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الأسئلة الشائعة حول تطبيق أسلوبي الـ Bracketing والـ Matrixing في دراسات الثبات

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جدول المحتويات

- **قائمة الاختصارات**

ICH: International Conference of Harmonization
VICH: Veterinary International Conference of Harmonization
MDI: Metered Dose Inhalers
TDS: Transdermal Devilry Systems
API: Active Pharmaceutical Ingredient
DPI: Dry Powder Inhalation
OOS: Out of Specification
OOT: Out of Trend
CTD: Common Technical Document
COA: Certificate of Supplier

FAQ on Bracketing and Matrixing in Stability Studies

1-Is bracketing and matrixing applied to both human and veterinary products?

Yes, reduced designs can be used following ICH Q1D, VICH GL45

2-What are the key considerations when applying bracketing and matrixing designs in stability testing?

- The key considerations include:
- The type and level of justification needed to prove a reduced design is safe and appropriate.
- The variability and predictability of the stability data.
- The availability of existing stability studies and supporting data.
- The careful scientific justification required if you plan to use both bracketing and matrixing designs together in the same study.

3-Define bracketing in the context of stability testing designs.

Bracketing is defined as the design of a stability schedule where only samples on the extremes of certain design factors, such as strength, container size, and/or fill, are tested at all time points, similar to a full design.
The hypothesis here is based on the assumption that the intermediate stability is concluded by the stability of the extremes tested.

4-What is the basic requirement for a bracketing design?

The basic requirement for a bracketing design is that the testing protocol must always include the extremes of the intended commercial sizes, fills, and/or product strengths (e.g., the lowest and highest doses, or the smallest and largest bottles). If a large number of sizes or strengths are involved (four or more), it is recommended to also include either one batch of each intermediate size/strength or three batches of the exact middle size/strength.

5 Can bracketing be used to reduce the number of batches required for stability testing?

No. Bracketing does not reduce the regulatory requirement for the number of stability batches. Each tested bracketing configuration should include the required number of primary stability batches as defined in ICH Q1A(R2).

Bracketing applies only to design factors such as container size or strength and should not be used to justify a reduction in batch numbers.

6 Can bracketing be used to reduce annual ongoing (commitment) stability testing?

Bracketing may be used to reduce the number of pack sizes included in annual stability testing; however, it does not eliminate the requirement for ongoing stability studies. At least one marketed worst-case configuration should continue to be included in the annual stability program to verify continued product performance.

7 Can a bracketing design be used in the case of complex drug delivery systems?

Bracketing Design applies to most types of drug products, including immediate-and modified-release oral solids, liquids, semi-solids, and injectables. Certain types of drug products, such as metered-dose inhalers (MDIs), drug powder inhalers, and transdermal delivery systems (TDSs), may not be eligible for bracketing design. This is due to the potential of complex drug-device interactions, device functionality changes across different sizes, or variations in specialized packaging that can directly impact product performance and stability.

If bracketing is attempted for these complex systems, applicants must provide an exceptionally scientific justification and take extreme care during study design.

8 **Is the use of bracketing design acceptable in a stability study design for different dosage forms?**

Yes. Bracketing is an acceptable reduced stability study design for most drug products when applied in accordance with ICH Q1D/ VICH GL 45. The approach is considered scientifically appropriate provided that the tested configurations represent the true extremes of the relevant design factors and that those extremes adequately represent intermediate configurations. The use of bracketing must be supported by a clear scientific justification and should not compromise the ability to establish a reliable shelf life or retest period.

However, the use of bracketing in API is generally not applicable.

9 **Under what circumstances can bracketing be applied to stability studies with multiple strengths, packed in the same container closure system?** Bracketing can be applied to studies with multiple strengths when clinical or development batches demonstrate comparable stability profiles, and the strengths share the same qualitative formulation, manufacturing process, and critical quality attributes. This remains acceptable for multiple strengths packed in the same pack, provided that strength differences do not introduce formulation- or process-related stability risks. However, bracketing generally should not be applied if different excipients are used among strengths. If excipient ratios differ or strength-specific degradation pathways are identified, a separate stability justification may be required.

10 Is the use of bracketing design acceptable in a stability study design across different formulations?

Generally, no. Bracketing across different formulations is not acceptable unless the formulations are identical or closely related, and the applicant demonstrates comparable stability behavior.

11 How do assessors distinguish acceptable "closely related formulations" from unacceptable formulation changes when evaluating a bracketing design, and what product or submission factors apply?

Assessors evaluate the scientific relationship between product strengths, packaging configurations, and submission types using the following criteria:

I- General Principles of Assessment

Assessors review formulations and configurations to ensure that:

The ratio of active ingredients to excipients remains relatively constant throughout the range of strengths.

The materials and components of the container/closure system are identical across the packaging range.

Excipient functionality, degradation pathways, and critical quality attributes (e.g., moisture sensitivity, dissolution) must remain unchanged.

Critical geometric dimensions of intermediate packaging sizes (such as surface area/volume ratio, dead-space/volume ratio,

container wall thickness, and closure geometry) are safely bounded by the extreme configurations selected.

2- General Formulation matrix

Assessment Category	Criteria/Examples Allowed	Unacceptable/ Justification required
Identical Formulations	Different Compression weights of common granulation (tablets) Different Plug fill weights of the same composition filled into different size shells (Capsules)	Changing active levels while holding excipient weights or total unit weight constant (requires justification of comparable stability via supportive batches).
Very Closely related formulation	- Minor adjustments where the basic composition remains similar throughout the range - Purely non-functional aesthetic changes such as the addition or deletion of colorant or flavoring -Same tablet core with a different colorant; same powder blend with a different capsule fill weight.	-Significantly different formulations such as the addition or deletion of any excipient other than colorant or flavoring agent (generally not applicable) -Switching binder systems or disintegrants, -Altering the functional coating composition -Addition or removal of a desiccant-like excipient or moisture scavenger.

3- Product Type and Submission Applicability

Applicable Product Types: Most standard dosage forms, including immediate-and modified-release oral solids, liquids, semi-solids, and injectables. Specialized systems like MDIs, DPIs, and transdermal patches require additional justification.

Applicable Submission Stages: Primary stability batches in original applications, post-approval commitment batches, annual batches, or supplemental changes.
Strict Exclusions: Bracketing must not be applied to clinical batches during the investigational new drug stages while the product
is still under active development.
Regulatory Endorsement: Before applying a bracketing protocol to primary stability batches, the design must be formally endorsed by regulatory staff through preassessment; appeal for review of the bracketing design before the start of the stability studies.

- **12 Can bracketing be applied when formulation is the same, but batch composition ratios change slightly?**

Potentially yes, with justification. If changes in excipient ratios are:

- Proportional
- Not expected to affect stability
- Supported by comparative data

13 Why is fill level considered a critical design factor in bracketing, and which fill level is usually considered the worst case for solid dosage forms?

Fill level is considered the primary stability risk driver because it directly determines the headspace volume above the packed dosage form. An increased headspace volume directly elevates oxygen availability and enhances moisture ingress. For solid dosage forms packaged in plastic containers, this expanded headspace leads to greater moisture exchange and significantly increased stability variability during repeated opening, making it a critical design factor that must be addressed explicitly in stability protocols.

Assessors do not assume a standard worst case; the applicant must scientifically justify which extreme represents the highest stability risk based on the product's dominant degradation mechanism:

- Lowest fill level: Often considered the worst case due to the highest headspace-to-fill ratio, which maximizes oxygen and moisture exposure.
- Highest fill level: May represent the worst case if the configuration introduces risks such as increased mechanical compaction, reduced desiccant efficiency, or product segregation.

14 Can bracketing be applied when only the fill amount varies, and the container size is the same?

Yes. Bracketing may be applied when the fill amount varies within the same container size, provided that the container-closure system remains identical and the selected fill levels represent the true extremes of relevant stability risks.

In such cases, the applicant should evaluate whether the smallest and largest fill levels represent worst-case conditions with respect to:

- Headspace-to-fill ratio
- Oxygen exposure
- Moisture ingress per unit dose

If justified, testing only the extreme fill levels is acceptable, and intermediate fill levels may be bracketed.

Regulatory basis: ICH Q1D- VICH GL 45 allows bracketing across container size and/or fill, provided extremes are appropriately justified.

15 Can bracketing be applied to different container sizes of the same container-closure system, and what conditions must be met for these systems to be considered "identical" for stability testing?

Yes. Bracketing can be applied to different container sizes within the same container-closure system, provided that the systems are structurally identical, and the chosen sizes represent the worst-case conditions affecting product stability.

To utilize this design, the following conditions must be met:

-Identical System Characteristics: The container-closure systems across all bracketed sizes must be identical in every attribute that could influence stability. This includes container material and grade, wall thickness, container geometry, closure design, liner composition, sealing mechanism, and the method of manufacture. Any variation in these attributes introduces a new design factor, which invalidates the bracketing assumption.

-Evaluation of Stability Risk Drivers: The selected sizes must represent the worst-case extremes. Manufacturers must carefully evaluate factors like surface area-to-volume ratio, headspace-to-fill ratio, container wall thickness, closure integrity, and permeation characteristics.

16 How do assessors expect fill and formulation bracketing to be justified together?

When both fill and formulation are discussed, assessors expect a layered justification:

1. Confirmation that the formulation is identical (or closely related)
2. Identification of the worst-case fill level
3. Explanation of how fill level influences headspace and moisture exposure
4. Confirmation that intermediate configurations introduce no additional risk

Failure to clearly separate formulation sameness from fill-related risk is a common cause of deficiencies.

17 Can bracketing be applied when both container size and fill volume/level vary?

Yes, bracketing may be applied when both container size and fill volume/level vary; however, this scenario requires additional scientific justification. Assessors do not accept the assumption that the smallest and largest container configurations automatically represent the true worst-case conditions.

The applicant must evaluate and assess critical risk factors across all configurations, including:

- Surface area-to-volume ratio
- Headspace-to-fill ratio
- Moisture and oxygen permeation characteristics per unit dose

If the evaluation shows that an intermediate configuration (such as a mid-size container with a low fill volume) represents a higher risk, that specific configuration must be included in the stability testing. Failure to demonstrate that the selected extremes adequately represent all packaging

configurations may result in the bracketing design being rejected.

18 How are different quantities and scaling of desiccants used evaluated in the context of a bracketing design?

When desiccants are used, they are considered integral components of the container-closure system. Bracketing is acceptable only when the same desiccant type is used across all container sizes. Differences in desiccant quantity may be acceptable if scientifically justified; however, the applicant should demonstrate that the selected desiccant quantities adequately control moisture exposure across all bracketed configurations. The use of different

desiccant types across container sizes is generally not acceptable.

19 Is it acceptable to use scaled desiccant quantities across bracketed sizes?

Scaled desiccant quantities may be acceptable if the same desiccant type is used and the scaling approach is scientifically justified. Assessors expect evidence that the selected desiccant quantities adequately control moisture exposure across all bracketed sizes. Inadequate justification may lead the assessor to conclude that desiccant performance represents an additional
variable, thereby undermining the bracketing assumption.

20 Under what circumstances is bracketing unacceptable to assessors, and what are the common deficiencies identified in justifications?

Assessors consider bracketing unacceptable when the selected configurations fail to represent true worst-case scenarios, or when multiple complex factors are combined—such as varying container sizes alongside different strengths or excipients—meaning the largest and smallest sizes no longer represent the extremes for all combinations. It is also rejected if there are differences in container materials, changes in closure or liner systems, inconsistent fill levels affecting headspace, or when applied to highly moisture-sensitive products without sufficient data.

The most common deficiencies identified during regulatory reviews stem from a lack of proper justification rather than a flaw in the bracketing concept itself.

Manufacturers frequently fail by providing generic "blanket statements" instead of a product-specific scientific defense. Other typical errors include inadequate explanations of worst-case selections, failing to address moisture permeation risks for plastic containers, omitting proof of container-closure sameness, and
providing no supportive stability data, such as historical moisture trends

21 What key elements do regulatory assessors expect in a robust scientific justification for a bracketing design?

Assessors expect a comprehensive, product-specific scientific rationale rooted in ICH Q9 (Risk Management) and aligned with ICH Q1D or VICH GL45 guidelines to prove that the selected extremes truly represent the worst-case stability scenarios. A robust justification must include four core elements:

- Identification of Extremes: A clear, data-driven explanation of why specific strengths or container sizes were chosen as the worst-case (e.g., configurations with the highest surface-area-to-volume ratio or highest headspace risk).
- System Sameness: Definitive confirmation that all container-closure components, materials, and integrity grades are identical across the entire product range.
- Risk Analysis: A detailed evaluation of critical stability risks, specifically addressing factors like moisture ingress, oxygen permeation, or active ingredient adsorption for plastic containers.

Supportive Data: Inclusion of existing stability trend data (such as historical moisture gain/loss profiles) to back up the theoretical risk assessment and minimize follow-up regulatory questions.

22 Is the bracketing design for highly moisture-sensitive drug products/Solid dosage forms acceptable?

For highly moisture-sensitive drug products, bracketing may be considered acceptable only when supported by enhanced justification and data. Assessors expect direct evidence demonstrating that moisture exposure is adequately controlled across the tested extremes. This typically includes moisture content trending, evaluation of degradation products, and confirmation that critical quality attributes remain within specification under both long-term and accelerated
conditions. In the absence of such data, bracketing is likely to be challenged.

23 **How do assessors evaluate moisture trend data in support of bracketing?**
Assessors evaluate moisture trend data primarily for consistency and predictability rather than identical values. Acceptable trends typically show
gradual and controlled moisture uptake without abrupt increases or inflection points. Moisture content should remain within established limits throughout the proposed shelf life.
Inconsistent or accelerating moisture uptake in one extreme may indicate size-dependent permeation behavior and weaken the bracketing justification.

24 **Is container weight gain considered an acceptable indicator of moisture ingress?**
Yes. Container or package weight gain may be used as a supportive indicator of cumulative moisture ingress, particularly for plastic containers.
Weight gain data are considered complementary to direct moisture measurements such as Karl Fischer or loss on drying. Weight gain alone is not sufficient to replace direct moisture analysis's but may strengthen the
overall bracketing justification when presented alongside other stability data.

25 **How is headspace evaluated as a risk factor in bracketing designs?** Headspace is evaluated as a potential risk factor for oxygen exposure and moisture ingress. Regulatory assessment typically considers both absolute headspace volume and headspace-to-fill ratio. In many cases, the largest container size represents the worst-case condition for headspace-related risks; however, this assumption should be supported by a scientific rationale, particularly for oxygen- or moisture-sensitive products.

26 Does a change in liner thickness or liner composition affect the acceptability of bracketing?

Yes. Changes in liner thickness or liner composition are generally considered changes to the container-closure system. Such changes may significantly affect moisture permeation and sealing performance. Unless adequately justified with supporting data, these changes would invalidate the assumption of identical container-closure systems and, therefore, compromise the acceptability of the bracketing approach.

27 **Is accelerated stability testing expected for all bracketed extremes?**
Yes. As a general expectation, accelerated stability testing should be conducted on all bracketed extremes. Accelerated data provide early confirmation of worst-case behavior and support the scientific validity of the reduced design. The absence of accelerated data on one of the extremes may result in additional information requests during regulatory assessment.

28 **Is photostability testing required for all bracketed container sizes?** Photostability testing is not required for all bracketed container sizes. Testing of a single worst-case configuration is generally considered sufficient, provided that container material, opacity, and thickness are identical across sizes. If differences exist that could affect light protection, additional photostability evaluation may be required.

29 **How should shelf life be assigned when a bracketing design is applied?** When a bracketing design is applied, the shelf life assigned to all intermediate configurations should not exceed the shelf life supported by the least stable tested extreme. If different stability behaviors are observed between the tested extremes, the shelf life for all bracketed configurations should be based on the worst-performing configuration. This approach is consistent with the assumption underlying bracketing that intermediate levels are no more stable than the extremes.

30 How should differing degradation trends between bracketed extremes be handled?

Differing degradation trends between bracketed extremes do not automatically invalidate the bracketing design; however, they require careful evaluation. The applicant should assess whether the observed differences impact the reliability of shelf-life estimation for intermediate configurations. In such cases, a conservative shelf-life assignment based on the least stable trend is expected. Significant divergence in degradation behavior may prompt a request for additional data or inclusion of an intermediate configuration.

31 Is bracketing acceptable if one of the tested extremes is not intended to be marketed?

Yes. Bracketing may be applied using a non-marketed extreme container size, provided that it represents a valid worst-case condition. In such cases, the stability data generated may be used to support the marketed intermediate configurations. A commitment should be provided to conduct post-approval stability studies on the marketed extremes if the marketing strategy changes. If the stability of extremes is different from the retest set for the extremes, then the intermediate should not be more stable than the least stable extreme. The shelf life assigned to intermediate sizes should not exceed that supported by the least stable tested configuration.

32 How is bracketing assessed during post-approval variations affecting packaging?

During post-approval variations, the acceptability of an existing bracketing design depends on whether the original assumptions remain valid. Changes to container material, plastic grade, closure system, liner composition, or desiccant type generally invalidate the original bracketing justification and require reassessment. Variations that do not affect the container-closure system, such as labeling or secondary packaging changes, typically do not impact bracketing acceptability.

33 Can bracketing be used to support the addition of a new intermediate pack size post-approval?

Yes. Bracketing may be used to support the addition of a new intermediate pack size post-approval, provided that the new size falls within the range of the previously approved extremes and uses the same container-closure system. The applicant should confirm that the original bracketing rationale remains applicable and that no new worst-case conditions are introduced.

34 Is bracketing acceptable for initial registration but not for shelf-life extension?

Bracketing is commonly acceptable for initial registration; however, shelf-life extensions often require additional real-time data. As the proposed shelf life exceeds the period originally supported at approval, assessors may request confirmatory data on marketed configurations to ensure the continued validity of the bracketing assumptions.

35 How are out-of-specification (OOS) or out-of-trend (OOT) results handled under a bracketing design?

An OOS or significant OOT result observed in one of the bracketed extremes is considered indicative of a potential worst-case failure. In such cases, all intermediate configurations supported by the bracketing design are considered at risk. Stability data should be presented for all intermediate configurations. A thorough investigation should be conducted to assess the impact on the bracketing assumptions, and corrective actions may include shelf-life reduction or additional stability testing.

36 What constitutes a concise, regulatory-acceptable summary statement supporting bracketing?

A concise, acceptable summary statement should identify the applied guideline, the selected worst-case configurations, and the rationale for representativeness. For example:
The bracketing design was applied in accordance with ICH Q1D and VICH GL45. Stability studies were conducted on the smallest and largest plastic container sizes, representing worst-case conditions for surface area–to–content ratio and moisture ingress. All intermediate sizes use identical container-closure systems
and are therefore considered represented by the tested extremes.

37 How is the bracketing data presented in the CTD file, protocols, justifications, and what are the mandatory data to be presented?

Bracketing data and justifications must be systematically distributed across four distinct sections of the Common Technical Document (CTD), primarily within Module 3 (Quality):

1. **Section 3.2.P.2.4 (Container Closure System in pharmaceutical Development)**
   - Purpose: The Packaging Rationale.
   - Mandatory Content: Physical and chemical justification proving the intermediate sizes are represented by the extremes. Includes material equivalence data, geometric matrices (surface-area-to-volume ratios), and moisture/oxygen permeation rates.
2. **Section 3.2.P.7 (Container Closure System)**
   - Purpose: The Packaging Specifications.
   - Mandatory Content: The technical identification and regulatory criteria of the commercial packaging line. Includes full descriptions, engineering schematics, analytical testing methods, material specifications, and pharmacopeial compliance certificates for all primary and functional secondary packaging components and the COA of suppliers.
3. **Section 3.2.P.8.1 (Stability Summary and Conclusion)**
   - Purpose: The High-Level Overview.
   - Mandatory Content: A concise summary of the bracketing design, a clear matrix table identifying which configurations are tested/untested, and the proposed shelf-life/storage conditions for the entire product line.
4. **Section 3.2. P.8.2 (Post-Approval Stability Protocol and Stability Commitment)**
   - Purpose: The Future Framework.
   - Mandatory Content: The formalized stability protocol demonstrating how commercial, post-approval batches will continue to be monitored using the reduced bracketing design.
5. **Section 3.2.P.8.3 (Stability Data)**
   - Purpose: The Analytical Results.
   - Mandatory Content: The actual raw stability data tables, statistical trend lines, regression/ poolability analyses, and photostability data proving that the extreme bracket configurations safely support the intermediate configurations

38 What is matrixing in stability testing?

Matrixing is a reduced stability design used to decrease the total number of samples tested by selecting specific subsets for evaluation at different time points. The hypothesis here is based on the assumption that the stability of the tested samples represents the stability of all samples at any given interval.

39 What factors can and cannot be matrixed?

- **Can be matrixed:** Batches, strengths with identical formulations, container sizes, fill sizes, and intermediate time points.
- **Cannot be matrixed:** Initial and final time points, test parameters (attributes), different dosage forms, and different storage conditions.

40 What stability factors can be matrixed in a stability study design? Matrixing can be applied to the following factors, provided that supportive data justifies their similarity in stability performance:

- Strengths: Formulations that are identical or closely related (e.g., the same granulation mix used for different strength tablets).
- Batches: Multiple batches manufactured using the same process and equipment.
- Container/Closure: Different container sizes or fill volumes within the same closure system.
- Packaging Systems: Different container-closure systems, or variations in the secondary packaging system that could affect the stability of the product

41 Is the use of Matrixing an acceptable stability study design for different dosage forms?

Yes, Matrixing as a reduced design can be applied to most types of drug products, but additional justification is required for complex drug delivery systems with many potential drug-device interactions. For drug substances,
matrixing is of limited utility.

42 What are the time point requirements for a matrixing design?

For original applications, you must always include the initial (0-month) and final time points. Additionally, there must be at least two other time points
within the first 12 months. Every combination of factors under accelerated conditions must also have at least three time points (initial, middle, and end).

43 How is matrixing designed and what is its significance? What are the core design requirements for using a matrixing approach in stability studies?

Matrixing designs must be designed in a balanced manner, so that each combination of factors is tested equally over the study duration. Full testing of all factor combinations at initial and final time points, while a fraction of the total combinations is tested at intermediate time points. By the end of the study, the matrix ensures that every combination has been tested enough to build a reliable stability profile for the entire product range to ensure comprehensive stability data with acceptable shelf-life estimation to ensure safety and efficacy of the products.

44 What should be ensured when conducting matrixing at accelerated or intermediate storage conditions?

Each Storage condition should be treated separately under its own matrixing design. When conducting matrixing at accelerated or intermediate storage conditions, it is essential to ensure that testing occurs at a minimum of three time points, including the initial and final time points, for each selected combination of factors.

45 • How is the "size" of a matrixing design determined?

The Size is expressed as a fraction (e.g., ½, ⅝, ¾) of the total number of samples that would be tested in a full design; the appropriate fraction depends on the total number of factor combinations and the amount of the supportive data available; a larger number of combinations and substantial supportive data allow for a smaller matrix size. Example:

Number of combinations	**Amount of Supportive data available [c]**		
Factors[a]	**Substantial**	**Moderate**	**Little or none**
Large (e.g., 3x3x3 or greater)	Fractional (e.g., 1/2)	Fractional (e.g., 5/8)	Full (i.e., no martixing[c])
Moderate (e.g., 3x2)	Fractional (e.g., 5/8)	Fractional (e.g., 3/4)	Full (i.e., no martixing[c])
Very Small (e.g., 3x1)	Fractional (e.g., 3/4)	Full (i.e., no martixing[c])	Full (i.e., no martixing[c])

[a] Expressed as a fraction of the total number of samples to be tested in the corresponding full design.
[b] Excluding time points
[c] No matrixing means that matrixing is not suitable
* Cumulative stability data obtained from clinical / development batches, primary stability batches, and /or production batches as appropriate to form the basis to support the stability profile of the product.

46 What is the mandatory testing protocol for pre-approval submissions involving matrixed designs? What are the mandatory design rules, testing frequencies, and size requirements for implementing a matrixing protocol in a stability study?

Mandatory Time Points:

-The study must always include the initial (0-month) and final time points.

-For long-term data, you must include at least two additional time points through the first 12 months, ensuring a minimum of three time points (including the initial and 12-month points) for every selected combination of batch, strength, container size, and fill.

-If the full study is unfinished at the time of submission, you must test every single selected combination at the 12-month mark (or the last point before submission).

- Accelerated conditions also require a minimum of three time points, including initial and end points.

Design Setup: Matrixing must be treated separately for each individual storage condition. It should never be performed across different testing attributes, though different attributes can have different testing frequencies if justified.

Sample Management & Reversion: All samples—including those not scheduled for testing under the matrixing plan—must still be physically placed on stability. The protocol must be followed without deviation, with the sole exception that you may revert to full stability testing if needed. Once you revert, full testing must continue until expiry.

Determining Matrix Size: The size is expressed as a fraction of the total samples in a full testing protocol. Size is determined by multiplying factor combinations (e.g., 3 batches × 3 strengths × 3 sizes = 27 combinations or 3x3x3) against available supportive data. More factor combinations paired with "substantial supportive data" allow for smaller fractional testing designs (such as a 1/2 design)

47 What is the regulatory requirement for continuing stability testing on a factor (strength or container size) that is no longer intended for marketing?

According to ICH Q1D, if a specific strength, container size, or fill is withdrawn from your marketing plan, you may—and often should—continue its stability testing within the matrixed design. The data from all factors are interconnected. Continuing to test the "non-marketed" version provides critical statistical support for the remaining strengths or sizes. This ensures the integrity of the overall data set and maintains the validity of the shelf-life projections for the products you do intend to market.

This requirement is based on the following structural principles:

-Interconnected Factor Dependence: In a matrixing model, data points from all batches, strengths, and sizes are statistically interdependent. The matrix relies on the entire structural web of data to predict shelf-life profiles.

-Preserving Statistical Power: Continuing to test the "non-marketed" configuration provides critical mathematical and trend support for the remaining strengths or sizes that will be commercialized.

-Preventing Design Collapse: Abandoning testing for the withdrawn factor mid-study can create data gaps that weaken or invalidate the overall statistical pooling and shelf-life projections of your marketed products.

- **48 What are the potential risks of using a matrixing design?**

The risks include reduced precision in shelf-life estimation due to fewer data points.
Insufficient power to detect differences among factors, leading to incorrect data pooling. Excessive reduction in factor combinations may fail to estimate the shelf life for missing combinations.

- **49 What factors determine the applicability of matrixing designs?**

Matrixing designs are applicable when:

1. Supporting data indicate predictable product stability.
2. Data variability is small or moderate (with statistical justification for moderate variability or a high degree of confidence that the tested subsets accurately present the stability of the entire group), as presented in the table
3. Stability differences within or among factors are minimal.

Data Variability	**Product Stability[a]: Excellent**	**Product Stability[a]: Moderate**	**Product Stability[a]: Poor**
Very Small	Applicable	Applicable	Applicable, if justified
Moderate	Applicable	Applicable, if justified	Generally, not applicable
Large	Applicable, if justified	Generally, not applicable	Not Applicable

[a] In general, *moderate* and *excellent* stability mean little or no change in product test results for a period of 2-3 years and 4-5 years, respectively, as indicated by supportive data. *Poor* stability means measurable changes in test results within 1 year.

[b] Variability in supportive stability data within a given factor or across different factors.

Generally, justification is required when matrixing across factors such as different strengths, container closure systems, or excipients. Supporting data must demonstrate predictable product stability and minimal variability. However, if the supporting data show moderate variability, extensive statistical justification is required (proposed matrixing vs. differences detected), and matrixing should not be applied if the data exhibit large variability.

In general, justification is necessary to ensure that the reduced design can adequately predict the product's stability and shelf life while minimizing risks associated with reduced data collection.

50 Can matrixing designs be used for biotechnological or biological products?

Yes, but they may need additional justification. Matrixing should only be applied to biological products when documentation confirms that the stability of the tested samples truly represents the stability of all samples. If it cannot be confirmed that different strengths or containers respond similarly, matrixing should not be used.

51 How should stability data from these designs be evaluated?

The data should be subjected to the same rigorous statistical analysis as a full study. This includes testing for batch similarity (poolability) before combining data into an overall estimate. If the extremes in a bracketing study are found to be dissimilar, the intermediate sizes are considered only as stable as the least stable extreme

52 What is the difference between matrixing and bracketing in the context of reduced stability testing?

Matrixing is a stability testing design that allows for the testing of a subset of samples from a larger set of combinations of factors, such as different strengths and container sizes. Unlike bracketing, which tests only the extremes, matrixing involves testing a selected combination of samples to provide a representative assessment of stability across the entire range.

53 Is it acceptable to use both bracketing and matrixing designs simultaneously in a single stability study?

Yes. It is allowed the combined use of bracketing and matrixing in a single stability protocol under ICH Q1D (and VICH GL45 for veterinary products). However, doing so requires a high level of scientific justification. When combining both designs, the applicant must demonstrate that the study remains statistically valid. Because combining a bracketed extreme with a matrixed subset drastically reduces the total amount of data collected, any unexpected stability failure in the remaining test points could invalidate the entire study and prevent the establishment of a reliable shelf life.

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جدول التعديلات

رقم الإصدار	تاريخ الإصدار	ملخص التعديلات
1	2026/9/14	الإصدار الأول للإشعار