

## **A Practice to Create Executable SAS® Programs for Regulatory Agency Reviewers**

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### **ABSTRACT**

Providing executable SAS programs (in connection with the statistical analysis data sets and clinical table outputs) is presently not required with a NDA submission; however they are of great benefit to a regulatory agency reviewer for expediting the review process. This paper will discuss basic considerations, challenges, approaches and examples of practices on how to create executable SAS programs for regulatory agency reviewers.

### **INTRODUCTION**

Over the past few years, sponsors have been increasingly asked to provide executable SAS programs to the FDA for their NDA submissions in order to help reviewers understand complicated statistical analyses faster and better than without such programs. The belief is that providing such information would help improve the quality and efficiency of the agency review process. Information for such practice is very limited and no standard processes are publicly available.

For one of our recent submissions, we provided executable SAS programs for the main efficacy analyses of pivotal studies for a submission. This paper will discuss some of our basic considerations, challenges, approaches and examples of executable SAS programs for regulatory agency reviewers.

### **BASIC CONSIDERATIONS**

#### **1. PROGRAMS SHOULD BE EXECUTABLE WITH MINIMAL MODIFICATIONS NEEDED**

Given the uncertainty in the level of SAS programming expertise among agency reviewers, all SAS programs should be created with zero or minimal modification to be executable. If there are necessary code changes for executing such programs all changes should be located at the top of the program after the program header description for making it simple and easy for the reviewer to understand and implement.

One common programming change is specifying the location/path of the SDTM/analysis data sets. All pathing in our programs was 'relative' rather than 'absolute'. The SAS path for the data has to be modified by the FDA reviewer to point to data within the submission staging area at the FDA (either to the SDTM data sets or to the analysis data sets within the submission). Given that the clinical data sets were located in a different folder than the programs within the submission staging area of the FDA, this modification was necessary for the reviewer to access the data for any type of analysis that he/she wanted to do. Other changes might be optional. For example, reviewers might want to output and save their analyses to a certain location, or perform different efficacy analyses by building new models. Such basic options were built into the beginning of the program with clear comments.

#### **2. ALL FILES SUBMITTED SHOULD BE IN ONE FOLDER PER THE ECTD FOLDER STRUCTURE**

Unlike our standard programming environment that includes separate directories for SDTM and analysis data sets as well as tables, listings, graphs, and documentation, all the reviewer files (8 analysis data set programs, 15 table programs, a SAS Program Code User's Guide, and a couple of reference data sets for each pivotal trial) had to be placed in one flat directory. This was necessary so as to align with the electronic Common Technical Document (eCTD) structure defined by the Vertex Submissions group. In particular, they were placed in Module 5 of the eCTD for each study, parallel to the Analysis Data sets directory and the Data Tabulations (SDTM) directory. This was a

change to our standard development of data sets and TFLs, since our development environment at Vertex relies heavily on assumptions about our development and production multi-level directory structure.

### **3. ALL MACROS SHOULD BE EMBEDDED INTO INDIVIDUAL PROGRAMS**

Separate macros were not submitted in this process so that individual programs could be run independently without having any impact on any other program. To accomplish this, macro code was identified and embedded into individual submitted SAS programs completely. Our analysis data sets programs from the Primary Programmer. Therefore, these required programmers a somewhat time-consuming process in some cases, especially for certain table programs, but not for analysis data set programs.

### **4. PROGRAMS SHOULD POINT TO/USE THE DATA SUBMITTED TO THE FDA**

We took an elegant approach in terms of what inputs and outputs the programs used. As mentioned, the input data reviewers use would come from the FDA's own data sets that we had submitted to it. A step to avoid including any clinical data sets in the programs directory (Module 5), we decided that the reviewers were to point to the data already included in the submission. To accomplish it, the reviewer would just specify at the beginning of each SAS program the proper path location of the data sets. This meant we did not have to send any data sets in our programming code directory. This also meant that our programs could be run in any order without any dependencies between programs, minimizing any confusion or potential problems.

### **5. PROGRAMS SHOULD BE EXECUTABLE WITHOUT WRITING ANY OUTPUT TO DISK**

As for outputs, we didn't want to leave any "footprints." We wrote all output data sets and results to the SAS interactive, temporary work library. We assumed (and documented this in the SAS Code User's Guide) that the FDA reviewer would be using interactive SAS but we made no assumption about the operating system platform he/she would be using. If the FDA reviewer wanted to save a data set or table output to disk, then he/she would have to make another small modification.

Note: for each table program, all the statistical analysis from the SAS procedure was outputted and displayed interactively for the reviewer, not just the output found in the table.

## **CHALLENGES**

### **1. NO STANDARD SOP TO FOLLOW AND LIMITED INFORMATION PUBLICALLY AVAILABLE**

We didn't have a standard guideline, work instruction, or SOP to handle this type of FDA request, so we decided to create our own new process based on a lot of internal discussions.

### **2. USER'S SAS ENVIRONMENT UNKNOWN**

Given that no information was provided to us concerning the reviewer's operating system, version of SAS, or preferred mode of running SAS, no dependencies were factored into the program code, except for the need to specify the program/data set path at the top of each program

### **3. USER'S SAS KNOWLEDGE UNKNOWN**

We assumed very little about the SAS skill level of the agency reviewer except that he/she would be able to follow the user's guide and be able to find the proper data sets and programs within the submission.

### **4. SCOPE OF PROGRAMS TO BE INCLUDED**

To better understand the scope of the programs to be sent to the FDA, Vertex sent a clarifying letter to the FDA, proposing that only the SAS programs for the 3 pivotal registration trials would be sent. In particular, we proposed

that we would only send the SAS programs for the primary and secondary efficacy analysis data sets, and tables. As stated previously, our plan was to have the reviewer access the SDTM data sets (.xpts) from the submission, create the analysis data sets in WORK using our programs. And then to run the table programs, using SDTM and analysis data sets (.xpts) from the submission. Again, they merely changed the paths to point to their own data (in the submission staging area presumably) and the programs would run to create either data sets or table output in WORK.

## 5. HOW AND WHAT TO QC TO ENSURE THAT PROGRAMS ARE EXECUTABLE

To ensure the programs were properly created and executable, we followed a 2-step internal and external QC process.

For the internal QC, primary programmers compared their own executable program outputs with the outputs from the clinical study report (CSR). The QC programmers also compared these outputs, but also reviewed the code for clarity and provided comments to the code (where necessary).

For the external QC, an independent contractor was hired to execute the process. The 3 flat (no subdirectories) zip packages were created, one for each of the aforementioned registration studies. The contractor ran the programs on one's server (independent of Vertex) by following the reviewer's guide, and compared the results between the outputs (data and statistical analysis) from the executable programs and the outputs (data and statistical tables) from the NDA submission.

## APPROACHES AND PROGRAM EXAMPLES

Set up a core executive team, including both statisticians and programmers who are familiar with the project. This was critical for our success due to the short timeline and complexity of the projects. Have the team define program guidelines/scopes, create a working guideline/plan, and execute the plan.

Along with the SAS programs, we included a simple user guide to help further explain the process. The first part dealt with the contents of the executable SAS program package, listing and describing all the file names making it easy for the reviewer to find a specific program. The second part contained general instructions. The third and last part described a step-by-step guide on how to use the executable SAS programs for data sets, tables and figures.

Below is an example of the user guide, showing sections 2 and 3.

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### GLOBAL NOTES TO REVIEWER

1. All programs are independent and can therefore be executed in any order;
2. All programs were designed to be executed in an interactive SAS session;
3. All programs must be modified prior to execution; instructions are provided in Section 3;
4. When executed in default mode, these programs do **not** generate permanent output on disk;
5. When executed in default (interactive) mode, the output data product (analysis data set, table, or figure) is generated in the WORK library or the temporary OUTPUT window;
6. All programs were created under SAS Version 9.2 and may not run correctly in other versions of SAS;

### STEP-BY-STEP PROGRAM EXECUTION INSTRUCTIONS

#### ANALYSIS DATA SETS

1. Copy the SAS program and 3 SAS transport files to the execution location;

2. Modify the program to indicate system-specific information:
  - a. Replace the sample data set program directory path (specified to the right of the equal sign in the %LET PROGPATH statement) with the FDA reviewer directory path where the data set programs will be run.
  - b. Replace the sample SDTM program directory path (specified to the right of the equal sign in the %LET SDTMDATAPATH statement) to specify the location where the SDTM data sets (transport/.xpt files) reside on your system.
  - c. Replace the sample analysis data set program directory path (specified to the right of the equal sign in the %LET ADDATAPATH statement) to specify the location where the analysis data sets (transport/.xpt files) reside on your system.
3. Execute the program.

#### **TABLES**

Options and instructions are provided within the table programs to allow users to run the programs in batch mode and/or save output as rtf files. Notes are embedded within the programs to guide the user to make use of the existing program to conduct additional analyses (e.g., conducting similar analysis through Week 48).

1. Copy the SAS program to the execution location;
2. Modify the program in the following ways to indicate system specific information:
  - a. Replace the sample table program directory path (specified to the right of the equal sign in the %LET PROGPATH statement) with the FDA reviewer directory path where the table programs will be run.
  - b. Replace the sample analysis data set directory path (specified to the right of the equal sign in the %LET ADPPATH statement) with the FDA reviewer directory path where the analysis data sets (transport/.xpt files) will reside on your system.
  - c. Determine how the table programs will be executed (either in interactive or batch mode) and how the statistical output will be displayed (either on the monitor screen, in .lst format, or in .rtf format) by choosing the \*\*\* string (the default option specified to the right of the equal sign in the %LET RTF statement) or the null string. (See the table programs for more details and further clarification.)
3. Execute the program.

#### **FIGURE**

1. Copy the SAS program to the execution location.
2. Modify the program in the following ways to indicate system specific information:

Replace the string to the right of the equal sign in the first %LET statement to specify the location where the Study 102 analysis data sets (transport/.xpt files) reside on your system.

3. Execute the program.

The following is a screen snapshot showing files of the executable program package sent to the FDA reviewer.

Name	Type	Compressed size	Passw...	Size	Ratio
UserGuide102.pdf	Adobe Acrobat Document	35 KB	No	54 KB	36%
ADCECD_102.sas	SAS Program	7 KB	No	27 KB	77%
ADCETF_102.sas	SAS Program	7 KB	No	28 KB	77%
ADQS_102.sas	SAS Program	8 KB	No	28 KB	72%
ADSL_102.sas	SAS Program	10 KB	No	37 KB	74%
ADSP_102.sas	SAS Program	8 KB	No	28 KB	74%
ADSW_102.sas	SAS Program	6 KB	No	20 KB	73%
ADV5_102.sas	SAS Program	4 KB	No	11 KB	69%
f_tf_pulmo_48.sas	SAS Program	3 KB	No	9 KB	65%
t_102_f_clinevt_48.sas	SAS Program	4 KB	No	14 KB	74%
t_102_f_clinevt_normdy_48.sas	SAS Program	3 KB	No	9 KB	73%
t_102_f_clinevt_tf_48.sas	SAS Program	4 KB	No	15 KB	75%
t_102_f_qs_cf_mmrn_24.sas	SAS Program	2 KB	No	7 KB	72%
t_102_f_qs_cf_pooled_sens_24.sas	SAS Program	3 KB	No	9 KB	69%
t_102_f_sp_ppfev1_mmrn_a_24.sas	SAS Program	2 KB	No	7 KB	73%
t_102_f_sp_ppfev1_mmrn_b_24.sas	SAS Program	2 KB	No	7 KB	73%
t_102_f_sp_ppfev1_sensitivity_24...	SAS Program	3 KB	No	11 KB	72%
t_102_f_swcl_mmrn_24.sas	SAS Program	2 KB	No	7 KB	73%
t_102_f_swcl_sensitivity_24.sas	SAS Program	3 KB	No	8 KB	70%
t_102_f_vs_weight_lmm_48.sas	SAS Program	2 KB	No	6 KB	72%
bmizscor.xpt	SAS Xport Transport File	12 KB	No	19 KB	38%
trts_102.xpt	SAS Xport Transport File	3 KB	No	12 KB	78%
zscore.xpt	SAS Xport Transport File	12 KB	No	19 KB	38%

The following program is an example of the executable code sent to the FDA, where the necessary program and data paths are specified at the top of the program.

```

*****
*
*PROJECT:          VXxx-xxx-xxx
*
*PROGRAM:          ADSL_xxx.sas
*
*DESCRIPTION: This program is for generation of ADSL_xxx analysis data set
*
*SPONSOR:          Vertex Pharmaceuticals Incorporated
*
*INPUTS:   dm.xpt suppdm.xpt mh.xpt suppmh.xpt ds.xpt  ex.xpt sw.xpt sp.xpt
*
*OUTPUTS:   ADSL_xxx (Temporary SAS Data set)*
*****

***Reviewer, before running this program please replace the path 'x:\..\SASCode\VXxxx-
xxx\Submission' with the path
      where the submission package is situated for execution;
%let progpath   = x:\..\SASCode\VXxxx-xxx\Submission;

***Reviewer, before running this program please replace the path ' x:\..\VXxxx-
xxx\xpt' with the path
      where the submitted SDTM Transport (XPT) Data sets for Study xxx Reside at the FDA;
%let sdtmdatapath = x:\..\VXxxx-xxx\xpt;

***Reviewer, before running this program please replace the path ' x:\..\VXxxx-xxx\ad'
with the path

```

where the submitted Analysis Transport (XPT) Data sets for Study xxx Reside at the FDA;

```
%let adddatapath = x:\..\VXxxx-xxx\ad;
```

```
*****;  
**** !!!! Reviewer, no changes required below this line !!!! ****;  
*****;
```

## SUMMARY

This paper represents only one approach to a rather new and non-standard process. The most important principle to keep in mind when defining your own process is to keep it simple (in program form, content, structure, requirements, etc.). Spending more time up front in the design process definitely paid off for our company. By the end of the submission and subsequent drug approval, we hadn't received any comments, problems, or clarifications concerning the executable code process.

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## CONTACT INFORMATION

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