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Review Article

## Stability Matrix Designs: A Boon for Stability Testing of Pharmaceutical Drug Products

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### ABSTRACT

Long term stability is done in a matrix approach after manufacturing of drug for ensuring the stability of drugs. Using the matrix basic design which is useful for testing 3 lots under one storage condition can be expanded to multiple presentation of products or multiple storage conditions. The design shows full testing at the end points (0 and 36 months) and shows partial testing at the interim time points (3, 6, 9, 12, 18 & 24 min). With the assistance of a statistical search algorithm, the test points are selected. 37.5% reduction in analytical testing, while permitting a reliable interim expiry estimate. Based on 12 months stability data it is provided by the proposed matrix design. The matrix approach obtained by expiration dating periods is typically more conservative than the approaches derived from the full testing estimate. The comparison of expiration dating estimate for meter dose inhaler and capsules is presented using the matrixed and full testing approaches.

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### Introduction:<sup>[1]</sup>

Stability studies were managed to exhibit how the quality of drug substances varies with time under the capacity of different environmental factors like temperature, humidity, light etc to initiate and re-examine the drug substance to recommend strong conditions. The drug product is defined as the dosage form in the final package. Stability studies must be applicable to all strengths and all packages. For new drug product accelerated testing is necessary for six months and long term testing is required to determine the shelf life. Thus the cost of stability studies is essential leading to statistically designed stability studies, which are called matrix design where "a selected subject total number of possible samples for all combinations is tested at a specified time point

### History:

Statistically in early 1980s designed stability studies were first used (E. Nordbrock, 1981, stability protocols) and it was accepted by US food and drug administration. (W. Fairweather, 1982, personal communication). Nakagaki<sup>[4]</sup>, who was first person to use the terminologies matrix and bracket<sup>[9-28]</sup>. Nordbrock<sup>[2,3,5]</sup>

was the one who appeared in first journal articles in 1992<sup>[6-8]</sup>. Bracketting and matrixing guidance was issued in 2003<sup>[29]</sup>. A guidance on evaluation of stability data was issued in 2004<sup>[30]</sup>.

### Designs:

#### Background

Basic analysis which is applied to stability data is linear regression of the parameter of the time therefore the selection of observations in the slope is to take first half in beginning of the study which gives the minimum variance and second half is at the end. The statistically designed stability designs are analysed for several times either they can be during the new drug product or either can be yearly for market product.

#### Basic Matrix 2/3 on Time Design

For one dosage form the strength has to be studied for long term study. In a single package there are three batches, which should be tested for every three months in first year and for every six months in second year. Later they must be tested annually that is yearly once until the expiry date period. Thus the shelf life of the period must be thirty six

months so that for complete study can be done, so each of the three batches was tested at 0,3,6,9,12,18,24 and 36 months(Table 1). This matrix 2/3 time design can be tested

only for the intermediated time points that are designed only for two of the three batches. This design can be tested for 18 months in all batches

**Table 1: Basic Matrix 2/3 on Time Design**

Batch	Test Times
A	0,3,9,12,24,36
B	0,3,6,12,18,36
C	0,6,9,18,24,36

#### Matrix 2/3 on Time Design With Multiple Package

In this designed a single strength is packed unto three packages with equal balance in each of three packages. Balance means each batch have been tested twice at

intermediate time point and analysis will be done after completion of eighteen months .These design can be modified by telling all package combinations at 18 months(Table 2).

**Table 2 Matrix 2/3 on Time Design With Multiple Package**

Batch	Pkg 1	Pkg 2	Pkg 3
A	T1	T2	T3
B	T2	T3	T1
C	T3	T1	T2

Pkg 1= package 1, etc

#### Matrix 2/3 on Time Design with Multiple Packages and Multiple Strengths

Further extension of the above is the three strengths are manufactured using same formula with different weights and divided into 9 sub batches and each strength consists of 3 packages. This design is applied for 9 sub batches in

balanced fashion. Each sub batch at the intermediate time point is tested twice in such a manner that each batch is tested 6 times during this intermediate interval and the analysis is done after 18 months. By testing all batches by strength by package combinations these design can be modified at 18 months(Table 3).

**Table 3 Matrix 2/3 on Time Design with Multiple Packages and Multiple Strengths**

Batch	Strength	Pkg 1	Pkg 2	Pkg 3
A	10	T1	T2	T3
A	20	T2	T3	T1
A	30	T3	T1	T2
B	10	T2	T3	T1
B	20	T3	T1	T2
B	30	T1	T2	T3
C	10	T3	T1	T2
C	20	T1	T2	T3
C	30	T2	T3	T1

Pkg 1= package 1, etc

**Table 4 Test Code Definitions**

Batch	Test Times after Time 0
T1	3,9,12,24,36
T2	3,6,12,18,36
T3	6,9,18,24,36

**Matrix 1/3 on Time Design:**

The design forms are reduced from 2/3 to 1/3 by reduction in amount of testing. For example one of the 3 batches are

tested during intermediate time point during basic 1/3 time design and analysis is done after 18 months. these basic 1/3 design can be further modified by testing several batches at the time of completion of 18 months.(Table 5)

**Table 5 Matrix 1/3 On Time Design**

Batch	Test Times
A	0,3,12,36
B	0,6,18,36
C	0,9,24,36

**Matrix on Batch ×Strength×Package Combination:**

This design is done for multiple strengths and multiple packages. To test the batch only single portion of the batch – by –strength by package combinations are taken . for

example ; in 3 batches it is divided to two strengths giving 6 sub batches, the batch size is small and only 2 packages can be manufactured in each sub batch . The design should be balanced because each of 2 packages of sub batch are tested(Table 6).

**Table 6 Matrix on Batch ×Strength×Package Combination**

Batch	Strength	Pkg 1	Pkg 2	Pkg 3
A	10	T1	T2	-
A	20	T2	-	T1
B	10	T2	-	T1
B	20	-	T1	T2
C	10	-	T1	T2
C	20	T1	T2	-

**Table 7 Test Code Definitions**

Batch	Test Times after Time 0
T1	3,9,18,36
T2	6,12,24,36

**Uniform Matrix Design**

Another type of design is uniform matrix design “ the same time protocol is used for all combinations of the other design factors.” This testing is done only during 12 ,24 and 36 months. Advantage of this study design is this design is more simplified with reduced variability of slope of the regression line. Disadvantage is major stability problems . therefore this model is not acceptable majority of areas.

**Analysis Background <sup>[30]</sup>**

Long term based data the ich q1e guidance for single package and single strength specifies that 95% one sided lower confidence bound for the mean regression line must be according to ich q 1 e . in case of multiple strengths / multiple packages there are three possible approach for analysis

the first approach : package by strength combination separately

second approach : all data to model with one analysis with separate intercepts and slopes for each batch by its strength and package without poolability testing

third approach: model all data with one analysis and test for probability for selection of appropriate reduced model.

**Separate Analysis Approach**

Multiple analysis are conducted in first approach ,with separate analysis of each package- by-strength-by batch. For each of separate analyses shelf life is calculated and product shelf life minimum of all package by strength by batch shelf lives.

**One Analysis Approach, Without Testing Poolability**

It is a second approach, out of which one analysis is done that includes complete data by using individual intercepts a shelf life is estimated and pooled mean square error from the entire set. Shelf life for each batch by package by strength is taken as the time the batch by package by strength acceptable within limits .For multiple batches only one package and one strength the SAS model is

$$y = BAB * A$$

Where B is a class term for batch A is covariate for age .For multiple batches and multiple packages only one strength. SAS model is

$$Y = BAB * AP * AB * P * A$$

Where B is class term for batch ,p is class term for package and A is the covariate for age . This model consist of separate slopes for every batch by package . The shelf life of the product is the minimum of all batch by package shelf lifes.

#### One Analysis: Testing Poolability<sup>[14,27,28]</sup>

It is very important that full model reflects manufacturing process. For exact formulation by using different weights it is assumed that there are multiple strengths and multiple packages so granulation batches split into sub batches, where it is manufactured into a different strength of the product using different weights of granulation . Zero samples are collected from each sub batch of the tablet and every tablet is packaged into sub batch products. Process validation provides proof that entire tablet sub batch is uniform

SAS model is

$$Y = BSB * SAB * AP * AS * AB * P * AB * S * AP$$

With B as a class term for granulation batch,

P= package

S= strength

A= covariate for time

This model testing begins the slope two way interactions determine by using a significance level of 0.25 when the batch is a part of the term and 0.05 otherwise .By using final model 95% one sided lower confidence bound to mean regression line and shelf life is assigned for each package by strength.

#### Factors Acceptable To Matrix

- It is acceptable for NDA
- Investigational new drug application studies
- Supplements and marketed products
- It is acceptable to matrix for product such as solids
- It is acceptable to matrix for product such as semisolids
- It is acceptable to matrix for product such as liquids
- It is acceptable to matrix for product such as aerosols
- It is acceptable to matrix after bracketing
- It is acceptable to matrix when there are multiple sources of raw material
- It is acceptable to matrix if there are multiple sites of drug product manufacture
- It is acceptable to matrix when identical formulations are manufactured into several strengths
- It is acceptable to matrix if formulation are cosely related
- Matrixing is applicable to the orientation of container during storage
- Matrixing may be applicable to in certain cases when closely related formulations are used in different strengths
- Matrix across container and closure systems may be applicable if justified
- It is acceptable to matrix within a package composition

- It is not acceptable to matrix across storage conditions
- It is not acceptable to matrix across parameters , such as dissolution and potency

#### General Rules

- Matrix designs are balanced exactly
- For each batch - by - strength - by - package combination is not tested , strength - by-package combination should be tested at least for 2 batches
- Unless there are manufacturing restrictions such as batch ×strength×package combination only more than 3 strengths there is a combination.

#### CONCLUSION

In many situations matrix designs are applicable generally for stable products 1/3 matrix on time readily acceptable .2 Basic approaches when analyzing data from a matrixed design . There are several methods used to evaluate and compare potential designs.

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