chemical characteristics of the dosage form, e.g. magnesium stearate (dissolution), sodium benzoate, (microbiological preservative), etc.

3.6 Liquids

Dosage forms intended for oral administration or cutaneous use, e.g. solutions, emulsions, creams, or suspensions. They may contain one or more active ingredients in a suitable vehicle. They may contain suitable antimicrobial preservatives, antioxidants and other auxiliary substances such as stabilizers, emulsifiers and thickeners.

3.7 Bracketing

The design of a stability schedule so that at any time point only the samples on the extremes, for example of container size and/or dosage strengths, are tested.

3.8 Matrixing

The statistical design of a stability protocol such that only a fraction of the total number of samples are tested at any specified point in time. The tested samples for the same product should cover e.g. different batches, different strengths, different sizes of the same container and closure.

3.9 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 an Active Pharmaceutical Ingredient (API) in a single specified market. It should include time points and conditions employed, and methodology used to generate stability data

3.10 Integrated Stability Protocols

A detailed plan used to generate and analyze stability data in support of the retest period of an Active Pharmaceutical Ingredient (API) 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 API and/or the requirements of more than one market in a single plan/document.

3.11 Manufacturing Change Management

Manufacturing Change Management. This is the process that facilitates the tracking, review and approval/rejection of changes that may impact on the registered data and on the international supply of products.

3.12 Stability Master Plan (SMP)

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

3.13 Primary Package

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.

25^0C/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.

30^0C/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.

40^0C/75%RH = Accelerated storage condition as defined by ICH.

30^0C/65%RH = Intermediate condition to replace 40^0C/75%RH where allowed by ICH Guidelines; also where the product is of a flammable nature making studies at elevated temperatures inappropriate from a safety aspect.

These study conditions and testing schedules are geared to meet general ICH and tropical market requirements for products without a specific labeled storage statement or with a labeled storage statement of 'store below 30^0C'. If it is known from earlier studies that the product will not remain in specification when stored for 48 months at the long term storage conditions included in the table, the duration of long term studies can be reduced.

If there is a cautionary labeling statement of 'store below 25°C' for a package marketed in Zones III/IV, the only long term storage condition required is 25^0C/60% RH.

The study conditions and testing schedules may be further modified depending on specific drug product characteristics. For example, if the product is not sufficiently stable, physically or chemically, at 25^0C to justify a commercially

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.

The use of bracketing or matrixing (e.g. strengths, primary packages) may be considered where technically justified and agreed with RA.

Studies shall be conducted more frequently if required to meet specific regulatory requirements, e.g. on product/strength/primary package combinations marketed in USA and Canada.

5.3.2 Stability Protocols and Integrated Stability Protocols

Integrated Stability Protocols, or individual market specific stability protocols, for studies on each product/primary package combination, shall be defined to meet the regulatory requirements of each country where it is marketed. Each study shall be referenced to the appropriate Integrated Stability Protocol or individual study protocol.

The following sub-sections in Section 5.3 of this procedure summaries the general requirements of annual maintenance stability studies.

5.3.3 Study Conditions and Testing Schedules (Annual & Bulk Product Stability)

The number of lots of drug product placed on stability and the frequency of testing shall be designed to confirm that commercial products continue to exhibit the same stability characteristics that were demonstrated in primary stability studies and the studies on the 3 first, or early, commercial scale batches.

5.3.3.1 Solid Dosage Forms

The following table describes a reduced pull schedule for annual maintenance stability testing dependent on the expiry life of the product, ranging from 18 to 60 months. Application of this reduced pull schedule is dependent on the availability

1 Where product supplied in Zones I/II only, studies need to be stored and evaluated at the 25°C/40% RH condition. Where product supplied only in Zones III/IV only, studies need to be stored and evaluated at the 30°C/70% 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 Impact Assessment Report) shall be raised before implementation.

2 If product is stored in a hermetically sealed container, humidity control is not needed.

3 25°C/60% RH may be used if the appropriate development work has been done to determine the ration of water loss between 40% and 60% relative humidity at 25°C. This can be achieved by experimentally determining the permeation coefficient for the container closure system or, as shown in the example below, using the calculated ratio of water loss rates between the two humidity conditions at the same temperature. The permeation coefficient for a container closure system can be experimentally determined by using the worst-case scenario (e.g., the most diluted of a series of concentrations) for the proposed drug product. Examples can be found in the ICH Q1A(R2) reference.

4 30°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.
For products packaged in hermetically sealed containers that are stable for at least 3 years at 30°C and that are marketed in both Climatic Zones II and IV, the 25°/60° condition can be omitted.

The need to include the Ph. Eur. Freedom from Microbiological Contamination Test in the protocol for stability studies on oral dosage forms products (e.g. at the beginning and end of long term study) should be considered and included in the protocol if necessary.

5.3.3.3 Bulk Primary Package Stability

Stability data on bulk package(s) intended to be used for new formulated product will have been generated during the development phase of a new product. However, there may be occasions when studies on formulated products in bulk packages may be required in Operations, e.g.

When a new or modified bulk container is introduced

When no such data on established/mature products exist

Typically, a 'once only' study, on each product /MF. or Article No./dosage strength/bulk package type combination shall be conducted to support transport and/or storage in the bulk container types intended to be used in commercial operations for storage over time periods of more than 30 days. The study

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[1]	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)	
Months	0	12	18	24	36	48	60	3	6
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

[1] 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.

5.7 New Primary Package Introductions

