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STABILITY PROGRAM FOR MARKETED BATCHES

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ABSTRACT

The organization and implementation of a stability program for marketed batches is addressed by answering the questions: (1) What is a stability program?, (2) Why are stability programs necessary?, and (3) How do we conduct the program? Comments will be made regarding historical considerations and remarks will be directed toward the tools that are necessary for the program. There is no documented cookbook describing how to organize and perform your stability program. There are indications however, and these will be incorporated into a discussion of how one program is being used.

INTRODUCTION

It is difficult to talk about a subject in which there are many experts. This topic falls into the realm of politics or Monday morning quarterbacking. However, the risk is worth taking because one can always be sure about the things that are a matter of opinion. There is no system identified as the absolute right way to organize and conduct a stability program. There are however, certain characteristics that all systems should have.

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First, it is worthwhile clearly defining WHAT is meant by the title, and then proceeding with WHY and HOW (which includes WHERE, WHEN, WHO). Historical Considerations are discussed before concluding with the "Tools" required to perform a stability program.

WHAT is a Marketed Product Stability Program

Marketed product stability programs are concerned with the physical, chemical, microbiological and/or biological evaluation of pharmaceutical product which has been distributed to the field; i.e., released for human use. This is a simple and straight forward definition which is the topic of this paper. Although a relationship exists with R&D stability studies as well as clinical supplies information, this discussion will primarily deal with marketed batches (finished product).

Reasons for Conducting Marketed Product Stability Programs

The stability program policy evolves from an understanding of why the work is done. Later the organization and wording of HOW will demonstrate a correlation with WHY.

There are several reasons why firms conduct a marketed product stability program. Three areas are identified as: (1) NDA requirements, (2) CGMP requirements, and (3) Business requirements.

1. NDA Requirements:

NEW DRUG APPLICATION
FD Form 356H
Section 8P

This document requires a complete description of, and data derived from, studies of the stability of the drug, including information showing the suitability of the analytical method used. Additional stability studies underway or contemplated should be described. Stability data should be submitted for any new-drug substance, for

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the finished dosage form of the drug in the container in which it is to be marketed, including any proposed multiple-dose container, and if it is to be put into solution at the time of dispensing, for the solution prepared as directed. It is necessary to state the expiration date(s) that will be used on the label to preserve the identity, strength, quality, and purity of the drug until it is used. (If no expiration date is proposed, the applicant must justify its absence.)

This paragraph also includes some indications of how to organize and report a stability study, although this would not apply to every situation encountered.

2. CGMP Requirements: Excerpts from 21CFR 211.137 and 211.166 are shown below:

211.137 Expiration dating

a. To assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use, it shall bear an expiration date determined by appropriate stability testing described in 211.166.

b. Expiration dates shall be related to any storage conditions stated on the labeling as determined by stability studies described in 211.166.

211.166 Stability Testing

a. Talks to a stability protocol.

b. Talks to accelerated stability data and expiration dates.

Again, each of these excerpts includes some indications of how - but it is not explicitly spelled out in a checklist format.

The previous two WHY reasons, NDA and CGMP, can be classified as regulatory requirements. However, even without these legal constraints, there is a third reason why a

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marketed product stability program is necessary. Simply stated, GBP's, Good Business Practices, make sense.

3. Good Business Practices

   a. The following excerpt from J.M. Juran's book, Quality Control Handbook [1], talks about a concept of quality which is essentially a business reason.

      "All human institutions (industrial companies, schools, hospitals, churches, governments) are engaged in providing products or services to human beings. This relationship is constructive only if the goods and services respond to the overall needs of the user in price, delivery date and fitness for use."

   b. The author's explanation of WHY a stability program is essential from a business requirement is indicated below:

      Stability data can be used to make decisions relative to: (1) batch release, (2) batch recall, (3) complaint responses, and (4) process improvements.

All of the above requirements include legal, ethical, moral and business issues relating to the manufacture and sale of medicinal product. Additional ideas could probably be added to the list. No matter how the reasons are listed however, it is clear that the purpose of the marketed product stability program is to assure that drug products meet appropriate standards of identity, strength, quality, and purity at the time of use, and to provide data for the validation of expiration dates.

Before proceeding from WHY to HOW, it is necessary to determine what other work has been done, i.e., normally by R&D, in the development of the formulation and justification data for the expiration date.

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Ideally, accelerated stability studies exist; i.e., extremes of light, temperature, humidity (and possibly pressure) on pilot batches and production size batches. These studies will also be continued under ambient conditions for a period of time at least up to the expiration date.

If these data do not exist, Get Them. The marketed product stability program then is not concerned about extremes of humidity and temperature, etc., but only room temperature and the marketed package. If some change or deviation occurs during the production process, then it is possible to go back and do accelerated studies for a given time period before releasing the batch, which is also placed on long term room temperature stability.

The argument that these conditions do not adequately reflect the real life situation of storage in a non-air conditioned warehouse, or transportation in a trailer truck across the southwest portion of the country has been avoided. The reasons for not entering into that discussion are simply that: (1) these conditions are short term, (2) the R&D stability data, i.e., accelerated data which was generated early on, provided information which justifies allowing product to be stored or transported under these conditions for a short time period. Furthermore, the statistical evaluation of the R&D stability data has been used to determine the expiration date. The marketed product stability program needs only to validate that expiration date.

Conducting A Marketed Product Stability Program

It is appropriate to discuss HOW, with the assumption that the previous R&D data has been generated, and that the procedural part of the program is consistent with the following criteria:

1. Samples have been sampled properly.

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2. A stability indicating assay is in place and has been validated and transferred to the stability testing group.
3. Stability specifications are defined - i.e., the product must meet all release specifications. However, it may not be necessary to perform all of these tests during the stability program. All test methods must be meaningful and validated.
4. Reporting format of data is defined. For example: statistical treatment, reassay criteria, etc. These parameters can be clearly defined in a Stability Protocol which is completed and approved prior to the testing of samples.

   Remember that HOW involved WHERE, WHEN and WHO.

WHERE

In this particular case, where refers to physical conditions as opposed to physical or organizational location. Unless otherwise specified, e.g., a refrigeration requirement, marketed product stability samples are stored between 15° and 26°C, and the relative humidity is between 15 and 60%. All temperature and humidity conditions are recorded.

WHEN

Unless only one batch is made per year, no fewer than two batches representing each type of container in each manufacturing site are placed on stability the first year a product is marketed. Two batches are also placed on stability the second year and one batch each year thereafter. Any major change in formulation, manufacturing directions, manufacturing site, or immediate container restarts the clock.

Unless otherwise specified, the samples with three or more years of expiration dating are assayed at intervals of 3, 6, 12, 24, 36, 48, 60 months and a point not to exceed 1 year

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past the expiration date. For those products with less then 3 years of expiration dating, samples are assayed at 3, 6, 12, 18, 30 and 42 months.

WHO

The Quality Assurance/Control laboratories are responsible for release of product. In some organizations, QA also does the stability testing. Adherence to one important factor is necessary.

The stability testing group must be dedicated (time/head-count/equipment) to conducting the stability program.

There are obvious advantages to having the same laboratory performing both release and stability testing; but these advantages can be undermined if, in fact, personnel and equipment are not available at the necessary time.

HISTORICAL CONSIDERATIONS

The purpose of this topic is simply to emphasize the message: USE YOUR STABILITY DATA. This information should not be generated and filed without review and discussion. There are times when it may be necessary to open Pandora's box. Decisions regarding: (1) product release, (2) extension of expiration dates, (3) decrease of expiration dates, (4) formulation changes, (5) manufacturing changes, (6) specification changes, (7) responses to complaints, (8) increasing or decreasing testing intervals, (9) recalls, etc., can be made with the proper statistical evaluation of stability data and stability trends. Some of these decisions may need FDA approval before implementation, while others are internal business negotiations; but the fact remains, a better decision can be made if a meaningful marketed product stability program is conducted.

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TOOLS

Now that the philosophy regarding the marketed product stability program has been discussed, the mechanism for implementing and monitoring the program will be addressed. These tools are:

1. Standard Operating Procedure for the Stability Program and Batch Sample Survey
2. Stability Protocol
3. Statistical Evaluation of Expiration Periods and Release Limits

1. Standard Operating Procedure for the Stability Program and Batch Sample Survey

It is not necessary to explain how to write an SOP, but only to outline the contents of one to serve as an example.

Title - Stability Program and Batch Sample Survey

Major headings include:

1.0 Purpose
2.0 Scope
3.0 Procedure
    3.1 Marketed Product Stability Program
    3.2 Special Stability Program
    3.3 Batch Sample Survey
    3.4 Computer Data Control Procedures
4.0 Attachments
    A. Batch Sample Survey Schedule
    B. Checklist for Stability Test Results Reported To Be Out of Specifications

1.0 Purpose

The purpose of the Stability Program and Batch Sample Survey is to assure the drug products we produce meet appropriate standards of identity, strength, quality and purity at the time of use and to provide data for the validation of expiration dates.

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2.0 Scope

2.1 Stability Program

This includes all marketed product stability studies conducted by Quality Assurance. Included in this program are batches of product placed on stability to represent normal production, as well as those batches placed on stability because of significant changes in formulation, raw material suppliers, equipment, assays, manufacturing directions, immediate containers, etc. Unless otherwise specified on the product label, retained samples are stored between 15° and 26°C, and at a relative humidity between 15 and 60%. This program does not include accelerated stability samples.

2.2 Batch Sample Survey

This includes every batch of every product manufactured. A properly identified reserve sample of units selected at random from each batch is stored under conditions consistent with product labeling. These samples are inspected annually for physical evidence of deterioration unless such inspection would violate the integrity of the sample (211.170).

3.0 Procedure

3.1 Marketed Product Stability Program

Unless only one batch is made, no fewer than two batches representing each type of container and each manufacturing site are placed on stability the first year a product is marketed. Two batches are also placed on stability the second year and one batch each year thereafter. Any major change in formulation, manufacturing directions, manufacturing site, or immediate

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container restarts the clock. The clock will not restart unless the change affects every batch manufactured after the change occurs.

Unless otherwise specified, the samples are assayed at intervals of 3, 6, 12 months and then annually to a point 10-12 months past the expiration date.

3.2 Special Stability Program

Any batch with a new (additional) raw material supplier, a new (additional) immediate container, or manufactured with a deviation is recommended for the Special Stability Program.

One additional section to highlight concerns the guidelines for the decision process of placing batches into the Special Stability Program.

a. If the change is not significant, the batch may not be placed on stability.

b. If one or more stability studies have been completed or are in progress for this same change, this batch may not be placed on stability.

c. If the change is major and it is determined that it is permanent in nature, the batch may be placed on the Marketed Product Stability Program and the clock restarted.

d. If several product changes are contemplated, a batch may be judiciously chosen to cover more than one change.

Because the product is in the field, it may be necessary to react according to information resulting from the special stability program.

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3.3 Batch Sample Survey

3.31 A properly identified reserve sample of units selected at random from each batch of product are placed in the retained sample storage area. The samples are stored in the same immediate container - closure system in which the drug is marketed and stored under conditions consistent with product labeling. The quantity of material to be retained is twice the quantity sufficient to perform all testing for a period of one year beyond the expiration date of the product.

3.4 Computer Data Control Procedure

This section is included because computer data handling systems are becoming state of the art laboratory equipment. The contents of this section are an item by item cook book description of how to handle the system. You are all familiar with the concept that a computer will only do what you tell it to do. Three major areas that are explained include explicit instructions for data entry, data verification and data approval.

4.0 Attachments

A. The Batch Sample Survey Schedule indicates the pull dates for the annual batch sample survey. The schedule is on an 11 month basis so that over a period of time, we will survey batches pulled for different months of the year.

B. Checklist

There are times when unacceptable results may be obtained during a routine stability testing interval. The cause of the poor results can range

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from analyst error to poor sampling to an actual batch stability problem. In an effort to properly identify the cause and extent of the initially generated out of specification result, A Checklist for Stability Test Results Reported To Be Out of Specifications can be utilized (see Appendix).

After completing the checklist, the Laboratory Director passes on the results to the Director of Quality Assurance for review and action. This checklist completion and upper management review process is required to take place within a 5 working day period, in the event that FDA notification would be appropriate.

2. Stability Protocol

This document is really a subsection of the SOP and includes the following major headings.

I. Sample Requirements

II. Interval for Chemical Testing

III. Stability Specifications

IV. Methods for Testing

I. Sample Requirements

All marketed containers are included and identified in 3 major categories.

a. Units per Test Period
b. Total Number of Units Needed
c. Assays per Test Period

II. Interval for Chemical Testing

Specific time intervals are identified.

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III. Stability Specifications

Only stability specifications are included.

IV. Methods for Testing

Actual methods are documented or appropriately referenced.

The Quality Assurance laboratory is responsible for release of product and subsequent stability testing of marketed batches. Policy requires the transfer of all methodology (developed outside the QA laboratory) before using on a routine basis. This "Method Transfer Process" is not necessarily meant to validate the method because these data already exist. However, the transfer mechanism is in place to assure that the method can work in QA hands with QA equipment.

3. Statistical Evaluation of Expiration Periods and Release Limits

A statistical analysis of stability data is an absolute prerequisite. The particular statistical methodology used may differ for each firm. However, the approach used should be consistent.

One such approach is the Rate of Loss (ROL) program as part of a Stability Monitoring System. This program calculates the rate of loss for a given ingredient in percent label per year, the standard error of the estimate, and the upper 95% confidence limit on that rate of loss. Then, given the expiration period and lower specification limit, the program will compute the minimum release limit based on the rate of loss.

The concept of the minimum release limit is of no consequence during the stability testing program. However this value is used to set RED/YELLOW limits for product release. By only releasing product with an active ingredient assay above the RED limit, there is statistical assurance that this assay value will remain within label claim throughout the expiration period specified.

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The YELLOW limit is used to allow reassays in the event that the analytical value is too close to the RED limit based upon the method variability, which is determined during the "Transfer Process". The ROL program uses the nested error structure model of Fuller and Battese [2]. The mean assay at each age is determined by a linear effect of age plus group to group (age to age) variation. This group to group variation is due to the fact that each group of assays is performed at the same time by the same analyst using the same instruments and reagents. The estimates produced by ROL take this variability into account.

REFERENCES

1. Juran, J. M., Gryna Jr., F. M. and Bingham Jr., R. S., Quality Control Handbook, Third Edition, McGraw-Hill, Chapter 2, pp. 2-2 (1974).

2. Fuller, W. A. and Battese, G. E., "Transformation for Estimation of Linear Models with Nested Error Structure", JASA 68, No. 343, pp. 626-632 (1973).

APPENDIX

Check List for Stability Test Results Reported to Be Out of Specifications

1. Is the stability specification correct?

   A. What are the docket specifications?

      Release -

      Stability -

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B. What is the NDA specification?

Release -

Stability -

2. Do the expiration dates and batch numbers agree with the ones on the product container?

Expiration Date -

Batch Number -

3. Are the test results for the batches in question reproducible? Use controls and replication with different instruments and operators if possible.

4. Are the test results questionable form a scientific point of view?

5. How good is the method? Is it stability indicating? Did it go through method transfer? How did it do?

6. Is the method used precisely the same as the docket method? The NDA method?

7. Why are the affected batches on stability?

A. Marketed Product Stability?

B. Special Stability? Why?

8. From the data in our stability files, do other batches the

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same age give similar results? Do batches tested at the same time but of different ages give similar results?

9. Does there appear to be a trend over time?

   A. For these batches.

   B. For all batches on stability.

10. What is the complaint history for this batch? For all batches?

11. Can this problem be traced to a raw material? If so, what was the problem and should raw material have been used?

12. What additional tests are indicated, if any?

13. Should adjacent batches be tested from retained samples? Reason?

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