

Guidance for Industry

Bracketing and Matrixing Designs For Stability Testing of New Veterinary Drug Substances and Medicinal Products

VICH GL45 DRAFT GUIDANCE

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
July 20, 2009**

Contains Non-Binding Recommendations
Draft—Not for Implementation

VICH GL 45 (QUALITY) – BRACKETING AND MATRIXING

February 2008

For Consultation at Step 4 - Draft 1

QUALITY: BRACKETING AND MATRIXING DESIGNS FOR STABILITY TESTING OF NEW VETERINARY DRUG SUBSTANCES AND MEDICINAL PRODUCTS

Recommended for Consultation
at Step 4 of the VICH Process
on 11 February 2008
by the VICH Steering Committee

This Guidance has been developed by the appropriate VICH Expert Working Group and is subject to consultation by the parties, in accordance with the VICH Process. At Step 7 of the Process, the final draft will be recommended for adoption by the regulatory bodies of the European Union, Japan, and USA.

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BRACKETING AND MATRIXING DESIGNS FOR STABILITY TESTING OF NEW VETERINARY DRUG SUBSTANCES AND MEDICINAL PRODUCTS

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1. INTRODUCTION

1.1 Objectives of the Guidance

This guidance is intended to address recommendations on the application of bracketing and matrixing to stability studies conducted in accordance with principles outlined in the Harmonised Tripartite guidance VICH GL3(R) *Stability Testing of New Veterinary Drug Substances and Medicinal Products (Revision)* (hereafter referred to as the VICH GL3(R).)

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in Agency guidances means that something is suggested or recommended, but not required.

1.2 Background

VICH GL3(R) notes that the use of matrixing and bracketing can be applied, if justified, to the testing of new veterinary drug substances and medicinal products, but provides no further guidance on the subject.

1.3 Scope of the Guidance

This document provides guidance on bracketing and matrixing study designs. Specific principles are defined in this guidance for situations in which bracketing or matrixing can be applied. Sample designs are provided for illustrative purposes, and should not be considered the only, or the most appropriate, designs in all cases.

2. GUIDANCE

2.1 General

A full study design is one in which samples for every combination of all design factors are tested at all time points. A reduced design is one in which samples for every factor combination are not all tested at all time points. A reduced design can be a suitable alternative to a full design when multiple design factors are involved. Any reduced design should have the ability to adequately predict the retest period or shelf life. Before a reduced design is considered, certain assumptions should be assessed and justified. The potential risk should be considered of establishing a shorter retest period or shelf life than could be derived from a full design due to the reduced amount of data collected.

During the course of a reduced design study, a change to full testing or to a less reduced design can be considered if a justification is provided and the principles of full designs and reduced designs are followed. However, proper adjustments should be made to the statistical analysis, where applicable, to account for the increase in sample size as a result of the change. Once the design is changed, full testing or less reduced testing should be carried out through the remaining time points of the stability study.

2.2 Applicability of Reduced Designs

Reduced designs can be applied to the formal stability study of most types of new veterinary medicinal products, although additional justification should be provided for certain complex drug delivery systems where there are a large number of potential drug-device interactions. For the study of new veterinary drug substances, matrixing is of limited utility and bracketing is generally not applicable.

Whether bracketing or matrixing can be applied depends on the circumstances, as discussed in detail below. The use of any reduced design should be justified. In certain cases, the conditions described in this guidance are sufficient justification for use, while in other cases, additional justification should be provided. The type and level of justification in each of these cases will depend on the available supporting data. Data variability and product stability, as shown by supporting data, should be considered when a matrixing design is applied.

Bracketing and matrixing are reduced designs based on different principles. Therefore, careful consideration and scientific justification should precede the use of bracketing and matrixing together in one design.

2.3 Bracketing

As defined in the glossary to the VICH GL3(R), bracketing is the design of a stability schedule such that only samples on the extremes of certain design factors (e.g., strength, container size and/or fill) are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested.

The use of a bracketing design would not be considered appropriate if it cannot be demonstrated that the strengths or container sizes and/or fills selected for testing are indeed the extremes.

2.3.1 Design Factors

Design factors are variables (e.g., strength, container size and/or fill) to be evaluated in a study design for their effect on product stability.

2.3.1.1 Strength

Bracketing can be applied to studies with multiple strengths of identical or closely related formulations. Examples include but are not limited to (1) capsules of different strengths made with different fill plug sizes from the same powder blend, (2) tablets of different strengths manufactured by compressing varying amounts of the same granulation, and (3) oral solutions of different strengths with formulations that differ only in minor excipients (e.g., colorants, flavorings).

With justification, bracketing can be applied to studies with multiple strengths where the relative amounts of drug substance and excipients change in a formulation. Such justification can include a demonstration of comparable stability profiles among the different strengths of clinical or development batches.

In cases where different excipients are used among strengths, bracketing generally should not be applied.

2.3.1.2 Container Closure Sizes and/or Fills

Bracketing can be applied to studies of the same container closure system where either container size or fill varies while the other remains constant. However, if a bracketing design is considered where both container size and fill vary, it should not be assumed that the largest and smallest containers represent the extremes of all packaging configurations. Care should be taken to select the extremes by comparing the various characteristics of the container closure system that may affect product stability. These characteristics include container wall thickness, closure geometry, surface area to volume ratio, headspace to volume ratio, and water vapor permeation rate or oxygen permeation rate per dosage unit or unit fill volume, as appropriate.

With justification, bracketing can be applied to studies for the same container when the closure varies. Justification could include a discussion of the relative permeation rates of the bracketed container closure systems.

2.3.2 Design Considerations and Potential Risks

If, after starting the studies, one of the extremes is no longer expected to be marketed, the study design can be maintained to support the bracketed intermediates. A commitment should be provided to carry out stability studies on the marketed extremes post-approval.

Before a bracketing design is applied, its effect on the retest period or shelf life estimation should be assessed. If the stability of the extremes is shown to be different, the intermediates should be considered no more stable than the least stable extreme (i.e., the shelf life for the intermediates should not exceed that for the least stable extreme).

2.3.3 Design Example

An example of a bracketing design is given in Table 1. This example is based on a product available in three strengths and three container sizes. In this example, it should be demonstrated that the 15 milliliter (ml) and 500 ml high-density polyethylene container sizes truly represent the extremes. The batches for each selected combination should be tested at each time point as in a full design.

Table 1: Example of a Bracketing Design

Strength		50 mg			75 mg			100 mg		
Batch		1	2	3	1	2	3	1	2	3
Container size	15 ml	T	T	T				T	T	T
	100 ml									
	500 ml	T	T	T				T	T	T

Key: T = Sample tested

2.4 Matrixing

As defined in the glossary of the VICH GL3(R), matrixing is the design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations would be 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 medicinal product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and possibly, in some cases, different container closure systems.

When a secondary packaging system contributes to the stability of the veterinary medicinal product, matrixing can be performed across the packaging systems.

Each storage condition should be treated separately under its own matrixing design. Matrixing should not be performed across test attributes. However, alternative matrixing designs for different test attributes can be applied if justified.

2.4.1 Design Factors

Matrixing designs can be applied to strengths with identical or closely related formulations. Examples include but are not limited to (1) capsules of different strengths made with different fill plug sizes from the same powder blend, (2) tablets of different strengths manufactured by compressing varying amounts of the same granulation, and (3) oral solutions of different strengths with formulations that differ only in minor excipients (e.g., colorants or flavorings).

Other examples of design factors that can be matrixed include batches made by using the same process and equipment, and container sizes and/or fills in the same container closure system.

With justification, matrixing designs can be applied, for example, to different strengths where the relative amounts of drug substance and excipients change or where different excipients are used or to different container closure systems. Justification should generally be based on supporting data. For example, to matrix across two different closures or container closure systems, supporting data could be supplied showing relative moisture vapor transmission rates or similar protection against light. Alternatively, supporting data could be supplied to show that the medicinal product is not affected by oxygen, moisture, or light.

2.4.2 Design Considerations

A matrixing design should be balanced as far as possible so that each combination of factors is tested to the same extent over the intended duration of the study and through the last time point prior to submission. However, due to the recommended full testing at certain time points, as discussed below, it may be difficult to achieve a complete balance in a design where time points are matrixed.

In a design where time points are matrixed, all selected factor combinations should be tested at the initial and final time points, while only certain fractions of the designated combinations should be tested at each intermediate time point. If full long-term data for the proposed shelf life will not be available for review before approval, all selected combinations of batch, strength, container size, and fill, among other things, should also be tested at 12 months or at the last time point prior to submission. In addition, data from at least three time points, including initial, should be available for each selected combination through the first 12 months of the study. For matrixing at an accelerated or intermediate storage condition, care should be taken to ensure testing occurs at a minimum of three time points, including initial and final, for each selected combination of factors.

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

2.4.3 Design Examples

Examples of matrixing designs on time points for a medicinal product in two strengths (S1 and S2) are shown in Table 2. The terms *one-half reduction* and *one-third reduction* refer to the reduction strategy initially applied to the full study design. For example, a one-half reduction initially eliminates one in every two time points from the full study design and a one-third reduction initially removes one in every three. In the examples shown in Table 2, the reductions are less than one-half and one-third due to the inclusion of full testing of all factor combinations at some time points as discussed in section 2.4.2. These examples include full testing at the initial, final, and 12-month time points. The ultimate reduction is therefore less than one-half (24/48) or one-third (16/48), and is actually 15/48 or 10/48, respectively.

Table 2: Examples of Matrixing Designs on Time Points for a Medicinal Product with Two Strengths

One-Half Reduction

Time point (months)			0	3	6	9	12	18	24	36	
Strength	S1	Batch 1	T	T		T	T		T	T	
		Batch 2	T	T		T	T	T		T	
		Batch 3	T		T		T	T			T
	S2	Batch 1	T		T		T		T		T
		Batch 2	T	T		T	T	T			T
		Batch 3	T		T		T		T		T

Key: T = Sample tested

One-Third Reduction

Time point (months)			0	3	6	9	12	18	24	36	
Strength	S1	Batch 1	T	T		T	T		T	T	
		Batch 2	T	T	T		T	T		T	
		Batch 3	T		T	T	T	T	T	T	T
	S2	Batch 1	T		T	T	T	T	T	T	T
		Batch 2	T	T		T	T		T		T
		Batch 3	T	T	T		T	T			T

Key: T = Sample tested

Additional examples of matrixing designs for a medicinal product with three strengths and three container sizes are given in Tables 3a and 3b. Table 3a shows a design with matrixing on time points only and Table 3b depicts a design with matrixing on time points and factors. In Table 3a, all combinations of batch, strength, and container size are tested, while in Table 3b, certain combinations of batch, strength, and container size are not tested.

Tables 3a and 3b: Examples of Matrixing Designs for a Medicinal Product with Three Strengths and Three Container Sizes

3a Matrixing on Time Points

Strength	S1			S2			S3		
Container size	A	B	C	A	B	C	A	B	C
Batch 1	T1	T2	T3	T2	T3	T1	T3	T1	T2
Batch 2	T2	T3	T1	T3	T1	T2	T1	T2	T3
Batch 3	T3	T1	T2	T1	T2	T3	T2	T3	T1

3b Matrixing on Time Points and Factors

Strength	S1			S2			S3		
Container size	A	B	C	A	B	C	A	B	C
Batch 1	T1	T2		T2		T1		T1	T2
Batch 2		T3	T1	T3	T1		T1		T3
Batch 3	T3		T2		T2	T3	T2	T3	

Key:

Time-point (months)	0	3	6	9	12	18	24	36
T 1	T		T	T	T	T	T	T
T 2	T	T		T	T		T	T
T 3	T	T	T		T	T		T

S 1, S2, and S3 are different strengths. A, B, and C are different container sizes.

T = Sample tested

2.4.4 Applicability and Degree of Reduction

The following, although not an exhaustive list, should be considered when a matrixing design is contemplated:

- knowledge of data variability
- expected stability of the medicinal product
- availability of supporting data
- stability differences in the medicinal product within a factor or among factors and/or
- number of factor combinations in the study

In general, a matrixing design is applicable if the supporting data indicate predictable product stability. Matrixing is appropriate when the supporting data exhibit only small variability. However, where the supporting data exhibit moderate variability, a matrixing design should be statistically justified. If the supporting data show large variability, a matrixing design should not be applied.

A statistical justification could be based on an evaluation of the proposed matrixing design with respect to its power to detect differences among factors in the degradation rates or its precision in shelf life estimation.

If a matrixing design is considered applicable, the degree of reduction that can be made from a full design depends on the number of factor combinations being evaluated. The more factors associated with a product and the more levels in each factor, the larger the degree of reduction that can be considered. However, any reduced design should have the ability to adequately predict the product shelf life.

2.4.5 Potential Risk

Due to the reduced amount of data collected, a matrixing design on factors other than time points generally has less precision in shelf life estimation and yields a shorter shelf life than the corresponding full design. In addition, such a matrixing design may have insufficient power to detect certain main or interaction effects, thus leading to incorrect pooling of data from different design factors during shelf life estimation. If there is an excessive reduction in the number of factor combinations tested and data from the tested factor combinations cannot be pooled to establish a single shelf life, it may be impossible to estimate the shelf lives for the missing factor combinations.

A study design that matrixes on time points only would often have similar ability to that of a full design to detect differences in rates of change among factors and to establish a reliable shelf life. This feature exists because linearity is assumed and because full testing of all factor combinations would still be performed at both the initial time point and the last time point prior to submission.

2.5 Data Evaluation

Stability data from studies in a reduced design should be treated in the same manner as data from full design studies.