be constructed for each condition and market reporting group.

The schedule conditions, time points, and tests shall be based upon

- the stability protocols agreed with the various regulatory agencies for the early commercial batches and Annual Maintenance batches.

An example of a schedule for the three early commercial batches marketed only in Climatic Zones I and II is given below:

	25°C/60% RH									40°C/75% RH		
Test/Month	0	3	6	9	12	18	24	36	48	0	3	6
Test 1	X	X	X	X	X	X	X	X	X	X	X	X
Test 2	X	X	X	X	X	X	X	X	X	X	X	X
Test 3	X	X	X	X	X	X	X	X	X	X	X	X
Test 4	X				X		X	X	X			X
:												
Test n	X						X	X	X	X	X	X

An example of a schedule for Annual Maintenance is given below:

	25°C/60% RH						
Test/Month	0	6	12	18	24	36	48
Test 1	X	(X)	X	(Y)	X	X	(Z)
Test 2	X	(X)	X	(Y)	X	X	(Z)
Test 3	X	(X)	X	(Y)	X	X	(Z)
Test 4	X		X		X	X	(Z)
:							
Test n	X				X	X	(Z)

Note: (X) Only required if the shelf life is 18 months or less
(Y) Only required if the shelf life is 24 months
(Z) Only required if the shelf life is 48 months

Note that fewer or more time points may be required depending on the regulatory requirements.

A note, which references the initial test point, shall be included. The note shall state that initial results may be taken as the results of the batch release testing only when the results are obtained within the 30 days (60 days for annual studies providing that the first sample pull is 12 months or later) proceeding the start of

5.2.11 Revision of the Stability Protocol

If the Stability Protocol has had no revisions after two (2) years from the last signature (issue date) of the approved protocol, the DMG RO in consultation with the Stability Manager shall initiate a review of the protocol.

The following changes shall result in the creation of a new version of the Stability Protocol.

- Change in specification
- Change in the tests applied for example a test added or removed
- Condition change
- A new pack code added or an existing pack code removed
- Change in pull times
- A market reporting group is added or removed
- Change in Commercial Stability Site/Testing Site

The first and subsequent versions of the Stability Protocol shall be reviewed by all those required to approve the protocol.

5.3 Information to be included in a Stability Master Plan

In the SMP the DMG RO shall identify the studies required to meet regulatory requirements and GMP compliance and decide upon sample rotation among packaging sites.

5.3.1 Creating the SMP

To create the plan the following information which is contained in the protocol is needed:

- Identification of Drug Product or Drug Substance
- Market Reporting Group
- Study type
- Formulation site. (For liquid products the formulation site is the same as the packaging site)
- Drug Substance Site
- Packaging Site and Pack Details
- Composition code
- Length of study
- Protocol conditions

5.3.2 Studies to put in the SMP

- The first three commercial batches
- Annual Maintenance
- All Special Studies.

5.3.3 Information needed to decide on sample rotation

