1 Purpose

The purpose of this document is to provide recommendations for performing and documenting stability studies within R&D. Deviations from the recommended practice may be made providing

- The scientific rationale can be justified against regulatory requirements and expectations.
- There is no precedent that the scientific rationale will be unacceptable to regulatory authorities.
- For formal stability studies, the deviations and scientific rationale justifying them, do not conflict with, or undermine the validity of stability studies on similar commercial product types, particularly those belonging to the same therapeutic area.

In addition, this document describes the responsibilities of those involved with stability studies. These responsibilities are the mandatory elements of this guideline.

2 Scope and Applicability

This Guideline is applicable to all pharmaceutical drug Research and Development R&D functions when either conducting or outsourcing any stability study during drug development. For the drug development template refer to the Appendices, see 9.3.

Where stability data are provided in a regulatory submission, stability studies should meet the appropriate regulatory requirements.

This guideline is applicable to the following:

- Drug substances
- Drug products (including formulation intermediates and line extensions)
- Comparators
- Placebo products

The general principals within this guideline should be considered for biotechnology products however further guidance may be found in ICH guideline Q5C.

3 Definitions

3.1 Bracketing:

The design of a stability schedule such that only samples on the extremes of certain design factors, e.g., strength, package size, are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells).

development.

3.8 JNDA:

Japanese New Drug Application.

3.9 MAA:

Marketing Authorization Application including JNDA and NDA.

3.10 Matrixing:

The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system and possibly in some cases, different container closure systems.

3.11 NDA:

New Drug Application

3.12 Re-test date:

The date after which samples of the drug substance should be examined to ensure the material is still in compliance with the specification and suitable for use in the manufacture of a given drug product. Excipients normally have re-test dates.

3.13 Re-test period:

The period of time during which the drug substance is expected to remain within its specification and, therefore can be used in the manufacture of a given drug product, provided that the drug substance has been stored under the defined conditions. After this period, a batch of drug substance destined for use in the manufacture of a commercial drug product should be re-tested for compliance with the specification and then used immediately. A batch of drug substance can be re-tested multiple times and a different portion of the batch used after each re-test, as long as it continues to comply with the specification.

Drug substances destined for use in the manufacture of investigational medicinal products once re-tested for compliance with the specification at the end of the re-test period, may have the re-test period extended as appropriate, based on the long term accumulated data.

3.14 Shelf life:

The time period during which a drug product is expected to remain within the

applied when a range of strengths, and different drug/excipient ratios are being developed. One batch of each formulation, strength or pack type is typically tested. A matrixing design may also be appropriate.

Using development stability data, re-test periods for drug substances and shelf lives for drug products should be established for non-clinical and clinical material. Extrapolations may be used, see 5.14.

Stability studies in bulk packs used for intermediate storage of investigational medicinal products should be considered especially in Phase III. Prior to Phase III, a shelf life may be assigned to bulk material using appropriate open dish stability data.

For drug substances, development stability studies should also:

- Identify any change in physical characteristics and the solid state degradation products that are likely to occur under long term and accelerated storage conditions that will be encountered when stored as directed

For drug products, development stability studies should also:

- Identify formulation degradation products produced when stored in the primary pack under controlled conditions which model the real time storage conditions which are likely to be encountered when the product is stored as intended by a target commercial label

- Identify any interactions with excipients, packaging and container orientation to support formulation and/or packaging development.

- Monitor changes in product performance characteristics
- Test in-use stability and sensitivity to other types of stress refer to 5.10 and 5.11.

In addition, for both drug substances and products, stability studies should:

- Identify influences from production/processing parameters
- Identify any specific packaging or labeling requirements

It is recognized that changes may occur to raw material or intermediate sources, synthetic route and formulation composition and equipment and scale during development. Each change should be considered in the context of whether further stability testing of materials produced by the new process is required. If there is a significant change in formulation then additional stressed/forced degradation testing may be required.

If appropriate, results of development stability studies may be included in the MAA as supporting stability data.

For Phase IV (post approval) studies, material may be provided in a pack other than the commercial one. This should be covered by stability data.

the drug substance with other ingredients. Where necessary, consider providing cumulative stability data for the drug product in the first MAA.

5.8 Bracketing and matrixing

Refer to ICH guideline Q1D. It is acceptable to use bracketing and matrixing for formulations that are not so closely related with justification provided from supporting data. When applying bracketing and matrixing to different pack types and sizes etc, the bulk sample is normally tested instead of each variant at the initial time point.

5.9 Packaging

Global guidance and the local interpretation of this guideline should be considered when selecting the packaging for development studies. For formal stability studies drug substances should be packaged in a container closure system that is the same or simulates the packaging proposed for storage and distribution. For drug product the primary pack should be that of the proposed commercial drug product. Any secondary pack should be evaluated if it affords additional protection, other than physical, of the product. If it is found that the secondary package improves the stability of the product, the primary batches studied should be packed and stored with a representative secondary package in place. In some cases, stability data should be generated in the absence of a protective secondary pack to justify a suitable in use shelf life. Where a packaging device provides a specific functionality, consider the need to test the packaging performance alone in a separate stability study.

5.10 Transportation studies

To recommend special transportation and storage conditions for investigational medicinal products and justify temperature excursions consider if temperature cycling is also appropriate in development studies. Temperature cycling is normally conducted during formal stability studies. For certain drug products it is a regulatory requirement to submit temperature cycling studies in the MAA, eg for suspensions and creams this is a US regulatory requirement. Cycling conditions will depend on the conditions that the product may be exposed to once the product is in distribution and use. If temperature cycling is performed in early development and there is any change in formulation or analytical methodology consider repeating cycling studies in parallel to formal studies.

- A temperature cycling study for drug products that may be exposed to temperature variations above freezing may consist of three cycles of two days at refrigerated temperature (2-8°C) followed by a minimum of two days at 40°C.

- A temperature cycling study for drug products that may be exposed to sub-freezing temperatures may consist of three cycles of two days at freezer temperature (- 20°C± 5°C) followed by a minimum of two days at 40°C. Consider testing at the long term condition following temperature cycling.

5.14.1 Re-test/shelf life predictions for material used in non-clinical and clinical studies

During the development of a new drug substance and drug product, when only limited long term stability data are available, it is acceptable to evaluate stressed and accelerated stability data and if satisfactory, extrapolate a re-test period/shelf life for material used in non-clinical and clinical studies, which is longer than the amount of real time stability data accumulated. Guidance on extrapolation of data is provided in the Appendices, see 9.2.

Stability data available for similar drug product formulations or from investigational work may be used as supporting evidence for the assignment of an extrapolated shelf life.

The maximum extrapolated re-test period or shelf life should be based on there being 'no significant change' (ie the change is measurable but remains within the definition in ICH guideline Q1A) at the stated condition. It is acceptable to evaluate available stability data and extend the re-test period or shelf life longer than the accumulated real time stability data. This extended re-test period or shelf life should be confirmed with real time data.

For practical reasons a shelf life of at least 24 months is normally required for Phase III investigational medicinal products. For less stable or complex formulations more conservative extrapolations of stability data may apply.

Microbiological considerations should be taken into account when assigning a shelf life. The manufacturing procedure and the presence / absence of a preservative should be considered prior to assigning a shelf life and storage condition.

5.14.2 Re-test/shelf life predictions for commercial material

In addition to the commercial shelf lives proposed according to current ICH guideline Q1E, consideration should be given to any specific territorial requirements. Guidance on this and other territory specific requirements should be available from Regulatory CMC.

5.14.3 Re-test date for excipients

For commercially available excipients, published stability data should be available from the vendor and the recommended re-test date should be observed.

5.14.4 Shelf life for comparators

An unmodified product in the original primary pack or repackaged into a packaging giving equivalent protection should be given the shelf life assigned to the original product. Where stability data are generated on a modified product, extrapolations may be made and any shelf life assigned should not be beyond that of the shelf life of the unmodified commercial product.

Appendix 1

9.1 Protocols

Protocols should be prepared at all stages so that it is clear what should be done. The level of details will increase during development.

Example stability protocols are provided here for guidance.

9.1.1 Development protocols

Table 1 Example of a Stability Protocol for Packed Investigational Medicinal Products

Months	25°C/60%RH	30°C/65%RH	40°C/75%RH	50°C	Photostability
1	O		O	O	O[a]
3	T	O	T	O	
6	T	O	T		
9	O	O	O[c]		
12	T	O			
18	O	O			
24	T	O			
etc[b]					

T = testing
O = Optional
References should be stored at 5°C
[a] = Actual time depends on light intensity, maximum exposure detailed in ICH guideline Q1B
[b] = Longer storage time optional
[c] = May be required to support clinical studies conducted in Zone IV countries.

For sensitive formulations (e.g. solutions or suspensions) long term condition in the freezer or refrigerator may be necessary. For these studies refrigerator or 25°C/60%RH respectively are accelerated conditions.

Table 3 Example of a Stability Protocol for Worldwide Marketing of a Less Stable Drug Product

Months	25°C/60%RH[ae]	30°C/65%RH[af]	40°C/75%RH[ae]	50°C[b]	Photostability[b]
1	-		-	O	T[c]
3	T[d]	O	T	O	
6	T	O	T		
9	T	O			
12	T	O			
18	T				
24	T				
36	T				

T = testing
O = Optional
[a] = 3 batches
[b] = One batch only
[c] = Actual time depends on light intensity, maximum exposure detailed in ICH guideline Q1B
[d] = One batch stored open to support pharmacy dosing regimes
[e] = Where a more protective pack has been developed to protect a moisture sensitive drug product for Zone IV markets, conduct testing at the long term condition of 30°C/75%RH and accelerated testing at 40°C/75%RH, see Table 2.
[f] = ICH Intermediate condition if failure at 40°C/75%RH should occur

Allocation of re-test period/shelf life

Table 4 Allocation of Re-test period/Shelf life for Stable Non-clinical and Investigational Material

Storage condition	Extrapolation factor	Time point (months)	Maximum extrapolated re-test period / shelf life	Example
Thermal stressed (50°C)	x 6	a	6 * a	Where a = 1 month max shelf life = 6 months
Accelerated (40°C/75%RH)	x 4	a	4 * a	Where a = 6 months max shelf life = 24 months
Long term (25°C/60%RH) or Intermediate (30°C/65%RH) **AND** accelerated (40°C/75%RH)	x 2	a	2 * a (≤18 months data) a + 12 (>18 months data)	Where a = 18 months max shelf life = 36 months Where a = 24 months max shelf life = 36 months

Table 5 Recommended testing conditions for drug substances and drug products

Condition °C/%RH[1]	Comment
40/NMT25)	Evaluation of significant water loss at not more than 25% RH according to ICH Q1A
Inhalation Products	
25/60	Long term condition (Climatic zones I and II)
and/or	
30/75	Long term condition (Climatic zones III and IV)
25/75	Additional intermediate condition for US only, up to 6 months for use if significant change at 40/75 for any of the parameters delivered dose or fine particle size distribution
25/75	Additional condition for products using a protective, secondary package (e.g. foil over wrap). Storage in secondary package up to 1/3 of expiration dating period and without secondary pack for a period corresponding to the in-use shelf life.
30/65	Intermediate condition, up to 12 months, for use if significant change at 40/75, and if 25/60 is the long term condition (US and others)
40/75	Accelerated condition, up to 6 months

Note 1: Temperatures greater than 15°C should be controlled within the range ±2°C, for 5°C ±3°C and -20°C ± 5°C. Relative humidity should be controlled within the range ±5%.
Note 2: Stability studies on drug products in impermeable containers can be conducted at any controlled or ambient humidity condition
Note 3: Water loss rates should be determined by measuring weight loss, at least once for a specific semi-permeable pack at different conditions e.g. 25, 30 and 40°C with relatively low humidity. General case conditions can be used for stability studies once a linear water loss over time has been demonstrated. The effect of water loss should always be considered when evaluating stability data.