approved specification, provided that it is stored under the conditions defined on the container label.

4 Responsibilities

It is the responsibility of R&D to generate stability data to a scientific level that supports the development, production and worldwide marketing of a drug product.

4.1 R&D Line Management

R&D Line Management, as defined in local procedures, supported by or in conjunction with other relevant personnel where appropriate, is responsible for:

- The principles of a stability program for drug substances, drug products, comparators and placebo products at all stages of drug development

- An awareness of approved and draft stability guidelines
- Assessing if reduced stability programs can be applied
- Appropriate consultation with Regulatory CMC and subsequently if necessary with relevant authorities
- Ensuring that suitable batches are placed on stability
- Documenting and approving stability protocols according to local procedures
- Evaluating stability data against acceptance criteria and reporting data according to GEL templates and local procedures
- Assigning appropriate re-test periods, shelf lives and storage conditions for drug substances, investigational medicinal products, excipients and comparators and updating when more data become available
- Assigning re-test periods, shelf lives and storage conditions to be included in the MAA
- Ensuring the hand over of stability studies to Operations and agreeing together the stability protocols for commitment and annual maintenance batches in the MAA

4.2 R&D QA

QA is responsible for:

- Releasing batches of drug substances and drug products for formal (MAA) stability studies.

- It is not necessary for QA to release batches of drug substances and drug products prior to the start of a stability study, providing there is no undue delay. A risk assessment for the project is recommended under these circumstances.

5 Guideline

This section of the Stability Guideline provides recommendations on stability testing requirements, however provides the flexibility to use alternative

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 4

Recommended testing conditions for drug substances and drug products

Table 5 Recommended testing conditions for drug substances and drug products

Condition °C/%RH[1]	Comment
Drug substances and products, general case[2]	
25/60	Long term condition (Climatic zones I and II)
and/or	
30/75	Long term condition (Climatic zones III and IV). Consultation with regulatory authority required if used as the long term condition in zones I and II.
30/65	Intermediate condition (Climatic zones I and II), up to 12 months, for use if significant change at 40/75,
40/75	Accelerated condition, up to 6 months
50/Ambient	Stressed condition to cover extremely hot and dry conditions
Drug substances or products intended for storage in a refrigerator	
5/Ambient	Long term condition
25/60	Accelerated condition, up to 6 months
Drug substances or products intended for storage in a freezer	
-20/Ambient	Long term condition
Aqueous-based Drug Products packed in semi-permeable containers[3]	
25/60 (alt 25/40)	Long term condition (Climatic zones I and II). Water loss evaluation at 25/40 according to ICH Q1A
and/or	
30/65 or 30/75 (alt 30/35)	Long term condition (Climatic zones III and IV) Alternative to long-term storage condition for climatic zones I and II for stable products. Water loss evaluation according to ICH Q1F
30/65	Intermediate condition, up to 12 months, for use if significant change at 40/75, and if 25/60) (alt 25/40) is the long-term condition
40/75 (alt	Accelerated condition, up to 6 months

