1.4

ICH Q1D Guideline

Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products ICH Step 4

Comments for its application

1. Introduction

1.1 Objectives of the Guideline

Recommendations for application of bracketing and matrixing

1.2 Background

Q1A(R2) mentions only possibility

1.3 Scope of the Guideline

- Guidance on study designs
- Specific priniciples for applications
- Sample designs for illustrative purposes

2. Guidelines

2.1 General

- Full study design: samples for every combination, all design factors tested at all time points
- Reduced design ability to adequately predict retest period or shelf life
- Risk assessment, shorter shelf life possible
- Change to full testing or less reduced design can be considered.
- If changed full testing or less reduced testing through remaining time points.

2.2 Applicability of Reduced Designs

- Applicable to formal stability studies of most types of drug products
- Drug substances: matrixing limited, bracketing generally not applicable
- Whether bracketing or matrixing depends on circumstances
- Any reduced design should be justified.
- Type and level of justification depends on avaiable supporing data.
- Careful consideration and scientific justification, if bracketing and matrixing in one design.

2.3 Bracketing

- Bracketing is the design of a stability schedule such that only the extremes of certain design factors are tested al all time points
  - different strengths
  - different container size and/or fill
- Stability of intermediate levels represented by stability or tested extremes.
- Bracketing design not appropriate, if tested samples are not the extremes.
- Rationale for bracketing
  - Interpolation between extremes is logical
  - Useful where lage number of presentations
  - Fairly well accepted

2.3.1 Design Factors

- Design factors are variables to be evaluated for their effect on product stability

2.3.1.1 Strengths

- Applicable without justificationt to studies with multiple strengths with identical or closely related formulations
  - Capsules of different strengths with different plug size same powder blend
  - Tablets different strengths compressing varying amounts of same granulation
  - Oral solutions of different strenghts with formulations that differ only in minor
  - excipients (e.g. , colourants, flavourings)
- Applicable with justification to studies with multiple strengths where relative amounts of drug substance and excipients change in a formulation.
  Justification means that corresponding supportive data on the drug product are available, e.g. stability profiles of different strengths of clinical or development batches. If results indicate that different strengths, even with different compositions do not differ in stability behabiour justification is easy.
- Bracketing not applicable if different excipients are used amoung strengths.

2.3.1.2 Container Closure Sizes and/or Fills

- Applicable without justificationt for same container closure systemn where either size of fill varies
- If both container size and fill vary, largest or smallest containers may not represent the extremes of all packaging configurations.
- Extremes should be selected comparing various characteristics:
  - Container wall thickness
  - Closure geometry,
  - Surface area to volume ratio,
  - Headsspace to volume ratio,
  - Water vapour permeaton rate per dosage unit
- With justificaton applicable with same container but closure varies
  If investigations for physico-chemical stability for solid dosage forms have shown not sensitive to moisture, liquid dosage forms not senitive to oxygen, justificaton is easy.

2.3.2 Design Considerations and Potential Risks

- If during testing one of extremes no longer expected to be marketed, study maintained to support bracketing intermediates. Commitment post approval stability testing.
- If stability of extremes differ, intermediates not exceed least stable extreme.

2.3.3 Design Example

Three strengths, three container sizes

Container size	Dosage Strength								
	50 mg			75mg			100mg		
	1	2	3	1	2	3	1	2	3
HDPE/ 15ml	T	T	T				T	T	T
HDPE/ 100ml									
HDPE/ 500ml	T	T	T				T	T	T

T means sample is tested

2.3.2 Design Considerations and Potential Risks II

To reduce the risk applying bracketing the number of strengths or container sizes should be balanced with the total number of strengths or container sizes.

This should be especially considered if bracketing is applied during the development stage of the drug product.

Therefore the following general rules are fixed.

NUMBER OF STRENGTHS	STRENGTHS TO BE TESTED
1-2	all
3-4	lowest and highest
≥ 5+	lowest, middle, highest

NUMBER OF SIZES	SIZES TO BE TESTED
1-2	smallest
3-4	smallest , biggest
≥ 5+	smallest, middle, biggest

Savings by Bracketing

Full testing					Bracketing					
Strengths	Container Sizes	Batches	Total Batches	Total time Points	Strengths	Container Size	Batches	Total Batches	Total time Points	savings
1	1	3	3	36	-	-	-	-	-	-
2	1	3	6	72	-	-	-	-	-	-
3	1	3	9	108	2	1	3	6	72	33%
3	2	3	18	207	2	1	3	6	72	65%
3	3	3	27	306	2	2	3	12	138	55%
4	1	3	12	144	2	1	3	6	72	50%
4	2	3	24	276	2	1	3	6	72	74%
4	3	3	36	408	2	2	3	12	138	66%

2.4 Matrixing

As defined in the glossary to the parent guideline, matrixing is the design of a stability schedule such:

- that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point.
- At a subsequent time point, another subset of samples for all factor combinations is tested.

The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point.
The differences in the samples for the same drug product should be identified as, for example:

- covering different batches,
- different strengths,
- different sizes of the same container closure system,
- possibly in some cases, different container closure systems.

2.4.1 Design Factors

☐ Matrixing application without justification:

- Strengths with identical or closely related formulations as
  - capsules of different strengths made with different fill plug sizes from the same powder blend,
  - tablets of different strengths manufactured by compressing varying amounts of the same granulation,
  - formulations that differ only in minor excipients, e.g. colorants, flavourings
- Batches made using the same process and equipment,
- Container size and fill in the same closure system.

Matrixing application with justification:

- Strengths where the relation amounts of the drug substance and excipients change,
- Strengths where different excipients are used,
- Different container closure systems,

Justification means supporting data e.g. that different container closure systems are similar in moisture or oxygen permeation, or the product is not effected by moisture or oxygen

2.4.2 Design Considerations

- A matrix design should be balanced such that each combination of factors is tested to the same extend over the duration of the study.
- Initial and end point values should be included for all samples.
- Before application all samples should be retested at 12 months or at the last time point before submission.
- At least three time points, including initial, should be available through the first 12 months,
- For accelerated or intermediate storage conditions, a minimum of three time points are necessary
- Any matrix design should retain an adequately ability to detect stability differences within factors or among factors.
- If one strength or container size is no longer intended for marketing, testing should be continued, to support the design

2.4.3 Design Examples

Since only a fraction of the total number of samples are tested it is necessary to fix the stability protocol before the start of the testing to exclude any manipulation concerning selection of samples.

Many statistical designs are possible, often 1/3 or 2/3 designs are proposed.

At the initial time point 0 all strengths are analysed whereas at the following time points only a reduced number is investigated according the following designs:

Design; 1/3

Type	Analysis	Explanation
A	x ..- -	yes no no
B	- x -	no yes no
C	- - x	no no yes

These basic sequences are repeated 3 times

Type	Storage period (months) and time points										Total number
	0	3	6	9	12	18	24	36	48	60	
A	x	x	-	-	x	-	-	x	-	-	4
B	x	-	x	-	-	x	-	-	x	-	4
C	x	-	-	x	-	-	x	-	-	x	4

2.4.3 Design Examples

Design 2/3

Type	Analysis	Explanation
A'	**-** ..x x	no yes yes
B'	x **-** x	yes no yes
C'	x x **-**	yes yes no

These basic sequences are again repeated 3 times

Type	Storage period (months) and time points										Total number
	0	3	6	9	12	18	24	36	48	60	
A	x	-	x	x	-	x	x	-	x	x	7
B	x	x	-	x	x	-	x	x	-	x	7
C	x	x	x	-	x	x	-	x	x	-	7

2.4.3 Design Examples

These 1/3 and 2/3 designs should be extended as follows:

- According to ICH at least 12 months data of the registration batches should be included in the file for registration application. Therefore it is advisable to analyse all samples at 12 months
- The final time point 60 months (or at reduced shelf life 36 or 48 months) should also be tested since the results are decisive for fixing the shelf life
- Therefore the two designs may look like as follows

2.4.3 Design Examples

1/3 designs with extended testing:

Type	Storage period (months) and time points										Total number
	0	3	6	9	12	18	24	36	48	60	
A	x	x	-	-	x	-	-	x	-	x	5
B	x	-	x	-	x	x	-	-	x	x	6
C	x	-	-	x	x	-	x	-	-	x	5

2/3 design with extended testing:

Type	Storage period (months) and time points										Total number
	0	3	6	9	12	18	24	36	48	60	
A	x	-	x	x	x	x	x	-	x	x	8
B	x	x	-	x	x	-	x	x	-	x	7
C	x	x	x	-	x	x	-	x	x	x	8

If different strengths and container sizes are included the batches and samples have to be arranged in such a way that the sequences A.B,C are distributed equally.

The guideline mentions “one half reduction”, “one third reduction”, and an example for a Product with three strengths and three container sizes is given

2.4.4 Applicability and Degree of Reduction

The following should be considered:

- Knowledge of data variability
- Expected stability of the product
- Availability of supporting data
- Stability differences in the product within a factor or among factors
- Number of factor combination in the study

Generally matrixing is applicable if the supporting data indicate predictable product stability

Savings by matrixing, one storage condition 25°C/60%

Strengths	Container* sizes	Batches	Total time points	1/3 design extended	2/3 design extended
1	1	3	30	-	-
2	1	6	60	32 = 53%	46 = 77%
2	2	12	114	58 = 51%	86 = 75%
3	1	9	90	48 = 53%	69 = 77%
3	2	18	171	87 = 51%	129 = 75%
3	3	27	252	126 = 50%	189 = 75%
4	1	12	120	64 = 53%	92 = 77%
4	2	24	228	116 = 51%	172 = 75%
4	3	36	336	168 = 55%	252 = 75%

*For different container sizes initial analysis has to be determined only once, the initial value of 40°C/75% is not analysed either
The savings are 25 - 50%

2.4.3 Design Examples

It is also possible to combine the 2/3 and 1/3 designs whereas the different strengths are analysed according 2/3 design and the different container sizes 1/3 design.

When a matrix on design factors is applied, if one strength or container size fill is no longer Intended for marketing, stability testing of that strength or container size fill can be Continued in order to support the other strengths or container sizes and fills in the design.

3. Bracketing or matrixing

After the procedures have been discussed shortly the question arises whether there are preferences for the application.

With bracketing samples of one batch are analysed at all time points. Therefore it is easy to pursue a trend on instability.

If all selected batches or packaging materials tested show the same trend it can be concluded with high certainty, that the remaining strengths or packaging materials behave the same. Bracketing and matrixing are not limited to the registration batches.

Thereby bracketing will be the preferable procedure during development up to accelerated and long term testing as long as the available stability information is limited.

With matrixing the samples to be tested are selected statistically, they originate from different batches. Therefore this procedure is less sensitive. This procedure is preferred to confirm a prediction or a stability information.

Therefore matrixing will be applied in the later stage of development, if sufficient data are available, for on-going stability testing with production batches and after marketing authorisation for follow-up stability testing. Thereby the stability behaviour has to be mainly confirmed.

3. Bracketing or matrixing

The advantage of matrixing is that all strengths or packaging sizes or materials are included in the testing procedure.

In the following table the arguments are summarised.

Bracketing or Matrixing?

With bracketing samples are analysed at all time points therefore this procedure is preferred to pursue a trend.

With matrixing a statistically selected sample is investigated, therefore this procedure is preferred to confirm a prediction or a stability information.

Stage of development	Preferable procedure
Predevelopment	bracketing
Clinical phases I-III	bracketing
Accelerated and long term testing with registration batches	Bracketing/ matrixing
On-going stability testing	matrixing
Follow-up stability testing	matrixing

3. Bracketing or matrixing

Justification

Concerning justification the following can be said for the application of bracketing or matrixing during the different stages of development.

Application of bracketing or matrixing during the whole development

Stage of development	Applied to	Justification
Clinic phase I, II	• Testing specifications • Stability testing	no no
Clinic phase III	Stability testing	no
Accelerated and long term testing	Registration batches	Strongly recommended if: • No according closely related, • No according supportive data
On-going stability testing	• Registration batches • Production batches	Depending on available data
Follow-up stability testing	Production batches	no

Evaluation

The following table gives an overview on the number of data which are available at the time of filing the data after 12 months storage if the different procedures are applied.

The calculation is based on a formulation with 3 strengths:

Procedure	Strengths	Batches	Data after 12 months 25°C/60%	Data after 6 months 40°C/75%
Full testing	3	9	45	18
Bracketing	3	6	30	18
Matrixing 1/3 extended	3	9	27	18
Matrixing 2/3 extended	3	9	36	18

Prerequisite for Application

For the application of all procedures the following prerequisites should be fulfilled. ·

- Efficient concept of development ·
- Investigation of different strengths ·
- Investigation of moisture sensitivity

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- Investigation of tightness of different container sizes and/or closure systems
- Stability of drug product should be known before starting accelerated and Long term testing with registration batches
- Summary of supportive data

Proposal for a stability protocol for registration application applying Bracketing or Matrixing

- Introduction
- Summary of supportive data with conclusion
- Proposed stability protocol
  - Selection of batches, bracketing or matrixing
  - Test attributes and analytical procedures
  - Specifications
  - Storage conditions
  - Testing frequency
  - Acceptance criteria, specifications
  - Container-closure system, bracketing or matrixing
  - Summarised stability protocol
  - Evaluation
  - Stability information/labelling
  - Summary

Risk of applying bracketing or matrixing

Applied procedure	Evaluation	Consequences
Bracketing	Strengths influences stability	Registration application only with investigated strengths
	Container size has influence on stability	Registration application only with investigated container size
Matrixing	Strongly scattering data	• No shelf life prediction beyond storage period possible • Extension of long term testing to 18 or 24 months before filing registration application
Bracketing or matrixing	Assumption was wrong	Registration application has to be postponed but nor risk to patient