

SAS4383-2020

SAS® Knows Good Manufacturing Practice

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ABSTRACT

The two key system requirements for pharmaceutical manufacturers are electronic data storage and statistical process control, and both must comply with the electronic records requirements of Title 21 CFR Part 11. SAS® Life Science Analytics Framework is specifically designed for electronic records and electronic signatures. SAS Life Science Analytics Framework efficiently manages the transformation, analysis, and reporting of life science data. SAS/QC® software, operating within SAS Life Science Analytics Framework, provides the specialized tools required for analysis of manufacturing data. SAS/QC is designed for process and manufacturing engineers, as well as for directors of quality improvement. This presentation shows how these two SAS products, working together, satisfy the business needs of the pharmaceutical manufacturing industry.

INTRODUCTION

In 2018, more than 3.7 billion prescriptions were filled in the US, according to the Kaiser Family Foundation. When we open our prescription bottle, we trust that the pill we take out and ingest will treat our health issue, and we also trust that we won't be harmed by it. The US Food and Drug Administration (FDA) regulates the quality of pharmaceuticals; we expect the medicines we ingest to be safe and effective.

As manufacturers of these medicinal products, you must abide by the Code of Federal Regulations (CFR) issued by the FDA, two of which are critically important:

- Title 21 CFR Part 11 ensures the authenticity, integrity, and confidentiality of the electronic records produced during the manufacture of a drug product.
- Title 21 CFR Part 210 and Part 211 outline the minimum Good Manufacturing Practice (GMP) requirements for drug products to meet the guidelines for safety, quality, and purity.

Two SAS® software offerings, SAS Life Science Analytics Framework and SAS/QC, allow you to easily manage and comply with these FDA regulations. The regulatory features available in SAS Life Science Analytics Framework assist in addressing CFR Part 11, and the quality management process features available in SAS/QC assist in addressing CFR Part 210 and Part 211. The regulatory and quality management features of this software and how they meet the current needs of pharmaceutical manufacturers are the focus of this paper.

HISTORY

SAS has a long history of working with Life Science companies. We know Good Manufacturing Practice and have the validated system to manage multiple industry requirements.

SAS® transport (XPT) files have long been the standard for providing clinical trial study data to the FDA for regulatory review. In January 1999, the FDA issued guidance describing the need to use XPT files for electronic data set submission. Since 2002, SAS Life Science Analytics Framework has provided a centralized and auditable clinical information repository. The repository is optimized for data standardization, improves project management through workflow enablement, and streamlines the management of

compliance, transparency and traceability. Currently, more than 50 customers have an active license for SAS Life Science Analytics Framework.

Since 1986, SAS/QC has helped manufacturers across multiple industries identify and understand sources of variation during production by providing specialized tools to measure and control product quality. By monitoring the production process, measuring variation during production and analyzing the data with SAS/QC, aberrant behavior can be detected, and solutions found for production issues. Currently, more than 2,500 customers have an active license for SAS/QC.

While originally designed for clinical trial data management, SAS Life Science Analytics Framework is a perfect fit for managing quality control data. By using SAS/QC within the SAS Life Science Analytics Framework, you integrate the quality analysis capabilities into the information management, workflow management, and regulatory compliance capabilities, resulting in one comprehensive framework. Combined, the two products provide data integration, data analysis, report generation, processing of workflows, and the capability to provide notifications based on results from analysis of production data.

These two mature SAS products are now available together, in one validated system, to satisfy the ongoing needs of the pharmaceutical manufacturing industry.

FEATURES OF THE SYSTEM

The hosted SAS Life Science Analytics Framework platform provides a single, integrated environment that streamlines the management of compliance, transparency, and traceability. SAS/QC provides the specialized software tools needed to analyze the measurements produced in quality control laboratories. These analysis tools provide not only the standard control charts seen across the industry, but also the ability to incorporate more advanced statistical analyses for additional insights into process and product improvements.

To examine the regulatory and quality control features in our validated system we will use the following laboratory example:

A quality control laboratory measures the protein concentration during vaccine production. The six daily measurements are stored in the laboratory information management system (LIMS). The SAS validated system automatically pulls in any new data, runs the concentration analysis, generates a report, and alerts the appropriate staff members of the results.

REGULATORY FEATURES

SAS Life Science Analytics Framework allows you to analyze quality control data and store the resulting reports in a regulated environment. Key features of this environment are described in the following sections.

Controlled Environment

Users must log in to the hosted solution with unique and secure account credentials. Identification and authentication are managed with specific processes and policies. One example of the controlled environment is that users are required to change their password at a pre-determined time interval.

Data Integration

From the hosted SAS Life Science Analytics Framework environment, you can connect to data contained in different external repositories. These connections allow pull and push operations to consume data from or send data to different data sources for analysis in the SAS Life Science Analytics Framework platform as shown in Figure 1.

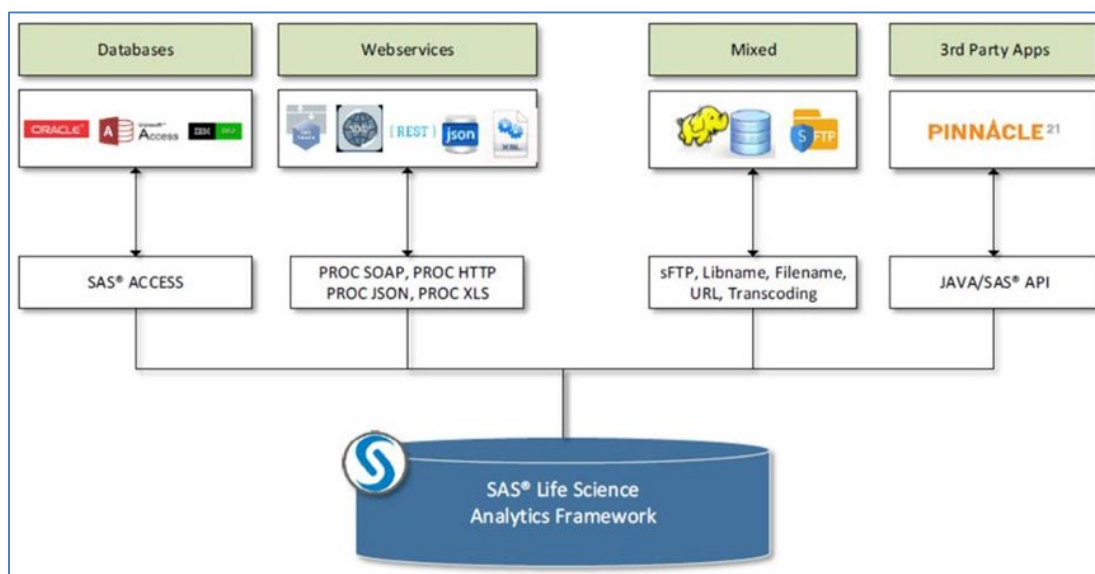


Figure 1: SAS Life Science Analytics Framework Data Integration Options

Because an ORACLE database was used to store the protein concentration data in LIMS for our laboratory example, SAS/ACCESS[®] software was used to connect the database with the SAS Life Science Analytics Framework server.

Check-in and Check-out Files

The SAS Life Science Analytics Framework repository, shown in Figure 2, is the production area, and it complies with Title 21 CFR Part 11, which ensures the integrity of the files. Data files, program files, and result files are stored in separate folders. A user must first check-out a file from the repository to their own personal workspace to make any changes to a file. When a user opens a program file in their workspace for modification, this action takes the user to a SAS session for code review and editing. After an editing session, the user must check the modified file back into the repository from their personal workspace to capture any changes made to the file in the production area. No other users in the system may edit a file that is checked out from the repository by another user; the file is in read-only mode. The ability to check-in and check-out files from the repository maintains the integrity of the validated system.

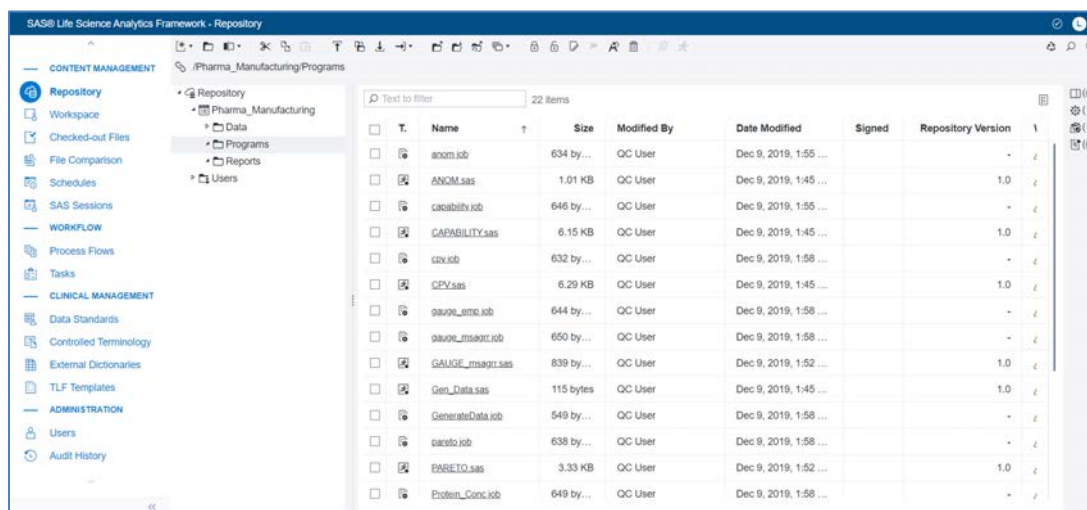
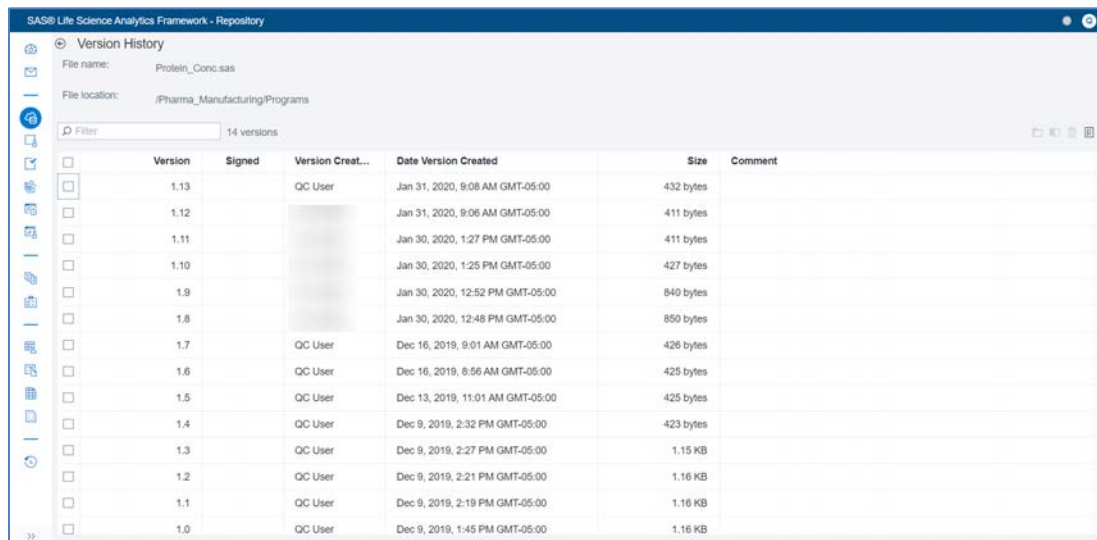


Figure 2: SAS Life Science Analytics Framework Repository View

Version Control

Modifications to files in any of the repository folders are tracked by the system, where each modification instance results in a different version number. Users can view and interact with prior versions of any file, as shown in Figure 3.



Version	Signed	Version Creat...	Date Version Created	Size	Comment
1.13		QC User	Jan 31, 2020, 9:08 AM GMT-05:00	432 bytes	
1.12			Jan 31, 2020, 9:06 AM GMT-05:00	411 bytes	
1.11			Jan 30, 2020, 1:27 PM GMT-05:00	411 bytes	
1.10			Jan 30, 2020, 1:25 PM GMT-05:00	427 bytes	
1.9			Jan 30, 2020, 12:52 PM GMT-05:00	840 bytes	
1.8			Jan 30, 2020, 12:48 PM GMT-05:00	850 bytes	
1.7		QC User	Dec 16, 2019, 9:01 AM GMT-05:00	426 bytes	
1.6		QC User	Dec 16, 2019, 8:56 AM GMT-05:00	425 bytes	
1.5		QC User	Dec 13, 2019, 11:01 AM GMT-05:00	425 bytes	
1.4		QC User	Dec 9, 2019, 2:32 PM GMT-05:00	423 bytes	
1.3		QC User	Dec 9, 2019, 2:27 PM GMT-05:00	1.15 KB	
1.2		QC User	Dec 9, 2019, 2:21 PM GMT-05:00	1.16 KB	
1.1		QC User	Dec 9, 2019, 2:19 PM GMT-05:00	1.16 KB	
1.0		QC User	Dec 9, 2019, 1:45 PM GMT-05:00	1.16 KB	

Figure 3: SAS Life Science Analytics Framework Version History View

Job Manifest

To execute the code in a program file in the repository, users run a job. A job is used to designate the inputs, one or more SAS programs, and the location to store the output. After completion of a job, new files are available in the repository. One of these files is the job manifest. The user can open this file to view all aspects of the execution, which are:

- the program or multiple programs that were executed
- input files referenced and their locations
- outputs produced and their locations
- the execution log

E-signature

A user may sign a file to signify their approval or disapproval of the status of a file in the repository. Signing a file denotes the state of the file for regulatory compliance. A user must provide the reason for their signature and the role that they represent. Customers can create reasons and roles that meet their regulatory requirements and standard operating procedures. To ensure their identity, a user must provide their password each time they sign a file.

In our laboratory example, shown in Figure 4, the User ID, qc_user, with the role of Biostatistician has approved the report titled Protein_Result.pdf.

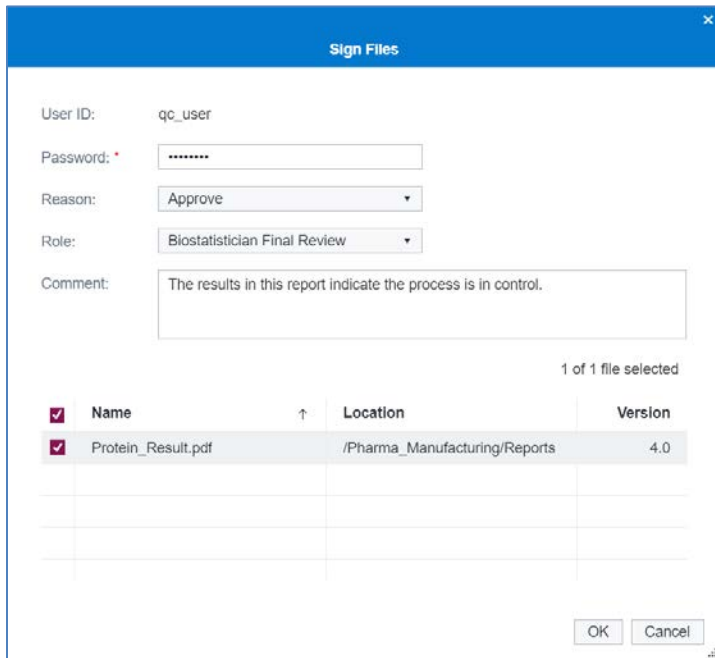


Figure 4: SAS Life Science Analytics Framework Version History View

Workflow

An executable business process consists of one or more tasks, gateways, and transitions between activities. You may create new process flows or edit existing process flows to satisfy your business process needs.

The process flow, called QC_Notification and shown in Figure 5, contains multiple tasks and gateways with directional connections between them. The black diamond is an event-based gateway that keeps the process from progressing until a user-designated event occurs. In our laboratory example, this event is any new data appearing in the protein concentration data file. The process then continues to the 'Run Job' task, which executes the code that analyzes the data in the file. A description of this code is described in the Control Chart Analysis section of this paper. Based on the results returned from this job, either a success email or a failure email is sent to staff members who are users of the system. You can configure which members receive the email.

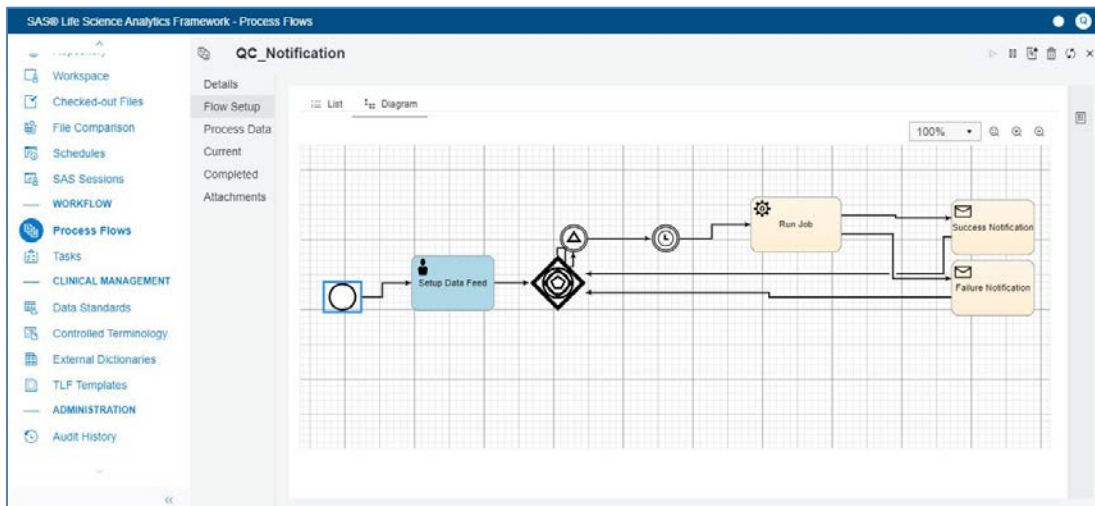


Figure 5: SAS Life Science Analytics Framework Process Flow Example

Figure 6 shows an example of the failure email notification using the messaging system in the SAS Life Science Analytics Framework environment. If desired, the email can be sent to an external messaging system and the report attached to that email.

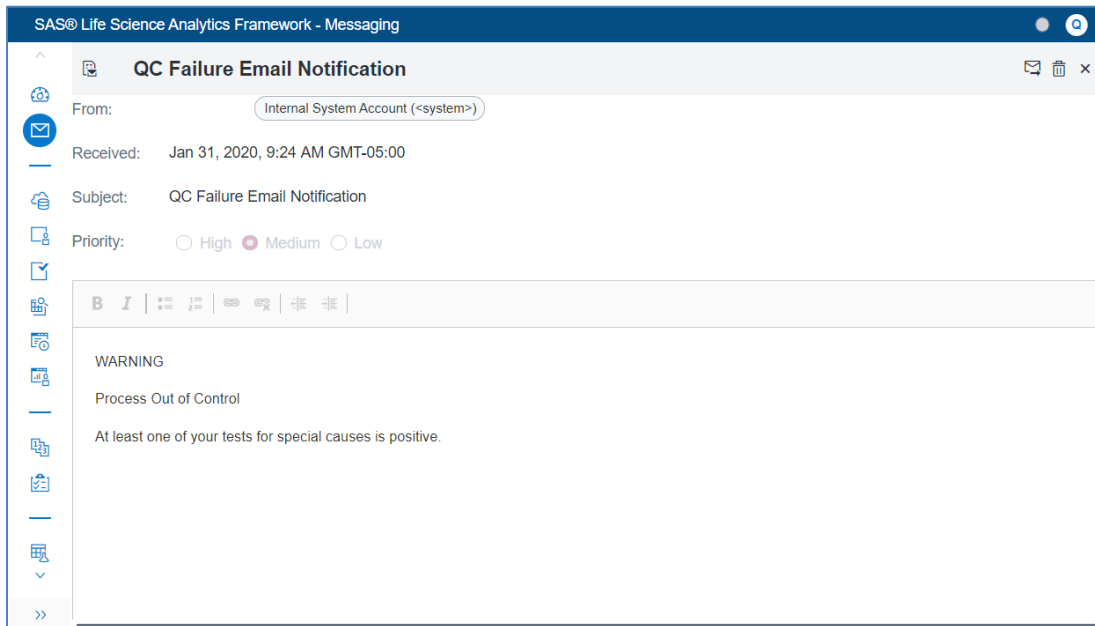


Figure 6: SAS Life Science Analytics Framework Failure Email Notification

Audit History

Figure 7 shows the audit history displayed in a table, where each row is a separate action. Columns include the date, the type of action, and the location of the action. Multiple query parameters are available to filter the audit history table to the desired search results. By default, the most recent month of activity is displayed. This audit history feature is crucial to provide proof of compliance and operational integrity.

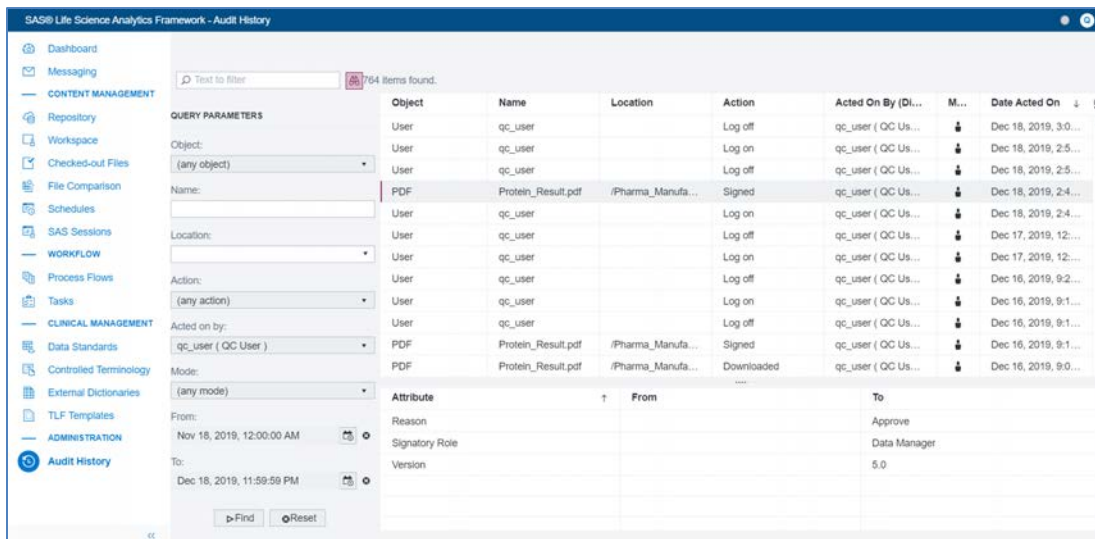


Figure 7: SAS Life Science Analytics Framework Audit History

QUALITY CONTROL FEATURES

SAS/QC allows you to analyze quality control data from the production line to identify and understand sources of variation. This ability enables you to improve product quality, optimize processes, and assess product reliability.

SAS/QC software provides a comprehensive set of tools for statistical quality improvement. You can use these tools to accomplish these tasks:

- establish statistical control of a process
- maintain statistical control and reduce variation
- organize quality improvement efforts
- design industrial experiments for product and process improvement

Table 1 lists the SAS procedures, by quality category, that are available in the SAS/QC offering.

Quality Category	SAS Procedure
Control Chart Analysis	SHEWHART CUSUM MACONTROL RAREEVENTS
Process Capability Analysis	CAPABILITY
Reliability Analysis	RELIABILITY
Analysis of Means	ANOM
Multivariate Process Monitoring	MVPMODEL MVPMONITOR MVPDIAGNOSE
Basic Quality Problem Solving	PARETO
Design of Experiments	FACTEX OPTX

Table 1. Quality Categories Corresponding SAS Procedures

See the SAS/QC 15.1 User Guide for details about each of the quality analysis capabilities provided by the SAS procedures in SAS/QC. Please note that the point-and-click interfaces that are typically included in SAS/QC software are not available when SAS/QC operates within SAS Life Science Analytics Framework.

Control Chart Analysis

Control charts are one of the many tools in your quality control toolbox. They help you decide whether a process is in a state of statistical control or requires attention and efforts toward process improvement. Four different SAS procedures are available for control chart analysis, as shown in Table 1. This section will focus on the SHEWHART procedure.

The SHEWHART procedure creates a single control chart in as few as two SAS statements:

```
proc shewhart data = tmp.measures;  
  xschart (Concentration) * Day (Machine) /  
run;  
quit;
```

The previous code analyzes the six daily measurements in the Measures data set, shown in Figure 8. The XSCHART statement produces a control chart displaying the daily mean in one

graph and the corresponding standard deviation in another graph. By default, the control limits shown are three standard error (3σ) limits estimated from the data. You can also read control limits from an input data set.

The screenshot shows a data table with the following columns: #, Concentration, Day, and Machine. The data is as follows:

#	Concentration	Day	Machine
1	3.97951	01MAY2018	A386
2	4.25553	01MAY2018	A386
3	4.61697	01MAY2018	A386
4	3.98198	01MAY2018	A386
5	4.63753	01MAY2018	A386
6	4.34473	01MAY2018	A386
7	3.72676	02MAY2018	A386
8	4.41562	02MAY2018	A386
9	4.45219	02MAY2018	A386
10	5.02473	02MAY2018	A386
11	3.67288	02MAY2018	A386

Figure 8: Measures data set

Many different control chart types are available within this procedure: BOXCHART, CCHART, IRCHART, MCHART, MRCHART, NPCHART, PCHART, RCHART, SCHART, UCHART, XCHART, XRCHART, and XSCHART. An example of the control chart produced by the XSCHART statement is shown in Figure 9.

Shewhart Control Chart

By adding a few optional statements in the SHEWHART procedure code, we can enhance the control chart. We can test for special causes of variation and alert the viewer by highlighting any positive results of the test with a contrasting color, as shown in Figure 9.

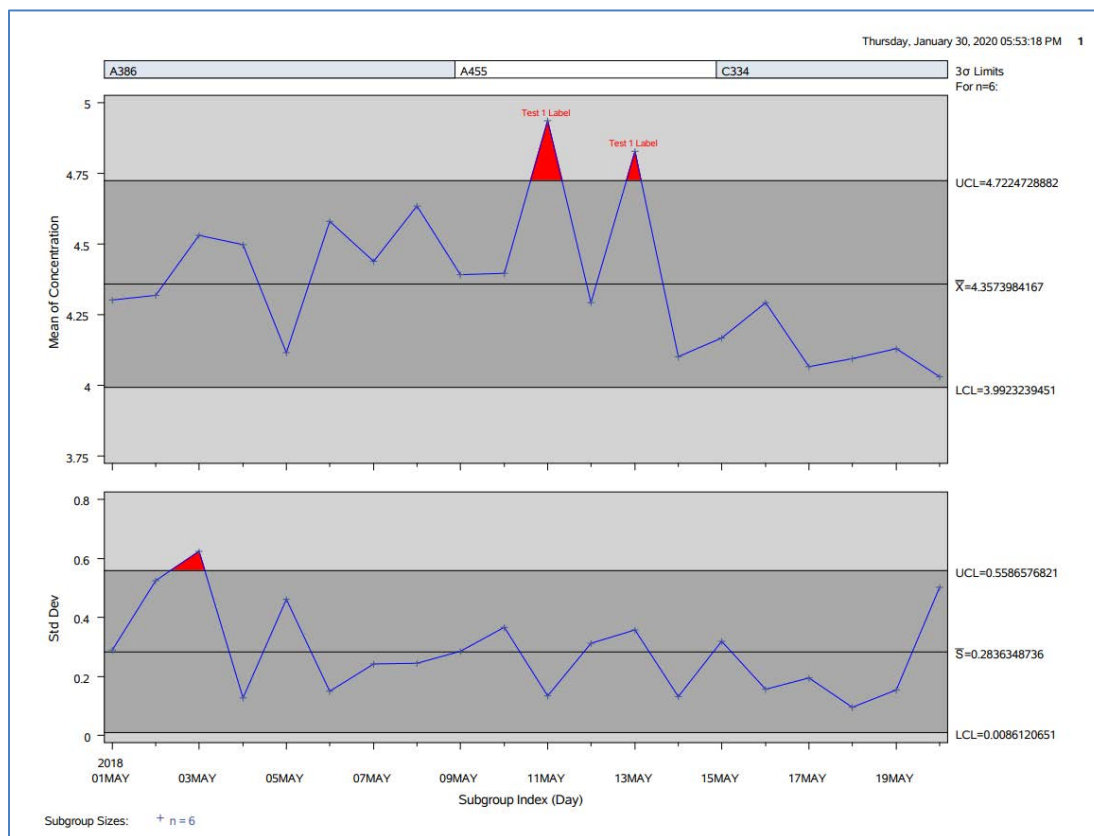


Figure 9: Control Chart with Test Results

The code below produced the chart shown in Figure 9:

```

proc shewhart data = tmp.measures;
  xschart (Concentration) * Day (Machine) /
  tests = 1 3 4 /*requests tests for special causes*/
  ctests = red /*specifies color for the test labels*/
  testlabel1 = 'Test 1 Label' /*assigns text to the test label*/
  testlabel3 = 'Test 3 Label' /*assigns text to the test label*/
  testlabel4 = 'Test 4 Label' /*assigns text to the test label*/
  sigmas = 3 /*specifies width of control limits in terms of multiple k of
standard error of plotted statistic*/
  caxis = black /*specifies color for axis lines and tick marks*/
  waxis = 1 /*specifies width of axis lines*/
  ctext = black /*specifies color for tick mark values and axis labels*/
  cinfill = cxa9a9a9 /*specifies color for area inside control limits*/
  climits = black /*specifies color of control limits, central line, and
related labels*/
  totpanels = 1 /*specifies number of pages or screens to be used to
display chart*/
  cconnect = blue /*specifies color for line segments that connect points
on chart*/
  coutfill = red /*specifies color for axis shading areas between the
connected points and control limits outside the limits*/
  cframe = cxd3d3d3 /*specifies fill colors for frame for plot area*/
  blocklabelpos = above /*specifies the position of the block-variable (in
this case 'machine') in the block legend*/
  cblocklab = white /*specifies fill colors for frames that enclose the
block-variable labels in the block legend*/
  blockpos = 1 /*specifies vertical position of the block-variable legend*/

```

```

tabletests(exception) /*restricts the tabulation of the tabletests
option to those subgroups for which the control limits are exceeded or a
test for special causes is positive*/
outtable=tmp.otl /*creates an output data set containing data based on
the tabletests(exception) option*/
;
run;quit;

```

The preceding code, using the SHEWHART procedure, analyzed the daily protein concentration measurements residing in the Measures data set. The XSCHART statement produced a control chart displaying the daily mean in the top graph and the corresponding standard deviation in the bottom graph, as shown in Figure 9. The TESTS= option provides eight standard tests for special causes. These tests, also known as Western Electric rules, search for patterns in the data. The results show a Test 1 label appearing in the control chart on May 11 and May 13, because these two values are outside the upper control limit. The TABLETESTS statement creates an extended version of the TABLES statement, to include the results from the TESTS= option. By adding the keyword EXCEPTIONS, the tabulation is restricted to the exceptional points only. The OUTTABLE statement captures these exceptional points in a data set.

The table, shown in Figure 10, is populated with the three exceptional points, found from the tests for special causes, that exceeded the upper limit - two points in the daily mean graph and one point in the standard deviation graph. This output table is produced if exceptional points are detected because the keyword EXCEPTIONS was included. Using the process flow capability example shown in Figure 5, a failure email is sent to appropriate staff if any row of the 'Special Tests Signaled' column is populated in this table of exceptional points. If all rows of this column are empty, then the success email is sent to the staff members.

Thursday, January 30, 2020 05:53:18 PM 2

The SHEWHART Procedure

Means and Standard Deviations Chart Summary for Concentration										
Day	Subgroup Sample Size	3 Sigma Limits with n=6 for Mean				Special Tests Signaled	3 Sigma Limits with n=6 for Std Dev			
		Lower Limit	Subgroup Mean	Upper Limit	Limit Exceeded		Lower Limit	Subgroup Std Dev	Upper Limit	Limit Exceeded
03MAY2018	6	3.9923239	4.5314233	4.7224729			0.00861207	0.622396060	0.55865768	Upper
11MAY2018	6	3.9923239	4.9352950	4.7224729	Upper	1	0.00861207	0.13436125	0.55865768	
13MAY2018	6	3.9923239	4.8266100	4.7224729	Upper	1	0.00861207	0.35814536	0.55865768	

Figure 10: Exceptional points resulting from Tests for Special Causes

This example of the analysis results prompting notifications to staff is just one of many possible ways you can use the process flow capabilities of SAS Life Science Analytics Framework in combination with SAS/QC to provide near real-time alerts from the production line. Any SAS programmer with the appropriate permissions can create their own process flow and triggers for notifications.

CONCLUSION

By integrating SAS/QC into SAS Life Science Analytics Framework, you can take advantage of all the regulatory features of a validated system and apply them to the quality control processes at the plants that manufacture your products. These features range from the security of a controlled environment with electronic signature and an audit trail to the plethora of control charts and other quality control tools. This combination of mature SAS products gives you the power to receive notifications of process issues as soon as possible

so that you can address any production issues. And because SAS programming code sits behind the features, you can modify code and customize process workflows to meet your specific manufacturing requirements. Contact us to discuss how SAS Life Science Analytics Framework and SAS/QC can meet your quality control process needs.

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