

## **1 Purpose**

The intent of this procedure is to provide to manufacturing and primary packaging sites the principles of a stability program.

## **2 Scope and Applicability**

This procedure applies to all drug products. The procedure covers:

1. New commercial products - the three first (or early) batches manufactured at each manufacturing site at full scale production
2. Annual Maintenance Stability Testing
3. Stability testing associated with product or 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 site that is accountable for conducting specified QA activities, notably QC analysis and release, and Stability Studies, as recorded in the QA agreement between the Lead Site and the Receiving Site.

### **3.2 Commercial Stability 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 Site allocates all or part of a stability study to another sister site or contractor the work will be managed by the Commercial Stability Site. The Lead Site and Commercial Stability Site may be the same.

Note: When all or part of a study is carried out at a contractor:  
COMMERCIAL STABILITY SITE = LEAD SITE

### **3.3 Commercial Packaging Site**

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

### **3.4 Commercial Secondary Packaging/Distribution Site**

Refers to the site at which packaged product is received and distributed to the market (possibly after secondary packaging and/or local labeling).

### **3.5 Key Excipients**

Those excipients used in drug product, that significantly impact upon the physical or

## Modified Release Solid Oral Dosage Forms

A significant body of information should include, for Modified Release Solid Oral Dosage Forms, a product-specific body of information. The product-specific body of information is likely to exist after five years of commercial experience for the original complex dosage form drug product, or three years of commercial experience for any subsequent complex dosage form drug product.

### **4 Responsibilities**

- 4.1** It is the responsibility of each Operations Site to establish stability testing procedures that are consistent with the regulatory requirements and to follow these procedures 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 stability protocols if no Integrated Stability Protocol exists.

### **5 Procedure**

#### **5.1 Introduction**

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

Ongoing surveillance of the stability of commercial drug products 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.

#### **5.2 Solid/Liquid Dosage Forms - New Product Introduction**

Shelf (expiry) lives of commercial products shall be established on the basis of a combination of:

- data from stability studies conducted by R&D on pilot batches (primary stability studies).
- data from stability studies conducted by Operations on early commercial batches.

Data from primary studies are included in first submissions for marketing approval and form the basis for an interim shelf (expiry) life for the new product.

If available, data from studies on commercial scale batches may be included in the first submissions to obtain an optimum interim life for the product. Shelf (expiry) lives may be further extended as a result of later regulatory submissions containing data obtained by Operations on commercial batches.

The following sections describe in detail the stability studies that will be

	<b>New Product Introduction (three 1<sup>st</sup>, or early, batches)</b>			
Frozen	-20°C	-20°C	5°C	N/A
Refrigerated	5°C	5°C	25°C/60%RH	N/A
Room Temperature	25°C/60% RH	30°C/75% RH	40°/75% RH	30°C/65% RH
Zones/Months	I & II	III & IV	I & II III & IV	I & II
Initial (Note 1)				
1				
2				
3	L	L	A	A
6	L	L	A	A
9	L	L		A
12	L	L		A
18	L	L		
24	L	L		
36	L	L		
48	L	L		

**Note 1**

Initial results may be taken as the results of the batch release testing only when the release methods are identical to those used for stability studies, e.g. assay.

Where differences exist between release methods and stability methods, re-analysis by the stability methods shall be conducted at set down. See also Section 5.2.4.5 .

L = Long Term Stability

A = Accelerated Stability

-20°C = Long term storage condition to support products that require freezing in all climatic zones as defined by ICH.

5°C = Long term storage condition to support products that require refrigeration in all climate zones as defined by ICH. Also, accelerated conditions for product that require freezing in all climate zones as defined by ICH.

25<sup>0</sup>C/60%RH = Long term storage condition to support marketing in Climatic Zones I and II and accelerated conditions for refrigerated product as defined by ICH. For product/package combinations for the US, it may be necessary to include an additional test at a time point corresponding to the expiration date. In these cases, the need for testing at pull times greater than the expiry date should be considered.

30<sup>0</sup>C/75%RH = Long term storage condition to support marketing in Climatic Zones III & IV. The 30°C/75% RH condition is only required by a portion of the Zone IV markets, most notably Brazil and the ASEAN (Association of South East Asian Nations), but is also acceptable for markets that would accept lower humidity conditions.

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when the release methods are identical to those used for stability studies, e.g. assay. Where differences exist between release methods and stability methods, re-analysis by the stability methods shall be conducted at set down. See also Section 5.2.4.5 .

Normally, the study period for bulk packages shall be: 12 months, or 50% of the product expiry life if this is expected to be greater, at the long term storage condition and 3 months at a more severe condition to cover potential short term excursions e.g. during transport; the conditions used being those selected for accelerated studies on the commercial primary packages.

These studies shall be conducted by Pharmaceutical and Analytical Research and Development (R&D) during the development phase of the product, on behalf of Operations.

The stability profile in the bulk container should be no worse than that observed in the best primary package for that product. Otherwise, a limited time in the bulk package needs to be established and the shelf (expiry) life in the primary packages reduced accordingly.

The 30°C/75% RH condition is only required by a portion of the Zone IV markets, most notably Brazil and the ASEAN (Association of South East Asian Nations), but is also acceptable for markets that would accept lower humidity conditions.

## 5.2.4 General Requirements for Studies on New Commercial Products

**5.2.4.1** Temperatures shall be controlled to  $\pm 2^{\circ}\text{C}$  and relative humidity at  $\pm 5\%$  RH. Excursions exceeding these ranges for more than 24 hours shall be recorded and evaluated and their impact assessed and documented.

**5.2.4.2** Normally, long term and accelerated stability studies shall be carried out on closed primary packages, without secondary packaging. Exceptions are:

- É When the secondary packaging affords additional protection for the product
- É When the secondary package affords no additional protection, but provides a convenient container for holding samples within the climate chamber, e.g. boxes of tablet blister strips.

**5.2.4.3** Primary packages chosen for stability shall be taken in such a way, as they are representative of the entire batch. This does not preclude taking primary packages from a specific portion of the packaging run, if these are deemed to be representative of the entire batch.

**5.2.4.4** All primary packages containing liquids shall be stored in an orientation that is the most stressful. This will be defined by R&D for each product. Provisions should be made for control samples for all primary packages to be stored in the upright position at the long term storage temperature/humidity condition. These control samples may serve as a reference in the event of a problem arising on stability.

samples other than the initial.

#### 5.2.5.8 Policy on P.E.T. (Preservative Effectiveness Testing)

- É For products marketed in the EU that contain a preservative and for which there is a quantitative specification and analytical method with sufficient precision and sensitivity to determine the concentration during commercial stability studies, compliance with the latest version of the European Pharmacopoeia, "Efficacy of anti-microbial preservation", at the lower expiry life concentration of the preservative shall be demonstrated only during development of the product.
- É For products marketed in the EU which contain a preservative for which there is no quantitative specification or analytical method with sufficient precision and sensitivity to determine the concentration during commercial stability studies, compliance with the latest version of the European Pharmacopoeia, "Efficacy of anti-microbial preservation", shall be demonstrated at the initial and final time point of the long term storage condition.
- É For products marketed in the USA that contain a preservative, the guidance issued by the FDA for post approval stability testing shall be followed.

5.2.5.9 Any reconstitution testing should be done in accordance with the protocol transferred from R&D.

5.2.5.10 Analytical results, which are numerical, shall have those results reported numerically instead of "complies" or "passes", to allow for data evaluations and analysis

### 5.3 Solid/Liquid Dosage Forms - Annual Maintenance Studies

#### 5.3.1 Selection of Batches/Primary Packages

Each distinct commercial product/MF or Art. No./strength/primary package/packaging site combination from the Stability Site and its aligned Primary Packaging sites shall be included in the stability program, as detailed in the Stability Master Plan (SMP).

When a product/dosage strength is manufactured (formulated) at more than one site, additional studies will be conducted so that data are available to support every manufacturing (formulation) site/product/MF or Art. No./strength/primary package/packaging site combination. For solid dosage forms formulated at a site and supplied to more than one packaging site for primary packaging, a stability study will be set down to cover every manufacturing (formulation) site/product/MF or Art. No./strength/primary package/packaging site combination at least once every 5 years, either as an individual study, or by inclusion in a bracketed or matrixed study.

	<b>Annual Maintenance Schedule<sup>1</sup></b>								
Market	Other Climatic Zone I & II Primary Packs			Climatic Zone III & IV Primary Packs					
Frozen	-20°C			-20°C					
Refrigerated	5°C			5°C					
Room Temperature <sup>2</sup>	25°C/60%RH			30°C/75%RH <sup>3</sup>					
Product Shelf Life ⇒	18	24	36	48	60				
Pull Month Initial (Note 1)	<p><i>AS</i></p> <p><b>FOR OTHER CLIMATIC ZONE ZONE I &amp; II PRIMARY PACKS</b></p>								
3									
6						L			
9									
12						L	L	L	L
18						L	L		
24							L	L	L
36								L	L
48									L
60 <sup>4</sup>					L				

Note 1

Initial results may be taken as the results of the batch release testing only when the release methods are identical to those used for stability studies, e.g. assay. Where differences exist between release methods and stability methods, re-analysis by the stability methods shall be conducted and set down. See also Section 5.2.4.4 .

L = Long Term Stability

-20°C = Long term storage condition to support products that require freezing in all climatic zones as defined by ICH.

5°C = Long term storage condition to support products that require refrigeration in all climate zones as defined by ICH.

25°C/60%RH = Long term storage condition to support marketing in Climatic Zones I and II defined by ICH.

- Where product supplied in Zones I/II only, studies need to be stored and evaluated at the 25°C/60% RH condition. Where product supplied only in Zones III/IV only, studies need to be stored and evaluated at the 30°C/75% RH condition only. Where product supplied in both Zones I/II and Zones III/IV, then studies must be stored and evaluated at both conditions unless the 30°C/75%RH data supports the product's registered shelf life in Zone I/II markets. However, if the removal of the 25°C/60% condition is considered, a RIAR (Regulatory

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solutions in plastic bags, nose drops in small plastic containers etc.) and consideration shall be given to appropriate testing under such conditions.

	<b>Annual Maintenance Schedule <sup>1</sup></b>							
Market	Other Climatic Zone I & II Primary Packs		Climatic Zone III & IV Primary Packs					
Frozen	-20°C		-20°C					
Refrigerated	5°C		5°C					
Room Temperature <sup>2</sup>	25°C/40%RH or 25°C/60% RH <sup>3</sup>		30°C/75%RH <sup>4</sup>					
Product Shelf Life ⇒	18	24	36	48				
Pull Month Initial (Note 1)	<b>AS FOR OTHER CLIMATIC ZONE ZONE I &amp; II PRIMARY PACKS</b>							
3								
6					L			
9								
12					L	L	L	L
18					L	L		
24							L	L
36								L
48								

Note 1

Initial results may be taken as the results of the batch release testing only when the release methods are identical to those used for stability studies, e.g. assay. Where differences exist between release methods and stability methods, re-analysis by the stability methods shall be conducted and set down. See also Section 5.2.4.4 .

L = Long Term Stability

-20°C = Long term storage condition to support products that require freezing in all climatic zones as defined by ICH.

5°C = Long term storage condition to support products that require refrigeration in all climate zones as defined by ICH. Also, accelerated conditions for product that require freezing in all climate zones as defined by ICH.

25°C/40%RH = Long term storage condition to support marketing in Climatic Zones I and II defined by ICH.

1 Where product supplied in Zones I/II only, studies need to be stored and

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conditions and length may vary according to how the bulk container is used in manufacturing operations.

In cases where the formulation range comprises the same excipients in slightly different proportions a bracketed study on the lowest and highest strength may be used to support the range.

In cases where the formulation range comprises different compression weights of a common granulation, a study on one compression weight may be used to support all compression weights.

The study period on bulk packages used to store product for 12 months or more, and/or for transportation between manufacturing (formulation) sites and packaging sites, shall be 12 months or 50% of the product expiry life, whichever is longer and shall follow the schedule described in section 5.2.3.3. at the appropriate long term temperate storage condition, and 3 months at a more severe condition to cover potential short term excursions e.g. during transport; the conditions used being those selected for accelerated studies on the commercial primary packs. If a significant body of information exist for the product, the number of time points may be reduced if the data supports such reduction.

The stability profile in the bulk container should be no worse than that observed in the best finished package for that product. Otherwise, a maximum storage time in the bulk package needs to be established and the shelf (expiry) life in the primary packages reduced accordingly.

### **5.3.4 General Requirements for Annual Maintenance Studies**

The general requirements for studies on new products (see Section 5.2.4) shall apply to annual maintenance studies, except that the requirement to repeat the initial analysis if the set down occurs more than 30 days after the release testing is relaxed to 60 days providing that the first sample pull is 12 months or later.

### **5.3.5 Data Generation and Analysis**

The details given for studies on new products (see Section 5.2.5) shall apply to annual maintenance studies.

## **5.4 Product / Process Modification**

Where a drug substance/product, process, or primary package has been modified in a way that requires stability information to support the change, additional batches shall be entered in the commercial stability program. The test protocol, number of batches and primary packages variants shall be dependent upon the magnitude of the change and local regulatory requirements. During the MCM process, Regulatory, Operations QA, and possibly PAR&D, shall determine what stability studies are required to support the change. The DMG Stability Manager shall identify an appropriate existing Integrated Stability Protocol or create a new protocol if needed.



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The duration at each condition was chosen to allow for scheduling within a week. Different times and temperature extremes may be used where justified by the product characteristics but the time shall not be less than two days at each condition for each cycle.

There should be no delays between cycles and once Cycle 3 is completed the exposed product shall be placed in the appropriate long term and accelerated conditions.

### 5.5.2 Testing Requirements

Testing of all normal protocol requirements should be performed before Cycle 1 and after Cycle 3. The testing before cycle 1 shall be used as the T=0 time point of the subsequent long term and accelerated studies.

The results from the pre-cycling and post cycling testing should be reviewed to determine if any significant changes have occurred as defined by ICH. If there has been no significant change, the long term and accelerated studies shall continue using the schedule that follows (5.5.3). If a significant change is observed, further storage at a long term and accelerated condition and testing shall be evaluated to determine if the studies should continue.

### 5.5.3 Schedule

Shelf-life <sup>1</sup>	Long Term (as defined by ICH for product type; e.g. 25°C/60% RH, 25°C/40% RH)							Accelerated (as defined by ICH for product type; e.g. 40°C/75% RH or 40°C/25% RH)	
	0	12	18	24	36	48	60	3	6
Months									
18	X	X	X					X	X
24	X	X		X				X	X
36	X	X		X	X			X	X
48	X	X		X	X	X		X	X
60	X	X		X	X	X	X	X	X

<sup>1</sup> The shelf life should be the expected or desired shelf life of the product

### 5.6 Additional Product/Package Combination Introduced to a Packaging Site

The first batch of an additional product/package combination introduced to a specific packaging site may be identified as a manufacturing change or may be included in the roll out plan for a new product introduction (Product Establishment Plan). In either case, the first batch packaged at each packaging site shall be set down as a special study incorporating appropriate accelerated and long term conditions. The time points should be the same as those described in sections 5.2.3.1 or 5.2.3.2. Fewer time points may be used if scientifically justified, and agreement with regulatory agency has been established.

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