Pharmaceutical Application for Stability (PASS) Analysis

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Abstract: PASS is a point-and-click answer to the key issues raised by “marketed products” and by accelerated stability testing in the QA/QC/QI area. The application virtually automates data entry, test scheduling, stability analysis (for both accelerated and marketed products), and FDA reporting.

I. Introduction and Overview

PASS (product analysis, shelf-life stability) is designed to remove the cumbersome drudgery (and therefore the potential for error) from the key tasks involved in marketed products shelf-life stability testing, namely: data entry, test scheduling, product trend analysis, and FDA (and other regulatory authorities) reporting.

PASS also has the capability to integrate accelerated testing outcomes with marketed product outcomes to remove much of the risk in the uncertainty surrounding final product approval.

Basically, PASS has been developed into a management decision making tool that follows FDA guidelines and allows for greater returns on up stream management of the R & D function (i.e., packaging, formulation, specification limits, supplier selection, product initiatives, etc.), and greater control over process improvement efforts.

The application has a number of time and money saving features; but details on only four key features and associated benefits are presented below:

1. “One time data entry” - much less labor and minimum data entry error,

2. Automatic scheduling - no labor, no errors, no missed deadlines,

3. Point and click analysis and reporting - no additional staff training in statistical analysis, no additional management and clerical time for reports creation (either electronic reporting/signatures, or hard copy reporting),

4. Integration of historic accelerated tests information with marketed products historic stability information (and optionally with final product release data) - risk reduction and uncertainty management for improving process quality.
II. PASS (Product Analysis for Shelf-life Stability)

1. One Time Data Entry

In many pharmaceutical and food companies data on stability testing (both for marketed products and accelerated testing) are not being systematically recorded. Therefore, PASS application provides for easy, point-and-click data entry of all relevant information about stability testing. There are 4 basic levels of data being entered, as follows:

- product data (e.g., product name, code, form, shelf-life, package, etc.)
- tested characteristic data (e.g., characteristic name, test type, method, lower and upper specification limits, etc.)
- batch data (e.g., batch ID, stability start date, stability testing plan, etc.)
- time data (e.g., test month, test value, etc.).

Figure 2. shows an example of batch data entry (level 3). After selecting a product from the list of products, batch ID and stability testing start date (i.e., production date), the user has to select a stability testing plan (e.g., 0, 3, 6, 12, 24, 36 months) from the list of all possible testing profiles (see blue frame below).
2. **Automatic Scheduling**

Pharmaceutical and food companies have, at any one time, many different products with many product characteristics (with a number of batches each) at different stages in the stability testing cycle. In any one month there are many different tests to be performed, and it is of course critical not to miss any deadlines.

Once all data on stability testing is entered into the PASS application (either through the PASS entry module or accessed from external databases using SAS accessing capabilities), the automatic scheduling module can create a listing of all tests that have to be performed in any future period (e.g. next month). The Figure 2 shows an example of a scheduler automatically created by selecting January 1999 to February 1999 for the scheduling period. The tests that have to be performed in that period are listed ordered by product name, code, batch and the characteristic to be tested.

Optionally, the user can also get a list of products/batches/tests that are missing, or have not yet been recorded... a very useful management control feature.
3. Stability Analysis and Reporting

Shelf life or expiration date of human drugs and biologics has to be a direct application and interpretation of the knowledge gained from stability testing. Therefore, FDA issues guidelines providing recommendations for the design, statistical analysis, and interpretations of results of stability studies to establish appropriate expiration dating period(s).

The original FDA proposed statistical analysis procedure for determining expiration dating period is implemented in the analysis module of the PASS application. As seen in Figure 4, the OLS method that treats effects (batches) as fixed is the default model. Under this model, it is automatically determined whether the degradation curves for the selected characteristic are the same for all the batches, or whether individual batch degradation lines have different intercepts and/or different slopes.

In addition to the FDA’s recommended ordinary least squared (OLS) method for analyzing shelf-life stability, PASS allows also for random effects modeling, and for models with prior transformations of variables.

Another important feature of the Analysis module is the possibility to select the output form:

- Analysis and Graphs (default) - Detailed analysis results and graph(s) are created in the output window in the graph window (e.g., see Figure 5), respectively. The user has the option to print or submit electronically.
- Analysis only - only detailed analysis results are created and can be printed.
- Export to word - graphs and interpretation of the analysis are automatically exported into MS Word for printing or electronic submission.
Since different batches are, in general, at different stages of stability testing, each time a batch is selected, a list of months at which that batch has been tested appears. The user can, thus, select only batches that are at the end (or close to the end) of their stability testing cycle.
Finally, each time the analysis is performed, results (i.e., estimated expiration date) are being recorded for later summary analysis and integration with accelerated testing results. This “data mine” becomes a source of quality improvement.

Statistical analysis and reporting of accelerated testing data (not shown here) are based on different set of models (e.g., Arrhenius model) for the estimation of shelf life. The Accelerated Tests Statistical Analysis module has the same input/ output capabilities as the Marketed Products Statistical Analysis module.

4. **Integration**

Integration of marketed products and accelerated stability testing can be done at the individual and summary (i.e., all products) level.

At the summary level, the PASS application compares marketed products to accelerated test shelf life predictions. In the Figure 6 “number of tests” with commensurate shelf life predictions (green bars) are compared to “number of tests” and incompatible predictions (red bars). These comparisons can be viewed over different product forms, test types, products, characteristics, batches, packages, suppliers, divisions, production lines, countries, time periods, etc.

Percentage of compatible predictions can be used as a critical success factor for stability testing, and monitored over time for quality improvement.

![Figure 6. Comparison of marketed products with accelerated test shelf life predictions.](image)

Since marketed products and accelerated testing data are linked together, their degradation curves can be easily compared and studied at the product level. In other words, we can compare accelerated predictions with marketed products estimates ... another valuable graphical learning tool for process improvement initiatives.
III. Summary

PASS is designed to reduce costs and efforts associated with the entry, scheduling, analysis, and reporting for both accelerated and marketed products stability information.

The cost saving can be enormous and are easily estimated for labor, training and overhead costs.

What is not so easily estimated is the bonus productivity and reduced stress on personnel that is achieved when PASS stability information from other previously manufactured batches of the same product can be used to predict the amount of potency loss that a particular batch of a drug (or food) product will experience ... before its expiration date.

PASS can help raise productivity by reducing the risk surrounding the uncertainty inherent in the final product release process.

The PASS Application has been developed using the following SAS modules: SAS Base, SAS/AF, SAS/STAT, SAS/GRAPH and SAS/EIS.

References:


Notes:

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