STABLE - A SAS/AF® SOFTWARE-BASED SYSTEM FOR PERFORMING
STATISTICAL ANALYSES OF DRUG STABILITY STUDIES
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ABSTRACT

Drug stability analyses obtained during the research phase are based upon assay values obtained from a number of lots of drug, which are stored under various conditions in possibly several different package configurations. Analysis of data is an iterative process, involving the pooling of parameters within and across different strengths to yield as simple a model as possible. Shelf life, expiration date, and release limits are estimated for specified conditions based upon the final model.

STABLE, a full-screen menu-driven system, was developed at PRI - Raritan using SAS/AF®, SAS/GRAPH® and the MACRO facility. It allows the statistician to perform one or more steps of a drug stability study at his terminal and return the results to the same terminal or optionally, to a local printer. Parameters are put into the analysis programs through fill-in-the-blank full-screens. The statistician may continue to perform analyses in an iterative fashion until he wishes to produce his final tables.

Introduction

In February 1987, the Center for Drugs and Biologics of the U.S. Food and Drug Administration issued guidelines on their suggested documentation regarding the stability of human drug and biological products. These guidelines contained recommendations for the design of stability studies needed to establish appropriate expiration periods and product storage requirements.

Depending upon the specific drug formulation involved, a number of physical, chemical, and microbiological characteristics of the drug product must be considered in addition to the physical properties of the container. Long-term studies with three lots of the drug product at the requested storage condition are recommended "in order to ensure a statistically acceptable level of confidence for the period proposed." Other short-term data at extreme storage conditions are usually required.

In the course of choosing the final formulation and storage condition, the pharmaceutical formulator may have also placed a number of additional lots of drug with alternative formulation and/or packaging components on long-term stability. These lots often have more long-term data than the final lots and can be used to answer a number of questions with regard to the effect of formulation and package differences on the stability of the product. Typically, all of these data are presented to the statistician for use in determining the shelf life, expiration dating period, and product release limits.

Drug stability analysis is therefore based upon assay values obtained from a number of lots of drug, which are stored in a variety of environmental conditions in possibly many different package configurations across a number of time periods. The essential unit for the analysis consists of a lot, package, conditions, and times and has been denoted at PRI - Raritan by its Stability Reporting Number (SRN). The goals of a stability analysis are:

1. Determine the degradation rates for each condition in each SRN.
2. Estimate the shelf life and expiration dating period for a given percentage of degradation for a specified condition in each SRN.
3. Estimate the release limits (mean initial assay value) needed to achieve a given expiration dating period for a specified condition in each SRN.
4. Use multiple SRNs to answer questions about possible lot and/or package differences in degradation rates.
5. Group SRNs in order to give overall estimates of shelf life, expiration dating period, and release limits within and across different strengths of drug for a specified condition.

The goal of the STABLE system was to help the statistician, who is knowledgeable in SAS® programming, perform individual SRN analyses, create and test poolability/grouping of SRNs, perform analyses of grouped SRNs, and produce summary plots and tables of results.
System Requirements

Much of the statistical methodology for performing the analyses had been developed outside of this system using base SAS, SAS/IML®, and the MACRO facility. However, the code still had to be modified for each analysis in order to accommodate the following technical considerations:

1. Rates needed to be estimated under zero, first, or second order degradation models, or perhaps all.
2. The number of SNRs and number of conditions per SRN were variable.
3. The total number of possible conditions was not known.
4. Conditions for expiration dating changed with the drug as did the percent of degradation allowed and how the estimates were constructed.
5. The list of possible lot and package identifiers changed with the drug.
6. Many possible poolings/groupings must be allowed and it must be possible to identify the SNRs used in the pooling.

The purpose of the proposed system was to generalize the process with SAS/AF software using the existing code as a basis for the analyses to be performed. This system should run under the CMS operating system and use SAS/GRAPH software for producing report graphics. Because the system is for use by statisticians familiar both with SAS and the desired analyses, little on-line help was anticipated.

System Development

The development of the system involved the following steps:

1. Identifying those aspects of a stability analysis to be included in the system and determining the generalizability of the programs available to do the analysis.
2. Creating the necessary menu and program screens.
3. Producing a prototype system to test screen layout and flexibility.
4. Testing and revising the prototype to include latest additions/changes.
5. Adding generalized programs to the prototype and repeating step 4.
6. Documentation and maintenance.

Any analysis performed is driven by two SAS data sets - one of which contains all assay values with their appropriate lot, SRN, time, and temperature identifiers; and the other which contains dictionary variables for the SRN. It is therefore reasonable that the user is first requested to specify the common library name for these files.

The types of analyses chosen under step 1 are best summarized on the main menu (Figure 1). Each choice leads to a selection menu where the user may specify modifications to the data by entering SAS statements, add additional titles, and make necessary choices which define an analysis. As each program to be generalized was finalized, they were placed in a MACRO library for inclusion at program invocation.

It was agreed that the system's menus be SAS/AF PROGRAM screens in order to more easily pass the statistician's choices for an analysis into the remaining code for immediate execution. SAS Display Manager is used to allow greater flexibility in reviewing the output at the terminal and managing disk copies of the results.

Conclusions

The STABLE system was designed to give the statistician enormous flexibility in arriving at a final analysis of stability data without burdening him with enormous amounts of SAS programming. It will help reduce the time required for an analysis, allow more time for interpretation of results, and provide good documentation of the analyses performed.

Through its use of SAS/AF, Display Manager, the MACRO facility, and other SAS products, the STABLE system demonstrates the power of the SAS system for integrating many facets of a complex statistical analysis into a timely, user-friendly system.

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