

## **Deploying SAS® as the Cornerstone of a Stability Monitoring Program: A Case Study**

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### **ABSTRACT**

Both US and international regulations require pharmaceutical companies to perform stability testing on all marketed active pharmaceutical ingredients (APIs; also referred to as drug substances) and finished drug products to provide evidence on how the quality of such products varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light. Data obtained during stability testing is used to establish a retest period or shelf life for a product as well as recommended storage conditions for the product.

Inherent challenges faced by stability personnel charged with managing the storage and testing of a high volume of products and/or product configurations include (1) difficulty in distinguishing variability in test results from changes in the product over time, and (2) resource constraints on the capacity for statistical analysis and evaluation of stability data in a timely manner. These challenges are critical to an organization's ability to detect changes in overall product quality over a protracted period of time, and can also preclude an organization's ability to strengthen a product's marketability and enhance inventory management in the event that the product's assigned expiration dating can be extended on the basis of data collected during stability testing.

Conventional laboratory information management systems (LIMS) have been largely deficient in addressing these challenges, primarily because of the unique nature of stability data and how it is collected and analyzed. This paper details the development and implementation of a strategy for leveraging SAS technologies to address the analytical needs of a stability monitoring program, and its impact on day-to-day operations for a stability testing laboratory in a major pharmaceutical company.

### **INTRODUCTION**

One aspect of pharmaceutical quality is consumers' expectation that a drug they intend to use to treat an ailment is as effective as advertised on the packaging on the product. They also need to know that the efficacy of the drug is not indefinite; if the product sits unused on the shelf there likely will come a time when its efficacy is not what it once was when first manufactured. Pharmaceutical manufacturers therefore place specifications around key product attributes, such as drug potency, to ensure that the quality of the product is consistent with the claims stated on its packaging. In addition, companies must repeatedly test the product over time, sometimes for as long as five years, in order to know how long the product can be expected to remain at its highest level of quality. This process of long-term product testing is referred to as stability testing, and the data acquired via this process requires several kinds of statistical analyses to not only demonstrate how long a product will last but also to identify potential product quality issues which may indicate a need to change the manufacturing process, methods of testing the product, or the environmental conditions in which the product can be stored.

The storage and testing of large samples of commercially viable drug product is expensive; companies therefore usually place only one or two lots of a given product on stability testing protocols per year. The handful of lots selected for testing are intended to represent the quality of all lots manufactured within that same year; this can be a tremendous burden if a product is manufactured routinely, say, daily or weekly. For this reason it is imperative that manufacturers have the ability to determine stability-related product quality issues as quickly as possible; there is neither time nor opportunity to corroborate evidence of a problem by testing other product samples. For a manufacturer of several hundred individual product offerings the task is made more daunting by the sheer volume of product samples to be tested and evaluated.

This paper highlights the development of a custom SAS application called STAN (Stability Trending & Analysis Node) which is specifically designed to handle tasks related to the evaluation of stability data. While stability data may be stored in some sort of database or laboratory information management system (LIMS), these repositories are either static or offer only a few basic statistical functionalities. And while commercial statistical software packages are capable of performing the requisite analyses, most require that a user first import already formatted data in order to perform analysis, and also require a user to know the specific task he/she wishes to perform. Through the power of SAS, STAN is able to quickly acquire and transform stability data as well as perform the specific tasks required in evaluating stability data. This means that a stability laboratory analyst no longer has to assemble a table of data, then pass it on to a statistician to work his/her numerical magic. Instead, STAN allows stability lab personnel to extract and perform all kinds of pertinent analyses on their own, exponentially improving the ability to evaluate data in a timely manner.

## USER REQUIREMENTS

In a most general sense, there are three main business drivers spurring the development and use of STAN. These drivers are best represented by three basic kinds of questions commonly asked of statisticians by stability lab personnel in everyday business contexts, questions such as:

- 1 – “We obtained a result for a lot at the 12-month interval that looks to us to be unusually high [or low]. What can we do to know whether this really is an issue or if the result just happens to be somewhat higher than normal?”
- 2 – “We obtained a low [or high] result for a lot at the 18-month interval, and when we look at the data we have for this lot since it was first manufactured it looks like it might fail specifications earlier than the assigned expiration date. It also doesn’t look the same as the other lots we have on stability. Is there a way we can test whether this lot is really that different and whether we need to investigate further?”
- 3 – “It’s time for us to submit our annual report for this product to the FDA, and we have all this data we’ve accumulated since last year. How do we demonstrate that the data we have continues to support the assigned expiration dating?”

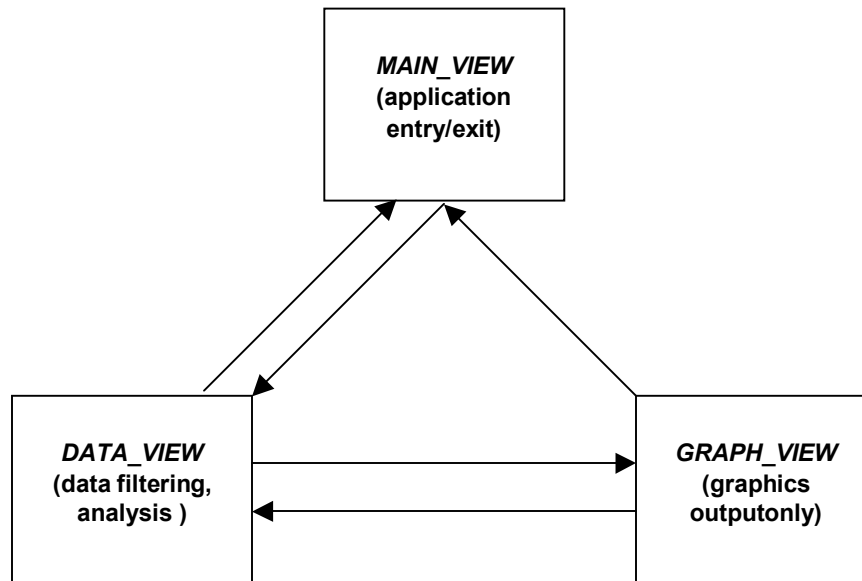
In other words, stability personnel need to be able to evaluate individual test results, individual lots, and the aggregate data from several lots, in order to make key decisions that may impact product quality and ultimately, perhaps, the company’s financial bottom line. For each of the questions above there is at least one statistical technique which may be employed as a standard tool for assisting analysts in making required quality decisions. These techniques have been bundled together within STAN to offer a very user-friendly interface that allows stability analysts to answer the specific question they are asking about their data.

## OVERVIEW

STAN is installed on a single PC workstation in a common area accessible to stability personnel, and is launched via a shortcut SAS icon which points to a configuration file called *stan.cfg*. This configuration file customizes the PC windowing environment so that STAN essentially has the look and feel of a standalone application.

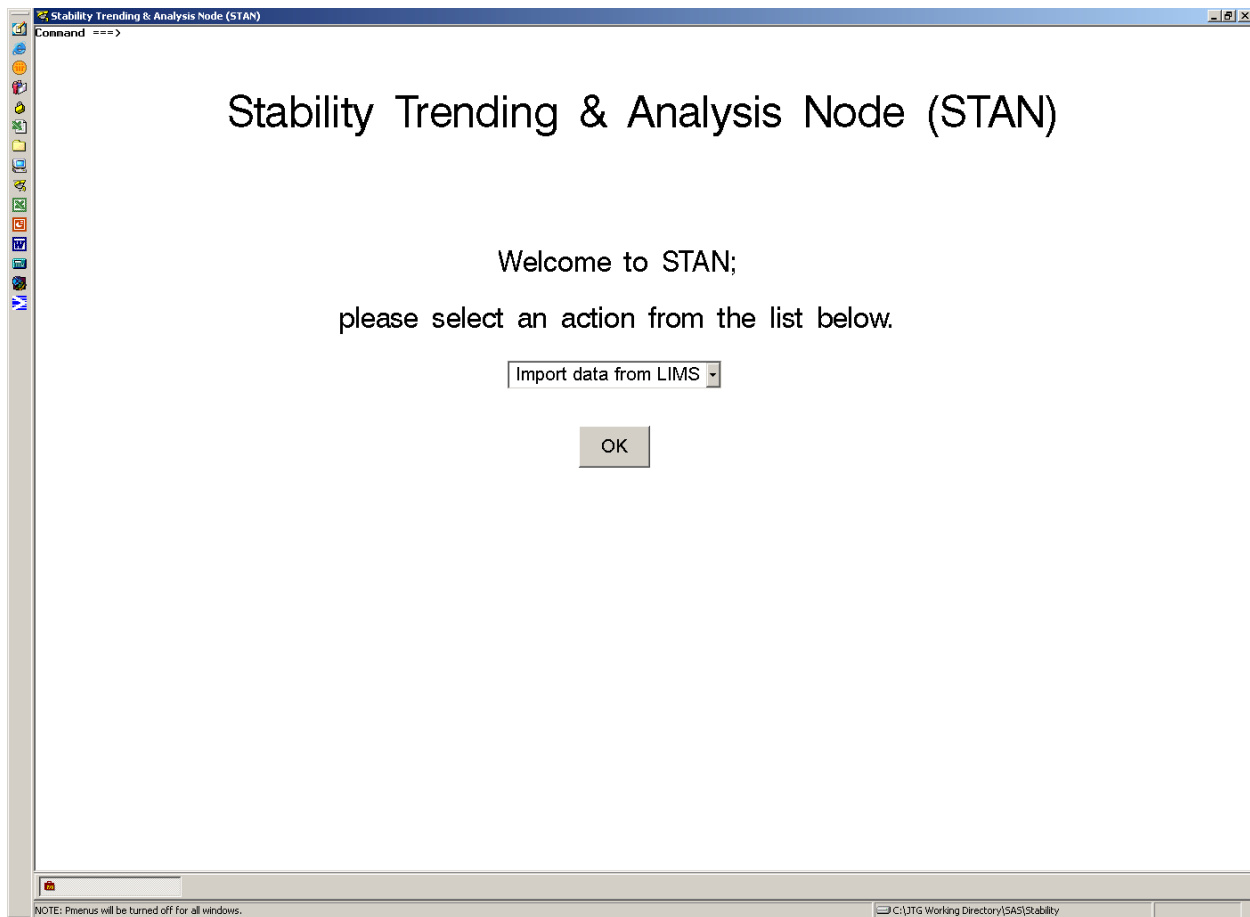
STAN is a simple application in that control passes between one of only three frames as shown in Figure 1 below. The point of entry into the application is the *MAIN\_VIEW* frame, where the user imports data for analysis or exits STAN. After importing data, control is passed to the *DATA\_VIEW* frame, where statistical analyses are requested. Graphical output from analysis requests are presented in the *GRAPH\_VIEW* frame, from which a user can either return to the *DATA\_VIEW* frame for additional analyses or return to the *MAIN\_VIEW* frame. The statistical output from requested analyses is displayed within the SAS RESULTS window.

**Figure 1. SAS/AF frames used in STAN.**



The subsections which follow provide detail regarding the functional options available to the user within each of these frames. Actual SAS code is only presented in brief where a particular procedure is called to perform a task that is central to a frame or option within a frame.

Figure 2. *MAIN\_VIEW* frame.



#### DATA IMPORT

In its development at the time of this writing STAN only accommodates import of Excel files containing data that has been extracted from a company LIMS system using another extraction tool external to SAS. Future development includes direct querying of LIMS systems to extract and transform data “on the fly”, thereby expediting data retrieval.

In the current version, once a data file has been selected, the data is imported and transformed by the application, and the user is prompted to select a directory for report output. This user-selected directory is subsequently used by the application to store PDF documents containing data, statistical analysis output, and graphics as records of the tasks the user performs within the application. At the end of a session the user can delete any undesired documents and retain the rest for relevant business purposes.

After selecting a storage directory, program execution passes to the *DATA\_VIEW* frame, where the transformed data is presented to the user as a data table in a window within the application. In this second screen the user has the option of either modifying the current data table (as shown in Fig. 3 below), opening a previously saved data table, performing statistical analysis, or returning to the main screen.

#### DATA FILTERING

Often a user may wish to restrict analysis to a subset of the data. The “Edit/Filter Data” task within the *DATA\_VIEW* frame provides an easy interface through which a user can construct a WHERE expression for including or excluding observations as desired. This is similar to the creation of WHERE expressions within the SAS VIEWTABLE window (invoked by issuing the command ‘VT’), except that in this case STAN only allows for logical operators in the expressions users create.

In order to accommodate changes requested by a user using the provided interface, the data table presented to the user is actually a copy of a background table which is the table processed if a user submits a WHERE expression. When a user submits an actual request by clicking “OK”, SAS code is processed via a submit block, creating a new background table which is a subset of the originating background table as specified by the WHERE expression. Each new table created in this fashion is named “Table\_Edit”, followed by a sequential number for unique identification. Three submissions of WHERE expressions within STAN, for example, will create data tables *Table\_Edit\_1*, *Table\_Edit\_2*, and *Table\_Edit\_3*.

Figure 3. Employing the filtering option within the *DATA\_VIEW* frame.

The screenshot shows the STAN (Stability Trending & Analysis Node) window. The main window title is "STAN (Stability Trending & Analysis Node)". Below the title is a table with the following columns: Study Number, Reason 1, Lot Number, Manuf Date, Date On Test, Protocol Id, Storage Condition, Drug Code/Descr, and STM Number. The table contains 25 rows of data. Below the table is a "Select task:" section with a dropdown menu set to "Edit/Filter Data". Below that is a filter dialog box with "Lot Number" selected, a dropdown set to "not equal to", and a text input field containing "A36701". An "OK" button is visible to the right of the dialog box.

	Study Number	Reason 1	Lot Number	Manuf Date	Date On Test	Protocol Id	Storage Condition	Drug Code/Descr	STM Number
1	36701001	Annual Lot	A36701	24JUN2000	24JUN2000	4436.M01	030CAMB	4436 - Sample Drug Code	7329023
2	36701001	Annual Lot	A36701	24JUN2000	23SEP2000	4436.M01	030CAMB	4436 - Sample Drug Code	7329023
3	36701001	Annual Lot	A36701	24JUN2000	23DEC2000	4436.M01	030CAMB	4436 - Sample Drug Code	7329023
4	36701001	Annual Lot	A36701	24JUN2000	19MAR2001	4436.M01	030CAMB	4436 - Sample Drug Code	7329023
5	36701001	Annual Lot	A36701	24JUN2000	21JUN2001	4436.M01	030CAMB	4436 - Sample Drug Code	7329023
6	36701001	Annual Lot	A36701	24JUN2000	19DEC2001	4436.M01	030CAMB	4436 - Sample Drug Code	7329023
7	36701001	Annual Lot	A36701	24JUN2000	15JUN2002	4436.M01	030CAMB	4436 - Sample Drug Code	7329023
8	36701001	Annual Lot	A36701	24JUN2000	14JUN2003	4436.M01	030CAMB	4436 - Sample Drug Code	7329023
9	37098001	Annual Lot	A37098	26JUL2001	26JUL2001	4436.M01	030CAMB	4436 - Sample Drug Code	7329023
10	37098001	Annual Lot	A37098	26JUL2001	03OCT2001	4436.M01	030CAMB	4436 - Sample Drug Code	7329023
11	37098001	Annual Lot	A37098	26JUL2001	04JAN2002	4436.M01	030CAMB	4436 - Sample Drug Code	7329023
12	37098001	Annual Lot	A37098	26JUL2001	29MAR2002	4436.M01	030CAMB	4436 - Sample Drug Code	7329023
13	37098001	Annual Lot	A37098	26JUL2001	17JUL2002	4436.M01	030CAMB	4436 - Sample Drug Code	7329023
14	37098001	Annual Lot	A37098	26JUL2001	31DEC2002	4436.M01	030CAMB	4436 - Sample Drug Code	7329023
15	37098001	Annual Lot	A37098	26JUL2001	24JUN2003	4436.M01	030CAMB	4436 - Sample Drug Code	7329023
16	37098001	Annual Lot	A37098	26JUL2001	23JUN2004	4436.M01	030CAMB	4436 - Sample Drug Code	7329023
17	37475001	Annual Lot	A37475	07AUG2002	07AUG2002	4436.M01	030CAMB	4436 - Sample Drug Code	7329023
18	37475001	Annual Lot	A37475	07AUG2002	07OCT2002	4436.M01	030CAMB	4436 - Sample Drug Code	7329023
19	37475001	Annual Lot	A37475	07AUG2002	06FEB2003	4436.M01	030CAMB	4436 - Sample Drug Code	7329023
20	37475001	Annual Lot	A37475	07AUG2002	01APR2003	4436.M01	030CAMB	4436 - Sample Drug Code	7329023
21	37475001	Annual Lot	A37475	07AUG2002	11AUG2003	4436.M01	030CAMB	4436 - Sample Drug Code	7329023
22	37475001	Annual Lot	A37475	07AUG2002	01FEB2004	4436.M01	030CAMB	4436 - Sample Drug Code	7329023
23	37475001	Annual Lot	A37475	07AUG2002	30JUN2004	4436.M01	030CAMB	4436 - Sample Drug Code	7329023
24	37475001	Annual Lot	A37475	07AUG2002	10JUL2005	4436.M01	030CAMB	4436 - Sample Drug Code	7329023
25	37850001	Annual Lot	A37850	17AUG2003	17AUG2003	4436.M01	030CAMB	4436 - Sample Drug Code	7329023

With the creation of each new table, the foreground table, which still mirrors the old table, is detached from the table viewer window, and overwritten as a copy of the new table via a data step in the same submit block. The new foreground table is then attached to the graph viewer for the user to see. This process is illustrated in Figures 4 and 5 below.

Since each new data table generated is stored within the *WORK* library, a user can therefore effectively undo a filtering operation by selecting a previous background table using the "Open table..." option in the *DATA\_VIEW* frame. All data tables are deleted when the session is ended.

Figure 4. Links between tables during *WHERE* processing.

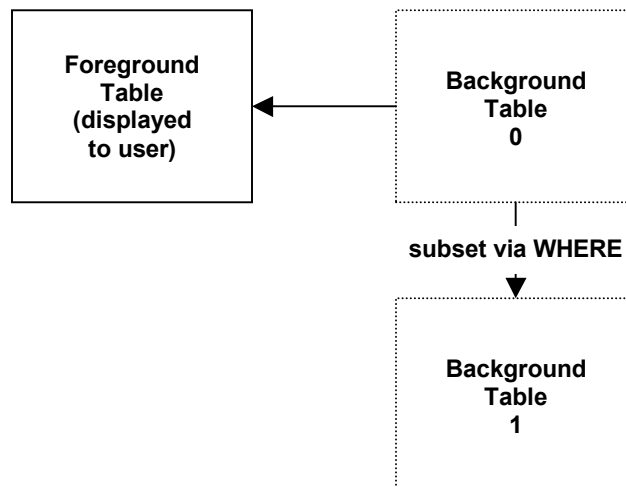
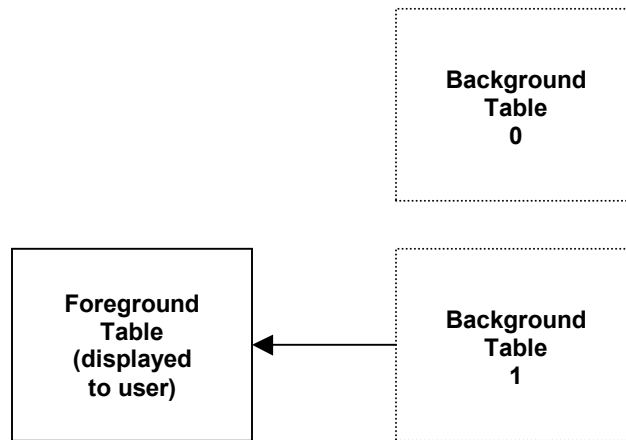


Figure 5. Links between tables after WHERE processing.



**STATISTICAL ANALYSIS: INDIVIDUAL TEST RESULTS**

The first of three types of statistical analyses STAN is designed to perform addresses the need to evaluate an individual test result for its consistency with the historical data for the respective product. Assessing the magnitude of the difference between a current test result and the result obtained when testing the same lot at the previous interval is complicated by the fact that the product itself is changing. The strategy employed by STAN for coping with this problem is to first fit a simple linear regression model (assuming the data warrants such a fit, which is usually the case) to the data, then construct individual and moving range (I-MR) charts using the regression model residuals ordered by test date. (I-MR charts are special types of statistical process control charts which, when used together, are effective in monitoring data produced by a process to ensure that the process remains consistent over time.)

Figure 6. Sample individuals chart for evaluating individual test results.

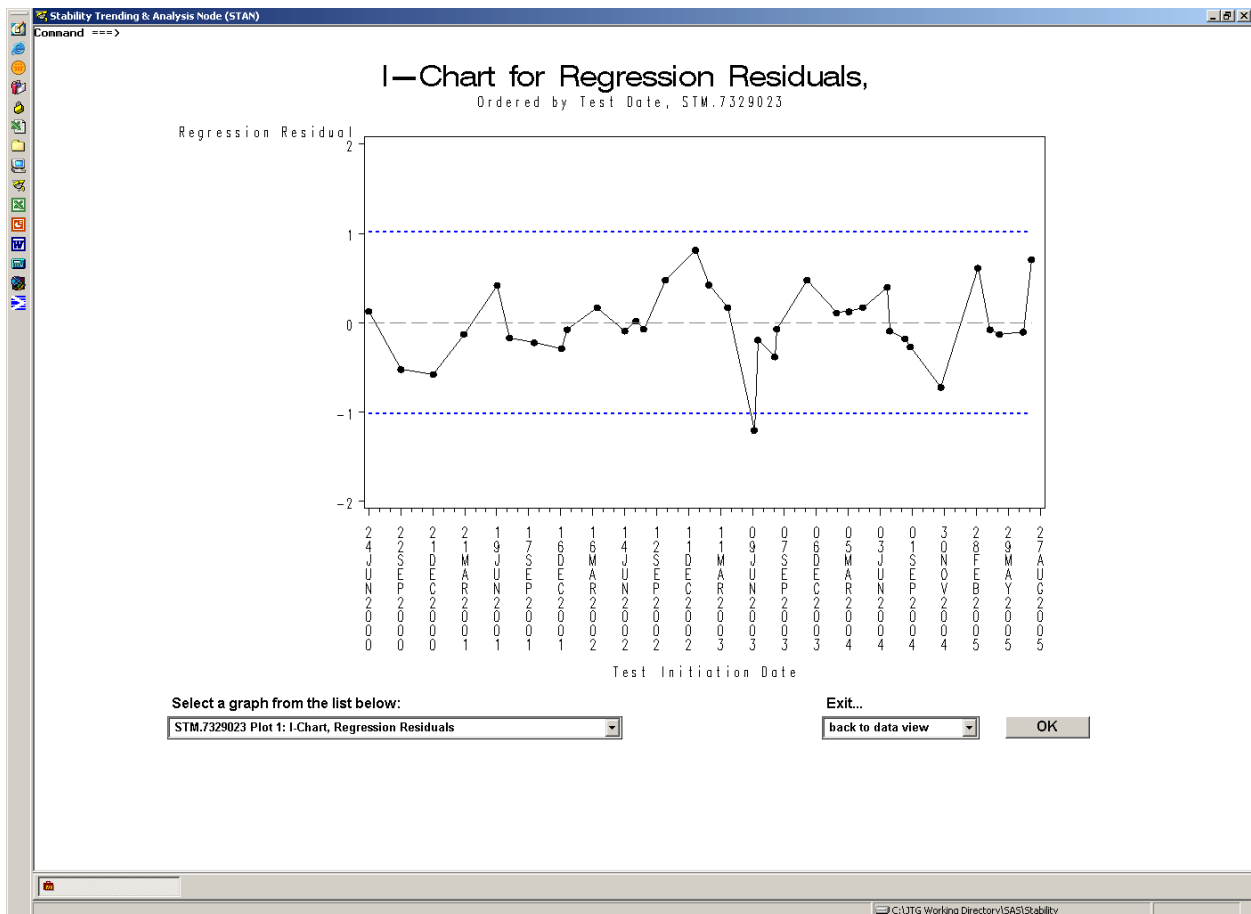
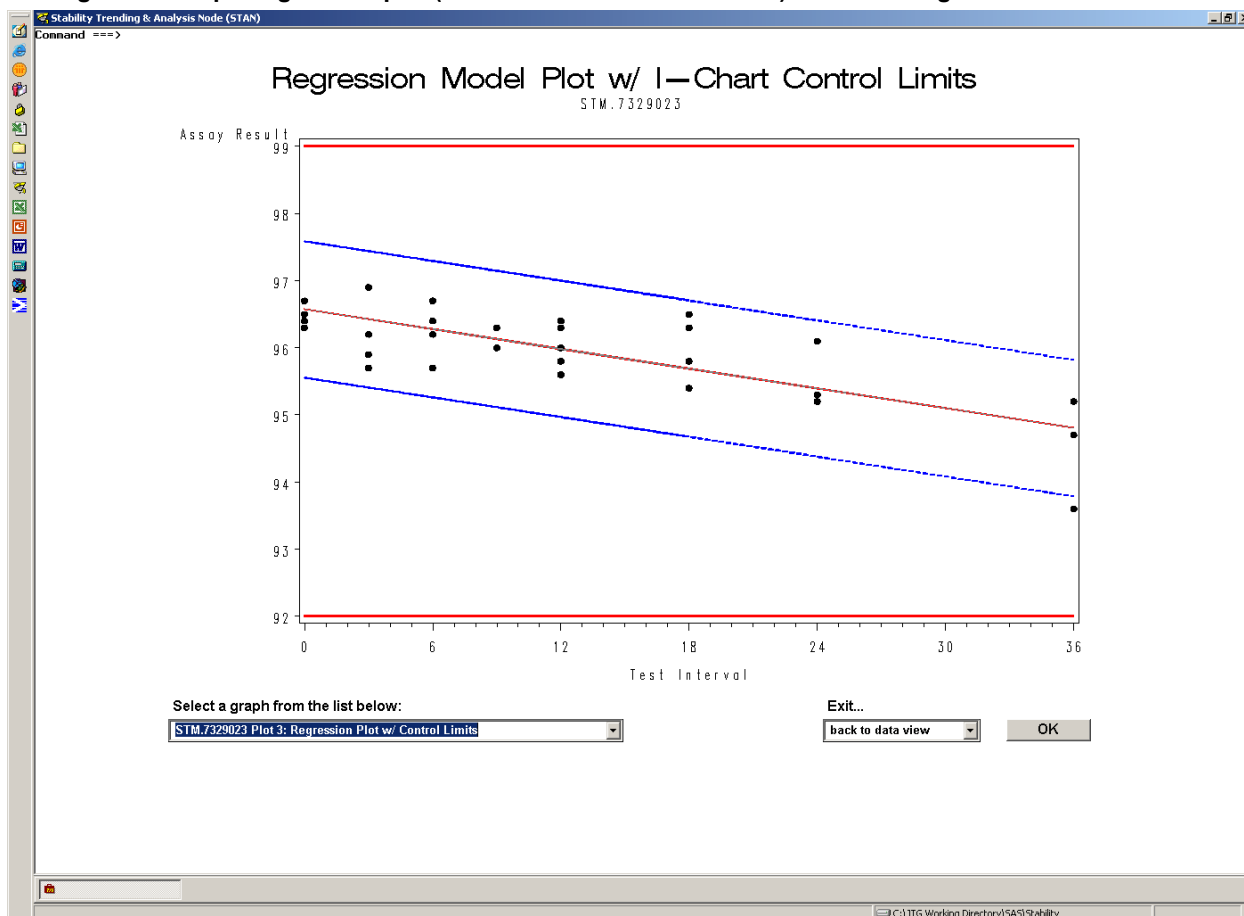


Figure 6 illustrates the individuals chart produced by STAN. On this chart there is one regression model residual that exceeds the lower statistical control limit which is based on the short-term variability of the stability testing process for this product. This out-of-control point indicates a test result which is extremely low even after accounting for the real change in the product over time. Out-of-control points on the accompanying moving range chart (not shown) indicate both this and another result display significant changes from the immediately prior test performed on the product, a sign that these results may not reflect the normal method variability.

The I-MR charts provide an excellent visualization, eliminating the subjectivity inherent in an analyst trying to make a decision about the appropriate disposition of a test result. However, there is a drawback to using these charts when assessing the validity of individual test results in that the charts are constructed using the regression model residuals, not the actual results themselves. While an observation may be clearly identified as atypical on the individuals or moving range charts, it is unclear what test interval produced the result. To address this deficiency STAN produces an additional plot displaying the original data, the regression line fit, the specifications for the given quality attribute, and the control limits from the individuals chart transformed via mapping onto the test interval domain (see Fig. 7). Any out-of-control points from the individuals chart can now be easily observed in their “real” context; that is, at the interval at which they occur. In the example above, the out-of-control point in Figure 3 can be observed in Figure 4 to have occurred at the 36-month interval. This is an especially significant bit of information considering that the assigned shelf-life for this product is 36 months. A low result at the final interval can have substantial impact on the estimated rate of product degradation (the regression line slope) and indirectly affect any internal specifications the manufacturer may have to ensure that the product remains within specifications for the full 36-month expiration period.

The I-MR charts and the regression model plot are produced by SAS code processed within a SUBMIT block contained in an SCL script. The SCL script is executed upon request when the user clicks the “OK” button. The SAS code within the SUBMIT block contains custom code for producing the statistical control limits for the I-MR charts as well as a PROC REG for producing a simple linear regression fit, while the graphics to be presented to the user are created using PROC GPLOT. For some products there may be data for several quality attributes; STAN generates the above set of graphics for each attribute present within the data set. Lastly, a list box containing the description of each graphic allows the user to select a specific graphic of interest for viewing.

**Figure 7. Sample regression plot (with individuals control limits) for evaluating individual test results.**



## STATISTICAL ANALYSIS: SINGLE LOT EVALUATION

The second type of statistical analysis STAN is designed to perform addresses the need to evaluate an individual lot for its consistency with other lots that have been placed on stability for a respective product. While an analyst may fit a regression line to the data for one lot and perhaps see some departure from the data produced by other lots, it is still a subjective endeavor to determine how much of a real difference exists between one lot and all others. STAN endeavors to objectify this kind of determination by statistically testing the regression line fit of a single lot's data via analysis of covariance (ANCOVA).

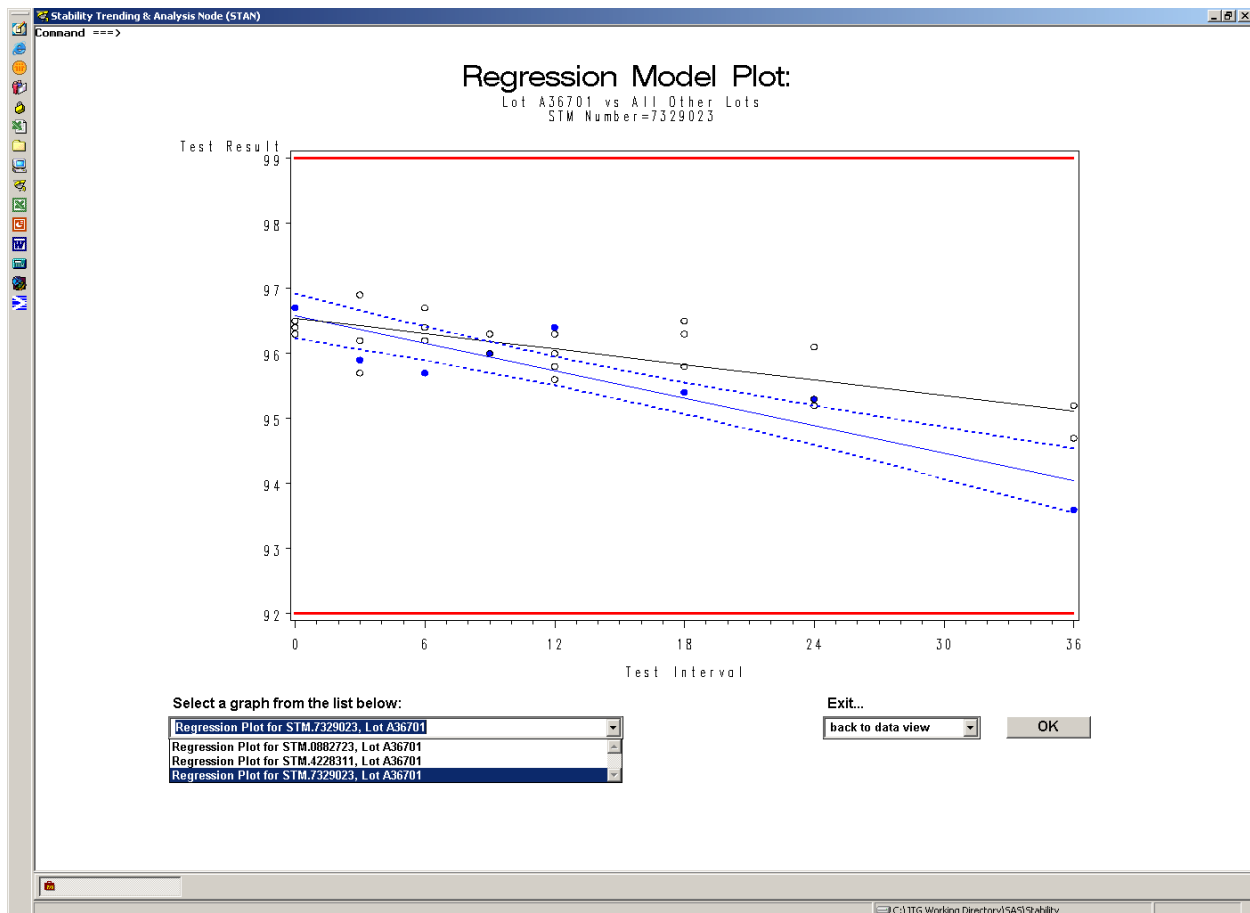
The ANCOVA is performed by splitting the data set into two groups. Data from the lot of interest, as designated by the user, constitutes one group, and all remaining observations in the data set are in the other group. Separate regression lines are effectively produced for these two groups and are overlaid within a single plot (see Fig. 8), along with any specifications the product data is intended to meet. The lot of interest is displayed in blue with the two-sided 90% confidence limits for the mean response for the lot also displayed. Where the statistical output from the analysis indicates numerically that there is a statistically significant difference in performance over time between the two groups, this plot allows the user to ascertain the magnitude of the difference and reach appropriate conclusions for subsequent actions to be taken.

Central to the ANCOVA and graphical display of the ANCOVA model is the TRANSREG procedure, which is called within the submitted SAS code as follows:

```
proc transreg data=work.type2_set;  
  by STM_Number;  
  model identity(Result)=class(group) identity(month) class(group)*identity(month)  
  / cl alpha=0.1;  
  output out=temp2 clm predicted;
```

Here, the variable *group* is a binary variable coded '1' for each observation matching the lot selected by the user or '2' for any other observation in the data set, and the variable *month* is the time interval at which the result for each observation is produced. The BY statement instructs STAN to perform the ANCOVA for each attribute present within the data set.

Figure 8. Sample ANCOVA model plot for single-lot evaluation.



When the analysis is completed and control is passed to the *GRAPH\_VIEW* frame, a list box is again presented to the user containing the description of each graphic, allowing the user to select a specific plot of interest for viewing.

### STATISTICAL ANALYSIS: MULTIPLE LOT EVALUATION

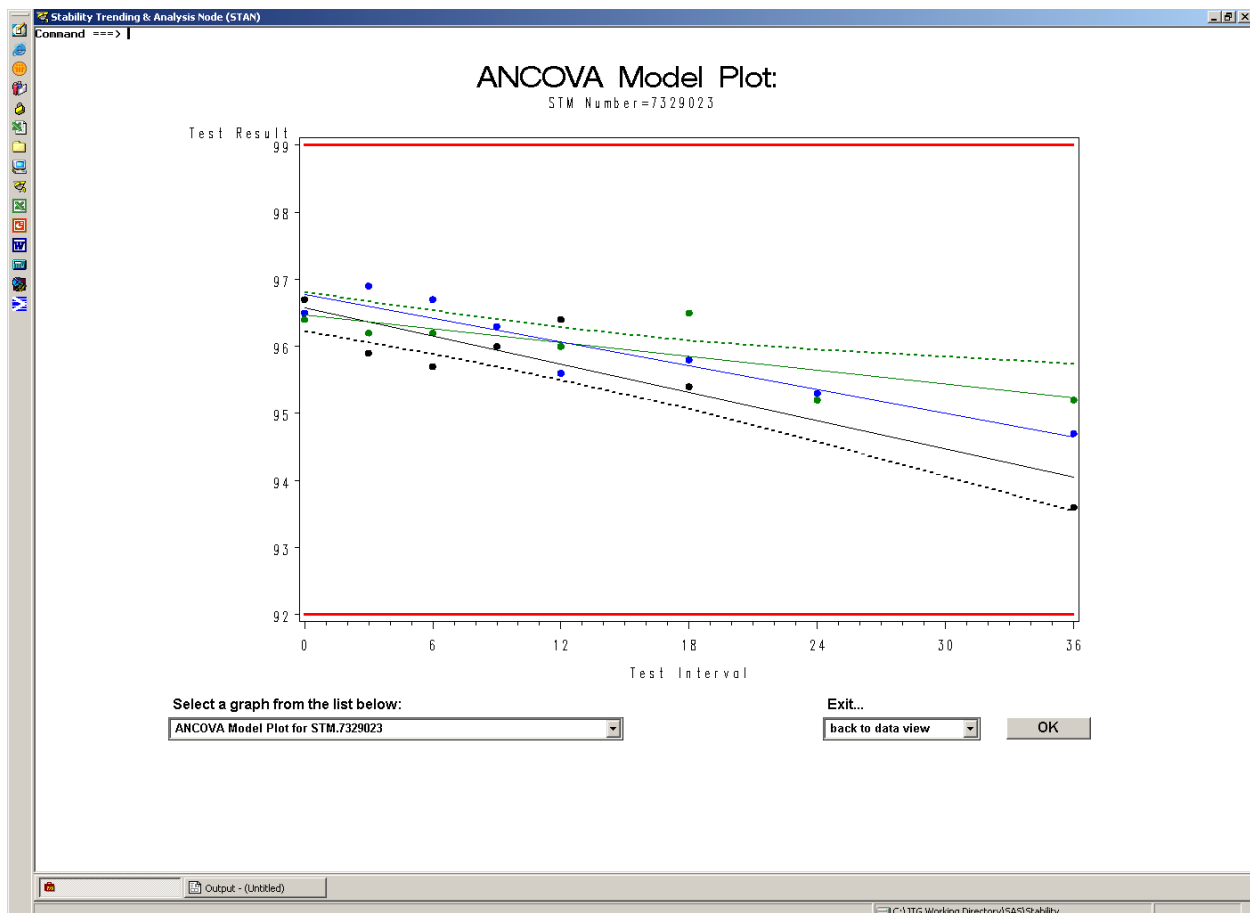
The third type of statistical analysis STAN performs addresses the need to evaluate aggregate data from multiple lots for a respective product. This analysis provides the basis for determining the product's shelf-life and therefore has some specific regulatory guidelines as to how it is performed. The International Conference on Harmonization (ICH) guideline Q1E, "Evaluation for Stability Data" details the hypothesis tests and level of significance this analysis should entail. STAN automatically performs the appropriate analysis by incorporating the decision rules outlined in ICH Q1E.

The analysis required for the evaluation of multiple lots is also the analysis of covariance, except that in this case each lot present within the data set is treated as an individual group. Separate regression lines are effectively produced for each lot; per ICH Q1E, analysis continues according to the following sequence:

- 1 – The null hypothesis that the slopes of the individual lots are all equal is tested at the 0.25 level of significance. If this test fails, separate regression estimates are calculated for each lot in the data set.
- 2 – If (1) passes, the null hypothesis that the intercepts of the individual lots are all equal is then tested at the 0.25 level of significance. If this test fails, separate regression lines having a common slope (i.e. parallel lines) are produced for the lots in the data set.
- 3 – If (1) and (2) pass, a single regression estimate is calculated for all the data in the data set.

STAN performs the analysis methodology described above by calling the GLM procedure, once for performing test (1) and again to perform test (2), if necessary. The TRANSREG procedure is then called to generate the final model in similar fashion to that described above for evaluating individual lots. The final model is displayed to the user in the usual *GRAPH\_VIEW* frame; in instances where the final model consists of multiple regression lines (as is the case in Figure 9 below) the maximum and minimum one-sided 95% confidence limits about the mean response are displayed. Under such circumstances up to eight individual lots can be simultaneously displayed for differences in performance over time. The incorporation of the confidence limits is essential to this analysis since per ICH Q1E the product's maximum shelf-life is earliest point at which the confidence limits intersect the specifications in place for the particular attribute.

Figure 9. Sample ANCOVA model plot for multiple-lot evaluation.





## **CONCLUSION**

At the time of this writing STAN is still in the pilot phase, with stability lab personnel using and challenging it with various data sets to detect errors in the application's operation and to recommend enhancements for improving its usability. Even in its current state, STAN has proven to be a simple yet powerfully effective tool in handling product stability data for a variety of purposes. Where the volume of data was previously prohibitive for much analysis, STAN's development now makes it possible to statistically evaluate all data produced by a stability testing laboratory while incurring little additional overhead in doing so. It also provides an opportunity for incorporating statistical expertise into everyday laboratory operations even if laboratory personnel lack such expertise.

Future developments of STAN include

- providing the user the option of extrapolating regression analyses to test intervals beyond those for which data is available;
- calculating internal control limits for ensuring compliance with specifications through a user-defined interval;
- "drill-down" or hyperlinked graphics to facilitate identification of key observations.

## **ACKNOWLEDGMENTS**

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## **CONTACT INFORMATION**

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