The Complete Stability Testing for a Successful Application

Strategies, Requirements, Basic Principles
Performance, Documents

2. Basic Principles of Stability Testing

2. Basic principles of stability testing

Introduction

11 basic principles have been established(1) which are decisive for stability testing and which are applicable to all stages of development, on all dosage forms

The 11 principles are as follows:

2.1 Selection of Batches and Samples
2.2 Test Attributes ✔
2.3 Analytical Procedures ✔
2.4 Acceptance Criteria, Specifications ✔
2.5 Storage Conditions
2.6 Storage Period
2.7 Testing Frequency
2.8 Number of batches
2.9 Container Closure System ✔
2.10 Evaluation ✔
2.11 Statements, labelling

2.2, 2.3, 2.4, 2.9, 2.10 are treated in detail whereas the others are discussed in chapter 3 during the continuous development.

2.2 Test Attributes

The selection of the test attributes is decisive to describe the quality, safety and efficacy. It is an evolving process during the steps 1 - 3 of development.

They should be finally fixed at step 4, before start of stability testing with the registration batches. They describe the quality of design at the time of submission.

Then it has to be decided which test attributes are required to describe the quality of reproduction after marketing authorisation.

For the application it has to be differentiated between:

- **In-process test attributes**
  In-process tests are performed during the manufacture of either the drug substance or drug
  product prior to release. They may be used for the purpose of adjusting process parameters
  within an operating range.

- **Release test attributes**
  They describe the quality after production to ensure consistency.

- **Shelf life test attributes**
  They describe the quality during stability testing

- **Skip testing**
  Periodic or skip testing is the performance at release
  - on pre-selected batches and/or
  - at predetermined intervals rather than on a batch-to-batch basis,

  during stability testing
  - on pre selected batches and/or
  - at predetermined storage intervals rather than on a batch-to-batch basis or at all storage intervals.

  It is advisable to establish a comprehensive list of test attributes for the drug substance and the different dosage forms of the drug product.

  This list may be based on

  - ICH Tripartite Guideline: Specifications: Test procedures and acceptance criteria for New Drug Substances and New Drug Products: Chemical Substances
  - Test Attributes listed in the different pharmacopoeias.
  - National or international Guidelines.

The required test attributes are selected from the comprehensive list according to the
- objectives,
- the step of development,
- the dosage form.

The resulting test attributes are then combined as follows:

- **Organoleptical properties**
  e.g.: appearance, odour

- **physico-chemical properties:**
  e.g.: hardness, disintegration, dissolution, pH, particle size ...

- **chemical properties**
  e.g.: assay, decomposition, antimicrobial preservative content

- **microbial properties**
  e.g. sterility, antimicrobial preservative effectiveness test

- **container closure system materials**
  e.g.: water permeation, extractables, functionality

- Examples:

In the following tables test attributes are listed for

- Drug Substances
- Drug Products
  - Solid Dosage Forms
  - Liquid Dosage Forms
  - Semisolid Dosage Forms

Drug substance

Group Test attributes	In-process control	Release Testing	Stability Testing	Skip Testing
1 Organoleptical attributes				
• Description	x	x	x	
• Odour	x	x	x	
2. Physicochemical attributes				
• Identification		x		
• Water content		x	x	
• pH of aqueous solution		x	x	
• colour of aqueous solution or organic solution		x	x	
• Clarity of aqueous solution		x	x	
• Melting point/range		x	x	
• Refractive index		x	(x)	
• Particle size	x	x	(x)	
• Solid state form				
- polymorphism		(x)	(x)	
- solvates		(x)	(x)	
3 Chemical attributes				
• Assay		x	x	
• Impurities				
- organic		x	x	
- inorganic		x		x
- residual solvents		x	(x)	x
4 Microbial attributes				
• Microbial limits		x	(x)	x
5 Container closure system attributes				
• Interaction with foil for bulk packaging			x	

Drug Products

Tablets

Group	Test-Attributes	In-process Control	Release Testing	Stability Testing	Skip Testing
1	Organoleptic attributes				
	• Description appearance	x	x	x	
	• Odour	x	x	x	
2	Physicochemical attributes				
	• Identification		x		
	• Uniformity of mass	x	x		
	• Average mass			x	
	• Water content	x	(x)	x	
	• Hardness (Resistance to crushing strengths	x		x	
	• Friability	x	(x)		
	• Disintegration		(x)	x	(x)
	• Dissolution		(x)	x	
3	Chemical attributes				
	• Content Uniformity		x		
	• Assay		x	x	
	• Impurities		x	x	
	- organic		(x)		(x)
	- residual solvents		(x)		
	- inorganic				
4	Microbial attributes				
	• Microbial limits		(x)		(x)
5	Container closure system attributes				
	• Functioning test			x	

Capsules

Group	Test-Attributes	In-process Control	Release Testing	Stability Testing	Skip Testing
1	Organoleptic attributes				
	• Description appearance	x	x	x	
	• Odour	x	x	x	
2	Physicochemical attributes				
	• Identification		x		
	• Elasticity		x	x	
	• Uniformity of mass	x	x	x	
	• Average mass			x	
	• Average mass of filling			x	
	• Water content of filling			x	
	• Water content of capsule		(x)	x	
	• Disintegration		(x)	x	(x)
	• Dissolution		(x)	x	(x)
3	Chemical attributes				
	• Assay		x	x	
	• Impurities				
	- organic		x	x	
	- residual solvents of filling		(x)	(x)	(x)
4	Microbial attributes				
	• Microbial limits		X	(x)	(x)
5	Container closure system attributes				
	• Functioning Test			x	

Oral liquid dosage forms

Group	Test Attributes	In-process control	Release Testing	Stability Testing	Skip Testing
1	Organoleptical attributes				
	• Description appearance	x	x	x	
	• Odour		x	x	
2	Physicochemical attributes				
	• Identification		x		
	• Uniformity of dosage units				
	• Weight variations	x	x		
	• Fill volume	x	x		
	• Uniformity of fill)	x	x		
	• Loss on mass			x	
	• pH	x	x	x	
	• Colour of solution		x	x	
	• Clarity of solution		x	x	
	• Viscosity		x	(x)	
	Orals suspension				
	• Particle size distribution		x	x	
	• Redispersibility		x	x	
3	Chemical attributes				
	• Assay		x	x	
	• Impurities				
	• Organic		x	x	
	• Antimicrobial preservative content		x	x	
	• Antimicrobial preservative decomposition			x	
	• Antioxidant preservative content		x	x	
4	Microbial attributes		X	(x)	
	• Microbial limits				
5	Container closure system attributes				
	• Interactions				
	Extractables				
	- rubber stopper			(x)	x
	- cap liner				x
	- plastic bottle				x

Injections, Parenterals

Group	Test Attributes	In-process control	Release Testing	Stability Testing	Skip Testing
1	Organoleptical attributes				
	• Description appearance	x	x	x	
2	Physicochemical attributes				
	• Identification		x		
	• Uniformity of dosage units				
	- Weight variations	x	x		
	- Fill volume	x	x		
	- Uniformity of fill)	x	x		
	• Loss on mass			x	
	• pH		x	x	
	• Colour of solution		x	x	
	• Particulate matters				
	- clarity of solution		x	x	
	• Osmolality		x	(x)	
3	Chemical attributes				
	• Assay		x	x	
	• Impurities				
	- organic		x	x	
	· Antimicrobial preservative content		x	x	
	· Antimicrobial preservative decomposition			x	
	· Antioxidant preservative content		x	x	
3	Microbial attributes				
	• Microbial limits		x		
	• Sterility		x	(x)	
	• Endotoxins		x		
	• Pyrogens		x		
5	Container closure system attributes				
	• Interactions				
	Extractables				
	- rubber stopper			(x)	x
	- cap liner				x
	- plastic bottle				x
	· Functioning test		x	x	

Creams, Ointments

Group	Test Attributes	In-process control	Release Testing	Stability Testing	Skip Testing
1	Organoleptical attributes				
	• Description appearance		x	x	
	• Odour	x	x	x	
	• Homogeneity		x	x	
2	Physicochemical attributes				
	• Identification		x		
	• Consistency		x	x	
	• Viscosity		x	x	
	• Crystallisation		x	x	
	• Recryistallisation			x	
	• Loss on mass			x	
	• Uniformity of content within container			x	
3	Chemical attributes				
	• Assay		x	x	
	• Impurities				
	- organic		x	x	
	• Antimicrobial preservative content		x	x	
	• Antimicrobial preservative decomposition				
	• Antioxidant preservative content		x	x	
4	Microbial attributes				
	• Microbial limits		x	x	
5	Container closure system attributes				
	• Interaction with packaging material			x	
	• Extractables				
	- plastic container			(x)	(x)
	- closure system			(x)	(x)

Considerations for selecting test attributes for release and stability testing from investigations during development

Step of Develop-ment	Investigations	Selection of test attributes
1	Stress and accelerated testing with drug substance	Test attributes for stability testing with registration batches
1-3	Drug substance batches for safety and clinical trials	Decision whether microbial testing is necessary for registration and production batches
2-3	• Preformulation and formulation finding, • clinical trial batches, • stress and accelerated testing with selected batches	Decision whether microbial testing is necessary for registration and production batches of solid dosage forms
3	Stress and accelerated testing with selected formulations of the drug product including final formulations	• Test attributes for stability testing with registration batches • Decision whether particle size of drug substance has to be followed

2.3 Analytical Procedures

2.3 Analytical Procedures

2.3.1 Introduction

The analytical procedure refers to the way of performing the analysis. It should describe in detail the steps necessary to perform each analytical test.

This includes:

- reagents
- sample preparation ·
- analytical method ·
- calibration
- calculation
- documentation

During the development of a new drug product in six steps from the stress- and accelerated testing with the drug substance up to the running production the analytical procedure has to be developed accordingly. It is not possible, to optimise and validate the analytical procedure at the beginning and then starting analysing the samples. The analytical procedure has to be developed step by step according to the objectives. The final version optimised and completely validated should be available before start of the stability testing with the registration batches of drug substance and drug product. That means all analytical procedures up to then are preliminary. The analytical data during development however are used to make decisions to release clinical trial batches of phase I - II1. Therefore the different steps have to be documented carefully and must be always traceable by a "history sheet".

For most of the organoleptic and physico-chemical test criteria pharmacopoeial analytical procedures or analytical methods are available.

For international registration it has always to be investigated whether the analytical procedures and methods are harmonised across the EP, JP and USP. There is a continuous process of harmonisation under way.

Examples

- Sterility
- Residue on ignition/sulphated ash,
- Bacterial Endotoxins
- Colour/Clarity
- Particulate matter
- Dissolution (apparatus)
- Disintegration

In this paper main emphasis is put on those analytical procedures which are applied for assay and the determination of impurities and degradation products, especially in stability testing.

The analytical procedures should be

- specific to determine the drug substance and the impurities, degradation products,
- sensitive to determine a fall in assay as early as possible.

Common analytical procedures are listed in the following table:

Analytical procedure	**RSD**	**Significant determination of fall in assay for N = 3**	**Assessment of specificity**
HPLC	1.2%	≥ 3%	specific
GC	1.2%	≥3%	specific
HPTLC	2.5%	≥ 6.3%	specific
UV spectroscopy	0.8%	≥ 2%	not specific
Polarographie	1.6%	≥ 4%	partly specific

Table 1 Common analytical procedures which are applied for assay and the determination of degradation products (1).

Table 2

n	**RSD**								
	0.1	0.2	0.3	0.5	1.0	1.5	2.0	2.5	5.0
2	0.90	1.80	2.70	4.5	9.0	13.5	18.0	22.5	44.9
3	0.25	0.50	0.74	1.2	2.5	3.7	5.0	6.2	12.4
4	0.16	0.32	0.48	0.8	1.6	2.4	3.2	4.0	8.0
5	0.12	0.25	0.37	0.6	1.2	1.9	2.5	3.1	6.2
10	0.07	0.14	0.21	0.4	0.7	1.1	1.4	1.8	3.6

Table 2: Number of replications n with dependence of RSD to determine a significant fall in assay (1).

The data listed in the tables 1 and 2 indicate that a fall in assay can often be determined only indirectly via quantifying the degradation products.
With a stable product no or only little degradation takes place. Stress investigations help to predict whether degradation will take place at accelerated and long term storage

conditions. In table 3 % of decomposition is listed for 3 months 70°C,/ 60 %, 3 and 6 months 40°C/75 % r.h. which has been calculated on the base of 0.2 % at 25°C/60 % after 12, 24, 36, 48 and 60 months. AE: 83 kJ' mol^{-1}, first order reaction. 0.2 % was chosen as the threshold for identification according to the ICH Guideline Impurities in New Drug Products for the maximum daily dose of > 10 mg -2 g. Most doses of the drug products fall in this range.

Stress storage conditions		**Accelerated storage conditions**		**Long term storage conditions Climatic zone II**
70°C/3 months	60°C/3 months	40°C/75%		25°C/60%
		3 months	6 months	
4% 2% 1.3% 1.0% 0.8%	1.7% 0.9% 0.6% 0.4% 0.33%	0.3% 0.15% < 0.1% < 0.1% < 0.1%	0.6% 0.3% 0.2% 0.15 0.1%	12 months 0.2% 24 months 0.2% 36 months 0.2% 48 months 0.2% 60 months 0.2%

Table 3: Calculated data for degradation on the base of 0.2 % at 25°C/60 %: ΔE 83 kJ · mol^{-1}, first order reaction.

2.3.2 Optimisation

Optimisation is the first step in developing an analytical procedure.
Since the HPLC is the most applied method the optimisation strategy will be shortly discussed:

☐ **Scientific aspects:**

- definition of separation problem
- information of the substances to be separated (structure, polarity, solubility, reactivity).
- availability of substances (decision on length of column for optimisation)

☐ **Economic aspects:**

- frequency of application, number of samples to be analysed
- required time for optimisation.

☐ **Optimisation procedure**

- Selection of stationary phase (standard: RP) and modifier (standard: methanol)
- estimation of elutionic strength (k' range 1 - 20)
- optimisation of pH (binary)
- optimisation of modifier (ternary)

- if necessary optimisation of further influencing factors (temperature ...)
- fixing elutionic strength, length of column and further chromatographic conditions.

☐ Stability testing aspects

- Sequence of peaks, degradation product ahead of active ingredient
- Extreme ratio of peak height 99.9% : 0.1% active ingredient : degradation product

The characteristic parameter of the HPLC and their influence on the separation should be also known

Characteristic parameter	Attributes
Retention time t_R	Dependent from: • flow rate • length of column
Capacity factor k'	Dependent from • type of sample • stationary phase • mobile phase Independent from: • dimension of column • flow rate
Relative retention α	Measure of selectivity of system $\alpha = \frac{k_2'}{k'_2}$, $k'_1 > k'_2$
Height equivalent of a theoretical plate, plate height H	Dependent from: • diffusion coefficient • particle size of packaging material • flow rate • partly dimension of column
Number of theoretical plates N	Describes efficiency of the chromatographic system
Chromatographic resolution Rs	Degree of separation of two adjacent peaks in a chromatogram Dependent from • relative retention • absolute retention $k', = \frac{1}{2} (k'_2 + k'_1)$
Tailing factor T	Measure for asymmetry of peak

2.3.2 Validation

Validation is the next step after the analytical procedure has been optimised.

The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose.

Pharmacopoeial analytical procedures and methods are generally validated according to definition. Whenever possible pharmacopoeial procedures should be applied. The table 4 gives a general overview on the test criteria, required optimisation and validation.

Test attributes	Pharmacopoeial method or procedure	Optimisation	Validation	Explanation
Organoleptic		-	-	-
Physicochemical, e.g. Hardness Particle size Disintegration Dissolution	 x x -	 - (x) (x) - x	 - - - - x	 - method depends on equipment - -
Chemical e.g. Identity Assay Impurities Degradation	 x - x - x - x -	 - x - x - x - x	 - x - x - x - x	
Microbial	x -	- x	- x	

Table 4: Overview of test attributes and required optimisation and validation x = yes, - = no

The validation is performed according to the ICH guidelines:

- Text on Validation of Analytical Procedures
- Extension of the ICH Text: «Validation of Analytical Procedures, Methodology".

A tabular summation of the characteristics applicable to identification, control of impurities, assay procedures is given in table 5

Validation characteristics	Type of analytical procedure			
	Identification	Quantitative test Impurity content	Limit test for impurities	Assay • Dissolution • Content/potency
Specificity	x	x	x	x
Linearity		x		x
Reporting threshold		x		
Detection limit			x[1]	
Range		x		x
Accuracy		x		x
Precision • Repeatability • Intermediate precision		x x[2]		x x[3]

Table 5: Tabular summation of the validation characteristics for identification and assay

Robustness is not listed in the table but should be considered at an appropriate stage in the development of the analytical procedure.

The following should be considered:

[1]Detection limit is only required for semi-quantitative methods. Otherwise it is covered by the range between reporting threshold and identification threshold.

[2]Repeatability is derived from the data of accuracy and range, that means out of 9 determinations: Therefore intermediate precision can be deleted if the RSD is in the range of 5 %.

[3]Intermediate precision for dissolution is not performed. The intermediate precision is superimposed by the scatter of the individual tablets. The repeatability is derived from the data of accuracy and range (9 determinations).

The various validation characteristics should be considered in distinct sections. The arrangement of these sections reflects the process by which the analytical procedure may be developed and evaluated.

The complete validation of the analytical procedures should be included as part of the registration application submitted within the EU, Japan and the USA.

Validation is a step by step procedure accompanying the development of the analytical procedure.

Three steps of validation are differentiated:

- orientational
- preliminary
- complete

The three steps concept reflects the objective of validation, to demonstrate that it is suitable for its intended purpose.

Validation characteristics	Extend of validation		
	orientational	preliminary	complete
Specificity	x	x	x
Linearity	x	x	x
Reporting threshold	x	x	x
Detection limit[1]	x	x	x
Accuracy	x[2]	x	x
Range		x	x
Repeatability		x	x
Intermediate precision			x
Robustness	x	x	x
Validation report			x

[1] Only for semi-quantitative procedures instead of quantitation limit.

[2] At this stage only for drug products and not for drug substance.

The extend of validation reflects the objective of the analysis in the six steps of development. At the beginning of the stress testing with the drug substance no information is available about the intrinsic stability of the molecule.

In step 2 with the preformulation and formulation finding, samples of different formulations or composition
may be analysed just once or only a few times, in phase I the different strengths of clinical trial samples are analysed once. In all these cases orientational validation with specificity (if possible) linearity, quantitation limit, accuracy for drug product formulations and robustness is sufficient to secure the analytical data, to draw conclusions for the further development or to release clinical trial batches for phase I.

As the stress investigations with the drug substance comes to an end, the final formulation evolves in the course of development, stress investigations are performed with selected formulations in step 3 of development, clinical trial batches have to be released in phase II or phase III the validation is extended to include range for assay and decomposition, and repeatability. Before start of step 4, the accelerated and long term testing with the registration batches, the validation should be completed to include also intermediate precision. The stability data should then be summarised in a validation report which should be available at the time of submission.
Finally a revalidation may be required in step 6 with variations.

The table lists the extend of validation in the steps 1 to 6 of development.

		Extend of validation	
Step	**Stage of development**	**Before starting**	**During or end of investigations**
1	Stress- and accelerated testing with drug substance	Orientational	preliminary
2	Preformulation and formulation finding	orientational	
3	Stress- and accelerated testing with selected formulations: • toxicological samples • clinical trial samples I • clinical trial phase II • clinical trial phase III • up-scaling pilot plant	Orientational (if possible from step2) orientational preliminary preliminary preliminary	preliminary
4	Accelerated and long term testing	complete	
5	On-going stability testing	complete	
6	Follow up stability testing. • continuous production • variations and changes	complete revalidation may be necessary	

In the following the extend of validation for the different validation characteristics is described in more detail based on the ICH guidelines on validation

Specificity.

Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. This might include impurities, degradants, matrix

For the mostly applied HPLC method representative chromatograms should be used to demonstrate specificity by the resolution of the different compounds:

Compound	Orientational	Preliminary	Complete
Drug substance	Pure drug substance spiked with appropriate levels of impurities (intermediates of synthesis) and degradants if already known	Pure drug substance spiked with degradation products if they are available now	= orientational
Drug Product	Pure drug substance is spiked with degradants and the excipients or placebo is spiked with drug substance and degradation products	= orientational	= orientational

Linearity

The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration of analyte in the sample.

A linear relationship should be evaluated across the range.
If there is a linear relationship evaluated by visual inspection, the test results should be evaluated by appropriate statistical methods.

Submitted should be:

- correlation coefficient,
- y-intercept,
- slope of regression line,
- residual sum of squares,
- derivation of the actual data points from the regression line itself.

A minimum of five concentrations is recommended for the establishment of linearity.

It may be performed by dilution of a standard stock solution or separate weighings of synthetic mixtures of the drug product components and adding dilutions of standard stock solution of drug substance.

Linearity has to be demonstrated for the drug substance, impurities and degradants which are determined quantitatively.

Compound	Orientational	Preliminary	Complete
Drug substance • Range • Impurities and degradation products • Pure drug substance if degradation product unknown	• 50-150% of test solution • 0.05-2% • 0.05-2%	• = orientational • 0.05-120% acceptance criterion	= orientational = preliminary
Drug product • range • Degradation product • Dissolution	• 50-150% of stated content • 0.1% - 5% (reporting threshold) • Q-30% - Q+30%	• = orientational • 0.1%-120 % of shelf life acceptance criteria	=orientational = preliminary = preliminary

Reporting thresholds/quantitation limit, detection limit

In the ICH guidelines on impurities in drug substances and drug products quantitation limit and detection limit are not mentioned any more but have been replaced by identification threshold and reporting threshold.

- **Identification threshold:**

  A limit above which (>) an impurity needs identification

  - Drug substance 0.1%
  - Drug product: 0.2-1% depending on maximum daily dose

- **Reporting threshold: A limit above which (>) an impurity needs to be reported**

  - Drug substance: 0.05%
  - Drug product: 0.1%

The reporting threshold levels for impurities in drug substances and drug products should be the lower limit of validation. It should be the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy
The reporting threshold can be determined with the active ingredient or the impurity res. the degradation product. Preferably the active ingredient is used. The amount to be injected should be estimated from the IU (Integration Units) of assay, that 0.05% rest. 0.1 can be integrated. Signal-to-noise 10:1
The threshold levels are definitions and not scientifically derived quantitation or detection limits.

The detection limits are applied only for semi-quantitative analytical procedures.

The reporting threshold for impurities in drug substances and drug products is determined at the orientational validation.

Accuracy/Range

The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found.

Accuracy should be established across the specified range of the analytical procedure.

Accuracy should be reported as percent recovery by the assay of known added amount of analyte in the sample or as the difference between the mean and the accepted true value together with the RSD.

The range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and range).

Minimum specified ranges which should be considered

Test attribute	Range
Drug substance • Percent of test solution • Impurity, degradation product	 • 80 - 120% • reporting threshold - 120% acceptance criteria
Drug product • Percent of test solution • Content uniformity • Dissolution testing • Degradation product • Assay and degradation as one test	 • 80-120% or 70-130% • 70-130% • Q ± 30% • Reporting threshold - 120 % shelf life acceptance criteria • Reporting threshold - 120% of assay acceptance criterion

Accuracy

Compound	Orientational	Preliminary	Complete
Drug substance assay	no accuracy, no range	80,100, 120%, 3 replicates each. Comparison to analyte of known purity (reference material)	=preliminary
impurity, degradation product	0.05%, drug substance spiked with corresponding amount of impurity, 3 replicates	0.05, 0.1, 120% (acceptance criteria)	=preliminary
Drug product assay	100% stated content 100% drug substance added to placebo, 3 replicates	70,100,130% (thereby assay and content uniformity can be combined - Known quantities of drug substance are added to placebo or synthetic mixture - Known quantities drug substance added to drug product 3 replicates each = 9 results	=preliminary
Degradation product	0.1%, drug product or placebo + drug substance spiked with corresponding amount of degradation product. 3 replicates	0.1%, 0.2-1% (identification limit) 120 % of shelf life acceptance criteria Placebo or drug substance are spiked with known quantities of degradants. 3 replicates each = 9 results	=preliminary
Dissolution	Q, 3 replicates	Q-30%, Q, Q+30%, 3 replicates each = 9 results	=preliminary

Repeatability

Repeatability expresses the precision under the same operating conditions over a short interval of time.

Repeatability should be assessed using

- a minimum of 9 determinations covering the specified range for the procedure or
- a minimum of 6 determinations at 100 % of test concentration.

Compound	Orientational	Preliminary	Complete
Drug substance Drug product Impurities and degradants	No repeatability No repeatability No repeatability	Data from accuracy Data from accuracy Data from accuracy	Intermediate precision instead of repeatability

Intermediate precision

Intermediate precision expresses within laboratory variations:

- different day,
- different analyst,
- different equipment

It is not considered to study these effects individually

Intermediate precision is determined under complete validation

Compound	Performance	Required data[1]
Drug substance Assay 100%	Two analysts with 6 replicates each = 12 determinations	X_{12} SD RSD
Impurities	It should be considered carefully depending on RSD of repeatability. Corresponding amount of degradation product acceptance criteria) is added to placebo or drug product Two analysts with 6 replicates each = 12 determinations	If RSD ≥ 5% the statistical evaluation is not performed, otherwise as assay
Drug product Assay 100%	Two analysts with 6 replicates each = 12 determinations	X_{12} SD RSD
Degradation product	It should be considered carefully depending on RSD of repeatability. Corresponding amount of degradation product (shelf life acceptance criteria) is added to placebo or drug product Two analysts with 6 replicates each = 12 determinations	If RSD ≥ 5% the statistical evaluation is not performed, otherwise as assay

[1]Statistical evaluation may be necessary according to Anderson S., Hauck WW (2)

Robustness

Robustness should show the reliability of an analysis with respect to deliberate variations in method parameters.

- Examples:

  Stability of analytical solutions
  - Extraction time

- Examples for HPLC
  - influence of pH on mobile phase
  - influence of variations in mobile phase composition
  - different columns
  - temperature
  - flow rate

Orientational and preliminary	Complete
Stability of analytical solutions	Influence of chromatographic variations

Validation of formulation with several strengths:

The extend of validation can be reduced if several strengths of a formulation have to be investigated. If the final concentration of the analyte is the same after sample preparation the validation can be limited to one strength. Selected is the most unfavourable (e.g. ratio of active ingredient: excipient). If more than three strengths have to be analysed the concept of bracketing can be applied by selecting the two extreme strengths, highest and lowest.

If several strengths are intended to be submitted and marketed the complete validation for each strength should be performed.

The following table gives an overview on the extend and performance of the validation for step 1 and 2.

Validation characteristic	**Step of validation**	
	Step 1 **Clinical phase I**	**Step 2 preliminary** **Clinical phase II,III**
Specificity	• lowest strength • bracketing	• lowest strength • bracketing
Linearity	• assay: 50 - 150% of test solution • degradation products: 0.1- 2% if degradation unknown, reference to drug substance	• assay: 50 - 150% of test solution • degradation products: 0.1-120 % (shelf life acceptance criteria)
Reporting threshold	• 0.1% of lowest strength	• bracketing: 0.1%of lowest and highest strength
Accuracy	• lowest strength: - assay 100% 3 replicates - degradation product: 0.1% 3 replicates • dissolution: Q, 3 replicates • bracketing additionally assay 100% of highest strength	• lowest strength: - assay: 70,100,130%, 3 replicates - degradation product: 0.1%, identification threshold, 120% shelf life acceptance criteria, 3 replicates • Dissolution: Q - 30%, Q + 30% • bracketing additionally assay of highest strength
Range	-	• assay: 70, 100, 130% • degradation product: 0.1%,identifivation threshold, 120% shelf life acceptance criteria
Repeatability	-	Derived from data of accuracy/range = 9 determinations
Robustness	• lowest strength • bracketing, additionally highest strength	• bracketing, lowest and highest strength

In part 4 documents a complete validation report is presented,

2.4 Specifications and Acceptance Criteria

2.4 Specifications and Acceptance Criteria

A specification is defined as a list of tests,
references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges or other criteria for the tests described.

It establishes the set of criteria to which the new drug substance or new drug product should conform to be considered acceptable for its intended use (1).

When a specification is first proposed, justification should be presented for each procedure and acceptance criteria included.

The justification should refer to relevant development data, pharmacopoeial standards, test results used in toxicology and clinical studies and results from stress, accelerated and long term stability studies as appropriate. Additionally a reasonable range of expected analytical and manufacturing variability should be considered

2.4 Specifications and Acceptance Criteria

Specifications are a decisive part of a total control strategy for the drug substance and drug product designed to ensure quality and consistency. Other parts of this strategy are**:**

- product characterisation during development, upon which specifications are based,
- adherence to GMP,
- a validated manufacturing process,
- validated analytical procedures,
- comprehensive stability testing

2.4 Specifications and Acceptance Criteria

In the end of development the new drug product is described by its quality of design with acceptance criteria for all test attributes and a validated manufacturing process for batches which should be at least pilot scale

Specifications after marketing authorisation are binding quality standards that are agreed to between the appropriate governmental agency and the applicant.

Consequently changes in the specification after approval may need prior approval by the regulatory authority.

Four steps for Specifications

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 focusing on safety and efficacy
Production batches after Marketing authorisation	Post-approval	Experience gained with manufacture of a particular drug substance or drug product

2.4 Specifications and Acceptance Criteria

For all four steps it has to be differentiated between

- **release specification**
- **shelf life specification.**

This concept of different acceptance criteria for release versus shelf life specifications applies to drug products only, not for drug substances.

- In the EU there is a regulatory requirement for distinct specifications for release and shelf life,
- in Japan and the USA this concept may be applicable to
  - in-house criteria (release specification), not to the regulatory release criteria (shelf life specification)

2.4 Specifications and Acceptance Criteria

Release specifications describe the quality after manufacture and include

- analytical variability
- manufacturing variability.

The variability is described by:

- RSD of repeatability or intermediate precision of the analytical procedure. Accordingly validation has to be performed, preliminary or complete.
- data of ≥ 3 batches to describe the manufacturing variability.

Shelf life specification describe the quality at the end of the shelf life and include:

- tolerable changes during storage and shipment.

Therefore corresponding stability data am required with organoleptical, physico-chemical, chemical and microbial tolerable changes.

2.4 Specifications and Acceptance Criteria

If testing specifications are submitted in the course of an IND or CTX documentation

It has to be stated very clearly:

The corresponding specifications are orientational or preliminary and may be cause of change during further development.

2.4 Specifications and Acceptance Criteria

❒ **Specifications in pharmacopoeias are always shelf life specifications**

In many cases they are not appropriate to secure the consistency of the quality.

An example is given:

- Disintegration time of tablets < 15 min as shelf life specification.
- The actual disintegration time may be
  min, correspondingly

➔ Release specification: ≤ 6 min.

It is not easy to derive the release specifications in the course of development-

but it is even more difficult fixing the shelf life specifications.

2.4 Specifications and Acceptance Criteria

Strictly speaking precise data are available not before the anticipated shelf life has been reached, e.g.

- two years after submission.

In reality this is not acceptable.:

- A systematically structured stability schedule is required with stress-and accelerated testing during development.

- From the stated changes shelf life specifications are fixed for the registration batches latest at the time of submission.

As a first step on this way it has to be investigated :

- whether a statistically significant change has taken place.

This is based on the confidence interval of the analytical procedures for the physico-chemical and chemical test attributes

Overview on the available data and information to derive the respective specification

Specifications

Statements	Orientational	Preliminary	Registration	Post-approval
Step of development	2-3	3	3-4	5-6
Stage of development	Formulation finding	Clinical phases II/III	Registration batches	• On-going • Running production
Formulation/ composition	Formulation finding	• preliminary • final	• final	• final • variations
Batch size	• laboratory	• pilot plant	• pilot plant • production	• production
Strengths	>3	preliminary >3	final ≥1	final ≥1
Manufacturing process	experimental not validated	preliminary partly validated	simulating final completely validated	final manufacturing process
Number of batches	>1	>3	>3	>3
Analytical procedure	orientational validation	preliminary validation	complete validated	complete validated
Stability data	• Stability profile drug substance • Stress-and accelerated testing - laboratory batches - clinical trial batches phase I	• Stress- and accelerated testing Clinical trial batches phases II/III • Confirmation at 25°C/60% Clinical trial batches phases I/II	• Stress- and accelerated testing Final formulation (clinical trial batches phase III) • Confirmation at 25°C/60% clinical phases II/III	• Accelerated- and long term testing • On-going registration batches • On-going production batches • Follow-up stability testing

2.4.1 Drug substance

❒ Description

A qualitative statement about the state (solid, liquid) and colour of the drug substance. Possible changes caused by stress testing have to be investigated for acceptance.

❒ Identification

Identification test should be specific

- HPLC/UV diode array,
- HPLC/MS,
- GC/MS.

If the new drug is a salt:
identification should be done for the individual ions.

2.4.1 Drug substance

❒ Particle size

Acceptance criteria are not required for:

- liquid dosage forms

Acceptance criteria are set if:

- particle size is critical to

  - dissolution,
  - solubility,
  - bioavailability,
  - drug product processability,
  - drug product stability,
  - drug product content uniformity.

If drug substance is milled acceptance criteria are fixed for the milled drug substance**.**

Where critical, the particle size distribution may be specified by upper and/or lower limits and the mean. The acceptance criteria should be justified by the results of the complete particle size distribution of pivotal batches used in toxicological and chemical trials and bioavailability/bioequivalence studies.

2.4.1 Drug substance

❒ **Particle size cont.**

Where critical, the particle size distribution specified by

- upper and/or lower limits and
- the mean.

The acceptance criteria should be justified by

- the results of the complete particle size distribution of pivotal batches used in toxicological and chemical trials and bioavailability/bioequivalence studies.

2.4.1 Drug substance

❒ **Particle size cont.:**

The acceptance criteria depend on the applied analytical procedure as:

- sieve,
- air jet sieving,
- laser granulometry.

Accordingly the results of the different procedures are

- not. comparable,
- cross validation is not possible because no reference standard is available.

Acceptance criteria are not required if:

- particle size has no influence on quality,
- the drug substance is dissolved in the course of the manufacturing process.

2.4.1 Drug substance

☐ **Solid state forms:**

Drug substance may exists in different solid state forms (polymorphs or solvates)

- which may differ in physical properties.

In cases where differences exist which have been shown to effect :

- drug product performance,
- bioavailability or
- stability,
  - then the appropriate solid state should be specified.

(The drug product may be controlled by dissolution since it is difficult or impossible to measure polymorph content in the drug product)

☐ **Assay**

Acceptance criteria: 100 % ± 1%
100 % ± 2 % (with justification)

- A single assay for free acid/base is sufficient.
- For salts, a single assay may be sufficient (e.g. the therapeutic moiety or the counter Ion).
- Both moieties must be assayed if stoichiometry is not reproducible

The acceptance criterion for assay can be fixed in the early stage of development.

It may not change.

2.4.1 Drug substance

❒ Impurities

Refer to the ICH Guidelines for detailed information:

- "Impurities in New Drug Substances",
- "Residual Solvents in Pharmaceuticals"

Impurities are classified as:

- organic impurities (process- and drug related)
- inorganic impurities
- residual solvents.

☐ Organic impurities include:

- unidentified
- identified
- specified
  - unidentified
  - identified
- qualified

☐ Specifications should include:

- Each specified identified impurity
- Each specified unidentified impurity $> 0.1\%$
- Any unspecified impurity, with a limit of $\leq 0.1\%$
- Total impurities $\leq 2\%$

❒ Prediction of impurities likely to occur in commercial product based on:

- Stability studies,
- Chemical development studies,
- Routine batch analysis.

Where no safety concern impurity specifications should be based on

- data generated on actual batches
- allowing sufficient latitude to deal with normal manufacturing and analytical variation.

The qualification thresholds for impurities are:

Maximum daily dose	Qualification threshold
≤ 2g/day	0.1% or 1mg per day intake (whichever is lower)
> 2g/day	0.05%

- Reporting threshold: ≤ 2g/day 0.05%
- Impurities limited at higher levels may have higher quantitation limit.

Impurities > 0.1% should be quantified and identified. Identification of impurities ≤ 0.1% (response factor of the drug substance) is generally considered not necessary.
Levels of impurities ≤ the reporting threshold need not to be reported (0.05 %).

2.4.1 Drug substance

☐ Acceptance criteria for impurities

Establishing acceptance criteria for a specified impurity in a new drug substance:

- Determine mean + upper confidence limit for the impurity = A.
  - Upper confidence limit = three times
  standard deviation of batch analysis data.

  Example:

  % impurity: 0.12, 0.09, 0.13, 0.14, 0.11

  $\bar{x}_5$:0.12, SD: 0.019, 3 x SD: 0.058
  A: 0.12 + 0.058 = 0.18

- Estimate maximum increase in impurity at retest date using data from relevant accelerated and long term stability data = B.

  Example: B: 0.2 %

  Acceptance criterion:

  A + B = 0.18 + 0.2 = 0.38
  if A + B $\leq$ qualified level

❒ Chiral impurities:

For chiral impurities acceptance limits of

$\leq$ 0.5 % rather than 0.1%

are acceptable if that Is the limit of analytical separation technology.

Higher limits would have to be justified.

If it is difficult to effect control of the drug substance itself, assurance of control could be given by appropriate

- testing of starting material or
- intermediate,

with suitable justification.
The following table summarises how Impurities in new drug substances should be handled in the different steps of development.

Impurities in new drug substances

Step of Development	Batches	Reference substances	Stage of validation	Reporting threshold	Impurities reported	Impurities identified	Impurities specified
Predevelopment < 1	First laboratory samples	Starting materials, intermediates if isolated	orientational	0.05%	>0.05%	–	–
1	Batches for safety studies	Starting intermediates if isolated	preliminary	0.05%	>0.05%	>0.1%	–
1	Stress testing with drug substances	Unstressed samples	orientational, preliminary	0.05%	>0.05%	≥0.5% at 5-10% >0.1% at <5%	–
2-3	Optimisation	Starting materials, key intermediates if isolated	preliminary	0.05%	>0.05%	>0.1%	–
3	Up-scaling	Starting materials, key intermediates, final intermediates if isolated	preliminary	0.05%	>0.05%	>0.1%	–
4	Registration batches Representative of proposed commercial process	Starting materials, key intermediates, final intermediates	complete	0.05%	>0.05%	>0.1%	Identified >0.1%, unidentified, qualified >0.1% unspecified ≤ 0.1% total ≤2% >0.1%

2.4.1 Drug substance

❒ **Residual Solvents**

According to the ICH Guideline they are classified as:

- Class 1: unacceptable toxicities

  - solvents to be avoided

- Class 2: less severe toxicity

  - solvents to be limited

- Class 3: less toxic solvents

  - no health-based exposure limit will be needed.

- Limits for class 2 are necessary,

- Class 3up to 0.5 % can be determined by loss on drying..

2.2.1 Drug substance

❒ Microbial properties, microbial limits

There may be a need to specify:

- total count of aerobic microorganisms,

- total count of yeasts and molds,

- absence of specific objectionable bacteria.

2.4.1.1 Reference Standards

Reference standards must be characterised according to the intended use.

- **Primary Standard:**

  Material which is accepted without reference to other standards.

  - It must have undergone complete analytical characterisation,
  - its identity must be proven (elucidation of chemical structure) ,
  - its purity must be sufficiently high and stated (> 99 %).

  Respective purification is not required:

  - related substances total 0.1%
  - residual solvents 0.05 %
  - assay: titration, DSC, chromatography.

It is acceptable that the manufacturing process of the primary standard differs from the final process of the drug substance.

- **Working Standard:**

  Material is designed for daily use in instrumental analysis such as routine quality control.

  It is characterised by:

  - comparison with the primary standard,
  - is of appropriate purity corresponding to a 'typical" batch.

❒ **Pharmacopoeial Standard:**

It is commonly used for certain tests and assays to achieve

- accuracy and precision of analytical results required in compendial monographs. It can be used only for the purpose for which it is intended. The same applies to other official standards.

❒ **Impurity Standard:**

This material is mainly needed for development and
analytical procedures (selectivity, recovery, reporting threshold, response factor compared to drug substance).

They are characterised to the extend necessary.

Impurity levels can be measured using the response factor compared to drug substance

All reference standards must be stored and used in a manner that will not adversely affect their quality and their stability. These aspects should be monitored by periodic examination.

2.4.2 Drug products

2.4.2.1 Tablets

❒ **Description appearance**

A qualitative description should be provided (size, shape, colour).

The acceptance criteria should include:

- the final acceptable appearance,
- that means also possible changes during storage.

If colour changes occur during storage a quantitative procedure may be appropriate. Most helpful and easy to handle am colour charts (3) where are differentiated:

- colour shade
- colour intensity
- depth of shade

The appearance can be described precisely and especially changes during storage can be followed easily.

2.4.2.1 Tablets

❒ Description appearance cont.:

To include changes in appearance in the acceptance criteria,

- samples are stressed to see, whether a change takes place,
- whether this change is tolerable.

The description of a tablet may be:

- release specification: white to off-white 1A
- shelf life specification: slightly brownish 4A2

❒ Identification

Identification testing should establish:

- the identity of the new drug substance in the new drug product,
- It should be specific for the new drug substance:
  - infrared spectroscopy or,
  - HPLC/UV-diode array

Usually comparison with reference standard.

2.4.2.1 Tablets

❒ **(uniformity of mass) Average mass**

Average mass is a test criteria for stability testing.

Adsorption or desorption of water is persued.

Loss or gain of water may cause changes in:

- appearance,
- hardness,
- disintegration time,
- dissolution,
- assay,
- decomposition,
- microbial properties.

The shelf life acceptance criterion is derived from the data of open. storage of samples at

- 25°C/60 % r.h.,
- 30°C/65%r.h.,
- 40°C/75 % r.h..

2.4.2.1 Tablets

❒ **(uniformity of mass) Average mass, cont.:**

Before the acceptance criterion is fixed, its influence must be known on:

- organoleptical,
- physico-chemical,
- chemical
- microbial properties

Mostly the acceptance criterion is one-sided, since loss in water can be usually tolerated.

Shelf life acceptance criterion: $\bar{x}20 + x\%$

❒ Hardness

It was found that each change in water content causes a change in hardness (4).

Mostly water adsorption means decrease in hardness.

Graphic of log hardness [N] versus increase in mass yields a straight line (5).

- It is therefore possible to Interpolate and extrapolate.

2.4.2.1 Tablets

❒ Hardness cont.

It is normally appropriate to perform hardness testing as an

- inprocess control test and
- during stability testing.

In stability testing the data should be presented as follows:

$\bar{x}10$, RSD

Thereby a significant change can always be determined.

Hardness is usually an IPC test attribute.

If it is a release test criteria the data may be differently:

$\bar{x}_{1O}$, $X_{maximum}$, $X_{minimum}$

If $X_{maximum}$ and $X_{minimum}$ are part of the acceptance criteria a statistical procedure should be included with two stages.

2.4.2.1 Tablets

❒ Hardness cont.

- Shelf life acceptance criterion

  $\bar{x}_{10} \geq 25$ N.

With this limit it is usually possible

- to push tablets out of a blister pack without breaking

On the base of this limit the release acceptance criterion ran be derived:

Tablets at an early stage of development are stored in the open at 25°C/60%, 30'C/65 %, and 40°C/75 %
until equilibrium is reached (2 - 4 weeks).
Then the change in hardness is determined:

- **Preliminary release specification:**

  $\bar{x}_{10}$, initial - change by adsorption $\geq$30 N.

  With this preliminary limit the tablet formulation is optimised in the pilot plant and the stress test repeated**:**

  $\bar{x}_{10}$, initial - change by adsorption $\geq$ 25 N.

Further considerations:

- packaging material proposed for marketing
- composition, manufacturing equipment
- influence of hardness on disintegration time or dissolution.

2.4.2.1 Tablets

❒ Disintegration

Shelf life acceptance criterion is fixed in the pharmacopoeias for tablets as:

- disintegration time $\leq$ 15 min.

The release acceptance criteria are derived stepwise:

- Orientational release target value:

  $\geq$ 3 batches x + 3x SD

  Example: $\bar{x}_6$: 3.5, 4.2, 1.9 min

  $\bar{x}_3$:3.2 min, SD: 1.2 x 3 = 3.6, 3.2 + 3.6 = 6.6 min $\cong$ 7min.

- Preliminary release specification

  > 6 batches, $\bar{x}$ + 3 SD

- Registration release acceptance criterion:

  pivotal-, pilot plant, registration batches

  $\bar{x}_6$+ 3 SD

In stability testing the data presented as follows:

$\bar{x}_6$, RSD

For release the data presented as follows:

$\bar{x}_6$, $x_{maximum}$, $x_{minimum}$, RSD

2.4.2.1 Tablets

❒ Dissolution

Deriving specifications it has to be differentiated between following forms:

- Rapidly dissolving immediate-release dosage forms:

Disintegration testing sometimes sufficient.

For this type of products an in vivo - in vitro correlation may not be possible.

- Immediately release dosage forms with a range for dissolution:

  75 - 85 % (Q + 5) after 30 - 60 minutes.

If the product is poorly water soluble an in vitro - in vivo correlation may be possible, otherwise not.

A correlation has always considerable advantages:

The in vitro test serves as a tool to distinguish between acceptable and unacceptable drug products.

Acceptable products are bioequivalent in terms of in vivo performance, whereas unacceptable products are not.

2.4.2.1 Tablets

❒ Dissolution, vivo-vitro correlation

To establish an in vitro- in vivo correlation, at least three batches should be available that differ in the

- in vivo as well as in the
- in vitro performance

Where a drug substance with low solubility has been developed into an immediate-release product with satisfying dissolution performance it may be difficult

➔ to provide the corresponding „side batches“

If the batches show differences only in the in vivo performance

➔ then the in vitro test conditions can be modified.

- Often the in vitro dissolution test is more sensitive and discriminating than the in vivo test.
- Thereby the test will indicate possible changes in the quality of the product before in vivo performance is effected.
- Over discrimination however may also mean that performance batches are rejected but would have good in vivo

2.4.2.1 Tablets

❒ **Dissolution, vivo-vitro correlation cont.:**

- Modified-release dosage forms
  - extended release
  - delayed release.

These products are generally better candidates for establishing

- in vitro- in vivo comparison

In these cases, normally,

- dissolution
- not absorption is the rate limiting step.

For extended-release products the categories of in vitro - in vivo correlation of the USP/FDA should be used.

2.4.2.1 Tablets

❒ USP/FDA categories vitro - in vivo

- Level A

A level A correlation is usually estimated by a two stage procedure: deconvolution followed by comparison of a fraction of drug adsorbed to the fraction of drug dissolved.

An alternative is based on a convolution procedure that models the relationship between in vitro dissolution and plasma concentration in a single step.

- Level B

A level B correlation uses the principles of statistical moment analysis. The mean in vitro dissolution time is compared either to the mean residence lime or to the mean in vivo dissolution time. A level B correlation does not uniquely reflect the actual in vivo plasma level curve, because a number of different in vivo curves will produce similar mean residence time values.

- Level C

A level C correlation establishes a single point relation-ship between a dissolution parameter.

Consequently a level C correlation does not reflect the complete shape of the plasma concentration curve, which in the critical factor that defines the performance of extended-release products.

2.4.2.1 Tablets

❒ Dissolution materials and methods

- Apparatus:

  basket method (apparatus 1) with 50-100 rpm stirring speed
  paddle method (apparatus 2) with 50/75 rpm stirring speed
  flow through cell system (apparatus 5)

- Volume:

  500, 900, 1000 ml

- Sink conditions:

  desirable but not mandatory.

- Medium:

  aqueous solutions

  - pH 1 (0.1 M HCI)
  - pH 4.5 (0.05 M acetate buffer or 0.05 M phosphate buffer)
  - pH 5.8 - 8 (0.05 M phosphate buffer)
    pH 6.8 should be always included.

  In special cases:

  - simulated gastric juice, pH 1.2 and pepsin may be appropriate for gelatine capsules
  - 1% sodium lauryl sulphate may be appropriate for poorly soluble drugs

2.4.2.1 Tablets

❒ **Dissolution: Setting Specifications**

- **Rapidly dissolving immediate release-dosage forms:**

  - Drug solubility high throughout physiological pH range pH 1 - 6.8
  - dose + solubility < 250 ml.

  - Dissolution > 80 % 15 minutes at pH 1, 4.5,
    6.8.

  - Relationship between disintegration and dissolution

  - disintegration acceptance criteria are established

2.4.2.1 Tablets

❒ **Dissolution: Setting Specifications**

- Immediate release dosage forms

Anticipated release range:

➔ 75 to 80% (Q) of label content within 30 - 60 min.

The relevant medium should be chosen to reach the anticipated release range.

If the dissolution test acceptance criterion is ≥60 minutes, a two point acceptance criterion should be fixed,

- one at 15 minutes with a range and
- the second at the later point of ≥60 minutes.

During development and for submission a profile of the dissolution should be prepared at 15 minutes intervals.

2.4.2.1 Tablets

❒ **Dissolution, Setting specification**

BP and USP requirements

Pharmacopoeia	Stage	Number tested	Acceptance criteria
USP BP	S1 S1	6 6	all ≥ Q + 5% all ≥ 70 % after 45 min
USP BP	S2 S2	6 6	$\bar{x}_{12} \geq Q$, none < Q - 15% all ≥ 70 % after 45 min
USP BP	S3 No S3	12 --	$\bar{x}_{24} \geq Q$, not more than 2 < Q - 15%, none < Q -25%, --

As long as the requirements are not harmonised the acceptance criteria should be set as follows:

- After x minutes not less than % of the stated content.
  Complies with the stages S1 and S2 of USP.

  The results are presented as follows:

- Release: S1: all $\geq$ Q + 5 %

  S2: S1 + S2: $\bar{x}12 \geq$ Q, $\leq$ one Q - 15 %

-Stability: $\bar{x}_6$ + RSD or $\bar{x}_{12}$ + RSD.

2.4.2.1 Tablets

❒ **Dissolution Setting specification, cont.**

The product is expected to comply with dissolution specification ,throughout its shelf life.

If dissolution characteristics change with time, whether or not the specification should be altered will depend on
➔ demonstrating bioequivalence of the changed product to the original biobatch or pivotal batch.

To ensure continuous batch to batch equivalence after scale up and post approval changes,
➔ dissolution profile should remain comparable. to those of the approved biobatch or pivotal clinical trial batch(es).

Generally for submission the dissolution specifications should be based on

- acceptable clinical pivotal bioavailability
- and/or bioequivalence batches.
- The three. registration batches (two pilot and one smaller scale) may also be used to set dissolution specification, provided a suitable bioequivalence relationship exists between theses batches and both the pivotal clinical trial batch and the drug product intended for the market.

2.4.2.1 Tablets

❒ **Dissolution, Setting Specification, cont.**

- **Modified release dosage forms**
- **Extended release dosage forms**

The in vitro dissolution methology should adequately discriminate among formulations.

Dissolution testing can be carried out during the formulation screening stage using several methods.

Once a discriminating system is developed,

- dissolution conditions should be the same for all formulations tested in the biostudy for development of the correlation and
- should be fixed before further steps towards correlation evaluation are undertaken.

2.4.2.1 Tablets

❒ Setting dissolution specifications without in vivo-in vitro correlation:

Specifications should be established on clinical/bio-availability lots. Widening specifications based on

- scale-up,
- stability,
- or other lots

for which bioavailability data are not available is not recommended.

A minimum of three time points is recommended to set the specification. These time points should cover

- the early,
- middle,
- later stages of the dissolution profile.
- The last time point should be the time point, where at least 80 % of drug has dissolved.

The recommended range of any dissolution time point is ± 10 % (absolute) deviation from the mean dissolution profile.
In certain cases reasonable deviations from the ± 10% range can be accepted provided that the range at any time point does not exceed 25%

Specifications should be established based on average dissolution data for each lot equivalent to USP stage 3 testing

2.4.2.1 Tablets

❒ Setting dissolution specifications without in vivo-in vitro correlation, cont.:

The following acceptance table according to USP 25 <724 should be applied

Stage	Number	Acceptance criteria
L1	6	No individual value outside stated ranges, no individual value less than stated amount at final test time
L2	12	X_{12} (L1 + L2) within stated ranges and not less than the stated amount at the final test time. None more than 10% of labelled content outside each of stated ranges, none is more than 10% of labelled content below stated content an final test time
L3	24	X_{24} (L1 + L2 + L3) within stated ranges and not less than the stated amount at the final test time Not more than 2 of 24 are more than 10% of labelled content outside each of stated ranges, not more than 2 of 24 are more than 10% of labelled amount at final test time, none is more than 20% of labelled content outside each of the stated ranges or more than 20% of labelled content below stated amount at final test time.

2.4.2.1 Tablets

❒ Assay

A specific, stability indicating assay to determine strength should be included for all new drug products.

In many cases it is possible to employ the same analytical procedure for both .

- assay of the new drug substance and
- quantitation of impurities.

If the formulation has shown not to degrade during manufacture it may be permissible to use a spectrophotometric procedure for release.

➔ Acceptance criteria:

- Release: 100 % + 5 % of labelled content.

  If justified an overage for production or stability:

- Shelf life: 100 % + 5%,-10% of labelled content.

- The shelf life specification must be justified by actual stability data.

2.4.2.1 Tablets

❒ Decomposition (Impurities)

In drug products only those impurities are followed which are classified as:

- degradation products of the drug substance.
- reaction products of the drug substance with excipient
- reaction products of the drug substance with immediate container/closure system.

Impurities present in the new drug substance need not to be monitored in drug products unless they are also degradation products.

The ICH Guidelines "Impurities in New Drug Products" do not address the regulation of drug products used during the clinical research stages of development. But the rationale, for the reporting and control of impurities should summarise any laboratory studies conducted to detect degradation products in the drug product including:

- test results of batches manufactured during the development process,
- batches representative of the proposed commercial process

The systematic approach of the .strategic planning is very effective in reporting and control of degradation products in drug products.

2.4.2.1 Tablets

❒ **The following influencing factors are investigated in the different steps of development**:

Step	Investigations	Influencing factors
1	Drug substance stability profile	Temperature, moisture, pH, ionic strength, light, O_2
2	Compatibility tests	Temperature, excipients
3	Stress tests with selected batches including clinical batches for phase I-III. Drug product stability profile	Temperature, light, moisture, excipients, batch size, packaging material
4	Accelerated- and long term testing with registration batches	Storage conditions 40/75%, 25°C/60%, 30°C/65%

2.4.2.1 Tablets

❒ **Specifications for degradation products in the course of development:**

Step	Investigations	Reporting threshold	Identification threshold
2	Compatibility tests	>0.1%	>0.5%
3	Stress tests with selected batches Including clinical batches phase I-III	>0.1%	>0.1% >1% depending on maximum daily dose
4	Accelerated and long term testing with registration batches	>0.1%	>1% (< 1mg) >0.5% (1-10 mg) >0.2% (>10mg-2g) >0.1% (>2g)

If degradation takes place measures should be considered to reduce or prevent it

2.4.2.1 Tablets

❒ **Possibilities to reduce degradation:**

Influencing factor	Measure
light	light protecting container closure system
O_2	N_2 gassing, antioxidant
moisture	tight container
Temperature	Reaction kinetic calculation

2.4.2.1 Tablets

❒ **Pursue of degradation products**

Only degradation observed in stability studies at recommended storage conditions should be pursued. Therefore reaction kinetic calculation from stress data is very helpful.

The following storage conditions must be considered:

Storage condition	Storage period [months]
40°C/75%	6
30°C/65%	12[1] (24-60)[2]
25°C/60%	12-60

[1]only if significant change at 40°C/75 % r.h.
[2] only if distribution in climatic zones III and I
If storage instructions are required in the label then the recommended storage condition is decisive to pursue degradation products.

2.4.2.1 Tablets

❒ **Setting specifications for degradation products**

The specifications for the new drug product should include limits for degradation products expected to occur under recommended storage conditions. The following information should be used to characterise the degradation profile:

- stability studies,
- knowledge of degradation pathway,
- product development studies,
- laboratory studies.

Specifications should be set taking into account:

- qualification of the degradation products,
- stability data,
- expected expiry period,
- recommended storage condition,
- normal manufacturing variation
- analytical and stability profile variation.

The specifications should include where applicable limits for:

- each specified degradation product,.
- any unspecified degradation product,
- total degradation products.

2.4.2.1 Tablets

❒ **Degradation, Setting Specification**

The ICH Guideline "Specifications" contains as attachment a decision tree. Establishing acceptance criteria for a degradation product in a new drug product:

- **Release acceptance criteria A + C**

  A = three times the standard deviation of batch analysis data of degradation products in drug substance if any.

C = Estimated increase in degradate during manufacture
from development, pilot and scale-up study batches.

- Shelf life acceptance criteria A + C + D.

D = estimated maximum increase in degradate at shelf life using data from relevant accelerated and long-term stability studies.

If acceptance criterion A + B + C is greater than qualified level:

- acceptance criterion = qualified level or.
- establish new qualified level o r
- new storage conditions.

2.4.2.1 Tablets

❒ **Degradation, Setting Specification cont.:**

With the systematic approach of the strategic planning the estimated maximum increase in degradate will be calculated from the data of stress investigations.

Also qualification of the individual degradation products or a given degradation profile at least at the level specified should have been performed during development studies with a stressed sample.

To reach mass-balance as closely as possible the acceptance criteria should include a limit for degraded active ingredient:

- Limit for degradation product A: 0.5 %
- Limit for degradation product B: 1.0 %

- Relative mol mass active ingredient: 520
- Relative mol mass degradation product A:449
- Relative mol mass degradation product B:472
- Ratio of the relative mol mass:

$$\frac{520}{449} = 1.16 \qquad \frac{520}{472} = 1.1$$

Total degraded active ingredient:

- degraded to A: 0.5 % x 1.16 = 0.58 %
- degraded to B: I.0% x 1.1 =1.1%
- Total 0.58 % + 1.1% = 1.68 % =1.7

2.4.2.1 Tablets

❒ Residual solvents

Testing should be performed when production or purification processes are known to result in presence of such solvents.

If the calculation results in levels below that
recommended in the ICH Guideline "Residual solvents" no testing need to be considered.

However drug products should be tested if a
class 1 or class 2 used in manufacture of purification of drug substance, excipients or drug product.

For class 3 solvents a non specific method such as loss on drying may be used.

2.4.2.1 Tablets

❒ Microbial limits

It is advisable to test the tablets unless its components am tested before manufacture and the manufacturing process is known, through validation studies, not to carry any risk of microbial contamination. Skip testing may be an appropriate approach.

Acceptance Criteria

- total count of aerobic microorganism
- total count of yeasts and molds
- absence of specific objectionable bacteria .

With acceptable scientific justification, it may be possible to propose no limit testing for solid oral dosage forma.

If the drug product is a dry dosage form and scientific evidence is provided, demonstrating growth inhibitory properties of the drug product microbial limits acceptance criteria and testing may not be necessary.

2.4.3 Testing Specifications

❒ **The Testing Specifications combine:**

- test attributes,
- analytical procedures,
- acceptance criteria

They accompany the development of the drug product within the six steps.

❒ **Structure and content of the test specifications**

All testing specifications are structured and written likewise.

The testing specifications contain the following elements:

- Table: Assignment of test attributes
  - all test attributes are listed and it is indicated which of them are applied for release and which are applied in stability testing.

- Table: Test attributes and acceptance criteria, specifications
  - All test attributes are listed with the corresponding release and shelf life acceptance criteria,
  - thereby it is differentiated between orientational, preliminary, registration and post-approval acceptance criteria

- Table: Test attributes, validation parameter and validation data.
  - This table gives an overview on the validation parameter of the relevant test attributes and the validation data.

After this general information
- the analytical procedures are described for all test attributes which have been developed for the drug substance or the drug product.
- If a monograph exists or the analytical procedure or method is described in a pharmacopoeia, the corresponding pharmacopoeia is cited.

The analytical procedures are described likewise with
- solvents and reagents
- procedure
- evaluation.

2.4.3 Testing Specifications

They contain all the information to apply them successfully as

- calibration curves
- UV spectrum to derive the wavelengths
- chromatograms demonstrating
  - specificity,
  - peak for assay ,
  - reporting threshold

The analytical procedures, the acceptance criteria with the corresponding testing specifications are developed systematically in the steps 1 - 4

In step 4 they are transferred to quality control which elaborates on this basis the testing specifications for quality control.

Therefore the registration application contains two types of testing specifications**:**

- Those which have been applied during development:
  - for release and stability testing of toxicological samples,
  - for release and stability testing of clinical trial samples,
  - for release and stability testing of the registration batches and the on-going stability testing.

These testing specifications are universally applicable and not specific for any country.

- Those which will be applied for quality control of the running production specific to the different requirements of the individual countries**.**

- The analytical procedures are usually equal, the format and the total content different.

In part 4 Documents under 4.1 an example of a complete testing specification for tablets is presented

Selection of test attributes, step of validation, step of specification during development

Step of development		Selection of test attributes		Step of validation		Step of specification	
		Start	Final	Start	Final	Start	Final
1	Stress and accelerated testing with the drug substance	corresponding objective	Selection of test attributes for registration batches	orientational	preliminary	-	preliminary
2	Preformulation and formulation finding	corresponding objective	-	orientational	-		-
3	Stress- and accelerated testing with selected formulations for • Toxicological samples	corresponding objective	-	Orientational (from step 2)	-	orientational	minimum shelf life
	• Clinical trial samples - phase I	corresponding objective (phase I)			-	Orientational (phase I)	minimum shelf life phase I
	- phase Ii/III - final formulation	corresponding objective (phase II/III)	Selection of test attributes for registration batches	preliminary	-	preliminary	preliminary minimum shelf life phase II/III
	• cleaning validation	corresponding objective	-	preliminary	-	preliminary	-
	• scaling up/validation	corresponding objective	Selection of test attributes for registration batches	preliminary	complete	preliminary	registration
4	Accelerated and long term Testing up to registration application	Selected in step 3	-	complete	-	registration	-
5	On-going stability testing	as step 4	-	as step 4	-	registration	-
6	Follow-up stability testing • continuous production • variations and changes	as step 4 corresponding objective	- -	as step 4 revalidation	- complete	final final	final

Testing Specifications in the course of development

	Step of development	Testing Specifications	Time of release
1	Stress- and accelerated testing with the drug substance	Preliminary testing specification for stability testing or the drug substance	After stress-investigations have been completed
2	Preformulation and formulation finding	Orientational testing specifications for the drug product	After investigations have been completed
3	Stress and accelerated testing with selected formulations for		
	• toxicological samples	Orientational testing specifications for release and stability testing of the drug product	Before release of toxicological samples
	• clinical trial samples phase I-III	Preliminary testing Specification for release and stability testing of the drug product with continuous versions as required	For the time being of release of the clinical trial batches for phase I-III
	• cleaning validation	Testing Specification for cleaning validation for the drug product	Before start of investigations
	• scaling -up/validation	Preliminary Testing specification for release and stability testing of the drug product (continuous versions)	After investigations have been completed
4	Accelerated and long term testing	Testing Specification for release and stability testing of the drug product	Before start of stability testing with registration batches
5	On-going stability testing	As for step 4	-
6	Follow-up stability testing	Testing Specification for quality control and stability testing (analytical procedure should be identical to step 4 and 5)	Before start of follow-up stability testing

2.9 Container Closure System

2. 9 Container Closure Systems

Possible influence of test attributes by insufficient Container Closure Systems

Dosage forms	Causes to be considered
Solid dosage forms	• Permeation of moisture • Light with blister
Semi-solid dosage forms	• Permeation of O_2 • Permeation of flavour • Sorption of preservatives • Interaction with internal lacquering
Liquid dosage form	• Permeation of moisture • Permeation of O_2 • Sorption of preservatives • Interaction with glass • pH shift • Precipitation • Light penetration • Interaction with elastomers - sorption - desorption - permeation

2.9.1 The main packaging materials

Plastics

Elastomers

Glass

Metal

2.9.1.1 Plastics

Most applied materials

- **Polyethylene PE**
  - High pressure polyethylene (HD-PE), large amorphous portion, density 0.92, melting range ca. 110°C.
  - Low pressure polyethylene (ND-PE), low amorphous portion, density 0.95, melting range ca. 135°C.
  - Linear polyethylene low density (LLD-PE), low value of migration and sorption, higher values for moisture and O_2 permeation, high chemical resistance.

- **Polypropylene (PP)**
  - Density 0.91, melting range ca. 165°C, low amorphous portion, contains stabilisers and antioxidants, lower permeation of moisture than HD-PE

- **Polyethylene terephthalate (PET**)
  high density 1.37

- **Polystyrol**
  High permeation of moisture, brittle, density 1.05

- **Polyvinyl chloride PVC**
  Contains stabiliser monomers are limited to 1 ppm vinylchloride

Problems with its application

- **Permeation**

Transport of moisture, gases, essential oils, flavours through the plastic. The rate of permeation can be described by the

1. Ficks law:: $\frac{dm}{dt} = \frac{DA(C1 - C2)}{d}$

A = cross section in cm^2 or m^2
d = wall sickness in mm or cm

D = diffusions coefficient in $\frac{cm^2}{s}$
m = mass in g or cm^3
t = time in s, min, or h

The permeation of a gas depends on the diffusion and solubility on the plastic material

The solubility of a gas is described by the law of Henry

Law of Henry: C = Lp L 0 solubility coefficient

$$\frac{dm}{dt} = \frac{DLA\,(p1 - p2)}{d}$$

D and L are combined as permeation coefficient: P = LD

This underlines the dependence of the permeation on the solubility and diffusion in the plastic material.
The temperature dependence of permeation on diffusions and solubility coefficient is described by the following equations(1):

$P = Poe^{-Ep/RT}$, $D = Doe^{-ED/RT}$, $L = Loe^{-\Delta Hs/RT}$

Different Plastic Foils	**Permeation of moisture** $[\frac{g}{m^2 \cdot 24\ h}]$	[bezogen auf Polyvinyliden-chlorid ≙ l
Polyvinylidenchlorid	0,4	1,0
Polypropylen biaxial verstreckt	0,7	1,75
Niederdruck-Polyethylen biaxial verstreckt	0,8	2,0
Niederdruck Polyethylen	0,9	2,25
Polypropylen	1,7	4,25
Hochdruck Polyethylen	2,5	6,25
Polyterephthalsäureester/HD-Polyethylen 12/50 µ	2,5	6,25
Zellglas/HD-Polyethylen (325 µ)	2,6	6,5
Polyterephthalsäureester	5,0	12,5
Zellglas wetterfest (350 µ)	5,1	12,75
Suspension PVC	6,0	15,0
Emulsion PVC	8,0	20,0
Weich PVC 22 % Weichmacher	10,0	25,0
Mipo-Vinylchlorid Vinylacetat	11,0	27,5
Polyamid L-Typ	14,0	35,0
Polystyrol	33	66,0
Polyamid technisch	35	87,5
Polycarbonat	40	100,0
Acetat	250	625

The permeation of O_2 is listed in table 3:

Different plastic foils	O_2 Permeation $\left[\frac{cm^3}{m^2 \cdot 24\ h}\right]$	[bezogen auf Zellglas $\triangleq$ 1]
Zellglas wetterfest (350 µ)	5	1,0
Zellglas/HD-Polyethylen (325 µ)	10	2,0
Polyvinylidenchlorid	10	2,0
Polyterephthalsäureester	29	5,8
Emulsion PVC	75	15,0
Polyterephthalsäureester/HD Polyethylen 12/50 µ	80	16,0
Suspension PVC	117	23,4
Polyamid technisch	130	26,0
Mipo-Vinylchlorid Vinylacetat	160	32,0
Polyamid (L-Typ)	200	40,0
Polypropylen biaxial verstreckt	600	120
Weich PVC 22 % Weichmacher	880	176
Niederdruck Polyethylen biaxial verstreckt	1100	220
Acetat	1200	240
Polypropylen	1470	294
Niederdruck Polyethylen	1500	300
Polycarbonat	1700	340
Polystyrol	2800	560
Hochdruck Polyethylen	3200	640

Table 3: O_2 permeation of plastic foils 40 µm (2).

The temperature dependence of moisture permeation [g/m² · 24 hrs] of polyterephthalate and polyethylene is presented in figure 1 of O_2 permeation m [cm³/m² · 24 hrs] in figure 2:

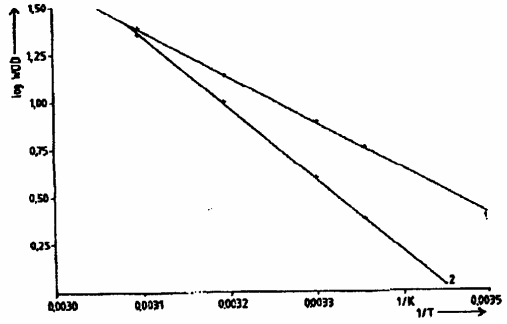


Figure 1: logWDD = f (1/T), WDD = permeation of moisture
1 = polyterephthalate, 2 = polyethylene (2)

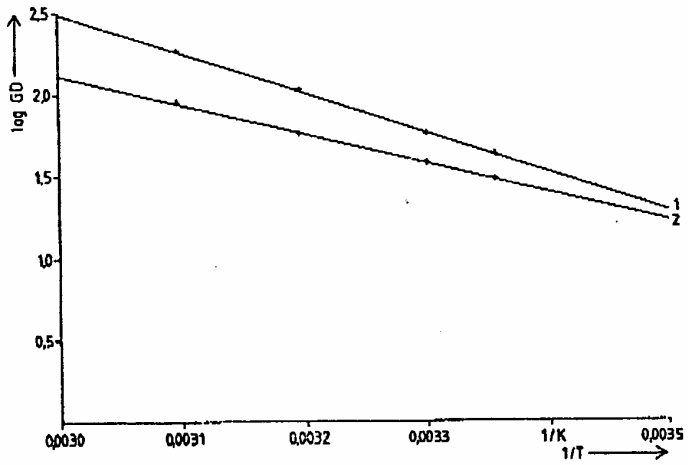


Figure 2: log GD = f (1/T), GL = O_2 permeation
1 = polyethylene, 2 = polyterephthalate (2)

The influence of the degree of cristallinity on permeation of moisture (4,5)

Plastic material	Moisture permeation	Degree if cristallinity
Polyvinylidene chloride	6	very high
Polytetrafluoroethylene	6	very high
Low pressure polyethylene	16	higher
Polyivinyl chloride	128	low
Polystyrol	532	very low

Influence of the thickness of the plastic foil on moisture permeation (4,5)

Thickness of foil polyethylene	Moisture permeation
0.15	2.47
0.1	0.90
0.15	0.816

Moisture permeation of plain and deep drawn foils (2)

Type of foil	Thickness [µm]	Plain [mg/day]	Plain P	Deep drawn [mg/day]	Deep drawn P	Ratio
PVC	250	5.10	1.02	7.93	2.17	2.1
PVC/Polyvinylacetet	250	5.58	1.11	9.81	2.71	2.4
PVC/PVDC	200/60g/m^2	0.62	0.12	0.68	0.18	1.5
PVC/PVDC	200/40g/m^2	0.61	0.12	0.68	0.17	1.4
PVC/PE/PVDC	200/20/40g/m^2	0.80	0.16	1.22	0.34	2.1
PVC/PCTFE	250/19	0.34	0.07	0.53	0.16	2.3

PCTFE= Polycholorotrifluoroethylene

Temperature dependence of moisture permeation (2)

Type of foil	Thickness [µm]	20°C/85%	30°C/75%	Ratio
PVC/PCTFE	250/19	1	3.07	3.1
PVC/PVDC	200/40g/m^2	1.21	4.35	3.6
PVC/PVDC	200/60g/m^2	1.8	5.71	3.2
PVC/PE/PVDC	200/20/40g/m^2	2.0		
PVC	250	14.7	31	2.1

❒ **Sorption**

- Loss of drug substance, preservatives or excipients
- Sorption takes place from the surface in the matrix of the plastic material by diffusion
- Especially the loss of preservatives by sorption ha to be considered
- Often sorption by polyethylene (6)

❒ **Desorption or migration**

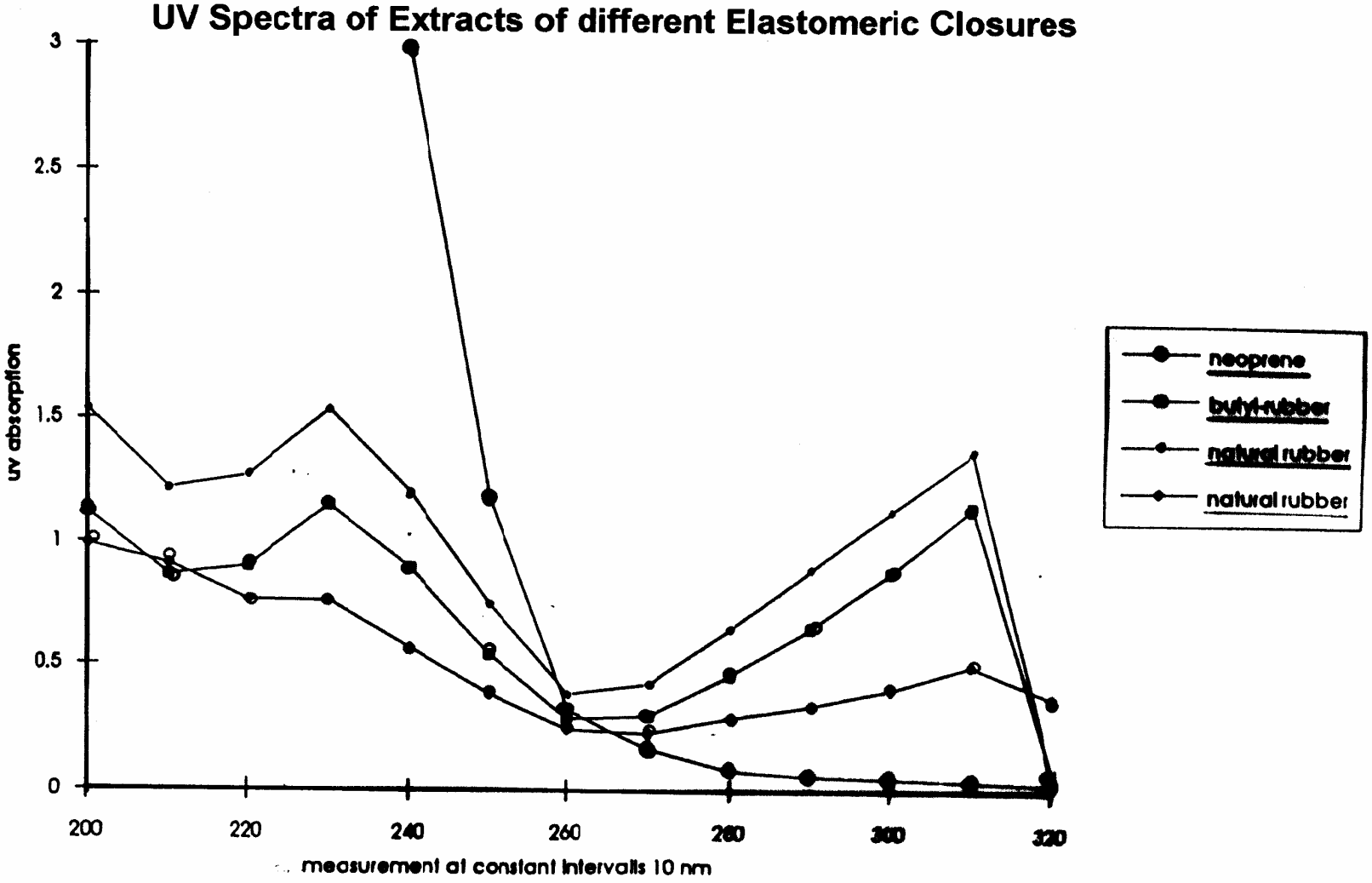
- Migration of components of the packaging materials into the packed product.
- Plastic material may contain monomers or oligomers, traces or catalysts, plastisisers, stabilisers, lubricants, substances added to improve processability and others(7)
- The migration depends on the solvent and the pH.
- The leached components may cause the following instabilities
  - Shift of pH
  - Oxidation or reduction
  - Discoloration of solution
  - Precipitation by interaction with drug substances or excipients

2.9.1.2. Elastomers

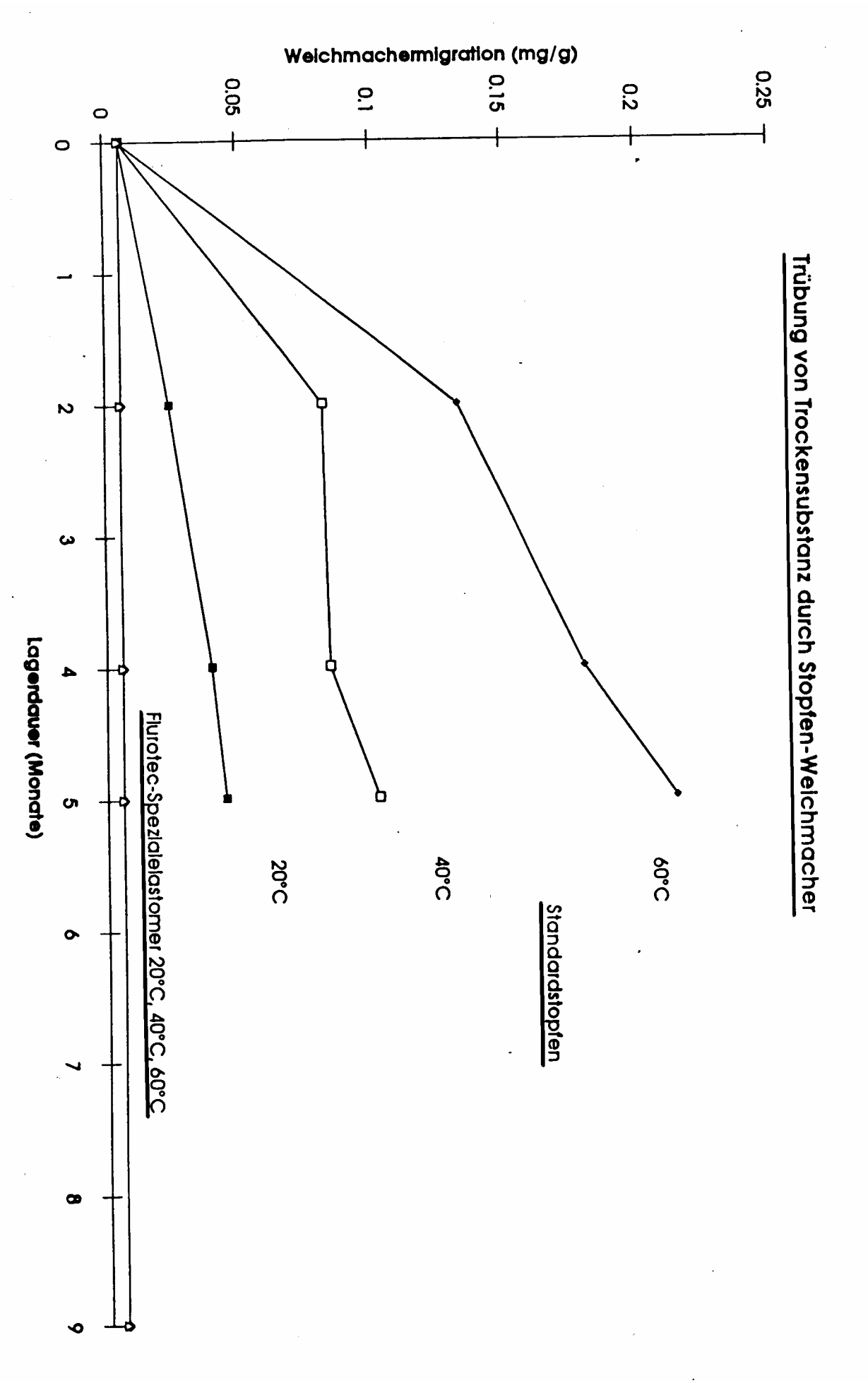
Elastomers have to be considered carefully

❒ **Migration or Leaching**

- Elastomers contain many additives which may migrate into the packed drug product
- Therefore migration or leaching investigations are generally required.
- Migration of consitituents of elastomers such as vulcanising agents should be studied extensively since non-negligible traces may appear short after contact times with the injectable solution (8)



Herrmann D, APV Kurs 158, 4. - 5. Mai 1995 (9)


Trübung von Trockensubstanz durch Stopfen-Welchmacher
Weichmachermigration (mg/g)
0
0.05
0.1
0.15
0.2
0.25
0
1
2
3
4
5
6
7
8
9
Lagerdauer (Monate)
Standardstopfen
60°C
40°C
20°C
Flurotec-Spezialelastomer 20°C, 40°C, 60°C

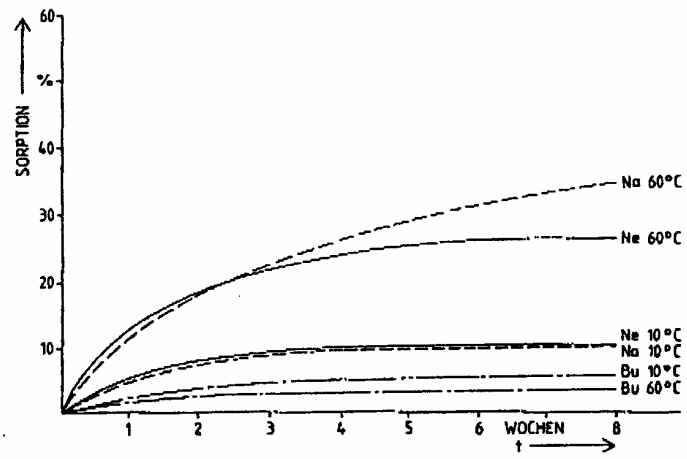


Figure 5: Sorption of benzylalcohol by natural rubber Na, moprene rubber Ne, and butyl rubber Bu at 60°C and 30°C (2).

❒ Permeation

Gas permeation through different types of rubber in ration to natural rubber as 100

Type of rubber	Permeation		
	H_2	O_2	CO_2
Butyl	15	5.6	4.0
Neoprene	27	17	20
Natural	100	100	100

Weight increase by moisture penetration

Type of rubber stopper	Increase in weight (mg/g desiccant)
Butyl	0
Neoprene	8
Natural	7

Residual moisture within stopper material (9)

Individual samples	Stopper Test No:	Batch 54083228	Mean	Stopper Test No:	Batch 54140610	Mean
	[%]	[%]	[%]	[%]	[%]	[%]
Stoppers as on receipt	0.20	0.19	0.19	0.21	0.17	0.19
Stoppers washed, sterilized and dried	0.27	0.21	0.24	0.23	0.20	0.22
As above after storage uncovered overnight (20.25°C/ 30-40%	0.33	0.33	0.33	0.33	Not tested	0.33
Overall mean	0.24					

2.9.1.3 Glass

Three different types of glass concerning changes which may be caused by:

- **Type 1**
  Boron silicate glass
  - low release of Na_2O ions,
  - little pH shift
- **Type 2**
  Sodium lime glass with surface treatment
  - Silicate particles may be released with may cause turbidity
- **Type 3**
  Sodium lime glass without treatment 10 times glass release of Na_2O ions compared to type 1 with corresponding change in pH

Chemical composition of different containers made from glass type 1 (11)

Proportion	Ampulle Röhren-glas	Vial Röhren-glas	Ampulle Röhren-glas	Ampulle Braun-Glas	Vial Hütten-Glas	Vial Hütten-Glas	Vial Braun-Glas	Vial Röhren-gas
SiO_2	75	74	74	71	67	69	67	80
B_2O_3	10	9	9	9	12	11	11	13
Al_2O_3	5	5	5	5	6	6	6	3
Na_2O	6	7	7	6	9	9	9	4
BaO	2	2	2	2	3	3	3	
CaO	1	1	1	1	1	5	1	
K_2O		0.8	0.8	0.8	2		1	
TiO_2				3				
ZnO					1	1	0.8	
PH shift	+0.8	+0.8	+0.6	+2.0	+1.0	+0.8	+0.7	+1.0

Released silicate-ions after autoclaving (60 min, 121°C, citrate buffer (1,12)

pH	4.0	5.0	6.0	6.5	7.0	7.5	8.0
Release of silicate-ions in ppm	0.5	1.2	1.9	4.7	14	28	37

Release of silicate ions by different organic acids

Organic acid	Content of Si (ppm)
Lactic acid	3
Acetic acid	5.6
Ascorbic acid	12
Tartaric acid	30
Oxalic acid	52
Gluconic acid	57
Citric acid	70

2.9.1.4 Metal

Aluminium is the most applied metal

- Aluminium container for semi-solid dosage forms
  The aluminium tube is protected by internal lacquering. Their interaction with the content has to be considered

- Aluminium tubes as moisture tight container
- Aluminium foil for blister

2.9.3 Regulatory requirement

2.9.3.1 EC

The Note for Guidance, plastic primary packaging materials has to be considered.

❒ **Solid dosage forms**

The risk of migration is low and generally does not require a content/container interaction study.

Solid forms intended for parenteral use may need interaction studies between the elastomer closure and the components of the formulation.

❒ **Semi-solid forms**

The risk of migration into aqueous or non-aqueous semi-solid requires suitable specific studies for each formulation.

The study should be performed under accelerated and long-term storage conditions.

❒ **Liquid dosage forms**

The risks of migration require suitable specific studies for each formulation.

Levels of extractives (e.g. antioxidants, plasticisers, catalysts, processing acids etc.) should be investigated mainly for parenteral and ophthalmic products.

❒ **General scheme:**

Samples

During the development stage, migration studies on initial formulations often allow the choice of a suitable packaging material for the finished product to be chosen.

The study should be performed on at least one batch of finished product.

Study condition

Studies should be performed under normal and accelerated conditions according to the current notes for guidance on stability.

Study methods

Simulation studies performed with extraction solvents (as in the case of food) can only be considered as predictive tests and do not preclude the need to perform a study on the finished product.

Migration and interaction studies should include:

- the control of technological characteristics for each pharmaceutical form.
- a study on the leaching of antioxidants, mono- and oligomers, plasticisers, mineral compounds likely to migrate (e.g. calcium, barium, tin for PVC) and other additives according to the composition of the packaging material. Maximum limits may need to be proposed.
- a study of the sorption of the formulation components to the packaging material.

2.9.3.2 FDA (draft)

(Guidance for Industry. Submission of documentation in Drug Applications for Container Closure Systems used for the packaging of Human Drugs and Biologics.

2.9.3.2.1 Phase 1 and 2

For the initial stage of the IND should be briefly described the container closure system.

The IND should also indicate that appropriate.

2.9.3.2.2 Phase 3

By the end of phase 3 the IND should contain complete information pertaining to the proposed market package for the drug product including corresponding compatibility and some stability data.

For drug products with complex container closure systems (e.g. inhalation aerosols), it is advisable to finalise the market package by the beginning of phase 3.

2.9.3.2.3 Qualification and Quality Control of Packaging Components

Each application is expected to contain enough information to show each proposed container closure system is suitable for the drug product in question.

2.9.3.2.3 General Consideration

Suitability for the intended use

Each proposed packaging system should be shown to be suitable for its intended use:

.

- adequately protect the dosage form
- be compatible with dosage form
- composed of material that are considered safe for use.

Examples of Packaging Concerns for Common Classes of Drug product

Degree of concern associated with the route of administration	Likelihood of packaging Component-Dosage Form Interaction		
	High	**Medium**	**Low**
Highest: Inhalation and Injection Drug Products	Inhalation aerosols and solutions; injections and injectable suspensions	Sterile powders and powders for injection; Inhalation powders	
High: Ophthalmic or Transdermal Drug Products	Ophthalmic solutions and suspensions; Transdermal ointments and patches;nasal aerosols and sprays		
Low: Oral or Topical Drug Products	Topical solutions and suspensions; Topical and lingual aerosols, oral solutions and suspensions	Topical Powders, oral powders	Tablets and capsules

2.10 Evaluation

Evaluation

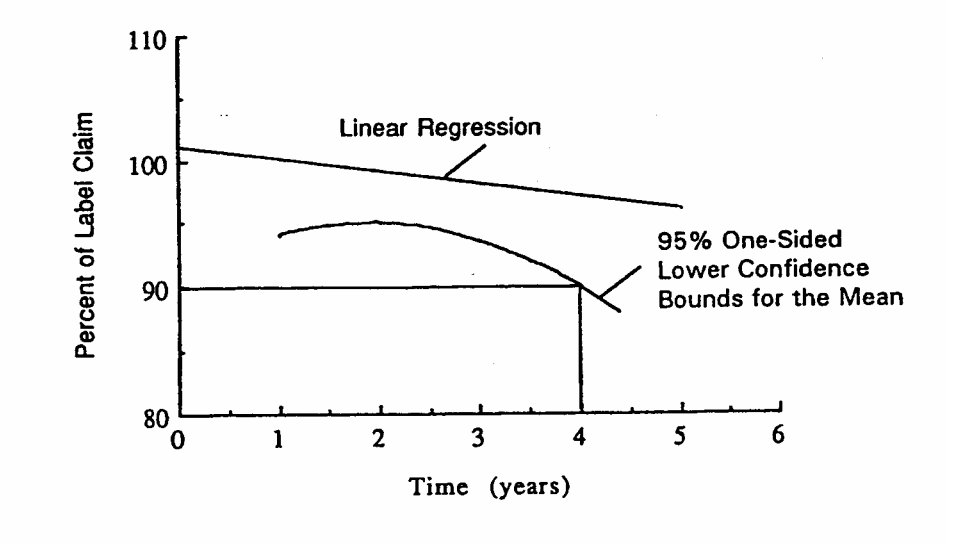
An acceptable approach for quantitative characteristics that are expected to decrease with time is

- To determine the time at which the 95% one-sided confidence limit for the mean degradation curve intersects the acceptable lower acceptance criterion limit (1)
- It is clearly limited to quantitative characteristics that are expected to change with time.
- This are mainly:
  - The chemical test attributes assay and degradation
  - It can be attributed only in rare cases to physico-chemical test attributes

Evaluation

This calculation is based on the assumption that the product characteristic (e.g. the strength will decrease with time.
For drug product characteristics expected

- To increase with time, the 95% one-sided upper confidence limit for the mean would be used.
- An alternative is the graphical presentation of the degradation instead of the content

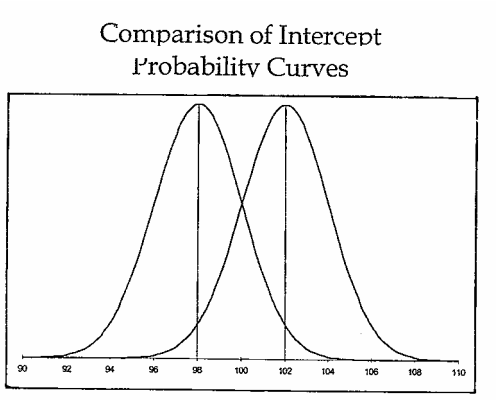


Pooling of data from batches

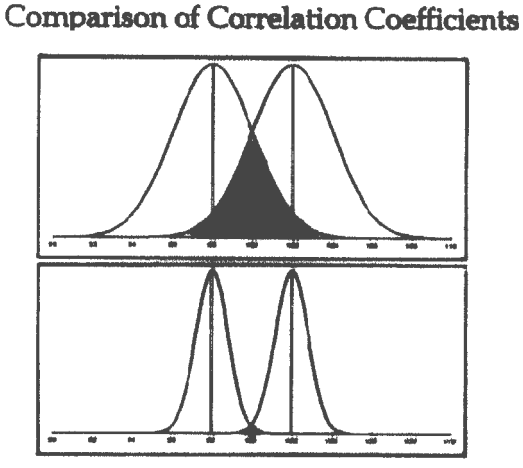
- **If analysis shows that the batch to batch variability is small, it is advantageous to combine the data into one overall estimate**
  This can be done by first applying appropriate statistical tests, for example:
  - p values for level of significance of rejection of more than 0.25
    - to the slopes of the regression lines and
    - zero time intercept for the individual batches

- **If it is a inappropriate to combine data from several batches**
  - The overall shelf life may depend on the minimum time a batch may be expected to remain within acceptable and justified limits

- **The probability is [100 (1-p)%], p = 0.25 means 75% probability of the data being different or the overlap to 25%**



Yarmschuk (4)



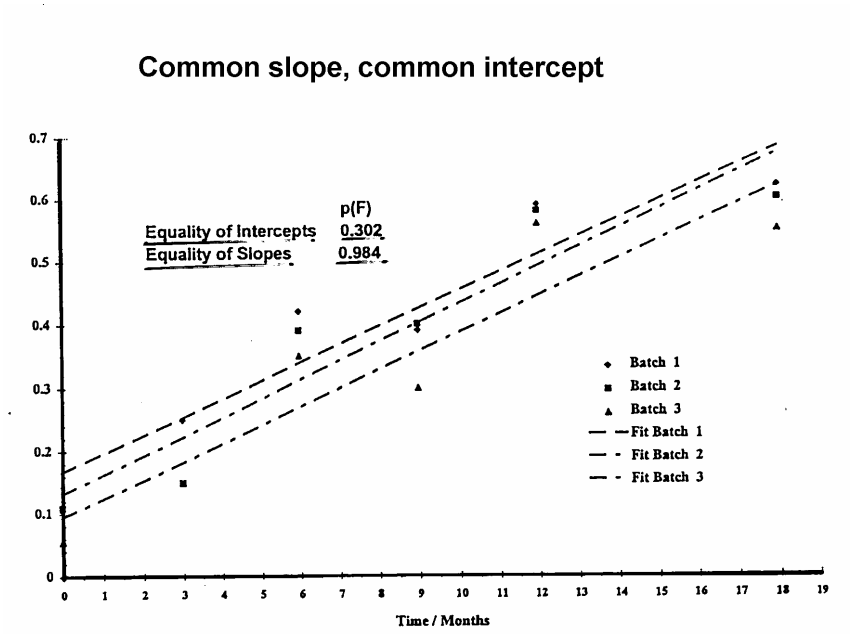
Yarmschuk (4)

To decide whether pooling is possible the uncertainty of regression lines with regard to slope and intercept has to be compared.

Common slope, common intercept

- **This is the ideal case, all data can be combined into one dataset**
  Usually resulting in longer shelf lives:
  - The larger N will be, the number of data,
  - The smaller the confidence limits on a calculated time point will be
  - The higher the number of batches

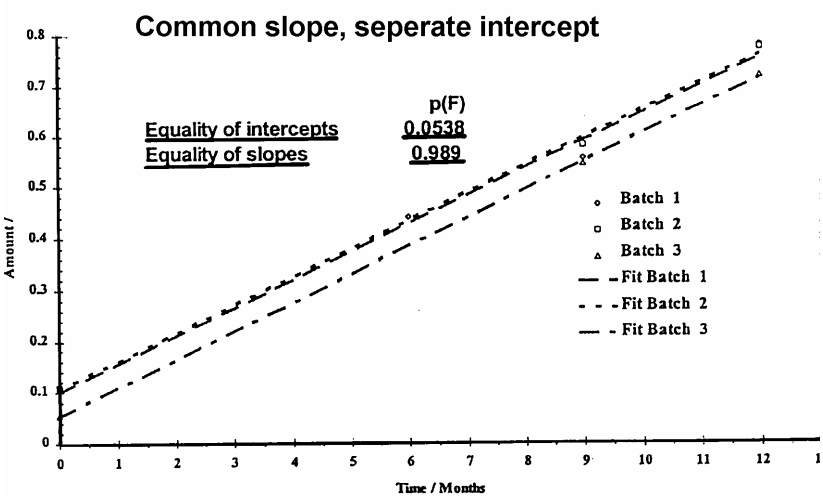
An example is given for three batches of degradation with common slope and common intercept (p (F) equality of intercept 0.302 and equality of slopes 0.984, that means both > 0.25.



Common slope, separate intercept

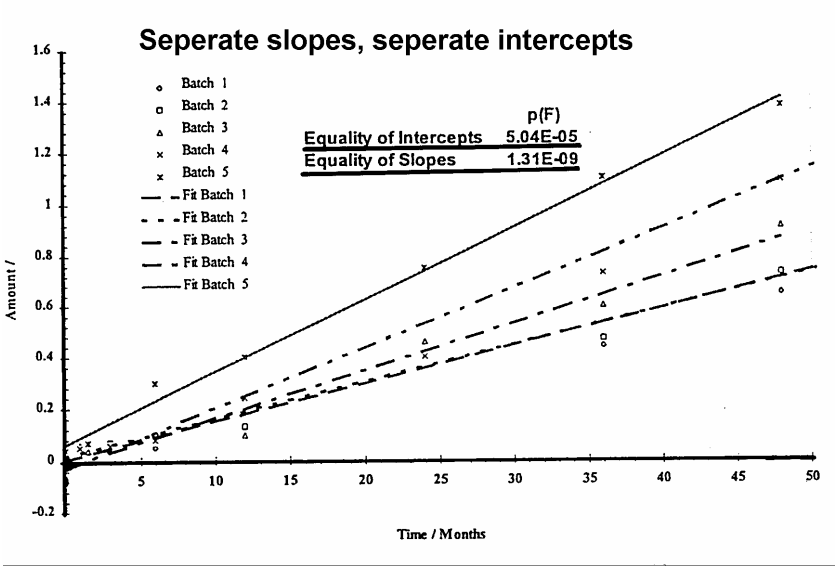
- **If the data indicate**
  - that the slopes are common
  - but the intercepts are different

  It is still possible to use all data, but the intercept from the worst batch

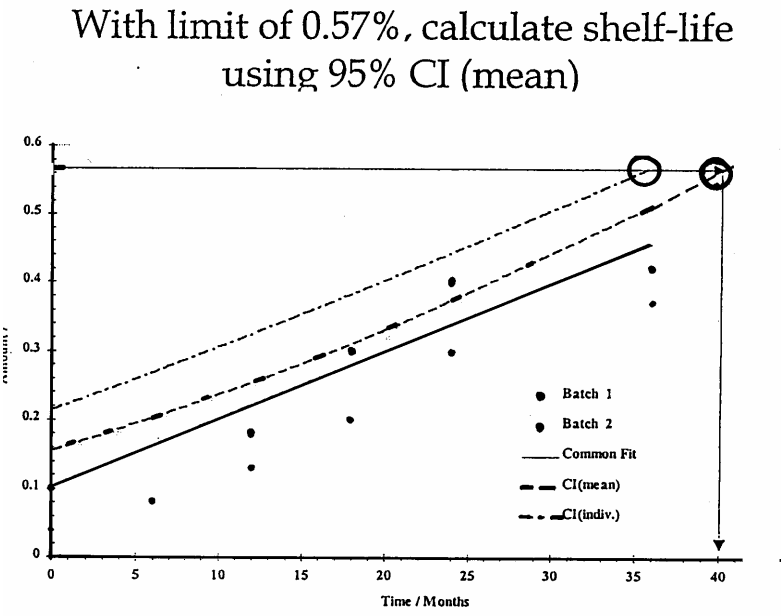


Separate slope, separate intercept

- **If data can't be pooled, only the worst batch can be used to determine the shelf life**



Finally an example is given with the calculated shelf life with a limit for degradation of 0.57%, using the 95% one-sided upper confidence limit for the mean Yarmchuck 4)



Evaluation

- **The nature of the degradation relationship will determine the deed for transformation of the data for linear regression analysis**
  Usually the relationship can be represented
  - by linear
  - quadratic
  - or cubic function
  - on an arithmetic or logarithmic scale

Statistical methods should be employed, to test the goodness of fit on all batches and combined batches (where appropriate) to the assumed degradation line or curve
The degradation may follow

- zero
- first or
- second order or
- broken one.

But up to 10-15% the order of reaction does not matter and all can be presented by linear relationship, therefore no transformation for linear regression analysis is necessary

Evaluation

Where the data show so little degradation and so little variability that it 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.

Evaluation

A formal statistical analysis is inapplicable with those data.
But even If the decomposition would take place in the range of 0.25-1% after 60 months

- it would be nearly impossible to recognise this decomposition as a significant change after 6 months at 25°C/60% when the results are filed for submission.

Calculated data for the drug substance assay

Fall in assay or decomposition	40°C/75% [months]		25°C/60% [months] [data in %]								
	3	6	3	6	9	12	18	24	36	48	60
0.25%	99.94	99.88	99.99	99.97	99.96	99.95	99.92	99.90	99.85	99.80	99.75
0.50%	99.88	99.75	99.97	99.95	99.92	99.90	99.85	99.80	99.70	99.60	99.50
0.75%	99.81	99.63	99.96	99.92	99.89	99.85	99.77	99.70	99.55	99.40	99.25
1.00%	99.75	99.50	99.95	99.90	99.85	99.80	99.70	99.60	99.40	99.20	99.00

Decomposition in the range or 0.25 – 1% after 60 months at 25°C/60% and the corresponding calculated data for the content of samples stored at 40°C/75% and 25°C/60%. ΔE: 83 kJ mol^{-1}, 1st order reaction

Calculated data for the drug substance degradation

Fall in assay or decomposition	40°C/75% [months]		25°C/60% [months][data in %]								
	3	6	3	6	9	12	18	24	36	48	60
0.25%	0.06	0.12	0.05	0.05	0.05	0.05	0.08	0.10	0.15	0.20	0.25
0.50%	0.12	0.25	0.05	0.05	0.08	0.10	0.15	0.20	0.30	0.40	0.50
0.75%	0.19	0.37	0.05	0.08	0.11	0.15	0.23	0.30	0.45	0.60	0.75
1.00%	0.25	0.50	0.05	0.10	0.15	0.20	0.30	0.40	0.60	0.80	1.0

Decomposition between 0.25% and 1% after 60 months at 25°C/60% and the calculated data for the samples stored at 40°C/75% and 25°C/60% ΔE: 83 kJ mol^{-1}, 1st order reaction

Evaluation

The release acceptance criterion for assay of drug products is 100% $\pm$ 5% the lower limit of shelf life acceptance criterion $\geq$ 90%, therefore a 5% fall in assay or decomposition is possible. In the following table data for the content are presented with 5% fall in assay after 5,4,3 and 2 years. To compare them directly the initial data start all

with 100% (according to the release specification a batch will also be released with an initial assay value of 95% , covering the range of 95-90% with 5 % decomposition)

Active ingredient content as a function of time and the corresponding shelf life

Fall in assay at 25°C/60%	**40°C/75% [months]**		**25°C/60% [months][data in %]**									**Shelf life**
	3	6	3	6	9	12	18	24	36	48	60	
≤ 5%	98.73	97.48	99.74	99.47	99.23	98.98	98.47	97.97	96.97	95.98	95.0	5 y
≤ 5%	98.42	96.86	99.68	99.36	99.04	98.73	98.09	97.47	96.23	95.0		4 y
≤ 5%	97.89	95.83	99.57	99.15	98.73	98.30	97.47	96.64	95.0			3 y
≤ 5%	96.86	93.81	99.36	98.73	98.09	97.48	96.22	95.0				2 y

The data were calculated : ΔE: 83 kJ mol^{-1}, 1st order reaction

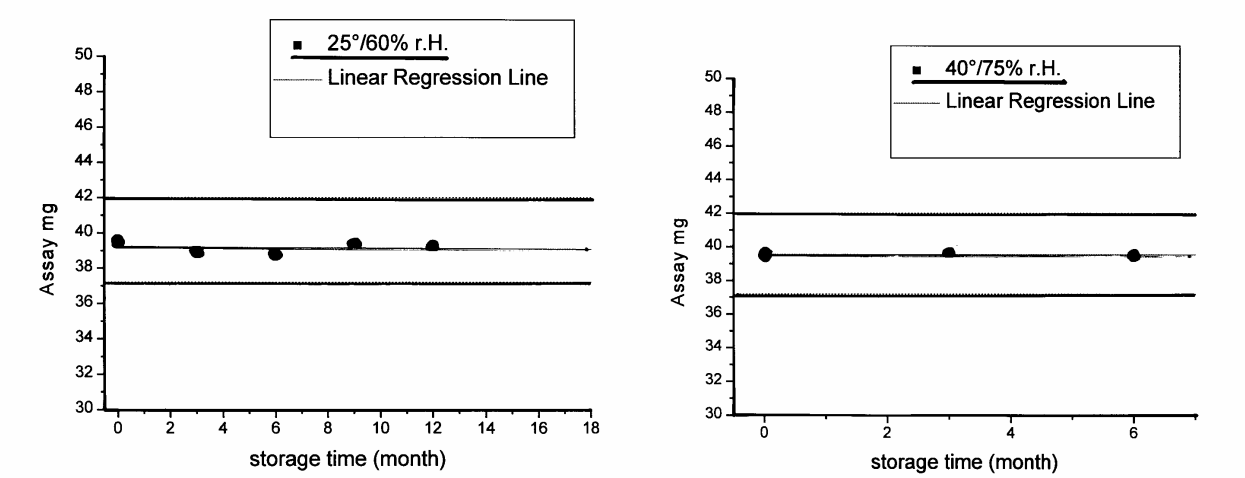
When the results are filed for submission 12 moths data are available..
As demonstrated in the table all data at 25°C/60% will be within the range of the standard deviation of the analytical procedure with anticipated shelf lives or 3-5 years and corresponding fall in assay of 1-1.7%.
Only for an unstable formulation with a maximum shelf life o 2 years a statistically significant change can be stated after 12 months.
This indicates that in many cases a linear regression analysis Is not possible after 12 moths storage.

- A statistically significant change can only be derived from the samples stored at 40°C/75%.
- An alternative would be again to evaluate the results of the corresponding decomposition product. Therefore they are presented in the following table:

Fall in assay at 25°C/60%	**40°C/75% [months]**		**25°C/60% [months][data in %]**									**Shelf life**
	3	6	3	6	9	12	18	24	36	48	60	
≤ 5%	1.27	2.52	0.26	0.51	0.77	1.02	1.53	2.03	3.03	4.02	5.0	5 y
≤ 5%	1.58	3.52	0.32	0.64	0.96	1.27	1.91	2.53	3.77	5.0		4 y
≤ 5%	2.11	4.17	0.43	0.85	1.27	1.70	2.53	3.56	5.0			3 y
≤ 5%	3.14	6.19	0.64	1.27	1.91	2.52	3.87	5.0				2 y

Decomposition of ≤ 5% after 2-5 years at 25°C/60% and the corresponding data for 40°C/75%.
These data were calculated with ΔE: 83 kJ mol^{-1}, 1st order reaction

If au to 12 months no significant fall in assay has taken place the data can be presented graphically not with the upper and power confidence limits but with the upper and lower specification limits as shown in the following figure:



Graphical presentation of assay data for 25°C/60% and 40°C/75% with the acceptance criteria limits.

When decomposition has taken place at higher temperature than the equations of the reaction kinetics can be applied:

Equations for zero order reactions:

Wanted	Given	**Equation**
k	Co, C, t	$k = \frac{Co - C}{t}$
t	Co, C k	$\frac{Co - C}{k}$
C	Co, t, k	C = Co - kt

Equations for 1st order reactions

Wanted	Given	**Equation**
k	Co, C, t	$k = \frac{1}{t} \ln \frac{Co}{C}$
t	Co, C k	$T = \frac{1}{k} \ln \frac{Co}{C}$
C	Co, t, k	lnC = lnCo - kt

k =rate constant
t = time in weeks, months or years
C = concentration in % at time t
Co = concentration in % at time O

Example: $k = \frac{1}{24\ m} \ln \frac{100\%}{95\%} = 0.00214/\ months$

Arrhenius equations

Wanted	Given	Equation
ΔE	k_1, k_2, T_1, T_2	$\Delta E = \ln \frac{k_1}{k_2} R \left(\frac{T_1 \times T_2}{T_2 - T_1}\right)$
k_x	$k_1, T_1, \Delta E$	$\ln k_x = \frac{\Delta E}{R}\left(\frac{T_x - T_1}{T_x \times T_1}\right) + \ln k_1$

Equations for the calculations of the temperature dependence of the reaction constant

ΔE= activation energy (kJ mol^{-1};
R = gas constant (0,008314 kJ mol^{-1} K^{-1})
T = temperature in K
k_1, k_2, k_x = rate constants

Example:

$T_1 = 314K, T_2 = 334$ K, $k_1 = 0.00272\ months^{-1}$, $k_2 = 0.01609\ months^{-1}$

Wantet ΔE, $\Delta E = \ln \frac{0.01609}{0.00272} \times 0.008314 \times \left(\frac{334 \times 314}{334 - 314}\right) = 77.50$ kJ mol^{-1}

If stress data are only available from one temperature then ΔE: 83 kJ mol^{-1} can be applied.

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