The Complete Stability Testing for a Successful Application

Strategies, Requirements, Basic Principles
Performance, Documents

3. Performance

3.1. Stress and accelerated testing with the drug substance

1.2.1 Objective

- ❒ Elucidation of the intrinsic characteristics of the drug substance with reference to chemical properties (physical properties are investigated separately).
- ❒ Establishment of the degradation pathway , leading to identification of degradation products and hence supporting the suitability of the proposed analytical procedure.
- ❒ Investigation of the following influencing factors: moisture, temperature, moisture + temperature, moisture + temperature + drug substance concentration, pH, ionic strength, oxidation, light.

1.2.2 Selection of the salt form

Before stability investigations are performed the optimal salt form should be selected

Typical salt forms

- ❒ Cationic drug substances
  - Hydrochloride
  - Methanesulfonate
  - Citrate
  - Tartrate
  - Oxalate
  - Fumarate
  - Acetate
- ❒ Anionic drug substances
  - sodium
  - potassium
  - calcium
  - magnesium
  - meglumine
  - tris

1.2.2.1 Test attributes for the selected salt form

❒ **Solubility**

- water all salt forms
- 0.1 N HCl, 0.1 N NaOH } only acid or base
- buffer pH 4.0, 7.4, 10.0 } only acid or base

❒ **Stability of solid drug substance**

- thermal stability (melting point, decomposition, DTA)
- short term stress (temperature, humidity, light)

❒ **Hygroscopicity**

Storage at 5, 40, 60, 75, 98 % r.h.

❒ **Grindability**

impact of intensive grinding on cristallinity

1.3 Application of the basic principles

❒ **Selection of batches and samples**:

Experimental batch, it must comply with the acceptance criteria of the preliminary testing specification, as far as they are available.

The impurity profile particle size distribution and the surface area are especially important.

❒ **Test attributes**

Appearance, physical properties, assay, decomposition

❒ **Analytical procedure**

- Specific for stability testing.
- Orientational validation at the beginning:
  Specificity, linearity, reporting threshold 0.05% of the drug substance.
- Preliminary validation at the end in addition:
  accuracy, range, repeatability, robustness for drug substance and decomposition products.

❒ **Acceptance criteria**

At the end: Preliminary release acceptance criteria

❒ **Storage conditions**

- Storage in open containers:
  25°C/60%, 25°C/75%, 30°C/65%, 40°C/75%

- Storage in standard packaging material
  40°C, 50°C, 60°C, 70°C

1.3 Application of the basic principles

❒ **Storage period**

- until equilibrium is reached at open storage
- ≤ 3 months

❒ **Testing frequency**

≤ 4

❒ **Number of batches per investigation**

1 to 2

❒ **Container closure system**

- Flask with ground-glass stopper,
- glass container with twist-off closure,
- glass container lined with polyethylene foil

❒ **Evaluation**

- Statistics and reaction kinetics are applied in evaluating the results.
- Assessment of observed decomposition products, whether they may be formed under accelerated and long-term testing.
- Establishment of degradation pathway of selected decomposition products, elucidation of their structure.
  Assessment of applied analytical procedures:

The data and the derived statements/labelling are summarised in a stability report, as the stability profile of the investigated drug substance. The stability report is part of CMC for CTX, IND and for the CTD registration application.

1.3 Application of the basic principles

❒ Statements/Labelling

The stability report contains the following stability information:

- Stability prediction drug substance
  - Preliminary prediction of the re-test period,
  - Storage instructions if required,
  - Test attributes,
  - container closure system,
  - assessed analytical procedure
  - stability test protocol for accelerated and long-term testing of registration batches.
- Stability predictions drug product
  - Orientational prediction of the chemical stability of the drug substance in solid, semisolid, liquid dosage forms.

1.4 Practical Example

The influencing factors to be investigated are now illustrated by means of a practical example.

To start the predevelopment as soon as possible, the investigations are carried out in two steps:

1.4.1 Preliminary investigation

1.4.2 Complete investigation

1.4.1 Preliminary investigation

The experiments are organised in such a way that the preliminary stability profile is available within 6 weeks.
Necessary amount: about 25 g.

1.4.1.1 Moisture

- **Sample**
  Drug substance stored in open container for 1 week
  at 25°C/75 % r.h.

- **Test attributes:**
  Appearance, mass, DTA

If the drug substance has absorbed water it is investigated further in 50 ml glass container with twist-off closure under 1.4.1.2.

1.4.1.2 Temperature, Moisture

- **Sample**:
  Drug substance with and without adsorbed water in
  50 ml glass container with twist-off closure.

- **Test attributes:**
  Appearance, decomposition, assay, DTA at the end

- **Analytical procedure:**
  Orientational validation at the beginning

- Storage temperature:
  70°C

1.4.1 Preliminary investigation

- **Storage period**:
  4 weeks

- **Testing frequency:**
  0, 2, 4 weeks

1.4.1.3 pH

- **Sample:**
  1 % aqueous solution or slurry in 0.1, 0.01 M HCl, in McIlvaine's buffers (0.1 M citric acid, 0.2 M disodium phosphate), pH 3, 4, 5, 6, 7, 0.01 M NaOH in volumetric flask with ground glass stopper

- **Test attributes**
  Appearance, decomposition, assay

- **Storage temperature:**
  60°C

- **Storage period:**
  3 weeks

- **Testing frequency:**
  0, 1, 3 weeks

1.4.1.4 Oxidation

- **Sample:**
  1 % aqueous solution or slurry in 0.3 % H_2O_2 solution in 25 ml glass flask with ground glass stopper.

1.4.1 Preliminary investigation

- **Test attributes:**
  Appearance, pH, decomposition, assay

- **Storage temperature:**
  50°C

- **Storage period:**
  3 weeks

❒ **Testing frequency:**
0, 1, 3 weeks

1.4.1 Preliminary investigation

1.4.1.5 Photostability

(Xenon lamp, Atlas Suntest, 250 W/m²)

❒ **Test sample:**

- Drug substance spread in colourless and brown glass across the container to give a thickness of not more than 3 mm.

- 1 % aqueous solution (or inert organic solvent) with and without N_2 gassing in colourless glass flask with ground glass stopper.

- 1 % aqueous solution (organic inert solvent) in brown glass flask with ground glass stopper as control.

❒ **Test attributes:**
Appearance, decomposition, assay

❒ **Storage period:**
48 hrs, Xenon lamp

❒ **Testing frequency:**
24, 48 hrs

Stability test protocol, preliminary investigation

Batch No.	Influencing factor	Test sample	Container closure system	Storage conditions	Storage times [weeks]	Anal. proce-dures
S95001	moisture	pure drug substance	open container	25°C/75%	0,1	No. 1
	temperature	pure drug substance	50 ml glass container with twist-off closure	70°C	0,2,4	No. 1
	temperature + moisture	pure drug substance with absorbed water at 25°C/75 %	50 ml glass container with twist-off closure	70°C	0,2,4	No. 1
	pH	1 % aqueous solution pH 1,2,3,4,5,6,7,8 0.1, 0.01 M HCl, McIlvaine's buffer (0.1 M citric acid, 0.2 M dibasic sodium- phosphate, 0.01 M NaOH)	25 ml glass flask with ground glass stopper	60°C	0,1,3	No. 1
	oxidation	1 % aqueous solution in 0.3 % H_2O_2 solution	25 ml glass flask with ground glass stopper	50°C	0,1,3	No. 1
	light	pure drug substance	open petri dish	Xenon lamp	24, 48 hours	No. 1
			brown glass flask	Xenon lamp	24, 48 hours	No. 1
		1 % aqueous solution gassed with N_2	colourless glass flask with ground glass stopper	Xenon lamp	24, 48 hours	No. 1
		1 % aqueous solution	colourless glass flask with ground glass stopper	Xenon lamp	24, 48 hours	No. 1
			brown glass flask with ground glass stopper	Xenon lamp	24, 48 hours	No. 1

Considerations

- If the drug substance decomposes fast > 10% after first test point), storage at lower temperature should be considered.
- If the drug substance is not wettable or does not dissolve at all, the stability information will be limited. The drug substance may appear very stable because it did not dissolve at all.

  In these cases the procedure has to be modified accordingly to reach wettability and increase the solubility.
- If an enatiomer is present, testing for racemisation is performed during the course of stability studies.

The results are summarized in the Stability Report as Preliminary Stability Profile of the Drug Substance.

1.4.1 Preliminary investigation

1.4.1.6 Required Capacity

Required capacity for a single analysis	Required capacity for an analysis in stress tests (serial factor 20 %)
5 hrs ≙ 0.19 weeks	4 hrs ≙ 0.13 weeks

Analytical procedures, orientational validation	Analysis of test samples documentation	Total required capacity
2 week	4 weeks	6 weeks

1.4.1.7 Time to availability of preliminary stability report

Storage period of sample	Evaluation of data Stability report	Total time period
4 weeks	2 weeks	6 weeks

1.4.2 Complete investigation

The stability protocol based on the results of the preliminary investigations has to be adjusted accordingly.
Necessary amount: about 50 g

1.4.2.1 Moisture

- **Sample:**
  Drug substance stored in open containers until equilibrium is reached at 25°C/60 %, 30°C/70 % (65%), 40°C/75 %. (The sample with the highest water absorption investigated further in 50 ml glass container with twist-off closure under 1.4.2.2)

- **Test attributes**
  Appearance, mass, DTA

1.4.2.2 Temperature, Moisture

- **Sample:**
  - Drug substance with and without moisture in 50 ml glass container with twist-off closure
  - Drug substance in 50 ml glass container lined with polyethylene foil with twist-off closure (70°C only)

- **Test attributes:**
  Appearance, clarity (70°C only), decomposition, assay, DTA of 70°C 12 weeks samples

- **Storage temperatures:**
  40°C, 50°C, 60°C, 70°C

- **Storage period:**
  12 weeks

1.4.2 Complete investigation

- **Testing frequency:**
  0, 4, 8, 12 weeks

1.4.2.3 Temperature, Moisture, Drug substance concentration

- **Sample:**
  1% and 5% aqueous solution or aqueous suspension or slurry (only 1%) in 25 ml glass flask with ground glass stopper.

- **Test attributes:**
  Appearance, pH, decomposition and assay

- **Storage temperatures:**
  50°C, 70°C

- **Storage perio**d:
  12 weeks

- **Testing frequency:**
  0, 4, 8, 12 weeks

1.4.2.4 pH and Buffer Concentration

- **Sample:**
  At the optimum pH obtained from preliminary investigation, 1% aqueous solution or slurry in McIlvaine's buffer, double buffer concentration (0.2 M citric acid,0.4 M disodium phosphate) in glass flask with ground glass stopper.

1.4.2 Complete investigation

- **Test attributes:**
  Appearance, decomposition and assay

- **Storage temperature**:
  60°C

- **Storage period:**
  12 weeks

- **Testing frequency:**
  0, 4, 8, 12 weeks

Stability test protocol, complete investigations

Batch No.	Influencing factor	Test sample	Container closure system	Storage conditions	Storage times [weeks]	Anal. proce-dures
S95004	moisture	pure drug substance	open petri dish	25°C/60% r.h 30°C/65 r.h 40°C/75% r.h	0,2	No. 1
	temperature	pure drug substance	50 ml glass container with twist-off closure	70°C 60°C 50°C 40°C	0,4,8,12 4,8,12 4,8,12 4,8,12	No. 1
			50 ml glass container lined with polyethylene foil and twist-off closure	70°C	12	No. 1
	temperature + moisture	pure drug substance with adsorbed water	50 ml glass container with twist-off closure	70°C 60°C 50°C 40°C	0,4,8,12 4,8,12 4,8,12 4,8,12	No. 1
	temperature + moisture + drug sub-stance con-centration	1 % and 5 % aqueous solution	25 ml glass flask with ground glass stopper	70°C 50°C	0,4,8,12 4,8,12	No. 1
	ionic strength	1 % aqueous solution pH 5, (0.1 M citric acid, 0.2 M dibasic sodium phosphate)	25 ml glass flask with ground glass stopper	60°C	0,4,8,12	No. 1
		1 % aqueous solution pH 5, double buffer concentration, (0.2 M citric acid, 0.4 M dibasic sodium phosphate)	25 ml glass flask with ground glass stopper	60°C	0,4,8,12	No. 1

1.4.2.5 Evaluation

- Degradation products are assessed whether they may be formed during storage, shipment and accelerated and long-term testing. Thereby reaction kinetic calculations and regression analysis are applied if scientifically justified.
- The structures of the selected degradation products are elucidated, the degradation pathway established. The applied analytical procedures are assessed.
- The test attributes, the container closure system, the stability test protocol are established for accelerated and long-term testing with the registration batches.
- All results, conclusions and the derived stability information are summarised in the Stability report ”xy drug substance active ingredient stability profile”.

1.4.2.6 Statements/Labelling

The Stability report contains the following stability information

- **Stability predictions drug substance**:
  - Preliminary re-test period
  - Storage instructions
  - Test attributes
  - Assessed analytical procedures
  - Container closure system
  - Stability test protocol for accelerated and long-term testing.
- **Stability prediction for drug products:**
  - Orientational stability prediction for drug substance in drug products.

The preliminary data are incorporated in the stability pro-file of the drug substance

1.4.3 Confirmation testing for the derived preliminary re-test period

- The results of the stress investigations are finally confirmed by the data of the registration batches.
- To bridge the time in between confirmation testing is performed under long-term storage condition of climatic zone II. These data support the re-test period for the reference samples and batches of drug substance applied during development and clinical trial investigation with the drug product.

Stability test protocol

Batch	Container Closure System	Storage condition	Storage period, testing frequency	Test attributes
Reference sample, laboratory or pilot plant batch	Selected from data of stress investigation	25°C/60 %	0, 6, 12, 18, 24 months	Selected from data of stress investigation

The re-test period of the reference sample is fixed to 6 months until the data of the confirmation testing are available.

Stability Report	
BIWG 98 SE drug substance	Number SSRS 200-01-01
Active ingredient stability profile	Date 24.05.2002
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Responsible Company	
Successful Pharma KG Biberach	

Responsible:

Analytical Sciences Department

Drug Product Analysis
Laboratory AZ 1

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1.2 Stability Results

The Stability Report comprises the stability data of stress investigations with the active Ingredient BIWG 98 SE. It represents the stability profile of the NME BIWG 98 SE

Two laboratory batches were included in the investigations

The analytical procedures were stability indicating and preliminary validated.

The following factors were investigated:
Moisture, temperature, moisture + temperature, moisture + temperature + drug substance concentration, pH, ionic strength, oxidation, light.

Three degradation products were formed:
BIWG 98 D1 by hydrolysis of the amide bond, the structure has been elucidated.
The structures of the two others

- BIWG 98 O caused by oxidation,
- BIWG 98 L caused by light

were not elucidated since they are formed only under stress conditions and will not appear under normal storage conditions.

The analytical results are presented in the following table.

1.2 Stability results

Overview of the summarized analytical results

Influencing Factor	Test sample Batch No	Container Closure System	Storage Con-ditions	Storage period	Test attributes	Analytical results
moisture+	1% and 5%	25 ml glass	70°C	12	appearance	no change
temperature+ substance	aqueous solution	flask with ground	50°C	weeks	degradation of BIWG 98 SE	**degradation up to 5%**
concentration (solution)	S95004	glass stopper			assay of BIWG 98 SE	**fall in assay**
pH	1% aqueous solution pH 1, 2, 3 S95001	25 m glass flask with ground glass stopper	60°C/--	3 weeks	appearance	no change
					degradation of BIWG 98 SE	**degradation up to 3.2%**
					assay of BIWG 98 SE	**fall in assay**
	1% aqueous solution pH 4,5,6 S95001				appearance	no change
					degradation of BIWG 98 SE	**degradation up to 0.38%**
					assay of BIWG 98 SE	no fall in assay
	1% aqueous solution pH 8 S95001				appearance	no change
					degradation of BIWG 98 SE	no degradation
					assay of BIWG 98 SE	no fall in assay
Ionic strengths	1% aqueous solution single and double buffer concentration pH 5 S95004	25 ml glass flask with ground glass stopper	60°C/--	12 weeks	appearance	no change
					degradation of BIWG 98 SE	no degradation
					assay of BIWG 98 SE	no fall in assay
oxidation	1% aqueous solution in 3% H_2O_2 solution S95001	25 ml glass flask with ground glass stopper	50°C/--	3 weeks	appearance	no change
					degradation of BIWG 98 SE	**degradation 0.14%**
					assay of BIWG 98 SE	no fall in assay

1.3 Stability predictions

1.3.1 Drug substance

- Test attributes for accelerated and long term testing with the registration batches:
  Appearance, colour of solution, clarity of solution, melting range, water content, impurities and degradation of BIWG 98 SE, assay of BIWG 98 SE, assessment of container closure system

- Analytical procedures:
  The applied analytical procedures are suitable after complete validation for the registration batches.

- Selection of container closure system
  Tight container lined with polyethylene foil 3020 D.

- Re-test period:
  Climatic zone I + II: 2 years

- Storage instructions:
  none.

1.3.2 Drug product

Solid, liquid and semi-liquid dosage forms can be developed concerning chemical stability:

- Solid dosage forms:
  Chemical stability of drug substance orientational prediction: $\geq$ 2 years

- Liquid and semi-liquid dosage forms:
  Chemical stability of drug substance orientational prediction: $\geq$ 2 years

  Antioxidants may be necessary
  Photostability of the dosage forms should be investigated.

3.4 Stability test protocol preliminary investigation

Batch No.	Influencing factor	Test sample	Container closure system	Storage conditions	Testing frequency [weeks]	Anal. proce-dure
S95001	moisture	pure drug substance	open petri dish	25°C/75%	0,1	No. 1
	temperature	pure drug substance	50 ml glass container with twist-off closure	70°C	0,2,4	No. 1
	temperature + moisture	pure drug substance + 3.8 % absorbed water	50 ml glass container with twist-off closure	70°C	0,2,4	No. 1
	pH	1 % aqueous solution pH 1,2,3,4,5,6,7,8 0.1, 0.01 M HCl, McIlvaine's buffer (0.1 M citric acid, 0.2 M dibasic sodium-phosphate, 0.01 M NaOH	25 ml glass flask with ground glass stopper	60°C	0,1,3	No. 1
	oxidation	1 % aqueous solution in 0.3 % H_2O_2 solution	25 ml glass flask with ground glass stopper	50°C	0,1,3	No. 1
	light	pure drug substance	open petri dish	Xenon lamp	24, 48 hours	No. 1
			brown glass flask with ground glass stopper	Xenon lamp	24, 48 hours	No. 1
		1 % aqueous solution gassed with N_2	colourless glass flask with ground glass stopper	Xenon lamp	24, 48 hours	No. 1
		1 % aqueous solution	colourless glass flask with ground glass stopper	Xenon lamp	24, 48 hours	No. 1
			brown glass flask with ground glass stopper	Xenon lamp	24, 48 hours	No. 1

4.1 Graphic of Test results

4.1.3 Influencing factor: pH

Degradation of BIWG 98 SE in aqueous solutions pH 1 - 8 at 60°C.

Sample: Batch No. S95001

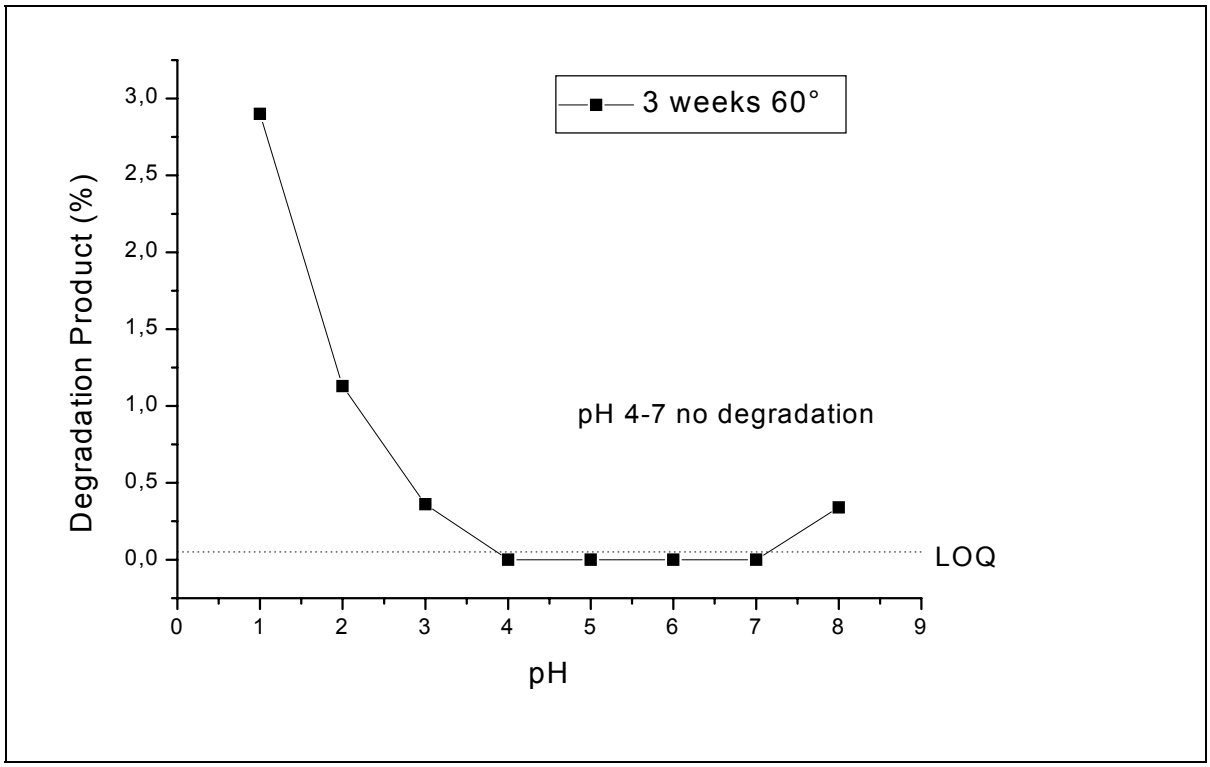
1 % solution pH 1, 2 (0.1, 0.01 M HCl)
1 % solution pH 3,4,5,6,7 (McIlvaine's buffer) 0.1 M citric acid, 0.2 M dibasic sodium phosphate
1 % solution pH 8 (0.01 M NaOH)

Container closure system:

25 ml glass flask with ground glass stopper

Storage time	Storage conditions							
3 weeks	60°C	60°C	60°C	60°C	60°C	60°C	60°C	60°C
	pH 1	pH 2	pH 3	pH 4	pH 5	pH 6	pH 7	pH 8

Assay of BIWG 98 SE	98.0 – 101.0%



4.2 Test results

4.2.3 Influencing factor: pH

Sample: Batch No. S95001

Container closure system:

1 % solution pH 1, 2 (0.1, 0.01 M HCl)
1 % solution pH 3,4,5,6,7 (McIlvaine's buffer) 0.1 M citric acid, 0.2 M dibasic sodium phosphate
1 % solution pH 8 (0.01 M NaOH)

25 ml glass flask with ground glass stopper

Storage time weeks	Storage conditions							
	60°C	60°C	60°C	60°C	60°C	60°C	60°C	60°C
	pH 1	pH 2	pH 3	pH 4	pH 5	pH 6	pH 7	pH 8

appearance								
0	clear, colourless	clear, colourless	clear, colourless	clear, colourless	clear, colourless	clear, colourless	clear, colourless	clear, colourless
1	clear, colourless	clear, colourless	clear, colourless	clear, colourless	clear, colourless	clear, colourless	clear, colourless	clear, colourless
3	clear, colourless	clear, colourless	clear, colourless	clear, colourless	clear, colourless	clear, colourless	clear, colourless	clear, colourless

degradation of BIWG 98 SE	(% BIWG 98 D1 $\triangleq$ % degraded BIWG 98 SE)							
1	0.96 % = 1.08 %	0.38 % = 0.43 %	0.10 % = 0.13 %	no degrad.	no degrad.	no degrad.	no degrad.	0.11 % = 0.12 %
3	**2.90 % = 3.28 %**	1.13 % = 1.28 %	0.36 % = 0.41 %	no degrad.	no degrad.	no degrad.	no degrad.	0.34 % = 0.38 %

Assay of BIWG 98 SE	98.0 – 101.0%							
1	98.5 %	98.9 %	98.9 %	99.3 %	98.9 %	99.8 %	99.9 %	99.7 %
3	97.1 %	98.5 %	99.4 %	99.7 %	99.6 %	99.9 %	99.8 %	99.5 %

4.3 Evaluation

4.3.3 Degradation pathway

Three degradation products were formed by the stress investigations:

- BIWG 98 D1
  This degradation product was formed by hydrolysis of the amide bond. Ratio of the relative molecular mass: 520 : 460 = 1.13. The degradation rate is influenced by the water content and the pH. In the pH range 5 - 7 no degradation is expected.

  The structure has been elucidated. It should be qualified up to 10% in a degraded sample together with the drug substance BIWG 98 SE.

  It is also expected to be formed in the different dosage forms at accelerated and long term storage conditions.

- BIWG 98 O
  This degradation product was formed in solution in 0.3 % H_2O_2, but not in the aqueous solutions alone. If it would appear nevertheless in liquid dosage forms an antioxidants can be applied.

  The structure was not elucidated since it is not expected to be formed at accelerated and long term storage conditions.

- BIWG 98 L
  This degradation product was formed by stress light (Xenon lamp). Under confirmation conditions according to the ICH Guideline "Photostability" it did not appear. There-fore the structure was not elucidated.

5. Conclusions

- ❒ The Stability Profile of the active ingredient the NME BIWG 98 SE has been established.

- ❒ The analytical procedures are stability indicating and preliminary validated.

The intrinsic stability characteristics are as follows:

No influence on stability:
Temperature, drug substance concentration and ionic strength.

Influence on stability:
Moisture (adsorption), moisture + temperature, pH, degradation (BIWG 98 D1), oxidation (BIWG 98 O), Xenon light (BIWG 98 L).

- ❒ No chemical instabilities are to be expected for the shipment and storage under accelerated and long term storage conditions of the drug substance.

- ❒ The samples should be stored in tight containers, during production no special precautions are necessary.

5.1 Stability predictions drug substance

- ❒ **Selection of test attributes for the accelerated and long term testing with the 3 registration batches:**
  Appearance, colour of solution, clarity of solution, melting range, loss on drying, impurities and degradations of BIWG 98 SE, assay of BIBW 98 SE, assessment of packaging material.

- ❒ **Analytical procedures**:
  The applied analytical procedures are suitable for the registration batches after complete validation.

- ❒ **Selection of container closure system**:
  Tight containers lined with polyethylene foil 3020 D are re-quired.

- ❒ **Re-test period**:
  Climatic zone I + II: 2 years.

- ❒ **Storage instructions**:
  None.

5.2 Stability predictions drug product

Solid, liquid and semi-solid dosage forms can be developed concerning the chemical stability

Liquid dosage forms:

Liquid dosage forms have to be investigated concerning oxidation.
Orientational stability prediction: $\leq$ 2 years

On the base of the stress data under 4.3.2.4. moisture + temperature + drug substance concentration in solution the degradation of BIWG 98 SE to BIWG 98 D1 was calculated:

ΔE: 83 kJ · mol^{-1}, first order reaction. pH of the solution about 3.

Storage conditions	Storage period [months]	% degraded BIWG 98 SE $\triangleq$ % BIWG 98 D1
40°C/75 % r.h.	6	0.7 %0= 0.62 %
30°C/70 % r.h.	12 24 36 48 60	0.5 % = 0.44 % 1.0 % = 0.88 % 1.4 % = 1.24 % 1.9 % = 1.68 % 2.4 % = 2.12 %
25°C/60 % r.h.	12 24 36 48 60	0.3 % = 0.27 % 0.6 % = 0.53 % 0.8 % = 0.71 % 1.1 % = 0.97 % 1.4 % = 1.24 %

For liquid dosage forms a pH between pH 5 - pH should be chosen. Under these conditions a stable formulation can be expected.

Semi-liquid dosage forms $\cong$ liquid dosage forms.

3.2. Preformulation and Formulation finding for the Tox-, Clinical Samples, and Final Dosage Form

The tests are based on the drug substance stability profile. Therefore it is a prerequisite for step 2.

This stage covers the process of development from the first preformulation tests to the toxicological and clinical samples and the potential final formulation for the desired dosage form. Consequently, it includes the actual pharmaceutical-technological development.

Since a different dosage form is frequently used for the clinical samples than is planned for later market introduction, e.g. capsules for clinical trials, tablets for the market, a double-tracked approach is necessary in some cases.

2.1 Objective

- ❒ Dosage form related tests with the drug substance.
- ❒ Acceptance criteria for individual excipients.
- ❒ Investigations of external factors that have an influence on individual excipients.
- ❒ Compatibility tests with the drug substance.
- ❒ Compatibility tests with preliminary formulations.
- ❒ Clarification of technological influencing factors.
- ❒ Selection of formulations for toxicological samples.
- ❒ Development of the analytical procedure for dissolution rate testing.
- ❒ Selection of formulations for clinical samples.
- ❒ Selection of formulation and optimisation of the potentially final formulation.

The requirements placed on the different dosage forms are highly variable. Furthermore, an individual approach is adopted for each specific case which is shaped by the corporate philosophy as well as the skill and experience of the developer.
A schedule of tests can thus only be sketched in very general terms:

2.2 Application of the basic principles

❒ **Selection of batches and samples**

- Drug substance, excipients,
- active ingredient-excipient mixtures,
- dosage forms.

The drug substance and excipients batches used must comply with the specifications of the quality control testing specifications.

❒ **Test attributes**

- Appearance,
- relevant physico-chemical parameters,
- drug substance decomposition and assay.

❒ **Analytical procedures:**
Specific to stability testing orientationally validated.
Methods for physico-chemical determinations are optimised and preliminarily validated, e.g. dissolution rate.

❒ **Acceptance criteria**
Not relevant, tests are performed to identify changes.

❒ **Storage conditions**
Standard storage conditions for stress tests and long-term tests, relevant for the dosage form

- ≥ - 10°C
- 5°C
- 5 - 40°C temperature cycle
- 25°C/60 %
- 30°C/65%
- 40°C/75 %,
- 40°C, 60°C

❒ **Storage period:**
Problem-orientated

- e.g. until equilibrium is reached for open storage
- not more than 3 months.

❒ **Testing frequency:**
Individually determined, depending on the stability behaviour

❒ **Evaluation and statements**

- Orientational testing specification
- Dosage form related drug substance stability profile
- Attributes and stability results of individual excipients.
- Research report of selected formulations for clinical samples and potential final formulations.
- Research report of rational for analytical procedure dissolution rate.
- These reports are part of the development report.

2.3 Practical Examples

The tests also depend on

- the active ingredient, its solubility and stability,
- the dosage form to be developed,
- the experience and skill of the developer.

Only a few points may be given as examples.

2.3.1 Dosage form related active ingredient profile

This concerns all the solubility problems of an active ingredient under consideration:

- dissolution profile with respect to pH, particle size, surface area,
- tests to improve the apparent solubility or dissolution rate.

2.3.2 Stability behaviour of excipients

- moisture sorption tests
- sensitivity to oxygen
- sensitivity to light
- sensitivity to pH

2.3.3 Selection of formulation

- compatibility tests active ingredient - excipients, preferably preliminary formulations
- planning of tests, factorial design
- technological influencing factors
- optimisation of pH for liquid, semisolid and, if appropriate, solid dosage forms
- evaluation of shelf life specifications for antimicrobial preservatives
- oxygen and sensitivity to light-discoloration
- content uniformity
- phase separation with semisolid forms
- solubility problems with semisolid and liquid dosage forms
- optimised in vitro procedure for determination of dissolution rate

3.3. Stress- and Accelerated Testing with selected formulations, selection of container closure system, up scaling pilot-plant, registration batches

These tests follow directly upon step 2.

This is the main area of focus in development analysis.

It is necessary to establish whether the formulation selected in screening in step 2 is not only stable in relative terms but also absolutely stable enough for toxicological investigations, clinical trials and possible commercialisation.

3.1 Objective

- ❒ Optimisation and validation of analytical procedures.
- ❒ Selecting those degradation products which may be formed under accelerated and long-term testing within the anticipated shelf life.
- ❒ Establishment of the degradation pathway and elucidating the structure of the selected degradation products.
- ❒ Identification of the weaknesses of the formulation and parameters that may have a limiting effect on the anticipated shelf life.
- ❒ Identification of problems that could arise during storage and especially during transport.
- ❒ Establishment of tolerances for changes during storage.
- ❒ Evaluation of the robustness of the formulation.
- ❒ Selection of suitable container closure systems.
- ❒ Establishment of minimum shelf lives (period of use) and if necessary storage instructions for
  - toxicological samples
  - clinical trial samples for the phases I – III.
- ❒ Selection of test attributes for accelerated and long-term testing with the registration batches in step 4.
- ❒ Establishment of the stability test protocol for the registration batches in step 4.
- ❒ Establishment of registration release- and shelf-life specifications for the registration batches in step 4.
- ❒ Establishment of the anticipated shelf lives for the stability investigations in step 4 and 5.

The stress tests must be thought out and planned very carefully. The individual stability protocol depends on the stage of development, the dosage form, the number of strengths and the anticipated shelf life.

Two aspects however must be considered for all stress investigations:

❒ **Storage conditions**

If a stability prediction of all test attributes is to be derived, a distinction must be drawn between storage for

- organoleptic and physico-chemical stability, where the laws of reaction kinetics do not apply,
- chemical (drug substance, preservatives) stability, where the laws of reaction kinetics are applicable.

❒ **Tight containers to prevent loss of moisture.**

3.2 Application of the basic principles

The drug product is in the process of development with different

- formulations,
- strengths,
- dosage forms,
- batch sizes
- equipment.

Therefore a variety of different batches is included in these stress investigations.

A prerequisite for all batches is that the used drug substances and excipients have been released by quality control.

3.2.1 Selection of batches and samples

The following batches may be included:

- Experimental laboratory batches
- Toxicological samples
- Experimental clinical batches
- Clinical or pilot plant batches
- Final formulation batches
- Representative primary registration batches

3.2.2 Test attributes

The relevant test attributes will become apparent during the course of development.

Included are the 4 groups of test attributes

- organoleptic
- physico-chemical
- chemical
- microbial

Overview on general test attributes for solid, semi-solid and liquid dosage forms used in stability testing.

3.2.2.1 Solid dosage forms: tablets, capsules

❒ **Organoleptic and physico-chemical stability**

Tablets: Appearance, average mass, water content, disintegration time, dissolution rate hardness (resistance to crushing strength).

Capsules: Appearance, elasticity, average mass, average mass of filling, water content capsule shell and filling, disintegration time, dissolution rate.

❒ Chemical stability

Tablets: Drug substance: decomposition and assay
Capsules: Drug substance: decomposition and assay.

3.2.2.2 Semi-solid dosage forms: Creams and ointments

❒ **Organoleptic and physico-chemical stability**

Appearance, odour, homogeneity, consistency, pH, particle size (if active ingredient is in suspension), recrystallization, content uniformity within container (tubes stored vertically are cut open, samples are taken from the beginning, middle and end of the tube and analysed).

❒ **Chemical and microbial stability**

Drug substance decomposition and assay, preservative assay.

3.2.2.3 Liquid dosage forms: solutions, ampoule

❒ **Organoleptic and physico-chemical stability**

Appearance, colour of solution, clarity, pH.

❒ **Chemical and microbial stability**

Drug substance decomposition and assay, preservative assay.

3.2.3 Analytical Procedures

The analytical procedures have to be stability indicating. They undergo a process of development. The same applies for the validation.

❒ **Three steps of validation are differentiated:**
- orientational
- preliminary
- complete.

The following table lists the extend of validation for the three steps:

Validation characteristic	Extend of validation		
	orientational	preliminary	complete
Specificity	x	x	x
Linearity	x	x	x
Quantitation Limit (Reporting threshold)	x	x	x
Detection limit (1)	x	x	x
Accuracy		x	x
Range		x	x
Repeatability		x	
Intermediate precision			x
Robustness	x	x	x
Validation report			x

(1) instead of quantitation limit for semi-quantitative procedures

3.2.4 Specifications, Acceptance criteria

Fixing specifications is an evolving process which accompanies the development of the new drug substances and drug products.

❒ **It has always to be differentiated between**
- release specifications
- shelf life specifications.

Fixing specifications can be described as a four step procedure as listed in the following table:

Step of development drug substance, drug product	Specifications	Characterisation
• Preclinical • Clinical phase I	Orientational	Target values
• Clinical phases II/III • Pivotal batches	Preliminary	Broader acceptance criteria, ranges, numerical limits.
• Pilot plant batches • Registration batches	Registration	Acceptance criteria focussing on safety and efficacy.
Production batches after marketing authorisation	Post-approval	Experience gained with manufacture of a particular drug substance or drug product.

3.2.5/6 Storage conditions, storage period

❒ **It has to be differentiated between:**

- stress,
- accelerated,
- long-term storage conditions.

Type	Storage condition
Stress	• Open storage at 25°C/60 %, 30°C/65% 40°C/75%, 40°C/25% • ≥ - 10°C • 5°C • Temperature cycle 5 – 40°C • Xenon lamp 48 hours • 40, 50, 60, 70°C
Accelerated	• 40°C/75% r.h. (30°C/65% r.h.)
Long-term	• 25°C/60% r.h. • 30°C/65% r.h.

If a stability prediction for all test attributes is to be derived, a distinction must be drawn between storage for

- ❒ organoleptic and physico-chemical stability where the laws of reaction kinetics do not apply,
- ❒ chemical stability (drug substance, preservatives) where the laws of reaction kinetics may be applicable.

Overview for solid, semi-solid and liquid dosage forms:

Stability investigation	Dosage form	Storage condition	Storage period
Organoleptic and physico-chemical stability	Solid	Storage in open container until equilibrium is reached at 25°C/60%, 30°C/70%(65%) 40°C/75 %	1 – 2 weeks
	Semi-solid	≥ - 10°C 5°C 5°C – 40°C temperature cycle within 24 hrs 40°C (content uniformity)	4 weeks 4 weeks 2 weeks 3 months
	Liquid	≥ - 10°C 5°C 40°C/≤ 25% (semipermeable container)	4 weeks 4 weeks 3 months
Photostability	all	Xenon lamp (Atlas Suntest, 250 W/m²)	48 hrs
Chemical	Solid	40°C, 50°C, 60°C, 70°C	3 months
stability	Semi-solid	30°C, 40°C, 50°C	3 months
	Liquid	40°C, 50°C, 60°C, 70°C	3 months

3.2.7 Testing frequency

- ❒ Individually determined, depending on the problem and stability behaviour.
- ❒ When testing for chemical and microbial stability ≤ 4 determinations including initial analysis.

3.2.8 Number of batches

- ❒ Basically 1 batch per formulation.
- ❒ If several strengths have to be investigated for clinical phase I or II bracketing is applied.

It is also used even if the composition of the individual strengths may differ.

A rational bracketing system for all dosage forms would be as follows:

Strength	Samples tested
1 – 2	all
3 – 4	highest lowest
> 4	highest middle lowest

Examples:

- If minimum shelf lives are required for 10, 20, 40, 60, 80, 120 mg, then 10, 40, 120 mg are tested.

- If 3–4 strengths have to be investigated the two extremes the highest and lowest are fully tested.
  The most probable final strength however will be a middle strength. Therefore also a middle strength will be included with a reduced stability protocol e.g. chemical stress testing only at 60°C.

3.2.9 Container Closure System

In selecting container closure systems, the following has to be considered:

At higher temperatures, desorption and loss of moisture also occurs at higher relative humidities.

- ❒ Unless packaging materials impermeable to water vapour are used for stress tests with solid dosage forms, the samples lose moisture at different rates in the temperature range 40 - 60°C and the results are not suitable for a reaction kinetics calculation.

- ❒ Packaging materials permeable to water vapour can however also result in a falsification of the results for semi-solid and liquid dosage forms if varying degrees of mass loss occur which lead to differences in the active ingredient concentration or ion strength.

- ❒ The use of inert standard packaging materials that are impermeable to water vapour is thus an important precondition for stress tests which are to be evaluated in terms of reaction kinetics, and on the results of which stability predictions are to be based.

- ❒ Most of the stress tests are carried out in standard packaging material.

The following Container closure systems are used:

Dosage form	Container closure system
Solid	• 50-ml glass container with twist-off closure, (tight container) • Polypropylene tube
Semi-solid	• Standard tube, • Small volumetric flask • Aluminium tube, inert lacquering
Liquid	• 25-ml volumetric glass flask with ground-glass-stopper

However, further investigations for the selection of the final container closure system are necessary.

3.2.9.1 Selection of container closure systems for solid dosage forms

- On the basis of the results of the stress tests for solid dosage forms, the sensitivity to moisture can be determined and suitable packaging materials can be selected.

As a rule, no interactions are to be expected.

- If the final container closure system has been selected and samples packed in the final packaging material are available, the investigation of photo-stability should be performed.

- Photostability
  - The samples with and without container are irradiated with a Xenon lamp (Atlas Suntest, 250 W/m²) for 24 hours.
  - Test attributes: appearance, drug substance decomposition and assay.

3.2.9.2 Selection of container closure systems for semi-solid dosage forms

Suitable tests have to be carried out.

- **Container closure systems:**
  Aluminium tube internally lacquered, plastic tubes.

- **Problems:**
  Corrosion of metal tube; interaction with internal lacquering; sorption; permeation of water vapour, oxygen, aromas, essential oils.

❒ **Tests packaging material - dosage form:**
To test for corrosion, the filled metal tubes are stored horizontally, upright and inverted at 40°C for 3 months and are then investigated.

❒ **Test for permeation and sorption**:
The filled plastic tubes are stored for 3 months at 50°C, 40°C, 30°C/70 % (65%)

The climatic zone in which the product is to be introduced must also be taken into account.

❒ Because of the problems arising with plastic tubes, aluminium tubes are preferred.

If the final packaging material has been selected the investigations on the photostability are performed.

❒ **Photostability:**
- The samples with and without container are irradiated with a Xenon lamp (Atlas Suntest, 250 W/m²) for 24 hours.
- Test attributes:
  Appearance, drug substance decomposition and assay.

3.2.9.3 Selection of container closure systems for liquid dosage forms

Suitable tests have to be carried out.

❒ **Container closure systems:**
Ampoule, injection vial with rubber stopper, glass bottle or plastic bottle with screw closure or pilfer proof closure with liner.

❒ **Problems:**
pH, leakage, desorption, sorption, permeation, interaction with rubber stopper, interaction with liner.

❒ **Tests packaging material - dosage form:**
To test for sorption, permeation, pH and leakage, the final formulation solution is filled in the container, and for desorption placebo solution is used. The samples are stored vertically and inverted under the following conditions: 50°C, 40°C, 40°C/25%, 30°C/70 % for up to 12 weeks. Testing intervals: 0, 1, 2, 3 months.

If the final container closure system has been selected the investigations on the photostability are performed.

❒ **Photostability:**
- The samples in colourless glass and the original packaging material are irradiated with a Xenon lamp (Atlas Suntest, 250 W/m²) for 24 hours.
- Test attributes:
  Appearance, (colour of solution), clarity of solution, drug substance decomposition and assay.

3.2.10 Evaluation

A systematic approach is adopted in the evaluation and presentation of the analytical results.

Thereby all test attributes are included.

- **Investigations for organoleptic and physico-chemical stability.**
  - Where possible the data are evaluated for significant changes with the aid of statistics.
  - Organoleptic and physico-chemical changes which have taken place at stress temperatures at 40–70°C are recorded but they are only of limited relevance for predicting stability.

- **Investigations for chemical and microbial stability**
  - If decomposition and fall in assay has taken place, the equations for a first-order reaction and the Arrhenius equation are used.
  - If decomposition levels are available for only one temperature, the activation energy Δt: 83 KJ x mol^{-1} (9) is applied.

    The decomposition levels for the required storage temperatures are calculated.

3.2.11 Statements/Labelling

All results and the stability information derived there-from are compiled in a stability report. The different stability reports are structured and written in the same format.

They contain

- Summary
- Introduction
- Material and methods
- Results and evaluation
- Conclusions
  - Statements

The stability information corresponds to the stage of development.

Stage of development	Stability information
General	- Assessment of the formulation - General prediction of shelf lives - Storage instructions if required - Proposal for the container closure system
Toxico-logical samples	- Minimum shelf life (period of use) for toxicological samples in climatic zone I and II
Clinical phase I	- Minimum shelf life (period of use) for phase I in climatic zones I and II - Storage instructions if required - Proposal of suitable container closure system - Robustness of the formulation
Clinical phase II	- Minimum shelf life (period of use) for phase II in climatic zones I and II - Storage instructions if required - Proposal of suitable container closure system - Robustness of the formulation
Clinical phase III	- Minimum shelf life (period of use) for phase III in climatic zone I and II - Storage instructions if required - Proposal of suitable container closure system - Selection of those decomposition products that may occur under accelerated and long-term testing of the registration batches in step 4. - Elucidated structure and degradation path way of the selected decomposition products. - Establishment of test attributes for accelerated and long-term testing of the registration batches in step 4. - Registration release and shelf life specifications for registration batches in step 4. - Establishment of storage conditions for accelerated and long-term testing in step 4 + 5. - Suitable container closure systems for the registration batches in step 4. - Expected shelf lives for the registration batches in step 4 and 5 and storage instructions if necessary. - Establishment of Stability test protocol for registration batches. - Robustness of the formulation
Registration batch	- Comparison and evaluation of the results of the stress investigation with laboratory, clinical trial and registration batches - Robustness of formulation

3.3 Practical examples

3.3.1 General

3.3.1.1 Solid dosage forms

Stability test protocols

Organoleptic and physico-chemical stress testing

Container Closure System	Storage conditions	Storage period, Testing frequency	Test attributes
Open container	25°C/60%	0, 2 weeks	organoleptic, physico-chemical
	30°C/70% (30°C/65%)	0, 2 weeks	organoleptic, physico-chemical
	40°C/75%	0, 2 weeks	organoleptic, physico-chemical

Photostability stress testing

Container Closure System	Storage conditions	Storage period, Testing frequency	Test attributes
Open container	Xenon lamp Atlas Suntest 250 W/m²	24, 48 hours	Appearance, drug substance decomposition and assay

Chemical stress testing

Container Closure System	Pre-treatment	Storage conditions	Storage period, Testing frequency	Test attributes
50 ml glass container with twist-off closure or equivalent tight container	none	70°C 60°C 50°C 40°C	1, 2, 3 months 1, 2, 3 months 0, 1, 2, 3 months 1, 2, 3 months	chemical chemical all all
	30°C/65%* or 25°C/60%* or 40°C/75%*	70°C 60°C 50°C 40°C	1, 2, 3 months 1, 2, 3 months 0, 1, 2, 3 months 1, 2, 3 months	chemical chemical all all

* Samples which have adsorbed the highest amount of water during open storage at 25°C/60%, 30°C/65%, 40°C/75 % are used.

3.3.1.2 Semi-Solid dosage forms

Stability test protocols

Organoleptic and physico-chemical stress testing

Container Closure System	Storage conditions	Storage period, Testing frequency	Test attributes
Standard tube	≥ - 10°C	0, 4 weeks	organoleptic, physico-chemical
	5 – 40°C in 24 hrs cycle	0, 2 weeks	organoleptic, physico-chemical
	40°C, tube stored vertically, with the neck of the tube pointing upwards	0, 3 months	content uniformity (homogeneous distribution of active ingredient, assay of material taken from the beginning, middle, end of the tube)

Photostability stress testing

Container Closure System	Storage condition	Storage period, Testing frequency	Test attributes
Open container	Xenon lamp Atlas Suntest 250 W/m²	24, 48 hrs	Appearance, drug substance decomposition and assay

Chemical and microbial stress testing

Container Closure System	Storage condition	Storage period, Testing frequency	Test attributes
Standard tube	50°C 40°C 30°C	1, 2, 3 months 0, 1, 2, 3 months 3 months	Organoleptic, physico-chemical all all

Selection of container closure system

Proposed Container Closure System	Compo-sition	Storage condition	Storage period, Testing frequency	Test attributes
metal tube	verum	40°C stored horizontally, upright, inverted	0, 3 months	Appearance, drug substance decomposition, appearance of internal surface of metal tube for corrosion, interaction with internal lacquering
plastic tube	placebo	50°C 40°C 30°C/65%	0, 1, 2, 3 months 1, 2, 3 months 3 months	Loss in mass (water permeation), aromas, essential oils, desorption
	verum	40°C	0, 3 months	Organoleptic, loss in mass, drug substance decomposition and assay

3.3.1.3 Liquid dosage forms

Stability test protocols

Organoleptic and physico-chemical stress testing

Container Closure system	Storage conditions	Storage period, Testing frequency	Test attributes
25 ml glass flask with ground glass stopper	5°C	0, 4 weeks	organoleptic, physico-chemical
glass bottle or equivalent	≥ - 10°C	0, 4 weeks	organoleptic, physico-chemical

Photostability stress testing

Container Closure System	Storage condition	Storage period, Testing frequency	Test attributes
25 ml colourless glass flask with ground glass stopper	Xenon lamp Atlas Suntest 250 W/m²	24, 48 hrs	Organoleptic, physico-chemical, drug substance decomposition and assay

Chemical stress testing

Container Closure System	Storage condition	Storage period, Testing frequency	Test attributes
25 ml glass flask with ground glass stopper	70°C 60°C 50°C 40°C	0, 1, 2, 3 months 1, 2, 3 months 1, 2, 3 months 1, 2, 3 months	all all all all

Selection of container closure system

Intended Container Closure System	Compo-sition	Storage condition	Storage period, Testing frequency	Test attributes
glass bottle with screw closure	placebo	50°C upright and inverted	0, 3 months	Desorption of liner components
or pilfer proof with liner	verum	50°C,40°C upright and inverted	0, 3 months	all
plastic bottle with closure semipermeable container	placebo	50°C 40°C 40°C/25% 30°C/65 % upright +inverted	0,1,2,3 months 1,2,3 months 1,2,3 months 3 months	Appearance, loss in mass, desorption of plastic components
	verum	50°C 40°C	0, 2,3 months 2,3 months	all all
ampoule	verum	50°C 40°C	0, 3 months 3 months	all all
injection vial with rubber stopper	placebo	50°C 40°C stored inverted	0, 3 months 3 months	Organoleptic, physico-chemical, desorption of rubber component
	verum	50°C 40°C stored inverted	0, 3 months 3 months	all

3.3.2 Toxicological samples

The anticipated minimum shelf life of 12 weeks is derived from the data of accelerated testing and confirmed by storage at 25°C/60 % r.h. (climatic zone II).

Stability test protocol

Accelerated and confirmation testing

Batch	Container Closure System	Storage condition	Storage period, Testing frequency	Test attributes
Experimental laboratory batch	Standard	40°C/75%	0, 2, 4, 6 weeks	all
		25°C/60%	12 weeks	all

3.3.3 Clinical trial samples, phase I - III

3.3.3.1 Solid dosage forms

3.3.3.1.1 Phase I

The anticipated minimum shelf life (period of use) is 3 to 6 months. The minimum shelf life is derived from data of stress- and accelerated testing after 6 weeks or 3 months, respectively, and then confirmed by the data of samples stored at 25°C/60 % (climatic zone II) up to 3 or 6 months.

Stability test protocols

Organoleptic and physico-chemical stress testing

Batch	Container Closure System	Storage condition	Storage period, Testing frequency	Test attributes
Experimental laboratory batch	open container	25°C/60 %	0, 2 weeks	organoleptic, physico- chemical

Chemical accelerated and confirmation testing

Batch	Container Closure System	Minimum shelf-life	Pre-treatment	Storage Condition	Storage period, Testing frequency	Test attributes
Experi-mental labora-tory batch	50ml glass container with twist-off closure	3 months	none	40°C	0, 2, 4, 6 weeks	all
			25°C/60 %	40°C	0, 2, 4, 6 weeks	all
			none	25°C/60 %	3 months	all
	PP tubes		none	25°C/60 %	3 months	all
	50 ml glass container with twist-off closure	6 months	none	40°C	0, 1, 2, 3 months	all
			25°C/60 %	40°C	0, 1, 2, 3 months	all
			none	25°C/60 %	6 months	all
	PP tubes		none	25°C/60 %	6 months	all

If several strengths are to be investigated bracketing is applied.

3.3.3.1.2 Phase II

The anticipated minimum shelf life (period of use) is 12 – 18 months. The minimum shelf life is derived from the data of stress testing after 3 months, firstly confirmed by 6 months data of 40°C and finally by 12 or 18 months data of samples stored at 25°C/60% for climatic zone II.

Stability test protocols

Organoleptic and physico-chemical stress testing

Batch	Container Closure System	Storage condition	Storage period, Testing frequency	Test attributes
Experimental laboratory batch	open container	25°C/60 %	0, 2 weeks	organoleptic, physico- chemical

Chemical stress and confirmation testing

Batch	Container Closure System	Pre-treatment	Storage condition	Storage period, Testing frequency	Test attributes
Experi-mental clinical batches	50 ml glass container with twist-off closure	none	60°C	0, 1, 2, 3 months	all
		none	40°C	1, 2, 3, 6 months	all
	"	25°C/60 %	60°C	0, 1, 2, 3 months	all
	"	25°C/60 %	40°C	1, 2, 3, 6 months	all
	"	none	25°C/60 %	12, 18 months	all
	PP tubes or test container closure system	none	25°C/60 %	12, 18 months	all

If several strengths are to be investigated bracketing is applied.

3.3.3.1.3 Phase III

The anticipated minimum shelf life (period of use) is 24 - 36 months. The minimum shelf life is derived from the data of stress testing after 3 months, firstly confirmed by 6 months data of 40°C and finally by 24 or 36 months data of samples stored at 25°C/60% (climatic zone II). Usually in phase III the final formulation is applied. Therefore the stability information for the registration batches has also to be considered.

Stability test protocols

Organoleptic and physico-chemical stress testing

Batch	Container Closure System	Storage condition	Storage period, Testing frequency	Test attributes
Clinical or pilot-plant, final formulation	open container	25°C/60% 30°C/65% 40°C/75%	0, 2 weeks 0, 2 weeks 0, 2 weeks	organoleptic, physico-chemical

Photostability stress testing

Batch	Container Closure System	Storage condition	Storage period, Testing frequency	Test attributes
Clinical or pilot-plant batch, final formulation	• open container • proposed test or commercial container closure system	Xenon lamp, Atlas Suntest 250 W/m²	24, 48 hrs	Appearance, Drug substance decomposition and assay

Chemical stress and confirmation testing

Batch	Container Closure System	Pre-treatment	Storage condition	Storage period, Testing frequency	Test attri-butes
Clinical or pilot plant batch, final formulation	50 ml glass container with twist-off closure	none	70°C 60°C 50°C 40°C	1, 2, 3 months 1, 2, 3 months 0, 1, 2, 3 months 1, 2, 3, 6 months	chemical chemical all all
		30°C/65%* or 25°C/60 % or 40°C/75 %	70°C 60°C 50°C 40°C	1, 2, 3 months 1, 2, 3, months 0, 1, 2, 3 months 1, 2, 3, 6 months	chemical chemical all all
	50 ml glass container with twist-off closure	none	25°C/60 %	12, 18, 24, 36 months	all
	PP tube or test packaging material	none	25°C/60 %	12, 18, 24, 36 months	all

* The samples which have adsorbed the highest amount of water during open storage at 25°C/60 %, 30°C/65% %, 40°C/75 % are tested

If more than one strength is included in phase III, full testing is performed with all strengths. On the base of these data it may then be possible to apply bracketing or matrixing with the registration batches in step 4.

3.3.3.2. Semi-solid dosage forms

3.3.3.2.1 Phase I

The anticipated minimum shelf life (period of use) is 3 - 6 months. The minimum shelf life is derived from the data of stress- and accelerated testing after 6 weeks or 3 months, respectively, and then confirmed by the data of samples stored at 25°C/60% (climatic zone II) up to 3 or 6 months.

Stability test protocols

Organoleptic and physico-chemical stress testing

Batch	Container Closure System	Storage condition	Storage period, Testing frequency	Test attributes
Experimental laboratory batch	Standard tube	5°C	0, 4 weeks	organoleptic, physico-chemical

Chemical and microbial accelerated and confirmation testing

Batch	Container Closure System	Minimum shelf life	Storage condition	Storage period, Testing frequency	Test attri-butes
Experimental Laboratory batch	Standard tube	3 months	40°C	0, 2, 4, 6 weeks	all
			25°C/60%	3 months	all
		6 months	40°C	0, 1, 2, 3 months	all
			25°C/60%	6 months	all

3.3.3.2.2 Phase II

The anticipated minimum shelf life (period of use) is 12 – 18 months. The minimum shelf life is derived from data of stress testing after 3 months, firstly confirmed by 6 months data of 40°C and finally by 12 or 18 months data of samples stored at 25°C/60 % (climatic zone II).

Stability test protocols

Organoleptic and physico-chemical stress testing

Batch	Container Closure System	Storage condition	Storage period, Testing frequency	Test attributes
Experimental laboratory batch	Standard tube	5°C	0, 4 weeks	organoleptic, physico-chemical

Chemical and microbial stress and confirmation testing

Batch	Container Closure System	Storage condition	Storage period, Testing frequency	Test attributes
Experimental clinical batch	Standard tube	50°C 40°C	1,2,3 months 0,1,2,3,6 months	Chemical, microbial all
	Standard tube, Proposed container closure system	25°C/60% 25°C/60%	12,18 months 12,18 months	all all

If several strengths are to be investigated in phase I or II bracketing is applied.

3.3.3.2.3 Phase III

The anticipated minimum shelf life (period of use) is 24 – 36 months. The minimum shelf life is derived from data of stress testing after 3 months, firstly confirmed by 6 months data of 40°C and finally by 24 or 36 months data of samples stored at 25°C/60 % (climatic zone II). Usually in phase III the final formulation is applied. Therefore the stability information for the registration batches has to be considered.

Stability test protocols

Organoleptic and physico-chemical stress testing

Batch	Container Closure System	Storage condition	Storage period, Testing frequency	Test attributes
Clinical or pilot plant batch, final formulation	Standard tube	≥ - 10°C	0, 4 weeks	organoleptic, physico-chemical
		5°C	0, 4 weeks	organoleptic, physico-chemical
		5 – 40°C in 24 hours cycle	0,2 weeks	organoleptic, physico-chemical
		40°C tube stored vertically, with the neck of the tube pointing upwards	0, 1, 3 months	Content uniformity within the tube. Assay of material taken from the beginning, middle, end of the tube

Photostability stress testing

Batch	Container Closure System	Storage condition	Storage period, Testing frequency	Test attributes
Clinical or pilot plant batch, final for-mulation	• Open container • Proposed test or final container closure system	Xenon lamp Atlas Suntest 250 W/m²	24, 48 hrs	Appearance, drug substance decomposition and assay, preservative assay

Chemical and microbial stress and confirmation testing

Batch	Container Closure System	Storage condition	Storage period, Testing frequency	Test attributes
Clinical or pilot plant batch, final formulation	Standard tube	50°C 40°C 30°C	1, 2, 3 months 0,1, 2, 3, 6 months 6,12 months	Appearance, chemical, microbial all all
	Standard tube, Proposed test or final container closure system	25°C/60% 25°C/60%	12,18,24,36 months 12,18,24,36 months	all all

3.3.3.3 Liquid dosage form

3.3.3.3.1 Phase I

The anticipated minimum shelf life (period of use) is 3 - 6 months. The minimum shelf life is derived from the data of stress- and accelerated testing after 6 weeks or 3 months, respectively, and then confirmed by the data of samples stored at 25°C/60 % (climatic zone II) up to 3 or 6 months.

Stability test protocols

Organoleptic and physico-chemical stress testing

Batch	Container-Closure-System	Storage condition	Storage period, Testing frequency	Test attributes
Experimental laboratory batch	25 ml glass flask with ground glass stopper	5°C	0, 4 weeks	organoleptic, physico-chemical

Chemical, microbial accelerated and confirmation testing

Batch	Container Closure System	Minimum shelf life	Storage condition	Storage period, Testing frequency	Test attri-butes
Experimental laboratory batch	25 ml glass flask with ground glass stopper	3 months	40°C	0, 2, 4, 6 weeks	all
	"		25°C/60%	3 months	all
	Proposed container closure system		25°C/60%	3 months	all
	25 ml glass flask with ground glass stopper	6 months	40°C	0, 1, 2, 3 months	all
	"		25°C/60%	6 months	all
	Proposed container closure system		25°C/60%	6 months	all

3.3.3.2 Phase II

The anticipated minimum shelf life (period of use) is 12 – 18 months. The minimum shelf life is derived from data of stress testing after 3 months, firstly confirmed by 6 months data of 40°C and finally by 12 or 18 months data of samples stored at 25°C/60 % (climatic zone II).

Stability test protocols

Organoleptic and physico-chemical stress testing

Batch	Container-Closure-System	Storage condition	Storage period, Testing frequency	Test attributes
Experimental laboratory batch	25 ml glass flask with ground glass stopper	5°C	0, 4 weeks	organoleptic, physico-chemical

Chemical, microbial stress and confirmation testing

Batch	Container Closure System	Storage condition	Storage period, Testing frequency	Test attri-butes
Experimental clinical batch	25 ml glass flask with ground glass stopper	60°C 40°C	0,1,2,3 months 1,2 3,6 months	all all
	25 ml glass flask with ground glass stopper	25°C/60%	12,18 months	all
	Proposed test container closure system	25°C/60%	12,18 months	all

If several strengths are to be investigated in phase I or II bracketing is applied

Phase III

The anticipated minimum shelf life (period of use) is 24 – 36 months. The minimum shelf life is derived from data of stress testing after 3 months, firstly confirmed by 6 months data of 40°C and finally by 24 or 36 months data of samples stored at 25°C/60 % (climatic zone II). Usually in phase III the final formulation is applied. Therefore the stability information for the registration batches has to be considered.

Stability test protocols

Organoleptic and physico-chemical stress testing

Batch	Container Closure System	Storage condition	Storage period, Testing frequency	Test attributes
Clinical or pilot plant batches, final formulation	25 ml glass flask with ground glass stopper	≥ - 10°C	0, 4 weeks	organoleptic, physico-chemical

Photostability stress testing

Batch	Container Closure System	Storage condition	Storage period, Testing frequency	Test attributes
Clinical or pilot plant batch, final formulation	• 25 ml colourless glass flask with ground glass stopper • Proposed test or final container closure system	Xenon lamp Atlas Suntest 250 W/m²	24, 48 hrs	Organoleptic, physico-chemical, drug substance decomposition and assay

Chemical, microbial stress and confirmation testing

Batch	Container Closure System	Storage condition	Storage period, Testing frequency	Test attri-butes
Clinical or pilot plant batch, final formulation	25 ml glass flask with ground glass stopper	70°C 60°C 50°C 40°C	0, 1, 2, 3 months 1, 2, 3 months 1, 2, 3 months 1, 2, 3, 6 months	all all all all
	25 ml glass flask with ground glass stopper	25°C/60% 40°C/25%	12, 18, 24, 36 months 0, 1. 2. 3 months	all Loss in mass
	Proposed test or final container closure system	25°C/60 %	12, 18, 24, 36 months	all

3.3.4 Comparator or reference drug products

According to the EU GMP Guideline (10) stability data are also necessary for comparator or reference drug pro-ducts.

The following cases are differentiated:

- ❒ The samples are repacked into packaging material which is as tight or tighter concerning moisture and light than the original packaging material:
  ➔ the original shelf life is used.

- ❒ The samples are repacked into packaging material which is less tight than the original packaging material. Then the samples are tested for moisture sensitivity in the open at 25°C/60 % and for photostability for 24 hours with the Xenon lamp (Suntest).
  Test criteria: average mass and appearance:
  - if no changes take place: ➔ original shelf life
  - if changes take place, tighter or more protecting container closure system must be selected. ➔ Then original shelf life is used.

- ❒ Samples are reworked (tablets are ground and filled into capsules). There the stability protocol for phase I is applied with the difference that the samples are stored at 25°C/60 % in the intended packaging material up to 18 months for phase II and 36 months for phase III.

If stability data are not available and it is not intended to consider or perform further stability investigations during the clinical trial then the minimum shelf life can not be longer than 25 % of the remaining shelf life of the comparator or maximal 6 months whichever is shorter..

Stability test protocol

Clini-cal Phase	Minimum Shelf-life	Container Closure System	Pre-treatment	Storage condi-tions [°C] [%]	Storage period, Testing frequency [months]
II	12-18 months	Twist-off Twist-off Twist-off Proposed Container Closure system	none 25°C/60% none none	40 – 40 – 25 60 25 60	0,1,2,3,6, 0,1,2,3,6 12,18 12,18
II	24-36 months	Twist-off Twist-off Twist-off Proposed Container Closure system	none 25°C/60% none none	40 – 40 – 25 60 25 60	0,1,2,3,6, 0,1,2,3,6 12,18,24,36 12,18,24,36

- **Testing specifications:**
  Testing specification for release and stability Testing of clinical samples.

It must be stated very clearly that this procedure fulfils an official requirement but has no scientific base since the analytical procedures, specifications and limitation of the shelf life are unknown.

3.3.5 Registration batches

The statements derived for registration application should be based on the results of preclinical development, the clinical batches and the registration batches. Thereby it can be assured that the patient after marketing authorisation gets the same quality as the patient during the clinical investigation.

Therefore it is important to confirm not only the predicted quality by the data of the accelerated and long-term testing with the registration batches but to compare stress data directly. Consequently stress tests are performed also with registration batches.

Usually the first registration batch is tested.
The extent depends on the available stress data but mostly a reduced stability protocol is sufficient.

3.3.5.1 Solid dosage forms

Stability test protocols

Organoleptic and physico-chemical stress testing

Batch	Container closure system	Storage condition	Storage period, Testing frequency	Test attributes
Primary Registration batch	open container	derived from available data where highest amount was adsorbed	0, 2 weeks	Organoleptic, physico-chemical

Chemical stress testing

Batch	Container Closure system	Pre-treatment	Storage condition	Storage period, Testing frequency	Test attributes
Primary Registration batch	50 ml glass container with twist-off closure	none	70°C 50°C	1, 2, 3 months 0, 1, 2, 3 months	chemical all
		30°C/65% or 25°C/60% or 40°C/75%	70°C 50°C	1, 2, 3 months 0, 1, 2, 3 months	chemical all

3.3.5.2 Semi-solid dosage forms

Stability test protocols

Organoleptic and physico-chemical stress testing

Batch	Container closure system	Storage condition	Storage period, Testing frequency	Test attributes
Primary Registration batch	Proposed final container closure system	≥ - 10°C	0, 4 weeks	organoleptic, physico-chemical
		5 – 40°C in 24 hours cycle	0, 2 weeks	organoleptic, physico-chemical

Chemical and microbial stress testing

Batch	Container closure system	Storage condition	Storage period, Testing frequency	Test attributes
Primary Registration batch	Proposed container closure system	50°C or 40°C	0, 1, 2, 3 months	appearance, chemical and microbial

3.3.5.3 Liquid dosage forms

Stability test protocols

Organoleptic and physico-chemical stress testing

Batch	Container closure system	Storage condition	Storage period, Testing frequency	Test attributes
Primary Registration batch	Proposed container closure system	≥ - 10°C	0, 4 weeks	organoleptic, physico-chemical

Chemical stress testing

Batch	Container closure system	Storage condition	Storage period, Testing frequency	Test attributes
Primary registration batch	Proposed container closure system*	70°C 50°C	1, 2, 3 months 0, 1, 2, 3 months	all all

* If plastic bottle, 25 ml glass flask with ground glass stopper is used for chemical stress testing.

3.4 Evaluation

The results of the stress tests are evaluated carefully.
Where scientifically justified statistics, reaction kinetics and linear regression analysis are applied.

The analytical procedures are assessed, then the data evaluated as follows:

- ❒ organoleptic properties
- ❒ physico-chemical properties
- ❒ chemical (and microbial) properties
- ❒ container closure system properties

The results of the stress investigations are also assessed relating to the robustness of the formulation.

During the development the formulation was challenged by the following factors:

- ❒ different batches of drug substance and excipients
- ❒ different strengths
- ❒ different compositions
- ❒ different manufacturing processes with different types and sizes of equipment
- ❒ different sites of manufacture
- ❒ scale of manufacture, laboratory, pilot plant
- ❒ batch size.

The resulting batches manufactured with all these different influencing factors have been investigated in stress- and confirmation testing. Therefore considerable information is available on the possible influence of these factors on the stability of the drug product and the robustness of the formulation can be evaluated.

These data are an important base to assess later during running production the influence of variations and changes on the stability.

Finally it is decided whether it is necessary to ensure compliance with the minimum shelf life which has been established by providing storage instructions to be placed on the packaging material.

❒ Stability reports

Compiled in stability reports are:
- All the results,
- the information on the tested batches,
- the applied analytical procedures,
- the derived stability information

All the stability reports are structured in written in the same format.

The following stability reports are written:

- Stress Testing and Long-Term Testing with the drug product phase I
- Stress Testing and Long-Term Testing with the drug product phase II
- Stress Testing and Long-Term Testing with the drug product phase III including registration batches

The stability information of these three reports is then summarised in the

- Stability profile of the drug product.

The following information is available:

- ❒ Assessment of the analytical procedures optimised and validated during development of the drug product.

- ❒ Establishment oft the degradation pathway under the influence of excipients, of degradation products that may be formed under accelerated and long-term testing.

- ❒ Establishment of shelf lives

  Minimum shelf lives which have been derived from the results of stress investigations and confirmed by the data of long-term testing:

  - clinical phase I: 3 - 6 months
  - clinical phase II: 12 - 18 months
  - clinical phase III: 24 - 36 months

- ❒ Expected preliminary shelf life for the registration batches in step 4: e.g. 24 months.

- ❒ Anticipated shelf life for the drug product in step 4 and 5: e.g. 5 years.

- ❒ Storage instructions

  - clinical phase I – III
  - registration batches in step 4

- ❒ Identification of problems that could arise during sto-rage and especially during transport.

- ❒ Selection of suitable container closure systems

  - clinical trial batches
  - registration batches for all relevant climatic zones in step 4.

- ❒ Selection of test attributes for the accelerated and long-term testing with the registration batches in step 4.

- ❒ Establishment of specifications for tolerable changes during storage, registration shelf life specifications.

- ❒ Establishment of stability test protocol for the registration batches.

- ❒ Robustness of the formulation.

3.5 Required capacity

Dosage form	Required capacity for a single analysis and documentation	Required capacity for an analysis in stress tests (- 15 % serial factor) and documentation
solid	17 h ≙ 0.45 weeks	15 h ≙ 0.40 weeks
semisolid	12 h ≙ 0.32 weeks	10 h ≙ 0.27 weeks
liquid	8 h ≙ 0.21 weeks	7 h ≙ 0.19 weeks
clinical trial for solid dosage forms	20 h ≙ 0.53 weeks	-

3.6 Time to availability of prediction of minimum shelf life in weeks

Stage of development	Storage period		Analysis and Evaluation	Stability report	Total period	
	Stress*	Acce-lerated			Preli-minary	final
Toxicological Samples	-	6	1	1	-	8
Phase I	-	6	1	2	-	9
Phase I	-	12	1	2	-	15
Phase II	12	24	1	2	15	27
Phase III	12	24	1	2	15	27
Registration batches	12	24	1	2	-	27

* In the clinical phase II and III a preliminary prediction can be made based on the data of samples stored at stress conditions.

3.4. Accelerated and Long-Term Testing with Registration batches up to Registration Application for drug substances and drug products

Step 4 is the central part of the stability testing.

4.1 Objective

- ❒ Confirmation of the results of stress and accelerated testing.
- ❒ Testing specification for release and stability testing.
- ❒ Complete Validation of analytical procedures.
- ❒ Determination of the influence of batch size on the stability.
- ❒ Derivation of re-test-periods for the drug substance.
- ❒ Derivation of holding time for the bulk drug product or intermediate stages
- ❒ Derivation of in-use life, overage, if necessary.
- ❒ Derivation of the shelf lives for the final formulation of the drug product.

4.1.1 Drug Substance

4.1.1.1 Application of the basic principles

- ❒ **Selection of batches and samples**

  Representative batch for registration application (primary registration batch):
  - The batches of a minimum of pilot plant scale,
  - should be by the same synthetic route,
  - use a method of manufacture and procedure that simulates the final process to be used on a manufacturing scale.
  - The overall quality of the batches of drug substance placed on stability should be representative of both
    - The quality of the material used in pre-clinical and clinical studies
    - and the quality of material to be made on a manufacturing scale.

Most important are the impurity profile, the particle size and particle size distribution, possibly surface area.

- **Test attributes**
  Appearance, physical test attributes, decomposition and assay.

- **Analytical procedures**
  Specific for stability testing, completely validated:
  Specificity, linearity, Reporting threshold, accuracy, range, intermediate precision, robustness.

- **Specifications, acceptance criteria**
  Release specifications

- **Storage conditions**
  According to the four climatic zones, the following storage conditions were established for these zones:

Climatic zone	Storage conditions
I and II	25°C/60 % r. h.
III and IV	30°C/65 % r. h.

  Which of these are used depends on where and how the drug substance will be stored, shipped and used. 30°C/65 % storage only if the drug substance is applied in climatic zone III or IV.
  If the drug substance is intended for storage in a refrigerator: 5°C ± 3°C

- **Testing frequency**

Long-term:	0,3,6,9,12,18,24,36,48,60 months
Accelerated:	0,3,6, if significant change: 0,1,3,6, or 0,3,2x6

- **Number of batches**
  3
  When available long term stability data on primary batches do not cover the proposed re-test period granted at the time of approval, a commitment should be made to continue the stability studies post approval in order to firmly establish the re-test period.

  - If the submission includes data from stability studies on at least three production batches a commitment should be made to continue these studies through the proposed re-test period.

  - If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue these studies through the proposed re-test period and to place additional production batches to a total of at least three, on long term stability studies through the proposed re-test period.

  - If the submission does not include stability data on production batches, a commitment should be made to place the first three production batches after marketing authorisation on long term stability studies through the proposed re-test period.

❒ **Container Closure System**

It should be the same or simulate the actual used for storage and distribution

- small fiber-drum lined with polyethylene foil for drug substance not sensitive to moisture
- glass bottle lined with polyethylene foil with screw cap or twist-off for drug substance sensitive to moisture to simulate tight containers.

Stability test protocols

Climatic zone II ≙ ICH

Batch	**Container Closure System**	**Storage conditions**	**Storage period, Testing frequency**		**Testing Specifi-cations**
			up to registration [months]	**on-going** [months]	
3 primary registra-tion batches	Simulating proposed bulk storage container	25°C/60 % 40°C/75 %	0, 3, 6, 9, 12,(18) 3, 6	(18), 24, 36, 48, 60	No.:

Climatic zone III and IV

Batch	**Container Closure System**	**Storage conditions**	**Storage period, Testing frequency**		**Testing Specifi-cations**
			up to registration [months]	**on-going** [months]	
3 primary registra-tion batches	Simulating proposed bulk storage container	30 °C/65% 40°C/75 %*	0, 3, 6, 9, 12,(18) 3, 6	(18), 24, 36, 48, 60	No.:

* Only if not yet performed for climatic zone II

Drug Substance intended for storage in a refrigerator

Batch	Container Closure System	Storage conditions	Storage period, Testing frequency		Testing Specifi-cations
			up to registration [months]	**on-going** [months]	
3 primary registra-tion batches	Simulating proposed bulk storage container	5°C±3°C 25°C/60%	0, 3, 6, 9, 12,(18) 1,2, 3, (6)	(18), 24, 36, 48, 60	No.:

❒ **Evaluation**

The data are evaluated carefully. If scientifically justified statistics, reaction kinetics and linear regression analysis are used.

The data may show so little degradation and so little variability that it is apparent from looking at the data that the requested re-test period will be granted. Under these circumstances, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient

All the results obtained during the course of development are then compared with the primary accelerated and long-term stability test results.
If they confirm fully the predicted data from the stress investigation the general stability information can be based on the following primary and supportive data and the derived stability information.

- Primary data and derived statements
  - The results of the three registration batches
    derived: the confirmed preliminary re-test period.

- Supportive data and derived statements
  - The results of stress testing, the stability profile
    derived: preliminary re-test period
  - The results of confirmation investigation
    derived: preliminary confirmation of preliminary re-test period.

❒ **Robustness**

The primary and supportive data are also assessed relating to the robustness of the manufacturing process.

During the development the manufacturing process was likely challenged by the following factors:

- synthetic route which changed during development

- method of manufacture and procedure with different types and sizes of equipment
- site of manufacture, laboratory, pilot plant
- chemical production with different types and sizes of equipment
- scale of manufacture and batch size.

❒ **Available information**

The resulting batches manufactured with all these different factors have been investigated in

- stress,
- confirmation,
- accelerated and long-term testing.

Therefore extensive information is available on the possible influence of these factors on the stability of the drug substance.

❒ **Storage instruction**

Finally it is decided whether it is necessary to ensure compliance with the re-test which has been established by providing storage instructions to be displaced on the label.

Stability Report

The Stability Report for the investigated Drug Substances
contains:

- All the results,
- the information on the tested batches,
- the applied analytical procedure,
- the derived stability information

According to the two different stability protocols for climatic zone II and the climatic zones III and IV two separate Stability Reports are written if required.

Structure of Stability Report
All the Stability Reports are structured and written in the same format.
An example for the table of contents, the proposed re-test period and the packaging information is given:

Stability Report	
Accelerated and long-term testing with registration batches BIWG 98 SE drug substance	Number SR 200-02-01 Date 20.05.2002 Page 1 of 29

Responsible Company Successful Pharma KG Biberach	

Table of contents

1.2 Stability results

The Stability Report comprises the primary stability data of the three registration batches of BIWG 98 SE drug substance.

The samples were stored up to 18 respectively 12 months at 25°C/60 % r.h. and up to 6 months at 40°C/75 % r.h..

No change in organoleptic, physico-chemical, chemical properties took place. Not sensitive to light. No inter-action with the packaging material took place.

1.2 Stability results

An overview is given in the following table

Batch No.	Test attributes	Storage conditions [°C]	[% r. h.]	Storage time [months]	Analytical results
S96013* S96014 S96015	Appearance	25	60	0,3,6,9,12,(18) *	no change
		40	75	3,6	no change
	Odour	25	60	0,3,6,9,12,(18)	no change
		40	75	3,6	no change
	Colour of solution	25	60	0,3,6,9,12,(18)	no change
		40	75	3,6	no change
	Clarity of solution	25	60	0,3,6,9,12,(18)	no change
		40	75	3,6	no change
	Melting behaviour	25	60	0,3,6,9,12,(18)	no change
		40	75	3,6	no change
	Loss on drying	25	60	0,3,6,9,12,(18)	no change
		40	75	3,6	no change
	Degradation of BIWG 98 SE	25	60	0,3,6,9,12,(18)	no degradation
		40	75	3,6	no degradation
	Assay of BIWG 98 SE	25	60	0,3,6,9,12,(18)	no fall in assay
		40	75	3,6	no fall in assay

1.2 Stability results

The primary Accelerated- and Long-Term Stability test results confirmed fully the data of the Stress Testing with the drug substance, documented in the Stability Report "Active Ingredient Stability Profile of BIWG 98 SE drug substance, No. SSRS 200-01-01 dated 24.06.2000".

Summarizing the primary and the supportive stability data, it can be concluded:

- The NME drug substance BIWG 98 SE is stable.
- It should be stored in a tight container.

1.3 Proposed Re-test period and Container closure system information

A preliminary re-test period of 24 months is derived from the resulting data. The stability testing will be continued up to 60 months, with the intention of extending the re-test period up to 60 months, if the data adequately support that conclusion. Drug substance stored for longer then the approved re-test period must be tested again before use and then used immediately within 30 days

Example: After release: re-test period: 24 months
After 2 years analysis before immediate use

Preliminary re-test period		
Container closure system	Climatic zone	Re-test period
Polyethylene bag in stainless steel container	II	24 months

Storage instructions

Countries	**Storage instructions**
EU	Keep the container tightly closed Store in a dry place
Japan	as EU
USA	Store at 25°C, excursion permitted to 15 - 30°C Keep the container tightly closed Store in a dry place

1.4 Commitment: On-going Stability testing

The stability testing will be continued as On-going Stability Testing according to the ICH Guideline Q1AR

Part 1
Continuation of the storage and investigation of the three registration batches up to 60 months.

Batches	Storage condition	Storage period, Testing frequency [months]	Testing specifications
S96013 S96014 S96015	25°C/60% r.h.	(18), 24, 36, 48, 60	TSS 90-A-01/02

Part 2
After marketing authorisation 3 production batches are put on stability.

Batches	Storage condition	Storage period, Testing frequency [months]	Testing specifications
3 production batches	25°C/60%	0, 6, 12, 18, 24, 36, 48, 60	TSS 90-A-01/02

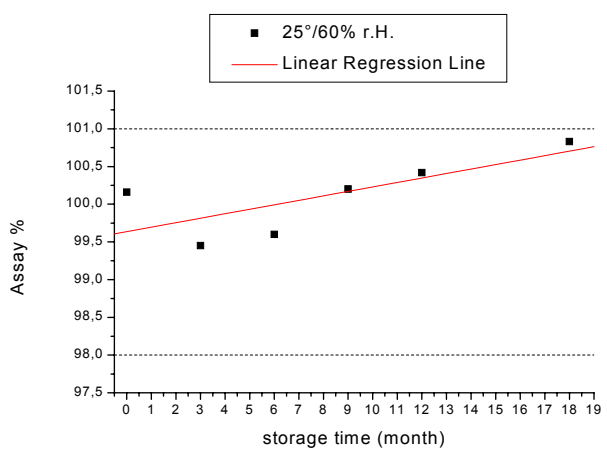
The available data will be submitted annually.

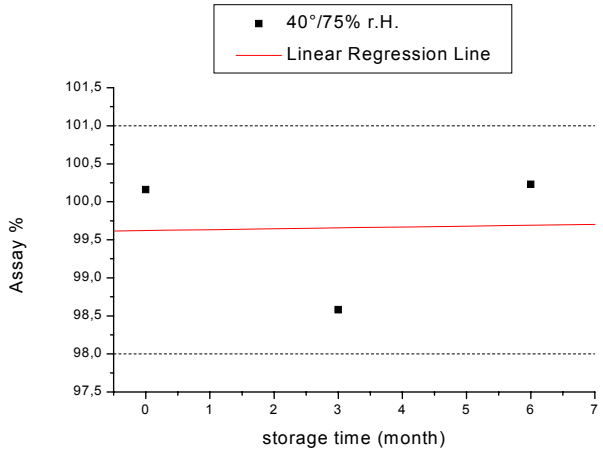
4. Results and Evaluation

4.1 Graphic of test results

Batch No.: S96013 Container closure system 500 ml glass flask with twist- off closure lined with polyethylene foil

Storage time [months]	Storage conditions 25°C/60%	40°C/75%
Assay of BIWG 98 SE	98.0 - 101.0%	





Assay of BIWG 98 SE	98.0 - 101.0 %	
0	100.16 %	
3	99.45 %	98.58 %
6	99.60 %	100.23 %
9	100.20 %	
12	100.42 %	
18	100.83 %	

4.1 Test Results

Batch No.: S96013 Container closure system: 500 ml glass flask with twist-off closure lined with polyethylene foil

Storage time [months]	Storage conditions 25°C/60%	40°C/75%
Impurities and degradation of BIWG 98 SE	Imp.I not more than 0.3 %, Imp.II not more than 0.3 %, any unspecified impurity (degradation) less than0.1%, total impurities not more than 0.7 %	
0	Imp.I 0.3 %; Imp. II 0.2 %; no unspecified impurity (degradation)	
3	Imp. I 0.2 %; Imp. II 0.2 %; no unspecified impurity (degradation)	Imp. I 0.3 %; Imp. II 0.2 %; no unspecified impurity (degradation)
6	Imp. I 0.3 %; Imp. II 0.2 %; no unspecified impurity (degradation)	Imp. I 0.2 %; Imp. II 0.3 %; no unspecified impurity (degradation)
9	Imp. I 0.3 %; Imp. II 0.2 %; no unspecified impurity (degradation)	
12	Imp. I 0.2 %; Imp. II 0.3 %; no unspecified impurity (degradation)	
18	Imp. I 0.3 %; Imp. II 0.2 %; no unspecified impurity (degradation)	

6. Statements

Storage instructions:
- Keep the container tightly closed
- Store in a dry place

In the EU and Japan no further storage instructions are necessary.

USA: Store at 25°C, excursions permitted (15 - 30°C)

During shipment 30°C can be exceeded (3 months 70°C have been investigated)

4.1.2 Holding time for intermediate stages or bulk drug product

4.1.2.1 Holding time period for intermediate stage

The expiration period of a production batch should be calculated from the date of release of the batch.

The date of such a release should, under normal circum-stances, not exceed 30 days from the date of production of that batch.

If batches are released exceeding 30 days from the production date, the date of production as defined below, should be taken as the start of the shelf life.

The date of production of a batch is defined as the date that the first step is performed involving combining the active ingredient with other ingredients. But there may be exceptions.

Intermediates are manufactured
- in big quantities
- at a different site of production
- over a longer period of time.

Accordingly they may be stored over a longer period of time and can be regarded as starting materials. Under
these circumstances, testing specifications are necessary.
A holding time has to be determined. These data may not be necessary for the registration application, it is mainly a GMP measure.

4.1.2.1.1 Application of the basic principles

- **Selection of samples**
  The samples should be part of representative batches (pilot plant batches).

- **Test attributes**
  The attributes are investigated which are potentially susceptible to change during the course of storage.

- **Analytical procedures**
  The analytical procedures for the dosage forms are applied or adapted accordingly.

- **Specifications, Acceptance Criteria**
  Release specifications

❒ **Storage conditions, testing frequency, storage period**

Production in climatic zones	Storage condition	Container Closure system	Storage period, Testing frequency [months]
I - IV	40°C/75%	intended for storage	0 1 2 3
I - II	25°C/60% 25°C/60%	open intended for storage	0.5 3 6
III - IV	30°C/65% 30°C/65%	open intended for storage	0.5 3 6

❒ **Number of batches**
2

❒ **Container Closure System**
The packaging should simulate the actual container closure system intended for storage. The steel container may be simulated by a tight glass container, lined with the applied polyethylene foil.

❒ **Evaluation**
Results should be within release specifications.

❒ **Stability report**
- Statements
  Holding time according to storage period at
  25°C/60 % or 30°C/65%

The shelf life is then calculated from the date of re-lease of the related batch of finished product, if this release date does not exceed 30 days from the date that the intermediate is introduced into the manufacture of the finished drug product. If this 30 day limit is exceeded, the shelf life is calculated from the date that the intermediate is introduced into the manufacture of the finished drug product.

One batch of the drug product should be produced from intermediate stored for the full holding period, and this batch should be monitored during on-going
stability testing under long-term testing conditions.

4.1.2.2 Holding time for bulk drug product

Usually the bulk drug product is not packed immediately after manufacturing or only partly or it is shipped for packaging to another site. Therefore corresponding stability investigations are necessary.

These data may not be necessary for the registration application it is mainly a GMP measure.

4.1.2.2.1 Application of the basic principles

- **Selection of samples**
  The samples should be part of representative batches (primary registration batches)

- **Test attributes**
  The test attributes are investigated which are potentially susceptible to change during the course of storage.

- **Analytical procedures**
  The analytical procedures for the dosage forms are applied or adapted accordingly.

- **Specifications, acceptance criteria**
  Shelf life specifications

- **Storage conditions, storage period, testing frequency**

Production in climatic zone or shipment	Storage condition	Container Closure System	Storage period*, Testing frequency [months]
I - IV	40°C/75 %	intended for storage or shipment	0 1 2 3
I - II	25°C/60% 25°C/60%	open intended for storage or shipment	0.5 3 6
III - IV	30°C/65% 30°C/65%	open intended for storage or shipment	0.5 3 6

*The storage period according to requirement.

- **Number of batches**
  2

- **Container Closure System**
  The container closure system should simulate the actual packaging intended for storage or shipment. The steel container may be simulated by a tight glass container, lined with the applied polyethylene foil.

❒ **Evaluation**

If results are out of release specifications the data have to be compared with those of the registration batches to investigate whether the stability is at least the same. Only under this precondition the same shelf life can be applied.

❒ **Statements/Labelling**

- Shelf life according to registration batches.
- The expiration period is calculated from the date of release,
- the storage period of the bulk has to be subtracted accordingly.

4.1.3 Drug product

4.1.3.1 In-use stability

The derivation of in-use stability is necessary for

❒ drug products which are reconstituted into a usable form before administration,
❒ drug products whose stability is jeopardized once the container is opened.

Reconstituted drug products are usually limited by the chemical stability
Drug products in multiple use containers may be limited by the microbial stability.

4.1.3.1.1 Application of the basic principles

❒ **Selection of batches and samples**
Representative pilot-plant batch, usually two primary registration batches which are put on stability for registration application.

❒ **Test attributes**
Usually the test attributes are derived from the results of the stress, the accelerated and long-term testing and only those should be followed, which are potentially susceptible to change due to reconstitution or opening of the container

- Reconstituted dry product:
  Appearance, clarity, pH, drug substance decomposition and assay, for suspension also dispensability and particle size distribution.
- Multiple use container:
  Appearance, drug substance decomposition and assay microbial preservative challenge test.

❒ **Analytical procedure**
The testing specification for the final formulation of the dosage form.

❒ **Specifications, Acceptance Criteria**
Shelf life acceptance criteria

❒ **Storage conditions, storage period, testing frequency**
To simulate also the in-use stabile at the end of the shelf life in is recommended to use one batch after storage for 6 months at 40°C/75%

Reconstituted dry product

Storage condition	**Storage period, Testing frequency** [weeks]
5°C	0, 2, 4

Reconstituted powder for injection with antimicrobial preservation

Storage condition	**Storage period** [days]
5°C	28

Injection with antimicrobial preservation

Climatic zone	**Storage condition**	**Storage period** [days]
I - II	25°C/60 %	28
III - IV	30°C/65 %	28

Multiple use container
Before storage, treatment is simulated for a duration of up to about 4 weeks whereas 1 dosage is withdrawn daily.

Climatic zone	**Storage condition**	**Storage period, Testing Frequency** [months]
I - II	25°C/60%	1* + 5
III - IV	30°C/65%	1* + 5

* This 1 month represents the period where 1 dosage is withdrawn daily. No analyses after this period.

❒ **Number of batches**
2

❒ **Container Closure System**
Commercial Container Closure System

❒ **Evaluation**
The results may be part of the stability report for registration application. If not, such results should be available in case the regulatory authorities request them.

❒ **Statements/Labelling**
In-use shelf life:

- at least 4 weeks after reconstitution store in the refrigerator 2 - 8°C,
- maximal 28 days,
- at least 6 months.

The in-use shelf life should be stated on the label. In addition (if space allows) there should be a space for the user to write the date of opening of the “use-by” date.
The in-use shelf life and the in-use storage recommendation - if applicable - should be included in SPC, leaflet and outer carton text.

4.1.3.2 Photostability

The investigations are undertaken as confirmatory investigations if data in the final packaging are not yet available.

4.1.3.2.1 Schedule of tests

❒ **Selection of batches and samples**
Representative registration batch in commercial container closure system. Preferably after storage for 6 months at 40°C/75%.

❒ **Test samples**

- Drug product outside immediate pack in colourless glass container,
- Tablets or capsules spread in single layer
- Drug product in dark container as control sample.
- Drug product in blister pack (if intended for marketing)

If decomposition:

- Drug product in immediate packaging

If decomposition:

- Drug product in marketing container closure system

❒ **Storage condition**

Xenon test or corresponding energy source (Atlas Suntest, 250 W/m²).

- Confirmatory studies > 400 nm 1.2 million lux hours Xenon lamp (250 W/ m²): 21,8 hours
- Confirmatory studies 300 - 400 nm W/ Xenon lamp (250 W/ m²): 8.9 hours

4.1.3.3 Accelerated and Long-Term Testing

4.1.3.3.1 Application of the basic principles

❒ **Selection of batches and samples**

Representative batches for registration application (primary registration batches).
The batches should be put on stability within 4 weeks after release.

- Manufacturing process:
  - Should meaningfully simulate that which would be applied to large scale batches for marketing.
  - The process should provide product of the same quality intended for marketing,
  - meeting the same quality specifications as to be applied for release of material.
- Batch size:
  - Two of the three at least pilot scale: One tenth that of full production or for solid dosage forms 100 000 tablets or capsules.
  - One of the three may be smaller, e.g. 25 - 50 000 tablets or capsules for solid dosage forms.

If the primary batches are no full size production batches, the first three production batches must be placed on long term and accelerated stability studies after approval.

- Drug substance
  - Where possible different batches should be applied for manufacturing
  - It is the best to use the three primary registration batches of the drug substance.

Requirements for the primary registration batches

- must be representative of the manufacture and packaging,
- should be produced by a validated manufacturing process,
- must meet the specifications required for the release of material,
- must be homogeneous and consist of random samples.
- The container put into storage must be representative of the batch.
- The samples investigated from a container must be representative of all the samples in the container at the time of analysis.

Other supporting data from batches investigated during development can be provided.

❒ **Test attributes**

In stability testing, the attributes of a drug product are investigated

- which are potentially susceptible to change during the course of storage,
- which are especially important for quality, safety, efficacy.

❒ **Analytical procedures**

The analytical procedures must be stability specific and fully validated, e.g. the following validation characteristics must be taken into account:

- specificity
- linearity for drug substance and decomposition product
- quantitation limit 0.1 % according to reporting threshold
- accuracy for drug substance and decomposition product
- range for drug substance and decomposition product
- intermediate precision for drug substance and decomposition product
- robustness

❒ **Specifications, acceptance criteria**

It has to be differentiated between

- Release specifications: Quality after manufacture.
- Shelf life specifications: Quality up to the expiration date.

To fix the shelf life specifications may be not easy. If possible the specifications are derived from the results of the steps 1 - 3. But it may happen that the shelf life specifications cannot be fixed before the 12 or 18 months data are available, especially for decomposition products.

❒ **Storage conditions**

- Climatic zones I and II: 25°C/60%, 40°C/75%
  If significant changes take place at 40°C/75% storage at 30°C/65% is necessary.
- Climatic zones III and IV: 30°C/65% 40°C/75%

It is differentiated between the stability protocol for the ICH countries (climatic zone II) and the extension to countries of the climatic zones III and IV with 30°C/65 % r.h. The following table contains all further storage conditions as:

- Refrigerator with 5°C ± 3°C
- Freezer: -20°C ± 5°C
- Semi-permeable container: 25°C ± 2°C/40%±5% + 40°C ± 2°C/not more than 25%

Storage test conditions

Study	Case	Storage condition	Minimum time period at submission	Testing frequency (months)	Climatic zones
Long -term	General	25°C ± 2°C/60% ± 5%	12 months	0,3,6,9,12	I and II
Accelerated	General	40°C ± 2°C/75% ± 5%	6 months	0,3,6	I to IV
Accelerated Intermediate	If significant change at 40°C/75%	30°C ± 2°C/65% ± 5%	6 moths	0,6(9,12) or 0,3.6,9,12	I and II
Accelerated	Aqueous based products in semi-permeable containers	40°C ± 2°C/not more than 25% or [1]	6 months	0, 1, 3, 6,	1 to IV
Long-term	General (semi-permeable container)	25°C ± 2°C/40% ± 5% or[2]	12 months	0, 3, 6, 9, 12	I and II
Long-term	General	30°C ± 2°C/65% ± 5%	12 months	0,3,6,9,12	III and IV
Long-term	refrigerator	5°C ± 3°C	12 months	0,3,6,9,12	I to IV
Accelerated	refrigerator	25°C ± 2°C/60% ± 5%	up to 6 months	0,1,2,3,(6)[3]	I to IV
Long Term	Freezer	-20°C ± 5°C	12 months	0,3,6,9,12	I to IV
Accelerated	Freezer	5°C ± 3°C	appropriate time	0, 1, 2,	I to IV

[1]Storage at 40°C/75% is possible, but loss in weight must be multiplied with 3, [2] Storage at 25°C/60% is possible, but loss in weight must be multiplied with1.5, [3] If significant change occurs between 3 and 6 months no extension of shelf life possible

❒ **Storage period**

- The long-term testing should cover at least 12 months duration at time of submission.
- It is continued up to the intended shelf life after registration application (on-going stability testing).
- The commitment should be made that investigation continues.

❒ **Testing frequency**

- Long term studies
  - first year every three months. 0, 3, 6, 9, 12
  - second year every six months: 12, 18, 24
  - third year and longer annually: 24, 36, 48, 60
- Accelerated studies
  - general minimum three time points: 0,3,6 months
  - expectation of significant change increases testing adding samples at final time point or forth time point: 0, 3, 2x6 or 0, 1, 3, 6 months
- Intermediate storage condition studies
  - Minimum four time points, including initial and final e.g.: 0,6,9,12 months**,**
  - at time of submission 0,6 months

Stability test protocols

Climatic zone II ≙ ICH

Batch	**Container Closure System**	**Storage conditions**	**Storage period, Testing frequency**		**Testing Specifi-cations**
			up to registration [months]	**on-going** [months]	
3 primary registra-tion batches	Final container closure system(s)	25°C/60 % 40°C/75 %	0, 3, 6, 9, 12,(18) 3, 6	(18), 24, 36, 48, 60	No.:

Batch	Container Closure System	Storage conditions	Storage period, Testing frequency		Testing Specifi-cations
			up to registration [months]	**on-going** [months]	
3 primary registra-tion batches	Final container closure system(s)	30 °C/65% 40°C/75 %*	0, 3, 6, 9, 12,(18) 3, 6	(18), 24, 36, 48, 60	No.:

* Only if not yet performed for climatic zone II

❒ **Number of batches**

3 batches

Stability studies should be performed on each individual strength and container size of the drug product unless bracketing or matrixing is applied.

Commitment and number of batches

- Proposed shelf life not covered:
  When long term stability data do not cover proposed shelf life granted at time of approval commitment should be made to continue post approval to establish the shelf life.
- Commitment not necessary:
  Submission includes data on three production batches covering proposed shelf life.
- Commitment required:
  Submission includes data from 3 production batches, commitment to continue through proposed shelf life:
- Fewer than three production batches:
  Commitment to continue with these studies through proposed shelf life and to place additional production batches to a total of three on long term and accelerated stability testing through proposed shelf life.
- No Production batches:
  Commitment to place first three production batches on long term and accelerated stability testing through proposed shelf life.

❒ **Container closure system**

Final container closure system proposed for marketing, or when justified in the container closure system that simulates the final one.

A drug product is frequently marketed in several container closure systems, all must be included. The stability programme can be however reduced by applying bracketing or matrixing, if justified

Solid dosage forms

The following container closure systems are used:

- blisters: PVC, polypropylene, composite film
- plastic tubes: polypropylene, polyethylene
- glass bottles
- aluminium foil, aluminium blister

If the drug products are known not to be extremely sensitive to moisture on the basis of the results of stress tests, the container closure systems can be used as follows in the individual climatic zones.

Container closure system	Climatic zones		
	I + II	III	IV
blisters	x	x	
plastic tubes	x	x	x
glass bottles	x	x	x
aluminium foil, aluminium blister	x	x	x

Semi-solid dosage forms

Frequently used packaging materials:

- aluminium tube, internally lacquered
- plastic tubes
- plastic containers

General suitability in the climatic zones.

Container closure system	Climatic zones		
	I+II	III	IV
plastic tubes	x		(x)
plastic containers	x		(x)
aluminium tubes, internally lacquered	x	x	x

Liquid dosage forms

Frequently used container closure systems

- glass bottles with closure
- ampoules
- ampoules, glass bottles with rubber stopper
- plastic containers

General suitability in the climatic zones:

Container closure systems	Climatic zones		
	II	III	IV
plastic containers	x		x *
glass bottles	x	x	x
ampoules	x	x	x

* application may be possible

❒ Evaluation

A Systematic in the presentation and evaluation of the stability information.

Storage period should cover at least 12 months duration at the time of submission.

Extrapolation of the proposed shelf life up to at 2 years may be acceptable, where supported by stress, accelerated and real time data.

An acceptable approach for quantitative characteristics that are expected to decrease with time is to determine the time at which the 95 % one sided confidence limit for the mean degradation curve intersects the acceptable lower acceptance criterion limit.

Statistics and reaction kinetics are also valuable approaches depending on the results.

The evaluation must consider all test attributes

Where the data show so little degradation and so little variability that is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the formal statistical analysis but only to provide a justification for the omission.

All the results obtained during the course of development are then compared with the primary accelerated and long-term stability test results. If they confirm fully the predicted data from the stress investigations during development, the general stability information for the drug product will be based on the following primary and supportive data and the derived stability information:

Primary and supportive data

- Primary data and derived statements/labelling:
  - The results of the three registration batches
    derived: The confirmed preliminary shelf lives.

- Supportive data and derived stability information:
  - The data of the drug substance stability profile
    derived: Preliminary re-test period.
  - The data of the three drug substance registration batches
    derived: The confirmed preliminary re-test period.

- The data of the stress- and confirmation investigation during the clinical development derived: Minimum shelf life (period of use) predicted and confirmed for the clinical trial phases I – III.
- The data of the stress investigations with the final formulation including one registration batch derived: Preliminary shelf lives for registration batches.

❒ **Robustness of the formulation**

- Different batches of drug substance and excipients.

Finally it is decided whether it is necessary to ensure compliance with the expiration date by providing storage instructions to be displayed on the pack.

❒ **Storage instructions**

- Storage instructions must be derived directly from tests.
- A logical relationship to the storage conditions

  - In the EU if there is evidence that batches of the stored product as packed for sale are stable at temperatures up to 30°C, the product need bear no special temperature storage instructions.
  - Within the USA all drug products require usually statements on storage conditions.
  - For Japan drug products shown to be stable up to 3 years need not necessarily carry specific storage statements

The following storage instructions should be used in the EU:

Testing conditions where stability has been shown		**Required label**	**Additional label where relevant**
25°C ± 2°C/60 % r.h. ± 5 % 40°C ± 2°C/75 % r.h. ± 5 % ↓	➔	No labelling to be used	Do not refrigerate or freeze
25°C ± 2°C/60 % r.h. ± 5 % 30°C ± 2°C/65 % r.h. ± 5 % ↓	➔	Do not store above 30°C	Do not refrigerate or freeze
25°C ± 2°C/60 % r.h. ± 5 % ↓	➔	Do not store above 25°C	Do not refrigerate freeze
5°C ± 3°C ↓	➔	Store at 2°C - 8°C	Do not freeze
Below zero	➔	-20°C ± 5°C	

General storage statements in the EU

In principle, medicinal products should be packaged in containers that ensure stability and protect from deterioration. A label statement should not be used to compensate for inadequate or inferior packaging. Nevertheless, the following statements may be used to emphasise the need for storage precautions to the patient.

No.	Storage Problem	Additional labelling statements depending on the package*	Comment
1	Sensitivity to moisture	Keep the container tightly closed	E.g. plastic bottles
2	Sensitivity to moisture	Store in the original package	E.g. blisters
3	Sensitivity to light	Store in the original container	
4	Sensitivity to light	Keep container in the outer carton	

* A rationale for the labelling statement should be given in the package leaflet.

Stability reports

They contain:

- All the results,
- the information on the tested batches,
- the applied analytical procedures and
- the derived statements drug product.

The stability report for the drug product is structured and written in the same format as those during development and for the drug substance. The requirements of the CTD with the two modules 2 and 3 are considered.

- According to the different storage conditions for the climatic zones I+II and III+IV with corresponding stability protocols two separate stability reports are written.
- For registration application in countries of the climatic zones III+IV the stability report for the climatic zones I+II can be used as supportive information.

❒ For the climatic zones III and IV different packaging materials and different acceptance criteria may be required.

The statements derived for registration application are based on the following results:

Batches	Investigations	Derived shelf life
Several strengths of laboratory batches	Stress and long-term	6 months phase I
Several strengths of clinical batches phase II	Stress and long-term	18 months phase II
One batch phase III	Stress and long-term	24 months phase III
One registration batch	Stress	24 months
Three registration batches	Accelerated and long-term	24 months

Thereby it can be assured that the patient after marketing authorisation gets the same quality as the patient during the clinical trial investigations.

Example of the main elements of a stability report:

Table of contents

Stability and container closure system information

A preliminary shelf-life of 24 months is proposed, it will be extended if corresponding data are available, 60 months are anticipated.

Preliminary shelf life		
Container closure system	Climatic zone	Preliminary shelf life
PVC/PVDC blister Applicable are further with justification: Polypropylene tubes with polyethylene closure, HDPE bottle with HDPE closure, Glass bottle with screw cap, Aluminium Blister, aluminium foil	II	24 months

Storage instructions:

According to the results no storage instructions are required, even if the shelf-life will be extended up to 60 months. Nevertheless storage instructions may be necessary due to national requirements.

Countries	**Storage instructions**
EU	none
Japan	none
USA	Store at 25°C, excursion permitted to 15 - 30°C

❒ **Statements/Labelling**

In the dossier for registration applications are included:

- Primary and supportive stability reports with the derived statements
- Testing specifications for release and stability testing.
- Validation report for the analytical procedures.

3. 5. On-going Stability Testing according to commitment

5.1 Objective

❒ Confirmation and extension of the anticipated re-test period, shelf life.

❒ Monitoring of the stability characteristics for as long as the anticipated re-test period/shelf life and the storage period are not yet identical, the data being generated by those studies already initiated or referred to in the registration application.

❒ Performing stability studies with the first three production batches after approval if no production batches were in the submission. If one or two were in the submission, it has to be added up to a total of three-

❒ The on-going stability testing is a continuation of accelerated and long-term testing, it concludes the development of a drug substance or drug product.

5.2 Application of the basic principles

❒ **Selection of batches and samples**

- Primary registration batches of step 4
- Representative production batches manufactured for marketing after approval

❒ **Test attributes, analytical procedure, specifications**
as for step 4

❒ **Stability test protocols**

Drug substance and drug product

Climatic zone II

Batches	Container Closure System	Storage condition	Storage period, Testing frequency [months]	Testing Specifi-cation
3 registra-tion batches	Simulating proposed bulk storage container (drug substance)	25°C/60%	18,24,36,48,60	Correspon-ding to step 4
3 production batches	Final container closure system (drug product)	25°C/60% 40°C/75%*	0,3,6,9,12,18,24,36,48, 60 3,6	Correspon-ding to step 4

*Drug Product only

Climatic zone III and IV

Batches	Container Closure System	Storage condition	Storage period, Testing frequency [months]	Testing Specifi-cation
3registration batches	Simulating proposed bulk storage container (drug substance)	30°C/65%	18,24,36,48,60	Correspon-ding to step 4
3 production batches	Final container closure system (drug product)	30°C/65% 40°C/75%*	0,3,6,9,12,18,24,36,48,60 3,6	Correspon-ding to step 4

*Drug Product only

❒ **Number of batches**

- 3 pilot plant batches from step 4
- 3 production batches,
  if registration batches already production batches not necessary

❒ **Container Closure System**

- Drug Substance: Simulating proposed bulk storage container.
- Drug Product: Container closure system for marketing.

❒ **Evaluation**

The same methods and procedures are applied as for the registration batches.
It may be necessary to derive post-approval specifications from the data.

❒ **Robustness**

- **Drug substance:**
  - Batch size of starting materials
  - Site of manufacture, chemical production
  - Synthetic route, method of manufacture and procedure: final process
  - Scale of manufacture: production scale
- **Drug product:**
  - Different batches drug substance from final process and production scale
  - Site of manufacture: pharmaceutical production
  - Manufacturing process: final manufacturing process
  - Scale of manufacture: production scale

Stability reports with the extended stability information are written on demand e.g.

- after approval to extend shelf life
- yearly updating of the stability report
- at the end of the anticipated shelf life/re-test period

❒ **Statements/Labelling**

Confirmation and extension of the shelf life/re-test period and storage instructions if necessary.

3.6. Follow-up stability testing, variations and changes

6.1 During continuous production

6.1.1 Objective

❒ Monitoring of the stability of the continuous production.
❒ Confirmation of the derived stability information.

6.1.2 Application of the basic principles

❒ **Selection of batches and samples**
Representative production batches. (Application of matrixing)

❒ **Test attributes**
Selection according to results of the steps 4 and 5.

❒ **Analytical procedures, specifications, acceptance criteria**
as for steps 4 and 5.

❒ **Storage conditions, storage period, testing frequency**

Climatic zone	Storage conditions		Storage period, Testing frequency [months]						
	[°C]	[%]							
I - II	25 40	60 75	0	6	12	24	36	48	60
III - IV	30 40	65 75	0	6	12	24	36	48	60

If the drug substance or drug product are distributed in the all climatic zones, then Storage should be only done at storage conditions of climatic zones III and IV besides at 40°C/75%

❒ **Number of batches**
Since the first year of production is covered by batches for the on-going stability testing, the follow up stability testing starts in the second year.

- drug substance: 1 batch per year
- drug product: 1 batch per year.

If several strengths are marketed, only the most sensitive is investigated or matrixing design (1/3 design) is applied.

It is advisable to start with the storage of the batch for a drug product in the same months every year.

❒ **Container closure system**
Commercial. If several are marketed, only the most sensitive is investigated or matrixing design (1/3)

❒ **Evaluation**
The results are compared with those of the steps 4, 5 and summarised in a yearly quality report.

❒ **Statements/Labelling**
Confirmation of the stability information, shelf lives, re-test periods.
The follow-up stability testing is not regulated by a stability guideline. It is a GMP measure to guarantee the quality.

6.2 Variations and Changes

The scope and design of the stability studies for variations and changes are based on the knowledge and experience acquired on active substances and drug products.

6.2.1 Drug substance

Variations and changes of the synthetic route or manufacturing process of the drug substance may influence

- impurity profile mainly by-products, intermediates, degradation products
- particle size and particle size distribution
- surface area.
- polymorphism

The following information is available

❒ **Justification of Specifications**

Justification for each analytical procedure and each acceptance criterion was derived from:

- relevant development data
- test data of batches used in toxicology and clinical studies
- results from stress testing
- results from accelerated and long-term testing
- results from production batches.

The batches for justification have been manufactured according to:

- different starting materials
- different synthetic route
- different method of manufacture and procedure
- different site of manufacture
- different scale of manufacture.

❒ **Statements**

The stability information is based on the following data and derived stability information:

- The results of stress testing, the stability profile with derived preliminary re-test period.
- The results of confirmation investigations with preliminary confirmed preliminary re-test period.
- The primary data with accelerated and long-term testing up to registration application with derived preliminary re-test period.
- The on-going stability data of the 3 registration batches, long-term testing with derived re-test period of 60 months.

- The on-going stability data of the 3 post-approval production batches, accelerated and long-term testing with confirmed re-test period up to 60 months.

❒ **Robustness of manufacturing process**

The batches investigated in stability testing were manufactured according to the following ”variations and changes”:

- different batches with different batches and batch size of starting materials
- different synthetic routes which changed during development
- different method of manufacture and procedure with different types and sizes of equipment
- different site of manufacture, development laboratory, pilot plant, chemical production with different types and sizes of equipment
- different scale of manufacture, laboratory, pilot plant, production scale.

On the basis of this detailed information it is usually possible to evaluate the influence of the variations and changes on the stability of the drug product. This is valid all the more for stable drug substances (stay within initial specifications 6 months 40°C/75 % r.h. and ≥ 2 years 25°C/60 % r.h.).

There may be an influence on the following test criteria which have to be investigated carefully after production at release: particle size, particle size distribution, surface area, polymorphy, purity, dissolution rate.

To be on the safe side the following general procedure is proposed after careful evaluation:

Drug Substance

Variation, Change in	**Possible influence on quality, release specifications. Immediate investigation**	**Assessment of results**	**Possible influence on stability, re-test period. Stability investigation**
Equipment	Particle size, Surface area Polymorphy purity, Dissolution rate	Quality unchanged, all data within acceptance criteria	none
Manufacturing site			none
Process			none
Route of synthesis			2 batches 40°C/75% 3 months

6.2.2 Drug Product

Basically the same amount of information is available as for the drug substance.

❒ **Justification of Specifications**
Justification was given for the selection of the test attributes, each analytical procedure and each acceptance criterion.

The justifications referred to

- relevant development data
- test data of batches used in toxicology and clinical studies
- results from stress- and confirmation studies
- results from accelerated and long-term testing
- results from production batches.

❒ **Statements**
The stability information is based on the following data and derived stability information:

- The results of stress- and confirmation studies during the clinical development:
  - different strengths and composition phase I
    derived: 3 or 6 months predicted and confirmed.
  - different strengths phase II
    derived: 12 or 18 months predicted and confirmed.
  - final formulation phase III including registration batch
    derived: 24 or 36 months predicted and confirmed, 24 months predicted for registration batches.
- The primary data of the registration batches, accelerated and long-term testing.
  derived: 24 months preliminary shelf life confirmed.
- The on-going stability data of the 3 registration batches long-term testing.
  derived: shelf life up to 60 months.
- The on-going stability data of the 3 post-approval production batches accelerated and long-term testing.
  derived: confirmed shelf life up to 60 months.

❒ **Robustness of formulation**
The batches investigated in stability testing had been manufactured according to the following ”variations and changes”:

- different batches of drug substance and excipients including drug substance from production,
- different strengths,
- different compositions,
- different container closure systems, type and size
- different manufacturing processes with different types and sizes of equipment

- different sites of manufacture: development laboratory, manufacturing site of clinical supplies, pilot plant, pharmaceutical production with different types and sizes of equipment
- different scale and batch site of manufacture laboratory, pilot plant, production.

On the basis of this detailed information it is very of-ten possible to evaluate the influence of the variations and changes on the stability. In the individual case it depends on the dosage form and the type of formulation.

By applying the strategic planning, scientifically based information can be provided in most cases. This information provides a higher degree of certainty than formal stability testing of 1 – 3 batches stored at 40°C/75 % 3 – 6 months.

It is always necessary to investigate these batches carefully after production to see whether all data are well within release specifications. It may be also necessary to perform special investigations.

Solid Dosage Forms

Variation, Change in	**Possible influence on quality, release acceptance criteria: immediate investigation**	**Assessment of results**	**Possible influence on stability, shelf life acceptance criteria Stability investigation**
Equipment	Appearance, Content uniformity, Dissolution rate	Quality unchanged all data within release acceptance criteria	2 batches 40°C/75% or 30°C/65% up to 3 months
Manufacturing site			none
Process			2 batches 40°C/75%
Excipients: - Qualitative - Quantitative			up to 3 months

Semi-Solid-Dosage Forms

Variation, Change in	Possible influence on quality, release acceptance criteria. Immediate investigation	Assessment of results	Possible influence on stability, shelf life acceptance criteria. Stability investigation
Equipment	Appearance, Homogeneity, Content Uniformity within container, Chemical stability preservation	Quality unchanged All data within release acceptance criteria	2 batches 40°C/75 % (30°C/65 %) up to 3 or 6 months
Manufacturing site			
Process			
Excipient: Qualitative, Quantitative			

Liquid Dosage Forms

Variation, Change in	Possible influence on quality, release acceptance criteria. Immediate investigation	Assessment of results	Possible influence on stability, shelf life acceptance criteria. Stability investigation
Equipment	Appearance, pH, Chemical stability preservation	Quality unchanged All data within Release acceptance criteria	none
Manufacturing site			2 batches 40°C/75% up to 6 months
Process			
Excipient Qualitative Quantitative			

Change in Container closure system

Variation, Change in	Possible influence on quality, release acceptance criteria, immediate investigation	Assessment of results	Possible influence on stability, shelf life acceptance criteria. Stability investigation
Immediate container closure system, Same material different size	<u>Solid Dosage Forms</u> Tightness of Container <u>Semi-Solid Dosage Forms</u> Homogeneity Content Uniformity <u>Liquid Dosage Forms</u> Chemical Stability	Quality unchanged, all data within release acceptance criteria	none none none
Different material	Solid dosage forms Permeability O_2, H_2O, Light	Equal or less permeable	none
		higher permeability	2 batches 40°C/75 % up to 3 months
	<u>Semi-solid, liquid d. f.</u> Permeability O_2, H_2O, Light, Interaction	Equal or less permeable, no interaction	none
		Higher permeability, Possible interaction	2 batches 40°C/75 % or 30°C/65 % up to 3 months
Test procedure	Specificity, Reporting threshold, Validation	Corresponding validation data equal or better	none

6.2.2.1 Application of the basic principles

❒ **Selection of batches and samples**

- drug substance: pilot plant
- drug product: The manufacturing process to be used should meaningfully simulate that which should be applied to large scale batches for marketing, the quality must meet all release acceptance criteria.

❒ **Test attributes**

Corresponding to original formulation

❒ **Analytical procedures**

Corresponding to original formulation

❒ **Specification, acceptance criteria**
Corresponding to original formulation

❒ **Storage conditions, storage period, testing frequency**

Storage condition		Storage period, Testing frequency			
[°C]	[% r.h.]	[months]			
40	75	0	1	3	(6)
30*	65*			3	(6)
25	60				6 up to shelf life

* only if at 40°C significant changes are expected

❒ **Number of batches**
2

❒ **Container Closure System**
Commercial unless packaging material has been changed.

❒ **Evaluation**
The results are compared with the corresponding data of the original formulation.
If no new data (≥ 3 years) are available 1 batch of the original formulation is investigated together with the changed formulation.

❒ **Statements/Labelling**
If the variation causes no influence on the quality, all data are within specifications the stability information of the original formulation is still valid.

The stability is pursued by the corresponding follow-up stability programme, but in the first year of production two representative batches are put on stability. Furthermore the testing frequency at 40°C is : 3 and 6 months.

If the changed formulation is less stable the shelf life has to be shortened accordingly.

7. Summary

The results of the analytical development and the stability testing for a New Molecular Entity (NME), the drug substance and the drug products form an important part for a registration application.

This paper describes the whole process of development from the preliminary experiments with the drug substance to the continuous production of the drug product.

The development is treated in six steps for each of which eleven basic principles have been defined. Combining the six steps and the eleven basic principles yields a systematically structured stability schedule.

Then it is shown that by strategic planning of the whole process including test criteria, analytical procedures and specifications,

- a successful marketing authorisation can be secured,
  - in the shortest period of time,
  - in the most efficient way.

The development is fully covered by stability data, therefore the quality, efficacy and safety of the finished medicinal product will be based on the results of

- preclinical experiments
- clinical samples
- NDA batches.

The quality of the clinical batches will correspond to those of the finished medicinal product. Statements gained by this broad based approach thereby acquires a completely new dimension.

For each step the necessary capacity has been evaluated and the time to availability of stability information. On this basis a development plan for a new drug product can be elaborated including the necessary analytical capacity and the schedule for registration application.
The paper is based on the ICH Tripartite Stability Guideline for the EU, Japan and the USA which has been extended to world-wide marketing. Furthermore all relevant ICH Guidelines have been considered.
The consistent application of the paper means considerable savings in capacity.

A prerequisite for a successful application is the open and close cooperation of all those involved in the development of the new drug product.

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