Drug Development and Industrial Pharmacy, 22(9&10), 851-871 (1996)

RESEARCH PAPERS

Stability Testing of Clinical Samples

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ABSTRACT

The stability program for clinical samples as presented is based on the ICH Tripartite Guideline for Stability Testing of New Drug Substances and Products and the same principles that the program followed throughout the development of a drug product. But the Guideline and the basic principles were adapted to deal with the specific problems encountered with clinical samples. The expiration dates represent minimum shelf lives, storage conditions, and storage periods, and the minimum shelf lives correspond the duration of the clinical trials in phases I to III. Shelf lives are established on the basis of stress and accelerated tests to provide all batches with an open expiration date. They are supported and confirmed by long-term tests conducted under the storage conditions presenting climate zone II, 25°C/60% RH. The self lives determined apply to all the batches of the relevant development stage, although only the batches in the final phase of development originate from a validated manufacturing phase. For different dosages, dosage forms, and packaging materials, the number of batches and analysis is reduced by scientifically based rationalization measures such as bracketing and matrixing. The stability results obtained with clinical samples are a major factor for achieving a comprehensive assessment of the quality of a finished medicinal product. In this way it is possible to establish a link between the quality of clinical batches for phases I-III and the quality of the finished drug product.

INTRODUCTION

General Requirements for Stability Testing

The aim of stability testing is to ensure the quality, safety, and effectiveness of drug products up to their expiration date. This means that all organoleptic, physicochemical, chemical, and microbial test results must be within the shelf-life tolerance ranges up to the end of the shelf life. Extensive studies are needed for this purpose. Stability testing accompanies the development of a medicinal product from the first preliminary trials with the drug substance up to continuous production. If the sta-

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bility program is scientifically well founded, systematically structured, and logically coordinated, stability information will be continuously augmented and become increasingly reliable.

The overall stability program can be divided into six stages (1):

Stage 1: Stress and acceleration tests with the drug substance

Stage 2: Preformulation and formulation finding for
- Toxicological test samples
- Clinical samples
- Final dosage form

Stage 3: Stress and acceleration tests with selected formulations
- Toxicological test samples
- Clinical samples
- Final dosage form

Stage 4: Acceleration and long-term tests on drug substance and drug products up to marketing authorisation

Stage 5: On-going stability testing of drug substance, drug products
- Marketing authorization batches
- Production batches

Stage 6: Follow-up stability tests on drug substance and drug products
- Continuous production
- Modifications during continuous production

Each stage covers 11 basic principles (2):

1. Selection of batches and samples
2. Test criteria
3. Analytical procedures
4. Specifications
5. Storage conditions
6. Testing frequency
7. Storage period
8. Number of batches
9. Packaging materials
10. Evaluation
11. Stability information

Some of these elements such as selection of samples and batches, number of batches, storage conditions, testing frequency, and storage periods are firmly established, while others such as test criteria, analytical procedures with validation, and specifications undergo further development. Combining the 6 stages and the 11 basic principles yields a systematically structured stability study schedule as shown in Table 1.

The stability program shown is valid for worldwide launch in climatic zones I–IV (3). If drug products are to be sold only in climatic zones I–II including the EU, Japan, and the USA, however, across-the-board storage at 30°C/70% RH is not necessary.

The ICH Tripartite Guideline for Stability Testing of New Drug Substances and Products will be binding for the EU, Japan, and the USA from January 1, 1998 onwards but can already be applied today instead of national guidelines.

This Guideline is also based on the 11 basic principles as presented in Table 2. The ICH Tripartite Guideline, however, does not make any reference to the stability testing of clinical samples.

Specific Requirements for Stability Testing of Clinical Samples

Similarly to the requirements for proprietary medicinals, the aim of stability testing in this area of clinical samples is to maintain the quality and safety of these materials up to the end of phase I, II, and III clinical trials. This means that all relevant test results must remain within the shelf-life specifications up to the end of the clinical trial. In systematically structured stability programs, stability tests are carried out on clinical samples in stages 2 and 3. Stability testing accompanies phase I–III clinical trials.

At first, neither the dosage, formulation, nor dosage form are definitely established, but these are gradually defined during the course of development. The same applies to analytical procedures and specifications.

The effort and scope of stability testing must be tailored to the specific problem. The stability program will always differ from that required to generate stability information (expiration date, etc.) for marketing authorization application documents for proprietary medicinals. The stability information is based on the results obtained with three representative pilot-plant batches put into storage after the end of development. The stability information is then applicable to all production batches.

The stability information for clinical samples is required only for a small number of batches and for the duration of the respective clinical trial. The shelf-life determined is thus not a maximum shelf-life (≤5 years) at the end of which the tolerance limits of the shelf-life specifications for individual test parameters are reached,

but a minimum shelf-life at the end of which the tolerance limits usually have not been reached. There are no official regulations stipulating effort, scope, and implementation, which are left to the manufacturer's discretion.

Like finished medicinal products, clinical samples in the EU are required to be marked with an open expiration date, a requirement which does not apply for Japan and the USA. Furthermore, in the UK (CTX) and the USA (IND), the provision of stability information is a precondition for the commencement of clinical trials.

Minimum shelf-lives must be available for the open expiration date before the batches are manufactured. Specific stress and acceleration tests will therefore be performed and stability predictions derived from the results because only this approach can guarantee continuous development without substantial time loss due to long-term testing.

Stability information for clinical samples plays a very important role in the general assessment of the quality and safety of a medicinal product. Continuous stability is assured for the transition from phase I to III, including pivotal and equivalence batches, to the finished drug product in the commercial form.

Stability programs for clinical samples now have to be based on the ICH Tripartite Guideline for Stability Testing of Drug Substances and Drug Products although the guideline itself, as already mentioned, does not apply to clinical samples. The basic principles of the ICH Tripartite Guideline correspond to the aforementioned 11 principles and now have to be adapted to deal with the specific problems encountered with clinical samples.

BASIC PRINCIPLES OF STABILITY TESTING APPLIED TO CLINICAL SAMPLES

Selection of Batches and Samples

The drug product is in the process of development. Several dosages are tested in clinical phase I, and the formulation and dosage form are modified in the transition to II and III.

This developmental process has to be taken into account when selecting the batches. Especially in the initial phase of development, no representative batches are available. The following batches are put into storage with the aim of establishing the minimum shelf-life for phases I to III:

Clinical phase I: experimental batches
Clinical phase II: clinical experimental batches
Clinical phase III: clinical or pilot-plant batches

Test Criteria

The criteria investigated are those that

- Are potentially subject to change during the course of storage
- Have a particular bearing on the quality, safety, or acceptance of the product

The relevant test criteria will become apparent during the course of development from phase I to phase III.

Analytical Procedures

The analytical procedures themselves undergo a process of development from phase I to phase III. The same applies for the validation. Three stages with the following criteria can be distinguished:

1. Orientational stage
   - Validation parameters: specificity, linearity, accuracy (= theoretical value), limit of quantitation
   - Data required: before start of clinical phase I
2. Preliminary validation
   - Validation parameters: Additional validation parameters: accuracy (= 75% and 125% of the theoretical value), limit of detection, reproducibility
   - Data required: before start of clinical phase II
3. Full validation
   - Additional validation parameters: intermediate precision, robustness
   - Data required: before start of phase III

Specifications

Generally, a distinction is made between the following:

- Release specifications: quality after manufacture
- Shelf-life specification: quality up to the expiration date

Compendial tolerance limits are shelf-life specifications.

Table 1

Principle	Stage 1: Stress and Acceleration Tests with Drug Substance	Stage 2: Preformulation and Formulation Finding	Stage 3: Stress and Acceleration Tests with Selected Drug Products
Selection of batches and samples	Experimental batches	Experimental batches	Experimental batches, clinical batches
Test criteria	Depending on problem	Depending on problem	Depending on problem
Analytical procedures	Relevant for stability, preliminary validation	Relevant for stability, orientational validation	Relevant for stability preliminary validation
Specifications	Guide value	Guide value	Preliminary
Storage conditions			-10°C
		4°C	4°C
	25°C/60%	25°C/60%	25°C/60%
	30°C/70%	30°C/70%	30°C/70%
	40°C/75%	40°C/75%	40°C/75%
	40°, 50°, 60°, 70°C	40°,60°C	40°, 50°, 60°, 70°C
Testing frequency	0, 1, 2, 3 months	Depending on problem	a. Depending on problem b. 0, 1, 2, 3, 6 months
Storage period	Up to 3 months	Depending on problem	a. Up to 3 months b. Up to 6 months
Number of batches	1	Depending on problem	a. Depending on problem b. 1
Packaging material	a. Open b. Standard packaging material	a. Depending on problem, standard packaging material	a. Depending on problem, standard packaging material
Evaluation	Statistics, reaction kinetics, stability report as drug substance stability profile	Statistics, research report	Statistics, reaction kinetics: a. Stability report for clinical samples b. Stability report as drug product stability profile
Stability information	a. Retest period b. Packaging materials c. Storage instructions d. Test parameters for long-term testing e. Preliminary stability prediction for drug products	a. Selection of drug product b. Minimum shelf-life for clinical phase I c. Minimum shelf-life for toxicological samples	a. Shelf-life predictions b. Storage instructions c. Test parameters for long-term testing d. Selection of packaging materials e. Minimum shelf-life for clinical phases II and III

Systematically Structured Stability Study Schedule

Stage 4: Acceleration and Long-term Tests up to Marketing Authorization, Drug Substance, Drug Products	Stage 5: Ongoing Stability Testing, Drug Substance, Drug Products	Stage 6: Follow-up Stability Tests, Drug Substance, Drug Products, Continuous Production, Modifications
Representative pilot-plant batches	Representative pilot-plant batches, production batches	Representative production batches
Depending on results obtained in stages 1–3	As for stage 4	Depending on results of stage 4
Relevant for stability, full validation	As for stage 4	Relevant for stability, full validation, or revalidation
Final shelf-life specifications	Final shelf-life specifications	Final shelf-life specifications
4°C 25°C/60% 30°C/70% 40°C/75%	4°C 25°C/60% 30°C/70% 40°C/75%	4°C 25°C/60% 30°C/70% 40°C/75%
a. 0, 3, 6, 9, 12, (18) months	a. (18), 24, 36, 48, 60 b. 0, (3), 6, (9), 12, (18), 24, 36, 48, 60 months	a. 0, 6, 12, 24, 36, 48, 60 months b. 0, 1, 2, 3, 6 months
a. Up to 12 or 18 months	a. Up to 60 months	a. Up to 60 months b. Up to 6 months
a. 3	a. 3 b. 3	a. 1 per year b. 1–3
Commercial packaging material	Commercial packaging material	a. Commercial packaging material b. Standard packaging material
Statistics, reaction kinetics, stability report	Statistics, stability report	Statistics, reaction kinetics, stability report
a. Shelf-life predictions b. Stability after opening the container c. Storage instructions	a. Confirmation of shelf-lives	a. Confirmation of shelf-lives b. Assessment variations

Table 2

Basic Principle	Stress Testing with Drug Substance	Stress Testing with Drug Product	Accelerated and Long-Term Testing with Drug Substance, Formal Studies
Selection of batches	Laboratory batch	Laboratory batch	Pilot-plant batches
Test criteria	As relevant	Depending on dosage forms	Depending on influence on quality, safety, efficacy. Physical, chemical, microbial
Test procedures	Stability-indicating, validated	Stability-indicating, validated	Stability-indicating, validated
Specifications	Preliminary release specifications	Preliminary shelf-life specifications	Release specifications
Storage conditions	open, e.g., 50°C, 60°C, 70°C	open, e.g., 50°C, 60°C, 70°C	40°C/75% 25°C/60%
Testing frequency	Open, not defined	Open, not defined	0, 3, 6, 9, 12
Storage period	Open, not defined	Open, not defined	40°C/75% → 6 months 25°C/60% → 12 months
Number of batches	1	1	3
Packaging, container	Not defined	Not defined	Final or simulated final
Evaluation	Open, not defined Physical, chemical quality characteristics. Kinetic and statistical calculations	Open, not defined Organoleptic, physical, chemical, microbial quality characteristics Kinetic and statistical calculations	Organoleptic, physical, chemical, quality characteristics; regression analysis where relevant
Statements, labeling	Prediction of retest period, storage instructions if necessary Stability profile of drug substance	Prediction of shelf-life, storage instructions if necessary Stability profile of drug product.	Prediction of retest period, storage instructions if necessary

Storage Conditions

A basic distinction is drawn between stress, and accelerated and long-term storage conditions:

Stress
- Temperature: 10°C higher than acceleration temperature 40°C; e.g., 50°C, 60°C, 70°C, -10°C
- Temperature cycle 4°-40°C

Accelerated storage
- 40°C/75%
- 25°C/60% open storage

Long-term storage
- 25°C/60%
- 30°C/70%

The conditions used in stress and accelerated tests are above those of the relevant climatic zones, allowing:

ICH Tripartite Guideline, Stability Testing of New Drug Substances and Products

Accelerated and Long-Term Testing with Drug Product, Formal Studies	Ongoing Testing, Accelerated and Long-Term with Drug Substance	Ongoing Testing, Accelerated and Long-Term with Drug Product
Pilot-plant batches	Pilot-plant and production batches	Pilot-plant and production batches
Depending on influence on quality, safety, efficacy. Organoleptic, physical, chemical, microbial	Depending on influence on quality, safety, efficacy. Physical, chemical, microbial	Depending on influence on quality, safety, efficacy. Organoleptic, physical, chemical, microbial
Stability-indicating, validated	Stability-indicating, validated	Stability-indicating, validated
Shelf-life specifications	Release specifications	Shelf-life specifications
40°C/75% (30°C/60%) 25°C/60%,	25°C/60%	40°C/75% (30°C/60%) 25°C/60%
0, 3, 6, 9, 12	18, 24, 36, 48, 60; (3), 6, (9), 12, 24, 36, 48, 60	18, 24, 36, 48, 60; (3), 6, (9), 12, 24, 36, 48, 60
40°C/75% → 6 months 25°C/60% → 12 months	25°C/60% → 60 months 25°C/60% → 60 months	25°C/60% → 60 months 40°C/75% → 6 months 25°C/60% → 60 months
3	3 ongoing 3 production	3 ongoing 3 production
Final or simulated final	Final or simulated final	Final or simulated final
Organoleptic, physical, chemical, microbial quality characteristics; regression analysis where relevant	Organoleptic, physical, chemical quality characteristics; regression analysis where relevant	Organoleptic, physical, chemical, microbial quality characteristics; regression analysis where relevant
Prediction of shelf-life, storage instructions if necessary	Extension and confirmation of retest period, storage instructions if necessary	Extension and confirmation of shelf-life, storage instructions if necessary

- Verification of the discriminatory power of the analytical procedure
- Identification of weaknesses of a formulation
- Generation of stability information

The last-named aspect is particularly important in designing a stability program for clinical samples. To ensure continuous development, specific stress and acceleration tests are carried out which are then verified by long-term tests.

If stress and acceleration tests are to be successful, two aspects must be paid special attention:

- Clear separation between the tests for
  -Organoleptic and physicochemical stability and
  -Chemical/microbial stability
- Use of packaging materials impermeable to water

vapor for stress tests at elevated temperatures, allowing application of the laws of reaction kinetics

Under these conditions the reaction mechanism must not change with increasing temperature. It is therefore necessary to use packaging materials which are impermeable to water vapor to prevent solid formulations becoming dehydrated at higher temperatures or the active ingredient concentration of liquid formulations increasing due to loss of moisture.

The laws of reaction kinetics cannot be used to make stability predictions for organoleptic and physicochemical changes. This is the reason why solid dosage forms, for example, are stored without packaging at 25°C/60%. This induces the maximum possible changes due to absorption or loss of water. Semisolid and liquid dosage forms are stored at -10°C in order to detect irreversible changes.

Storage at 30°C/70% RH is not usually necessary because most clinical trials are performed in countries of climatic zones I and II.

Testing Frequency

The testing frequency is established to suit the problem being studied. Retest periods are different for stress, acceleration, and long-term tests.

Storage Period

The storage period depends on the required minimum shelf-life.

Clinical phase I: 3–6 months
Clinical phase II: 12–18 months
Clinical phase III: 24–36 months

The storage period for stress and acceleration tests is considerably shorter.

Number of Batches

With all the different dosages, dosage forms, and packaging materials examined during the development phase, it is not possible to provide three batches for each dosage form. Reliable information can nevertheless be obtained by applying scientifically based rationalization measures. This includes the expedients mentioned in the ICH Stability Guideline:

- Bracketing
- Matrixing

Both methods are based on the assumption that a reduced number of investigated samples is representative of the stability behavior of all samples. In bracketing, only "limit samples" are tested, for example, the lowest and highest dosage, smallest and largest container. In matrixing, selection is performed according to a statistical procedure (random number). A rational bracketing system would be as follows:

- 1–2 dosages: Test all samples
- 3–4 dosages: Test highest and lowest samples
- >4 dosages: Test highest, middle, and lowest samples

A rational matrixing system would be as follows:

- Beginning and end test samples: Test all
- Intermediate values: Test statistically established, random numbers

For the implementation of rationalization steps it is important to definitively establish the stability program at the outset and to perform the tests strictly in accordance with the program.

As regards the number of batches, each clinical phase is covered by several batches as required by the rational bracketing system. The number of samples to be tested must always be considered in relation to the number of clinical batches.

Packaging Materials

The following are used in phases I to III (Table 3):

- Stress tests: Standard packaging material
- Acceleration tests: Standard packaging material
  Test packaging material
- Long-term test: Standard packaging material
  Test packaging material

Evaluation

EU regulations require each clinical sample to be marked with an open expiration date like a marketed drug product. (This does not apply in Japan or in the USA.) This expiration date is based on the results of the stability tests and must be available before starting manufacture of the clinical samples. The expiration date for clinical samples is based on the results of the drug substance stability profile which comprehensively describes the stability behavior of the active ingredient.

This active ingredient stability profile also includes preliminary predictions regarding the stability behavior of the drug substance in solid, semisolid, and liquid dosage forms. Stability tests on formulations for clinical phases I–III provide specific information regarding

Table 3

The Most Important Packaging Materials for Stability Testing of Clinical Samples

Clinical Phase	Dosage Form/Packaging Material		
	Solid	Semisolid	Liquid
I			
Acceleration tests	Standard packaging material • Glass container with twist-off closure	Standard packaging material • Standard tube	Standard packaging material • Ground-glass-stoppered flask or • Glass ampoule or • Injection vial with rubber stopper
Long-term test	Standard packaging material • Glass container with twist-off closure • PP tubes	• Standard packaging material • Test packaging material	• Standard packaging material • Test packaging material
II			
Stress tests	Standard packaging material • Glass container with twist-off closure	Standard packaging material	Standard packaging material
Acceleration tests	Standard packaging material • Glass container with twist-off closure	• Standard packaging material • Test packaging material	• Standard packaging material • Test packaging material
Long-term test	• Standard packaging material -Glass container with twist-off closure -PP tubes • Test packaging material: blister	• Standard packaging material • Test packaging material	• Standard packaging material • Test packaging material
III			
Stress tests	Standard packaging material • Glass container with twist-off closure	Standard packaging material	Standard packaging material
Acceleration tests	Standard packaging material • Glass container with twist-off closure	• Standard packaging material • Test packaging material	• Standard packaging material • Test packaging material
Long-term test	• Standard packaging material -Glass container with twist-off closure -PP tubes • Test packaging material: blisters	• Standard packaging material • Test packaging material	• Standard packaging material • Test packaging material

Table 4

Influencing Factors for Individual Dosage Form

Influencing factor	Possible Influence on Quality of the Dosage Forms		
	Solid	Semisolid	Liquid
Batch size	Appearance	Appearance	Appearance
Equipment	Content uniformity	Homogeneity	pH
Manufacturing process	Dissolution	• Homogeneity within a container • Preservation • Chemical stability after manufacture	• Preservation • Chemical stability after manufacture

the influence of excipients and the overall formulation on organoleptic, physicochemical, chemical and microbial stability.

It is of major importance for the evaluation to bear in mind the aim of the individual tests and maintain the clear separation of storage conditions. On the one hand, there is the test for organoleptic and physicochemical stability; on the other hand, for chemical or microbial stability. If, for example, discoloration, a decrease in hardness, an increase in dissolution, or phase separation is observed after 3-month storage at 70°C, these changes will be recorded but they are only of limited relevance for predicting stability. If there are no significant changes in the test for organoleptic and physicochemical stability, stability can be predicted by means of reaction kinetics calculations which are based mainly on the results obtained after storage at stress temperatures.

The predicted data will always be confirmed/substantiated by the concurrently performed long-term tests.

Stability Information

The results of stability tests on clinical samples are used to set minimum shelf-lives and not expiration dates.

The duration of each clinical trial, including logistics and provision of clinical supplies, must be fully covered. In many cases, therefore, the minimum shelf-life will not be determined by reaching a shelf-life tolerance limit. In all these cases the expiration date can be extended, if necessary, on the basis of suitable studies.

The following minimum shelf-lives are considered optimal:

Clinical phase I: 3–6 months
Clinical phase II: 12–18 months
Clinical phase III: 24–36 months

The established minimum shelf-lives are valid for all the batches of the relevant clinical phase.
Since the product is in the process of development, the shelf-lives are not based on three representative validation batches but on

- Batches comprising different dosages as tested by the bracketing procedure
- Batches comprising different dosage forms obtained as developmental progresses
- Batches of different origin and size; these are usually experimental and development batches

If a critical examination reveals that the batches exhibit similar stability behavior, the result can be applied to the "same" batches of the relevant clinical phase with a high level of reliability.

The following also applies to the minimum shelf-lives of clinical samples:

- They need cover only a short period, especially in phases I and II.
- They are not utilized to the full, and the risk inherent in the prediction is correspondingly smaller.
- They apply only to a small number of batches, especially in clinical phases I and II.
- They are additionally supported by concurrently implemented long-term tests.

Finally, it can be stated that the factors batch size, technology, and equipment used in the manufacturing process affect primarily the quality of manufacture and not that of stability. This means that they are identified in the analysis conducted immediately after manufacture, which determines the quality in relation to the release specifications (Table 4).

If all the analytical data obtained after manufacture are within the release specifications, the stability information obtained from the stress tests and acceleration tests can be considered generally applicable with a high degree of reliability. It may be necessary to ensure compliance with the minimum shelf-life by marking packs with storage instructions (Table 5). It is important to present this information unambiguously.

PERFORMANCE OF CLINICAL PHASES I–III

Solid Dosage Forms

Selection of Batches and Samples

For clinical phase I: experimental batches
For clinical phase II: clinical experimental batches
For clinical phase III: clinical or pilot plant batches

The samples to be put into storage must be sampled randomly.

Test Criteria

A clear distinction is made between the tests for organoleptic, physicochemical, and chemical stability. Tablets and capsules are examined as examples:

Table 5

Preferred Wording of Storage Instructions

Storage Instruction	Reason
Do not store above 30°C	Relevant changes were seen in the samples after storage at 40°C
Do not store above 25°C	Relevant changes were seen in the samples after storage at 30°C/70%, but not after storage at 25°C/60%.
Store at ≤8°C in a refrigerator	Relevant changes were observed in the samples after storage at 25°C/60%
2–8°C, store in a refrigerator, do not freeze	Relevant changes were observed in the samples after storage at 25°C/60% and −10°C.

- Organoleptic and physicochemical stability
  -Tablets: appearance, hardness, average weight, disintegration time, dissolution
  -Capsules: appearance, elasticity, average weight, average weight of capsule shells, average weight of capsule contents, disintegration time, dissolution
- Chemical stability
  -Tablets: appearance, hardness, dissolution, average weight, decomposition and assay of active ingredient
  -Capsules: appearance, elasticity, average weight, average weight of capsule shells, average weight of capsule contents, dissolution, decomposition and assay of active ingredient

The organoleptic and physicochemical test criteria are included in this case. The samples are tested accordingly and any changes are recorded, although they are not necessarily relevant for room temperature.

Storage Conditions, Storage Period, Testing Frequency, and Packaging Material

The same distinction is made for the storage conditions as for the test criteria. For organoleptic and physicochemical stability testing, the samples are stored without packaging under the climatic conditions of long-term testing at 25°C/60% until equilibrium is reached (Table 6). The maximum possible changes occur during this period. The test for chemical stability is performed using those samples which were stored without packaging at 25°C/60% until equilibrium was reached (Tables 7 and 8). With this approach, the influence not only of the temperature but also of humidity on the stability of the product can be examined.

Parallel to the stress and acceleration tests, samples are stored at 25°C/60% representing the conditions of climatic zone II. The storage period corresponds to the planned expiration date. These measures allow the stability prediction to be checked.

Table 6

Storage for Organoleptic and Physicochemical Stability

Clinical phase	Packaging Material	Storage Condition	Storage Period
I–III	Without	25°C/60%	Until equilibrium, 4 weeks

The samples are stored until equilibrium is reached, i.e., for about 4 weeks, independently of the planned expiration date.

Number of Batches and Samples

When there is one batch per clinical phase, bracketing is used if several dosages are tested. If one batch is stored in several packaging materials, the following rules are applied:

- If the product is not sensitive to moisture and no change was observed after storage without packaging material at 25°C/60%, only the least "protective" packaging material is studied.
- If the packaging materials are equivalent—e.g., polypropylene tubes, polyethylene tubes, aluminum/aluminum—matrixing is performed.
- If the product is "relatively" sensitive to moisture and the packaging materials are of differing quality—e.g., polypropylene tubes, polyethylene tubes, blister packs, etc.—all packaging materials are tested.

Table 9 shows the number of samples to be put into storage for various dosage forms and Table 10 lists the number of samples needed per batch.

Table 7

Storage for Chemical Stability

Clinical Phase	Minimum Shelf-Life	Packaging Material	Pretreatment	Storage Conditions, Storage Period, and Testing Frequency	
I	3 months	Twist-off	None	40°C:	0, 2, 4, 6 weeks
		Twist-off	25°C/60%	40°C:	0, 2, 4, 6 weeks
		Twist-off	None	25°C/60%:	12 weeks
		PP tubes	None	25°C/60%:	12 weeks
I	6 months	Twist-off	None	40°C:	0, 1, 2, 3 months
		Twist-off	25°C/60%	40°C:	0, 1, 2, 3 months
		Twist-off	None	25°C/60%:	6 months
		PP tubes	None	25°C/60%:	6 months
II	12–18 months	Twist-off	None	60°C:	0, 1, 2, 3 months
			None	40°C:	1, 2, 3, 6 months
		Twist-off	25°C/60%	60°C:	0, 1, 2, 3 months
		Twist-off	25°C/60%	40°C:	1, 2, 3, 6 months
		Twist-off	None	25°C/60%:	12, 18 months
		PP tubes or test packaging material	None	25°C/60%:	12, 18 months
III	24-36 months	Twist-off	None	70°C, 60°C, 50°C:	1, 2, 3 months
		Twist-off	None	40°C:	0, 1, 2, 3, 6 months
		PP tubes or test packaging material	None	40°C:	3, 6 months
		Twist-off	25°C/60%	70°C, 60°C, 50°C:	1, 2, 3 months
		Twist-off	25°C/60%	40°C:	0, 1, 2, 3, 6 months
		Twist-off	None	25°C/60%:	12, 18, 24, 36 months
		PP tubes or test packaging material	None	25°C/60%:	12, 18, 24, 36 months

Semisolid Dosage Forms, Creams, Ointments, Lotions

Selection of Batches

As for solid dosage forms.

Test Criteria

- Organoleptic and physicochemical stability: appearance, homogeneity, pH, particle size (for suspensions), recrystallization, consistency, content uniformity (tubes are stored vertically; they are cut open, and material from the beginning, middle, and end of the tube is tested).
- Chemical and microbial stability: Appearance, homogeneity, odor, pH, content uniformity (in the container), decomposition and assay of active ingredient, decomposition and assay of preservatives

Microbial stability is covered by the analysis of the preservatives.

Storage Conditions, Storage Period, Testing Frequency, and Packaging Material

Although the samples are stored differently for organoleptic/physicochemical and chemical/microbial stability, the tests overlap.

For organoleptic and physicochemical stability testing, samples are stored under two conditions (Table 11). Some of the samples are stored in standard tubes for up to 4 weeks at −10°C; the others are stored vertically in

Table 8

Chemical Stability

Clinical Phase	Minimum Shelf-Life	Packaging Material	Pretreatment	Storage Conditions, Storage Period, and Testing Frequency	
I	3 months	Twist-off	None	40°C:	0, 2, 4, 6 weeks
		Twist-off	25°C/60%	40°C:	0, 2, 4, 6 weeks
		Twist-off	None	25°C/60%:	12 weeks
		PP tubes	None	25°C/60%:	12 weeks
I	6 months	Twist-off	None	40°C:	0, 1, 2, 3 months
		Twist-off	25°C/60%	40°C:	0, 1, 2, 3 months
		Twist-off	None	25°C/60%:	6 months
		PP tubes	None	25°C/60%:	6 months
II	12–18 months	Twist-off	None	60°C:	0, 1, 2, 3 months
			None	40°C:	1, 2, 3, 6 months
		Twist-off	25°C/60%	60°C:	0, 1, 2, 3 months
		Twist-off	25°C/60%	40°C:	1, 2, 3, 6 months
		Twist-off	None	25°C/60%:	12, 18 months
		PP tubes or test packaging material	None	25°C/60%:	12, 18 months
III	24-36 months	Twist-off	None	70°C, 60°C, 50°C:	1, 2, 3 months
		Twist-off	None		0, 1, 2, 3, 6 months
		PP tubes or test packaging material	None	40°C:	3, 6 months
		Twist-off	25°C/60%	70°C, 60°C, 50°C,0°C:	1, 2, 3 months
		Twist-off	25°C/60%	40°C:	1, 2, 3, 6 months
		Twist-off	None	25°C/60%:	12, 18, 24, 36 months
		PP tubes or test packaging material	None	25°C/60%:	12, 18, 24, 36 months

standard tubes for up to 2 weeks at 4–40°C, the temperature varying within this range in a 24-hr cycle.

For the chemical–microbial stability tests, samples are stored under stress, acceleration, and long-term test conditions (Table 12). The storage period corresponds to the planned expiration date for clinical phases I–III, as described for the solid dosage forms.

Table 9

Number of Samples Required per Analysis

Dosage Form	Number of Samples/Analysis
Tablets, coated tablets	100 tablets
Capsules	80 capsules
Single dose containers—sachets (granules)	15 containers
Powder	3 containers

The standard tubes (aluminum tube with inert internal lacquering) are stored vertically with the neck of the tube pointing upwards. After 1 and 3 months the samples stored at 40°C are subjected to a threefold analysis for homogeneous distribution of the active ingredient (content uniformity) by testing material taken from the beginning, middle, and end of the tube.

Number of Batches and Samples

The number of batches is the same as for solid dosage forms. The number of samples per analysis and per batch are given in Tables 13 and 14, respectively.

Table 10

Number of Samples Needed per Batch

Clinical Phase	Pretreatment	Number of Samples at Storage Temperature		Total Number
I–II	25°C/60%	25°C/60% open:	1 + 1	2
I	None	40°C:	4 + 1	5
	25°C/60%	40°C:	4 + 1	5
	None	25°C/60%:	2 × 1	2
				12 + 2
II	None	60°C:	3 + 1	4
	None	40°C:	5 + 1	6
	25°C/60%	60°C:	3 + 1	4
	25°C/60%	40°C:	5 + 1	6
	None	25°C/60%:	2 × 2 + 2 × 1	6
				26 + 2
III	None	70°C:	3 + 1	4
		60°C:	3 + 1	4
		50°C:	3 + 1	4
	None	40°C:	5 + 1	6
	None	40°C/75%:	2 × 2 + 2 × 1	6
	25°C/60%	70°C:	3 + 1	4
		60°C:	3 + 1	4
		50°C:	3 + 1	4
	25°C/60%	40°C:	5 + 1	6
	None	25°C/60%:	4 + 1	5
	None	25°C/60%:	2 × 5 + 2 × 1	12
				59 + 2

Liquid Dosage Forms, Ampoules

Selection of Batches

As for solid dosage forms.

Test Criteria

- Organoleptic and physicochemical stability: appearance, clarity, and pH
- Chemical and microbial stability: Appearance, clarity, pH, decomposition and assay of active ingredient, decomposition and assay of preservative

Storage Conditions, Storage Period, Testing Frequency, and Packaging Material

A distinction is also made between the storage conditions for organoleptic and physicochemical stability (Table 15), and chemical/microbial stability testing (Table 16). The storage period depends on the planned/required shelf-life.

Number of Batches

As for solid dosage forms.

Table 11

Storage for Organoleptic and Physicochemical Stability Tests

Clinical Phase	Packaging Material	Storage Condition	Storage Period
I–III	Standard tube (aluminum tube) with inert internal lacquering	• -10°C	• 4 weeks
		• 4–40°C in a 24-hr cycle	• 2 weeks

Table 12

Storage for Chemical and Microbial Stability Tests

Clinical Phase	Minimum Shelf-Life	Packaging Material	Storage Conditions, Storage Period, and Testing Frequency	
I	3 months	Standard tube	• 40°C:	0, 2, 4, 6 weeks
			• 25°C/60%:	12 weeks
I	6 months	Standard tube	• 40°C:	0, 1, 2, 3 months
			• 25°C/60%:	6 months
II	12–18 months	Standard tube	• 40°C:	0, 1, 2, 3, 6 months
			• 25°C/60%:	12, 18 months
		Test packaging material	• 40°C:	0, 3, 6 months
			• 25°C/60%:	12, 18, 24, 36 months
		Test packaging material	• 40°C:	0, 3, 6 months
			• 25°C/60%:	12, 18, months
III	24–36 months	Standard tube	• 50°C:	0, 1, 2, 3, months
			• 40°C:	1, 2, 3, 6 months
			• 25°C/60%:	12, 18, 24, 36 months
		Test packaging material	• 40°C:	0, 3, 6 months
			• 25°C/60%:	12, 18, 24, 36

EVALUATION

As a first step, the drug substance stability profile data which comprehensively illustrate the stability behavior of the drug substance are examined. With a retest date of ≥2 years, this means that none of the test parameters of a drug substance undergo relevant changes over a period of ≥2 years.

The stress and acceleration tests are then evaluated for each clinical phase, taking into account the specific objective of the respective storage conditions. On this basis, the results of all test criteria can be included in the stability prediction.

The number of samples required per analysis is given for the different dosage forms in Table 17; and that per batch, in Table 18.

A critical examination is conducted to determine whether relevant changes have occurred and whether the shelf-life tolerance limits have been reached or exceeded by the criteria for the four test areas: organoleptic, physicochemical, chemical, and microbial.

It is then determined whether the dosages or the dosage forms exhibit different stability behavior or whether the batches can be combined to produce uniform stability information. The packaging materials and possible interactions with the packaging materials also have to be included in the assessment. In some cases, attention is focused on different aspects for the individual dosage forms.

Evaluation of Different Dosage Forms

Solid Dosage Forms

If all the results of the test for organoleptic and physicochemical stability are within the shelf-life specifications, the stability prediction depends exclusively on the chemical stability. If the water content of the pre-

Table 13

Number of Samples Required per Analysis

Dosage Form	Number of Samples Required per Analysis
Cream, gel, lotion, paste, ointment	• Approx. 50 ml or 9 containers for 5 g • 5 containers for 10–25 g • 2 containers for 50 g • 200 for preservative acceleration test
Suppositories	20 suppositories

Table 14

Number of Samples Needed per Batch

Clinical Phase	Number of Samples at Storage Temperature		Total Number
I–III	-10°C:	1 + 1	2
	4–40°C:	1 + 1	2
			4
I	40°C:	4 + 1	5
	25°C:	1 + 1	2
			7 + 4
II	40°C:	5 + 1	6
	25°C/60%:	2 + 1	3
	40°C/75%:	2 + 1	3
	25°C/60%:	3 + 1	4
			16 + 4
III	50°C:	3 + 1	4
	40°C:	5 + 1	6
	25°C/60%:	4 + 1	5
	40°C/75%:	2 + 1	3
	25°C/60%:	5 + 1	6
	+ preservative acceleration test		24 + 4

treated samples (open storage, 25°C/60%) has no influence or if the influence is acceptable, there is no restriction on the choice of packaging materials.

If the results of the test for organoleptic and physicochemical stability are outside the tolerance limits, or if the water content influences the chemical stability to an unacceptable degree, a packaging material impermeable to water vapor must be selected, e.g., glass bottle with screw closure, polypropylene or polyethylene tubes, aluminum/aluminum.

Semisolid Dosage Forms

If the results of the test for organoleptic and physicochemical stability are within the shelf-life specifications, the stability prediction is also determined by the chemical and microbial stability. Content uniformity within a container and possible interactions with the packaging material must also be considered. Generally, stability predictions are most difficult for semisolid dosage forms and this applies particularly to the use of reaction kinetics. It may also be necessary to ensure compliance with the minimum shelf-life by marking packs with storage instructions.

Liquid Dosage Forms

If the results of the organoleptic and physicochemical tests are within the shelf-life tolerance limits, reaction kinetics prediction presents few problems. The influence of the packaging materials also has to be considered, especially when elastomers are used.

Reaction Kinetics Extrapolations

Stability studies for clinical samples are based on stress and acceleration tests with the aim of speeding up, especially, chemical decomposition by storing samples at elevated temperatures. The results are then used to calculate the stability behavior at 25°C/60% based on the laws of reaction kinetics.

The equations for a first-order reaction and the Arrhenius model are used. If decomposition levels are available for only one temperature (4,5), the expression ΔE: 83 kJ $\times$ mol^{-1} is used for the activation energy.

Table 19 shows decomposition levels for 25°C/60% calculated from values obtained after storage at 40° to 70°C. Reported in Table 19 are the decomposition determined after storage at accelerated and stress temperatures, and the decomposition for 25°C derived from these data.

As mentioned above, a minimum shelf-life is determined for clinical trial samples and can be extended as necessary if the corresponding tests yield favorable results. Parallel to the stress and acceleration tests, samples are stored at 25°C/60% in order to confirm and support the predicted minimum shelf life.

If all the predicted data and the data confirmed in long-term tests are within the shelf-life tolerance limits, they can be extended if necessary. For this purpose, a

Table 15

Storage for Organoleptic and Physicochemical Stability Tests

Clinical Phase	Packaging Material	Storage Condition	Storage Period
I–III	25-mil ground-glass-stoppered bottle Glass ampoules Plastic bottle	-10°C	4 weeks

Table 16

Storage for Chemical and Microbial Stability Tests

Clinical Phase	Expiration Date	Packaging Material	Storage Conditions, Storage Period, and Testing Frequency	
I	3 months	25-ml ground-glass-stoppered glass bottle or glass ampoule or injection vial with rubber stopper, plastic bottle	40°C: 25°C/60%:	0, 2, 4, 6 weeks 12 weeks
I	6 months	Same as for phase I	40°C: 25°C/60%:	0, 1, 2, 3 months 6 months
II	12–18 months	Same as for phase I	40°C: 25°C/60%:	0, 1, 2, 3, 6 months 12, 18 months
		Test packaging material	40°C/75%: 25°C/60%:	3, 6 months 0, 12, 18 months
III	24–36 months	Same as for phase I	70,60,50°C: 40°C: 25°C/60%:	1, 2, 3 months 0, 1, 2, 3, 6 months 12, 18, 24, 36 months
		Test packaging material	40°C/75%: 25°C/60%:	0, 3, 6 months 12, 18, 24, 36 months

new prediction is performed and samples are stored at 25°C/60% to confirm the new minimum shelf life (Table 20).

Like the overall system of stability testing, the stability program for clinical samples is systematically structured in such a way that the aggregate available information is continuously augmented. Table 21 shows the individual stages with the derived information:

Stability Testing with Pivotal and Bioequivalence Batches

The stability information for a finished medicinal product is derived mainly from the primary data, i.e., the

Table 17

Number of Samples Required per Analysis

Dosage Form	Number of Samples Required per Analysis
Ampoules	Approx. 25 ml 25 ampoules for 1 ml 13 ampoules for 2 ml 5 ampoules for 5 ml 4 ampoules for >5 ml
Drops	Full analysis: approx. 50 ml Stress tests: 25 ml 10 containers for <10 ml 8 containers for 11–25 ml 5 containers for >25 ml
Unit-dose vials (eye drops)	Stress tests: 25 ml 100 containers each of 0.5 ml
Metered spray	Stress tests: 25 ml 10 containers each of 10 ml
Solutions, tincture, syrup, elixir	stress tests: 25 ml full analysis: approx. 50 ml 5 containers for 10–25 ml 3 containers for >25–50 ml 2 containers for >50 ml 200-ml preservative acceleration test

Table 18

Number of Samples Needed per Batch

Clinical Phase	Number of Samples at Storage Temperature		Total Number
I–III	-10°C:	1 + 1	2
I	40°C:	4 + 1	5
	25°C/60%:	1 + 1	2
			7 + 2
II	40°C:	5 + 1	6
	25°C/60%:	2 + 1	3
	40°C/75%:	2 + 1	3
	25°C/60%:	3 + 1	4
			16 + 2
III	70°C:	3 + 1	4
	60°C:	3 + 1	4
	50°C:	3 + 1	4
	40°C:	5 + 1	6
	25°C/60%:	4 + 1	5
	40°C/75%:	2 + 1	3
	25°C/60%:	5 + 1	6
	+ preservative acceleration test		32 + 2

results obtained from the three marketing authorization batches. Usually these are representative pilot-plant batches. After marketing authorization, three production batches are added.

Results from the development phase, supporting data, are also included in the application for marketing authorization to underpin the stability information. The stability results obtained with clinical samples are a major factor for achieving a comprehensive assessment of the quality of a finished medicinal product. In this way it is possible to establish a link between the quality of clinical batches for phases I, II, and III and the quality of the finished drug product. If development is fully covered by stability data, then the quality, efficacy, and safety of the clinical batches will correspond to those of the finished medicinal product. Stability information gained by this broad-based approach thereby acquires a completely new dimension.

Pivotal and bioequivalence batches are also required for this comprehensive general strategy unless they are covered by batches from clinical phase III. If this is not the case, pivotal and bioequivalence batches are included in the stability program.

Since the results are combined to produce a general statement, emphasis is placed not on the stress test but on the long-term test. The stability program combines acceleration tests with long-term tests in accordance with the ICH Guideline. The storage period, however is limited to 18 months:

- At 25°C, 60% RH: storage period and testing frequency is 0, 3, 6, 9, 12, and 18 months
- At 30°C, 70% RH: storage period and testing frequency is 3 and 6 months (These conditions are only used if significant change occurs after storage at 40°C (/75/%).
- At 4°C (75% RH): storage period and testing frequency is 3 and 6 months

Table 19

Reaction Kinetics Extrapolation

Clinical Phase	Storage Condition	Decomposition Found/ Extrapolated Decomposition (%) for 25°C					
I	• 40°C: 1.5 months	0.10	0.20	0.30	0.40	0.50	1.00
	• 25°C: 3 months	<0.10	<0.10	0.12	0.16	0.20	0.40
I	• 40°C: 3 months	0.10	0.20	0.30	0.40	0.50	1.00
	• 25°C: 6 months	<0.10	<0.10	0.12	0.16	0.20	0.40
II	• 60°C: 3 months	0.10	0.20	0.30	0.40	0.50	1.00
	• 25°C: 12 months	<0.10	0.18	0.27	0.35	0.44	0.89
	18 months	0.13	0.27	0.40	0.53	0.66	1.30
II	• 40°C: 6 months	0.10	0.20	0.30	0.40	0.50	0.60
	• 25°C: 12 months	<0.10	<0.10	0.12	0.16	0.20	0.40
	18 months	<0.10	0.12	0.18	0.24	0.30	0.60
III	• 70°C: 3 months	≤0.50	1.00	2.00	3.00	4.00	5.00
	• 25°C: 24 months	<0.10	0.10	0.20	0.30	0.40	0.50
	36 months	<0.10	0.15	0.30	0.45	0.60	0.76

Table 20

The Objective Is to Extend the Shelf-Life by 30%

Derived Minimum Shelf-Life (months)	Extension by 30% (total months)
3	4
6	9
12	16
18	24
24	32
36	48

The test criteria, specifications and analytical procedures are the same as those used for batches of clinical phase III and the marketing authorisation batches.

Stability Testing of Bulkware

The derived minimum shelf-lives for the clinical samples are valid from the date of manufacture/release after analysis. If the samples are stored without packaging this period is part of the minimum shelf-life. Depending on the containers used to store the bulkware, it is necessary to establish whether interactions are possible or can be ruled out. If such a risk is present, suitable stability tests are necessary: the samples are stored for 3 months at 40°C in a similar container and tested after 1, 2, and 3 months.

Reliability of Minimum Shelf-Lives

The shelf-lives for the batches of clinical samples are established to cover the duration of the clinical trial plus a supplement to allow for logistics and the provision of clinical supplies. The shelf-lives determined apply to all the batches of the relevant development stage, although only the batches in the final phase of development originate from a validated manufacturing phase and are therefore representative.

How reliable is shelf-life and stability information? This question can be answered as follows: The shelf lives for clinical phases I and II (and in some cases III) represent a minimum shelf-life; in other words, they still include a "reserve." A shelf-life of 3 months for a first clinical trial does not mean that the batch may not be stable for longer periods. The shelf-lives may be extended after appropriate storage and tests. Minimum shelf-lives are therefore associated with a lower risk than shelf-lives at the end of which the sample is always unstable.

Furthermore, the principle of "semicoverage" applies to clinical phase I; i.e., half the shelf-life (3–6 months) is covered by storage at higher temperatures.

If there are several dosages, bracketing is performed; i.e., two to three dosages are tested simultaneously for stability. If all two or three dosages exhibit the same stability behavior, a statement can be made regarding the reproducibility or the technological parameters. If the stability information for two to three batches of dif-

Table 21

Number of Dosages and Packaging Materials

Stage of Development	Tests[a]	Number of Dosages	Number of Packaging Materials	Total Number	Derived Information
Drug substance	Stress and acceleration tests	1	1	1	Retest date ≥ 2 years
Clinical phase I	40°C/1.5 months	≥2	2	≥4	3 months
	40°C/3 months	≥2	2	≥4	6 months
Clinical phase II	60°C/3 months	2[b]	2	4	12–18 months
Clinical phase III	70°C/3 months	1[b]	3	• 3	24–36 months
				• ≥16	

[a]A confirmatory long-term test is conducted concurrently to stress and acceleration tests.

[b]If more than 2 dosages are used in clinical phase II, ≥2 applies; if more than 1 dosage is used in clinical phase III, ≥2 also applies. The data in the table are therefore minimum limits.

Table 22

Time to Availability of Stability Information

Clinical Phase	Manufacture	Start of Storage and Initial Analysis	Storage Period	Analysis	Compilation of Documents	Total Period
I	2 weeks	1 week	6 weeks	1 week	2 weeks	12 weeks
I	2 weeks	1 week	12 weeks	1 week	2 weeks	18 weeks
II	2 weeks	1 week	24 weeks	1 week	2 weeks	30 weeks
III	2 weeks	1 week	24 weeks	1 week	2 weeks	30 weeks

ferent dosages or composition is identical, the information is naturally also applicable to identical batches.

As phases I–III progress, experience with analytical procedures and shelf-life specifications increases. The results and stability information derived from them become steadily more reliable.

Finally, the stability program is designed in such a way that stability predictions are verified by the results of long-term tests. There is thus still the possibility of replacing batches if necessary.

Furthermore, there is a clear overview of storage, dispatch, and transport ensuring continuous, full accountability.

Time to Availability of Stability Information

In the EU, clinical samples have to be marked with an open expiration date. The stability program for clinical samples is thus designed to produce stability information as rapidly as possible.

The time required until shelf-lives and the stability information are available is thus an important factor for planning clinical trials and establishing the date of manufacture. In addition to the actual storage time, the following time periods also have to be taken into account: time for analysis, establishing of expiration dates, and compilation of documents (Table 22).

SUMMARY

The stability program for clinical samples as presented in this document is based on the same principles as those used in the program operated throughout the development of a drug product. However, these principles have been adapted to suit the complex circumstances arising during ongoing development, as exemplified by the transition from clinical phase I to III.

Storage conditions, storage periods, and derived expiration dates correspond to the duration of clinical trials in phases I to III. The expiration dates represent minimum shelf-lives.

Shelf-lives are established on the basis of stress and acceleration tests. Only with this approach can shelf lives be established rationally and all batches provided with an open expiration date. By consistently separating the storage conditions for organoleptic, physicochemical and chemicomicrobial test criteria, all stability-indicating test criteria can be integrated in the stability information.

The number of analyses can be reduced by bracketing if phases I and II are performed using several dosages.

Stability predictions based on stress and acceleration tests are supported by long-term tests conducted under the storage conditions representing climatic zone II, i.e., 25°C/60%. The packaging material planned for commercial use is always included.

The analytical procedures and the specifications to be derived from the results also undergo a process of development. For example, at the outset the validation has a preliminary character and includes specificity, linearity, recovery, and limit of quantitation, whereas on completion there is the completely validated specification for clinical samples and stability testing. In the same way, the specifications initially serve as a general guide and then becomes increasingly specific. This flexible approach makes it possible to obtain reliable stability information while ensuring the rational use of resources.

Not carrying out stress and acceleration tests, and replacing them by long-term tests, would either cause major delays in clinical development or make it impossible to state an open expiration date. An alternative would be to include all batches in stability testing, running the serious risk of having to replace batches during the clinical trial and, in addition to the great analyti-

cal effort involved, of always having to keep up-to-date stable batches available in order to safeguard the continuity of the clinical trial.

Summarizing, it can be stated that the systematic approach of proceeding in logically coordinated steps represents the best way of supporting the clinical trial by stability testing. Furthermore, stability testing of clinical samples is a central factor for generating comprehensive stability information, i.e., an overall assessment of the quality of the finished medicinal product. By applying the same principles to the stability testing of clinical samples and the finished medicinal product, the marketed drug, it is ensured that the results of the clinical trial can be considered applicable to the finished medicinal product; both products have similar stability and therefore quality.

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