The Complete Stability Testing
for a Successful Application

Strategies, Requirements, Basic Principles Performance, Documents

Strategies

Introduction

- **Objectives**
- To secure the registration application and the successful marketing authorisation
  - in the shortest period of time,
  - In the most efficient way
- To apply all relevant guidelines and adapt them accordingly during the stage of development
- To include the whole process of development from the preliminary experiments with the drug substance to the continuous production of the drug product.
- To have an efficient procedure applicable to each stage of development
- To base the quality, efficacy and safety of the finished medicinal product on the results of
  - Preclinical experiments,
  - Clinical samples,
  - Primary registration batches
- To guarantee the patient after marketing authorisation the same quality as the patient during the clinical trial investigations

ICH Harmonised Guidelines

Number	Guideline	Status
Q1A (R2)	Stability Testing of New substances and Products	Step 5
Q1B	Photostability Testing of New Substances and Products	Step 5
Q1C	Stability testing, Requirements for New Dosage Forms	Step 5
Q1D	Bracketing and Matrixing Designs for Stability Testing of New Substances and products	Step 5
Q1E	Evaluation of Stability Data	Step 4
Q1F	Stability Data Package for Registration in climatic zones III and IV	Step 4
Q2A	Validation of Analytical Methods. Definitions and Terminology	Step 5
Q2B	Validation of Analytical Procedures: Methodology	Step 5
Q3A(R)	Impurities Testing Guideline: Impurities in New Drug Substances	Step 5
Q3B(R)	Impurities in New Drug Products	Step 4
Q3C	Impurities: Residual solvents	Step 5
Q6A	Specifications: Test Procedures and Acceptance Criteria for new Drug Substances and Drug Products: Chemical Substances	Step 5
M4	Common Technical Document for the Registration of Pharmaceuticals for human use: Organisation of CTC	Step 5
M4Q	CTD Quality Overall Summary and CTD Quality	Step 5

CPMP Note for Guidance

Number	Guidelines	Date for coming into Operation
CPMP/QWP/159/96	Maximum Shelf-life for Sterile Products for Human Use after first opening or following reconstitution	July 1998
CPMP/QWP/576/96	Stability Testing for a Type II Variation to a Marketing Authorisation	October 1998
CPMP/QWP/2934/99	In-Use Stability Testing of Human Medical Products	September 2001
CPMP/QWP/30015/96	Parametric Release	September 2001
CPMP/QWP/072/96	Start of Shelf-Life of the Finished Dosage Form	December 2001
CPMP/QWP/609/96/ Rev 1	Declaration of storage Conditions for Medicinal Products in the Products Particulars and Active Substances	March 2002*
CPMP/QWP/122/02	Stability Testing of Existing Active Substances and related Finished Products	December 2002

* These dates refer to deadlines for comments

6 Steps of Development

Step	Analytical Development and Stability Testing
1	Stress- and accelerated testing with the drug substance
2	Preformulation and formulation finding for: • toxicological samples • clinical trial samples • final dosage form
3	Stress- and accelerated testing with selected formulations: • toxicological samples • clinical trial samples • final formulation • registration batches • Selection of container closure system • up-scaling, pilot-plant
4	Accelerated and Long-Term Stability Testing with registration batches up to registration application: • drug substance • drug product • Transfer of analytical procedures to quality control
5	On-going Stability Testing with registration and production batches • drug substance • drug product
6	Follow-up Stability Testing • continuous production • variations and changes during continuous production

The 11 Basic Principles

- ❒ Selection of Batches and Samples
- ❒ Test Attributes
- ❒ Analytical Procedures
- ❒ Specifications, Acceptance Criteria
- ❒ Storage Conditions
- ❒ Storage Period
- ❒ Testing Frequency
- ❒ Number of Batches
- ❒ Container Closure System
- ❒ Evaluation
- ❒ Statements/Labelling

Basic principles	Step 1 Stress- and accelerated testing with the drug substance	Step 2 Preformulation and formulation finding	Step 3 Stress-and accelerated testing with selected formulations, up-scaling	Step 4 Accelerated and Long-Term Stability Testing up to registration application	Step 5 On-going Stability Testing	Step 6 Follow-up Stability Testing
Selection of batches and samples	experimental batch	experimental laboratory batches	experimental and clinical batches, representative pilot-plant batches	representative pilot plant batches	representative pilot plant and production batches	representative and experimental batches
Test attributes	corresponding to objective	corresponding to objective	corresponding to objective	corresponding to results of step 1 – 3	as for step 4	as for step 4
Analytical procedures	stability indicating, preliminary validation	stability indicating, orientational validation	stability indicating, orientational and preliminary validation	stability indicating, completely validated	as for step 4	stability indicating, completely validated or revalidation
Acceptance Criteria Specifications	orientational acceptance criteria	orientational acceptance criteria	preliminary	Release and shelf life Acceptance criteria Proposed for registration	Post approval release and shelf life acceptance criteria	Post approval release and shelf life acceptance criteria
Storage conditions	25°C/60 % 25°C/75 % 30°C/70 % 40°C/75 % 40°C,50°C,60°,70°C	5°C 25°C/60 % 30°C/65 % 30°C/35% 40°C/75 % 40°C, 60°C	- 20°C - 10°C 5°C 25°C/60 % 30°C/65 % 30°C/35% 40°C/25% 40°C/75 % 40°C, 50°C, 60°C, 70°C	- 20°C 5°C 25°C/60 % 30°C/65 % 30°C/35% 40°C/25% 40°C/75 %	- 20°C 5°C 25°C/60 % 30°C/65 % 30°C/35% 40°C/25% 40°C/75 %	- 20°C 5°C 25°C/60 % 30°C/65 % 30°C/35% 40°C/25% 40°C/75 %

Basic principles	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Testing frequency	0, 1, 2, 3 months	depending on problem	• depending on problem • 0, 1, 2, 3, (6) months	0, 3, 6, 9, 12, (18) months	• (18), 24, 36, 48, 60 months • 0, 3, 6, 9, 12, 18, 24, 36, 48, 60 months	• 0, 12, 24, 36, 48, 60 months • 0, 1, 2, 3, 6 months
Storage period	up to 3 months	depending on problem	• up to 3 months • up to 6 months	up to 12 or 18 months	up to 60 months	• up to 60 months • up to 6 months
Number of batches	1 to 2	depending on problem	• depending on problem • 1	3	• 3 • 3	• 1 per year • 1 - 3
Container Closure System	open, standard packaging material	•depending on problem •standard packaging material	• depending on problem • standard packaging material	commercial container closure system	commercial container closure system	• commercial container closure system • standard packaging material

Basic principles	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Evaluation	• Statistics, Reaction kinetics, • Stability report as drug substance stability profile • Preliminary testing specification for stability testing of drug substance	• Statistics, Reaction kinetics,, • Research reports • Orientational testing specifications	• Statistics, Reaction kinetics • Stability report and preliminary testing specification for release and stability testing of - toxicological samples - clinical trial samples - final dosage form	• Statistics, Reaction kinetics, • Stability report drug substance • Testing specification for stability testing of drug substance • Validation report • Stability report drug product • Testing specification for release and stability testing of drug product • Validation report	• Statistics, • Stability report	• Statistics, Reaction kinetics • Stability report
Statements/ Labelling	• preliminary Re-Test Period • Storage instructions • Selected test attributes for long-term testing • Orientational shelf life predictions for drug products	• Formulation selection	• Period of use - toxicological samples - clinical samples phase I - III • Shelf life prediction final dosage form • Storage instructions • Selection of container closure system • Selection of test attributes for long-term testing	• Re-test period prediction • Shelf life prediction • storage instructions • in-use stability • holding time for intermediates and bulk	• Post approval specifications • Confirmation and extension of re-test period • Confirmation and extension of shelf life	• Confirmation of re-test period • Confirmation of shelf life • assessment of variations

Drug Substance

Nummer	Thema	Entwicklungsanalytik Stabilitätsprüfung	Referenz ICH
3.2.S	**Drug Substance**		
3.2.S.1	**General Information**		
3.2.S.1.1	Nomenclature		
3.2.S.1.2	Structure	✔	
3.2.S.1.3	General Properties	✔	Q6Q
3.2.S.2	**Manufacture**		
3.2.S.2.1	Manufacturer(s)		
3.2.S.2.2	Description of Manufacturing Process And Process Controls		
3.2.S.2.3	Control of Materials	✔	Q6A
3.2.S.2.4	Controls of Critical Steps and Intermediates	✔	Q6A
3.2.S.2.5	Process Validation and/or Evaluation		
3.2.S.2.6	Manufacturing Process Development	✔	Q3AR
3.2.S.3	**Characterisation**		
3.2.S.3.1	Elucidation of structure and other Characteristics	✔	Q6A
3.2.S.3.2	Impurities	✔	Q3AR,Q3C,Q6A
3.2.S.4	**Control of Drug Substance**		
3.2.S.4.1	Specification	✔	Q6A
3.2.S.4.2	Analytical Procedures	✔	Q2A,Q6A
3.2.S.4.3	Validation of Analytical Procedures	✔	Q2A,Q2B,
3.2.S.4.4	Batch Analyses	✔	Q3AR,Q3C,Q6A
3.2.S 4.5	Justification of Specification	✔	Q3AR,Q3C,Q6A
3.2.S.5	**Reference Standards of Materials**	✔	**Q6A**
3.2.S.6	**Container Closure System**	✔	
3.2.S.7	**Stability**		
3.2.S.7.1	Stability Summary and Conclusions	✔	Q1AR,Q1B, Q1E, Q1F
3.2.S.7.2	Post-Approval stability Protocol and Stability Commitment	✔	Q1AR
3.2.S.7.3	Stability Data	✔	Q1AR, Q1B, Q1D, Q1F, Q1B,Q2A, Q2B

Drug Product

Nummer	Thema	Entwicklungsanalytik Stabilitätsprüfung	Referenz ICH
3.2.P	Drug Product		
3.2.P.1	Description and Composition of the Drug Product	✔	Q6A
3.2.P.2	Pharmaceutical Development	✔	Q6A
3.2.P.2.1	Components of the Drug Product		
3.2.P.2.1.1	Drug Substance	✔	
3.2.P.2.1.2	Excipients	✔	
3.2.2.2	Drug Product		
3.2.P.2.2.1	Formulation Development	✔	
3.2.P.2.2.2	Overages	✔	
3.2.P.2.2.3	Physicochemical and Biological Properties	✔	
3.2.P.2.3	Manufacturing Process Development	✔	
3.2.P.2.4	Container Closure System	✔	
3.2.P.2.5	Microbiological Attributes	✔	
3.2.P.2.6	Compatibility	✔	
3.2.P.3	Manufacture		
3.2.P.3.1	Manufacturer(s)		
3.2.P.3.2	Batch Formula		
3.2.P.3.3	Description of Manufacturing Process and Process Controls	✔	
3.2.P.3.4	Controls of Critical Steps and Intermediates	✔	Q2A, Q2B, Q6A
3.2.P.3.5	Process Validation and/or Evaluation		
3.2.P.4	Control of Excipients		
3.2.P.4.1	Specifications	✔	Q6A
3.2.P.4.2	Analytical Procedures	✔	Q2A,Q6A
3.2.P.4.3	Validation of Analytical Procedures	✔	Q2A, Q2B
3.2.P.4.4	Justification of Specifications	✔	Q3C
3.2.P. 4.5	Excipients of Human or Animal Origin		Q6B
3.2.P.4.6	Novel Excipients		
3.2.P.5	Control of Drug Product	✔	
3.2.P.5.1	Specification(s)	✔	Q3B,Q6A
3.2.P.5.2	Analytical Procedures	✔	Q2A,Q6A

3.2.P.5.3	Validation of Analytical Procedures	✔	Q2A,Q2B
3.2.P.5.4	Batch Analyses	✔	Q3BR, Q3C,Q6A
3.2.P.5.5	Characterization of Impurities	✔	Q3BR, Q6A
3.2.P.5.6	Justification of Specification(s)	✔	Q3BR, Q6A
3.2.P.6	Reference Standards or Materials	✔	Q6A
3.2.P.7	Container Closure System		
3.2.P.8	Stability		
3.2.P.8.1	Stability Summary and Conclusion	✔	Q1AR, Q1B, Q1D, Q1E. Q1F Q2A, Q2B,
3.2.P.8.2	Post-approval Stability Protocol and Stability Commitment	✔	Q1AR,
3.2.P.8.3	Stability Data	✔	Q1AR, Q1B, Q1D, Q1E. Q1F Q2A, Q2B,
3.2.R	Regional Information		
3.3	Literature References		

Overview of the documents which result during the development

Step of Dev.	Document	Needed for	Common Technical Document CTD	Guidelines
1	• Stability report : Preliminary Stability Profile of Drug Substance • Stability report: Stability profile of Drug substance • TS[1] for Stability Testing of Drug Substance, No. 1	• Preformulation • Regist. Appl.[2] • Regist. Appl.	 • 3.2.S.7.1, 3.2..S.7.3 • 3.2.S.4.2	• Q1AR2, Q1B • Q1AR2, Q1B • Q2A, Q2B. Q3AR
2	• TS for Stability Testing Drug Product, No. 1 • Development Report Compatibility	Base for further development • Compatibility	 • 3.2.P.2.6	
3	• Stability Report: Toxicological Samples • Stability Report: Clinical Samples Phase I • Stability Report: Clinical Samples Phase II • Stability Report: Clinical Samples Phase III • Stability Report: Stability Profile of Drug Product • TS for Release and Stability Testing Drug Product, Nr. 2 • TS for Release and Stability Testing Drug Product, Nr. 3/5 • TS for Cleaning Validation • TS for Intermediates Drug Product • TS for Release and Stability Testing Drug Product, Nr. 6 • Development Report Up-Scaling	• GLP • IND, CTX • IND, CTX • IND, CTX • Reg. Appl. • GLP • IND, CTX, • GMP • GMP, Reg. Appl. • Development Manuf. Procedure	 • 3.2.P.8.1, 3.2.P.8.3 • 3.2.P.8.1, 3.2.P.8.3 • 3.2.P.5.2 • 3.2.P.3.4 • 3.2.P.5.2 • 3.2.P.2.3	• Q1D • Q1AR2, Q1B, Q1D • Q1AR2, Q1B, Q1D • Q6A • Q2A, Q2B, Q3BR, Q3C, Q6A • Q2A, Q2B, Q6A • Q2A, Q2B, Q3BR, Q3C, Q6A

[1] TS= Testing Specification, [2] Reg- Appl. = Registration Application, [3] Reg. Auth. = Regulatory Authorities

4	• TS for Stability Testing of Drug Substance, No. 3 • Validation Report for TS No. 3 • Stability Report Drug Substance • TS for Intermediates Drug substance • Validation Report for TS Intermediates Drug Substance • Stability Report Intermediates • Rationale Specifications Drug Substance - Selection Test Attributes - Selection Analytical Procedures - Derivation of Acceptance Criteria	• Reg. Appl. • Reg. Appl. • Reg. Appl. • Reg. Appl. • Reg. Appl. • Reg. Appl. • Reg. Appl.	• 3.2.S.4.2, 3.2.S.7.1 • 3.2.S.4.2, 3.2.S.7.1 • 3.2.S.7.1, 7.2, 7.3 • 3.2.S.2.4 • 3.2.S.2.4 • 3.2.S.7.1, 7.2, 7.3 • 3.2.S.4.5	• Q3AR, Q3C, Q6A • Q2A, Q2B • Q1AR2, Q1B, Q1E,Q1F • Q3AR, Q3C, Q6A • Q2A, Q2B • Q1AR2, Q1F • Q3AR, Q3C, Q6A
	• TS for Release and Stability Testing Drug Product, Nr. 6 • Validation Report for TS No. 6 • Stability Report Drug Product • TS for Intermediates Drug Product • Validation Report for TS Intermediates Drug Product • Stability Report Intermediates • Stability Report Bulk • Rationale Specifications Drug Product - Selection Test Attributes - Selection Analytical Procedures - Derivation of Acceptance Criteria • Rationale Dissolution	• Reg. Appl. • Reg. Appl. • Reg. Appl. • Reg. Appl. • Reg. Appl. • Reg. Appl. • Reg. Appl. • Reg. Appl. • Reg. Appl.	• 3.2.P.4.2, 3.2.P.8.2 • 3.2.P.4.2, 3.2.P.8.2 • 3.2.P.8.1, 8.2, 8.3 • 3.2.P.3.4 • 3.2.P.3.4 • 3.2.P.8.1, 8.3 • 3.2.P.8.1, 8.3 • 3.2.4.1 • 3.2.4.1	• Q3BR, Q3C, Q6A • Q2A, Q2B • Q1AR2, Q1B, Q1D, Q1E, Q1F • Q3BR, Q3C, Q6A • Q2A, Q2B • Q1AR2, Q1F • Q1AR2, Q1F • Q3BR, Q3C, Q6A • Q6A
5	• Stability Report Drug Substance • Stability Report Drug Product	• Reg. Appl. • Reg. Appl.	• 3.2.S.7.1, 7.2, 7.3 • 3.2.P.8.1, 8.2, 8.3	• Q1AR2, Q1E, Q1F • Q1AR2, Q1D,Q1E,Q1F
6	• Stability Report Drug Substance • Stability Report Drug Product • Stability Report Variations Drug Substance • Stability Report Variations Drug Product	• Reg.Auth[3] • Reg.Auth. • Reg.Auth. • Reg.Auth.		• CPMP/QWP/576/96 • CPMP/QWP/576/96

Summarised required capacity in the steps 1 - 5

Step of Develop-	Stage of Development	Required [weeks]	Capacity [weeks x1.3]*	Capacity [weeks]	per step/ [weeks x 1.3]*	total capacity [years = 42 weeks]**
1	Stress- and accelerated testing with drug substance • Preliminary stability profile	8	10			
	• Stability profile	12	16	20	26	0.62
2	Preformulation and formulation finding	36	47	36	47	1.12
3	Stress- and accelerated testing • clinical phase I	24	31			
	• clinical phase II	24	31			
	• clinical phase III	32	42			
	• final formulation	18	23			
	• cleaning validation	5	7			
	• scaling-up	23	30	126	164	3.90
4	Accelerated and long-term-testing • drug substance	9	12			
	• drug product	17	22			
	• PAI preparation	6	8	32	42	1.00
5	On-going stability testing • drug substance	20	26			
	• drug product	42	55	62	81	1.93
Total 1 - 4				214	279	6.64
Total 1 - 5				276	360	8.57

- To calculate the actual time span the remaining work which is indirectly related with the NME's has to be considered, such as SOP's, qualifications, literature, therefore 0.75 % of a week is used corresponding to the factor of 1.3.
- **One year is calculated with 210 days $\triangleq$ 42 weeks.

Stability testing on the critical path

Step of development	Statements/ Labelling	Needed for	Time to availability from start
1	Preliminary stability profile of drug substance	Start of predevelopment	6 weeks
	Stability profile of drug substance	Base for minimum shelf life phase I	16 weeks
3	Minimum shelf life toxicological samples	Release of toxicological samples	8 weeks
	Minimum shelf life clinical samples phase I	Release of clinical trial batch phase I	9 or 15 weeks
	Minimum shelf life clinical samples phase II	Release of clinical trial batch phase II	15 weeks or 27 weeks
	Minimum shelf life clinical samples phase III	Release of clinical trial batch phase III	15 weeks or 27 weeks
4	Stability report for registration application	Filing data for registration application	(Release of 3rd batch for accelerated and long-term testing) 15 months