PhUSE US Connect 2019

Paper SA04

Submission of Software Programs to Regulatory Agencies

Maria Dalton, GlaxoSmithKline, Collegeville PA, USA

ABSTRACT

The FDA *Study Data Technical Conformance Guide* states that sponsors should provide the software programs used to 1) create ADaM datasets, 2) generate tables and figures for primary and secondary efficacy analyses, and 3) generate prescribing information presented in product labels.[1] In the pharmaceutical industry, there is sometimes confusion on how to meet the requirement to submit software programs. The paper will give recommendations for best practices for preparing software programs for submission. This paper will also discuss and answer frequently asked questions about submission of software programs, such as:

- Can sponsors submit programs with .sas extensions?
- Are sponsors required to submit executable programs?
- Should sponsors submit standard macros?
- What type of documentation should be included with the programs?
- Is the process different for software packages such as R or Python?
- What are the differences between FDA and PMDA requirements?

INTRODUCTION

This paper provides information to clinical programmers and statisticians in the pharmaceutical industry to help them fulfill the requirements for submission of software programs to regulatory agencies. The paper does not cover the topics of selecting statistical software packages or validating software programs. The paper will first give a high-level overview of the regulatory requirements for submission of software programs. The paper will then answer frequently asked questions and describe best practices for preparing and submitting software programs to regulatory agencies.

REGULATORY REQUIREMENTS FOR SUBMISSION OF SOFTWARE PROGRAMS

This section provides an overview of the regulatory requirements for submission of software programs to regulatory agencies. Information about the process of preparing and submitting software programs is covered in subsequent sections of the paper.

GENERAL GUIDANCE FOR STATISTICAL SOFTWARE PACKAGES

The US Food and Drug Administration (FDA) has written the following guidance documents to provide **general** guidance for statistical software packages. These documents explain the FDA's requirements and expectations that computer software used for statistical analysis be reliable, validated, and properly documented and controlled. Even though the topics of general requirements for software programs is beyond the scope of this paper, these references are provided to give a fuller picture of the regulatory guidelines for software programs.

Guidance Document	Guidance Relevant to Statistical Software Packages
Guidance for Industry E9 Statistical Principles for Clinical Trials (1998)[2]	"The computer software used for data management and statistical analysis should be reliable, and documentation of appropriate software testing procedures should be available."[2]
Guidance for Industry - Computerized Systems Used in Clinical Investigations (2007)[3]	"This document provides to sponsors, contract research organizations (CROs), data management centers, clinical investigators, and institutional review boards (IRBs), recommendations regarding the use of computerized systems in clinical investigations."[3] It describes requirements such as: design of computerized systems, security safeguards, audit trails, date/time stamps, recommended Standard Operation Procedures (SOPs), controls for system changes, and training of personnel.[3]

Guidance Document	Guidance Relevant to Statistical Software Packages
FDA General Principles of Software Validation; Final Guidance for Industry and FDA Staff (2002)[4]	This guidance outlines general validation principles for validation of medical device software or software used to design, develop, or manufacture medical devices. Even though the document was written for medical device software, the FDA states in the document that: • "This document is based on generally recognized software validation principles and, therefore, can be applied to any software." • "In addition, computer systems used to create, modify, and maintain electronic records and to manage electronic signatures are also subject to the validation requirements."[4]
FDA Position Statement - Statistical Software Clarifying Statement[5]	Clarifies that the FDA "does not require use of any specific software for statistical analyses". Also states that "software package(s) used for statistical analyses should be fully documented in the submission, including version and build identification should be available."[5]

GUIDANCE FOR SUBMISSION OF SOFTWARE PROGRAMS

At the current time, the FDA in the United States and the Japan Pharmaceuticals and Medical Devices Agency (PMDA) request that sponsors provide software programs as part of regulatory submissions.[1,6] Since additional countries, such as Canada and China, accept or will soon accept eCTD submissions, it is likely that additional countries will also request software programs in regulatory submissions in the future.[7,8]

FDA GUIDANCE FOR SUBMISSION OF SOFTWARE PROGRAMS

In addition to the general guidance documents listed above, the FDA has two documents that provide specific information about the submission of software programs to the FDA. Note that these guidance documents are not specific to any particular software language or package.

1. FDA Study Data Technical Conformance Guide (Oct 2018)[1]

The FDA *Study Data Technical Conformance Guide* contains the following section about software programs:

"4.1.2.10 Software Programs

Sponsors should provide the software programs used to create all ADaM datasets and generate tables and figures associated with primary and secondary efficacy analyses. Furthermore, sponsors should submit software programs used to generate additional information included in Section 14 CLINICAL STUDIES of the Prescribing Information[27], if applicable. The specific software utilized should be specified in the ADRG. Refer to FDA Statistical Software Clarifying Statement for more information[28]. The main purpose of requesting the submission of these programs is to understand the process by which the variables for the respective analyses were created and to confirm the analysis algorithms and results. Sponsors should submit software programs in ASCII text format. Executable file extensions should not be used."[1]

The FDA *Study Data Technical Conformance Guide* also specifies where to store software programs in the eCTD. For example, the programs to create ADaM datasets for clinical data are placed in Module 5 in folder /datasets/[study]/analysis/adam/programs. Programs to create legacy format datasets are placed in an equivalent location under the legacy folder.[1]

Table 2: Study Dataset and File Folder Structure and Description

Folder Name	Folder Level	Description/Contents
[module]	1	Refers to the eCTD module in which study data are being submitted. Name this folder m4 for nonclinical data and m5 for clinical data. Do not place files at this level.
datasets	2	Resides within the module folder as the top-level folder for study data (nonclinical or clinical) being submitted for the specified module (m4 or m5). Do not place files at this level.
[study]	3	Name this folder with the study identifier or analysis type performed (e.g., study123, iss, ise). Do not place files at this level.
analysis	4	Contains folders for analysis datasets and software programs; arrange in designated level 6 subfolders. Do not place files at this level.
adam	5	Contains subfolders for ADaM datasets and corresponding software programs. Do not place files at this level.
datasets	6	Place ADaM datasets in this subfolder.
split	7	Place any split ADaM datasets in this subfolder.
programs	6	Place software programs for ADaM datasets, tables and figures in this subfolder.

2. FDA Specifications for File Format Types Using eCTD Specifications[9]

This document lists the accepted file types within the eCTD and the eCTD locations where those file types should be stored. ".sas" and ".r" are acceptable extensions in eCTD Modules 3 – 5 for files used for "Modelling and Simulation Reporting". This document does not specify if ".sas" and '.r" are acceptable extensions for programs written for purposes other than Modeling and Simulation Reporting.

PMDA GUIDANCE FOR SUBMISSION OF SOFTWARE PROGRAMS

The PMDA also requests that sponsors submit software programs. The PMDA Revision of Technical Conformance Guide on Electronic Study Data Submissions document provides very helpful information about the PMDA's requirements for software programs.[6] This document is available on the PMDA website.

Here are excerpts from the PMDA *Technical Conformance Guide on Electronic Study Data Submissions*:[6]

4.1.6.1 Programs to be submitted

With respect to the programs related to the electronic study data conforming to the CDISC standards, the programs used to create the ADaM datasets and programs used for analyses must be submitted. The main purposes of requesting the submission of these programs are to understand the process by which the variables for the respective analyses were created and to confirm the analysis algorithms. Therefore, it is not necessary to submit the programs in a format or content that allows the PMDA to directly run the program under its given environment. Also, although the programs to be submitted are not limited to specific software or versions, information on the environment in which the programs were created or run (operation system and software used and their versions) must be provided together in the data guide. If programs with macros had been used, the macro programs should preferably be submitted together. However, if submission of the macro program is difficult or submission of the program itself is difficult because the creation of the dataset or program was outsourced, the submission of specifications that show the analysis algorithm would be sufficient.

4.1.6.2 File format of the programs

As stated in 4.1.6.1, although the programs to be submitted are not limited to specific software or versions, the file name should include the extension attached by the analysis software. If the file name does not contain an extension, an explanation about the file format should be included in the data guide."[6]

In addition, the PMDA *Technical Conformance Guide on Electronic Study Data Submissions* gives detailed information on the submission of programs for pharmacokinetic analyses and for PK population analyses (Sections 4.2.3 and Attachment 5). It also specifies where to store software programs in the eCTD.[6]

There are two additional documents on the PMDA website that also describe the requirement to submit software programs to the PMDA.

- Basic Principles on Electronic Submission of Study Data for New Drug Applications (2014)[10]
  In this document, the PMDA states that the primary analysis program for the primary endpoint in a confirmatory study should be submitted. The document also states that "additional programs may be required to be submitted even after an application if further evaluation is judged necessary during the process of review."

- Notification on Practical Operations of Electronic Study Data Submissions (2015)[11]
  This document contains similar information as in the PMDA *Technical Conformance Guide on Electronic Study Data Submissions*. It also contains the following text specific to software programs for PK population analysis, including simulations: "In principle, submit the programs of models that were important in the model building process, such as base model and final model, and files with the output of major results. If simulation was performed, submission of the program used for the simulation and program procedures is desirable. If it is difficult to submit the program itself, submission of specifications that demonstrate the analysis algorithm would be sufficient."

FREQUENTLY ASKED QUESTIONS

This section provides answers for many of the frequently asked questions about submission of programs to regulatory agencies.

Can sponsors submit SAS programs with .sas extensions?

For submissions to the FDA:

This question is often debated among programmers and statisticians in the pharmaceutical industry. The FDA *Study Data Technical Conformance Guide* states "Sponsors should submit software programs in ASCII text format. Executable file extensions should not be used."[1] But many programmers and statisticians contend that ".sas" is not an executable file extension and that SAS programs are inherently in ASCII text format. Therefore, they argue that sponsors should be able to submit SAS programs with a ".sas" extension to the FDA.

Since the FDA *Specifications for File Format Types Using eCTD Specifications* document states that ".sas" is an acceptable extension in eCTD Modules 3 – 5 for files used for "Modelling and Simulation Reporting"[9], sponsors should be able to include programs with a ".sas" extension in the eCTD without fear that eCTD gateway checks will reject the eCTD. However, the FDA has communicated informally (through responses to questions to the Center for Drug Evaluation and Research (CDER) eData team and through responses to sample eCTD submissions) that they would like SAS programs to be submitted with ".txt" file extensions in place of ".sas" file extensions.[12] Therefore, it is recommended that sponsors change all ".sas" file extensions to ".txt" before loading SAS programs to the eCTD.

For submissions to the PMDA:

The PMDA explicitly requests that "the file name should include the extension attached by the analysis software".[6] So, sponsors should not change ".sas" file extensions for SAS programs for submissions to the PMDA.

Are sponsors required to submit executable programs?

For submissions to the FDA:

The *FDA Study Data Technical Conformance Guide* states that the "main purpose of requesting the submission of these programs is to understand the process by which the variables for the respective analyses were created and to confirm the analysis algorithms and results. Sponsors should submit software programs in ASCII text format. Executable file extensions should not be used."[1] These statements imply that the FDA does not want executable programs – they do not want programs to have executable file extensions, and they will use the programs to better understand the process of creating the analyses. They will not necessarily try to execute the programs on their computer systems.

Despite this text in the FDA *Study Data Technical Conformance Guide*, some people still debate whether executable programs need to be provided, usually because people have different definitions of "executable" in mind. Some people have a very limited definition of "executable" – they think that any program we provide to the FDA will be executable because snippets of the code could be copied into FDA programs and executed.

However, this limited definition of "executable" is different from requiring that software programs be executable on the FDA's computer system without any modification by the FDA. It is challenging for sponsors to provide programs that are fully executable on the FDA's systems without modification because

- Programs usually contain LIBNAME statements that expect a specific directory structure that likely does not exist on the FDA's system. Also, the input datasets for the programs must be stored in the proper folders of this directory structure.
- Programs may need to be executed in a specific order to execute correctly.
- Some SAS statements may function differently in different environments (e.g. Linux SAS versus PC-SAS).

The text in the FDA *Study Data Technical Conformance Guide* makes it clear that the FDA does not expect sponsors to provide programs that will execute on FDA systems without modification.[1] The FDA eData team has confirmed that the FDA understands that they may need to modify programs to execute them (e.g. update LIBNAMEs, convert XPTs to SAS datasets, etc.).[12] So, by this definition of "executable", sponsors do not need to provide executable programs.

However, there have been times in the past when an individual review team at the FDA has requested programs that will execute on their systems without any modification by the FDA. If a review team requests these, be aware that it takes much more effort and time to provide executable programs. It is necessary to write a Program Guide that gives very detailed instructions to the regulators on how to set up the programming environment so that the programs will execute. This guide must contain information such as:

- How to setup the directory structure that the programs expect
- Which XPT files must be converted to SAS datasets and then loaded into the directory structure
- The correct order for executing the programs
- Instructions for modifying any statements that may execute differently on the FDA computer systems. For example, some SAS statements functions differently in PC-SAS than they do in Unix/Linux environment.

For submissions to the PMDA

The PMDA is more explicit than the FDA that executable programs do not have to be provided. The PMDA *Technical Conformance Guide on Electronic Study Data Submissions* states that "the main purposes of requesting the submission of these programs are to understand the process by which the variables for the respective analyses were created and to confirm the analysis algorithms. Therefore, it is not necessary to submit the programs in a format or content that allows the PMDA to directly run the program under its given environment."[6]

Should sponsors submit standard macros?

Most sponsors and CROs have a library of standard macros. These libraries can contain different types of macros – ranging from macros that create ADaM datasets to utility macros that perform tasks such as formatting tables and generating RTF files.

For submissions to the FDA:

The FDA does not have a specific requirement to submit standard macros. Sponsors will need to use judgement when deciding which standard macros to submit to the FDA. Utility macros will likely not be helpful in helping the FDA reviewers understand "the process by which the variables for the respective analyses were created and to confirm the analysis algorithms and results".[1] Therefore, there is probably not much benefit to providing utility macros. However, for macros that create ADaM datasets or that produce analyses, there is likely a benefit to providing these to the FDA.

For submissions to the PMDA

The PMDA *Technical Conformance Guide on Electronic Study Data Submissions* states: "If programs with macros had been used, the macro programs should preferably be submitted together. However, if submission of the macro program is difficult or submission of the program itself is difficult because the creation of the dataset or program was outsourced, the submission of specifications that show the analysis algorithm would be sufficient."[6]

If a sponsor does provide standard macros to either the FDA or PMDA, then it is a good practice to also provide clear documentation of the purpose and functionality of the macros.

What type of documentation should be included with the programs?

It is good practice to provide clear documentation of all software programs provided to the FDA, in order to help reviewers understand them. This documentation can be provided in the ADaM Reviewers Guide and/or in a separate Table of Contents file.

The PhUSE template ADaM Reviewers Guide contains *Section 7 Submission of Programs*.[13] Sponsors can provide documentation of submitted programs in this section. The following information can be added to Section 7:

- Description of which programs are being submitted.
- Table of Contents for the programs
- Software Version and Environment (e.g. PC SAS V9.3)

An example of a completed Section 7 Submission of Programs of the ADRG is available on the PhUSE Wiki at Analysis Data Reviewer's Guide (under the Samples folder).

Another option is to provide documentation of submitted programs in a stand-alone Table of Contents document. This document could contain information such as the purpose, functionality, and the input and output of each program. A simple example is given below for the purpose of illustration.

Type Program	Program	Output	Inputs	Macros Used	Description
ADAM	adsl.sas	ADSL	DM, EX, PD, etc.	%ru_ittpop.sas	Create ADSL from input SDTM datasets
Table	t_aesumm.sas	Table 8.3	ADAE, ADSL	None	Create Summary of AEs
Utility	t_addperiod.sas			None	This macro will derive ADaM period variables. It will create new variables on the output dataset: • APERIOD / APERIODC when EVENTTYPE=PL (planned, e.g. for laboratory data) • TPERIOD / TPERIODC when EVENTTYPE=SP (spontaneous, e.g. for adverse events)

Alternatively, the Table of Contents could be organized with Endpoint as the left-most column, in order to help reviewers find all the programs associated with an endpoint.

Analysis Results Metadata (ARM) is often provided in submissions as documentation for tables. ARM typically contains information needed to recreate a table, such as the analysis dataset, PARAM/PARAMCD values, subsetting criteria, and model statements.[14] ARM does provide valuable documentation to reviewers, but the FDA and PMDA guidance documents state that software programs are still requested for primary and secondary efficacy endpoints, even if ARM is provided.[1,6]

Is the process different for non-SAS languages, such as R or Python?

The FDA Position Statement - Statistical Software Clarifying Statement clarifies that the "FDA does not require use of any specific software for statistical analyses, and statistical software."[5] Also, all of the FDA and PMDA statements about software programs are written in a general way – they apply to any software program used to produce analyses.[1,6,10,11] SAS® is the most commonly used statistical analysis software used in the pharmaceutical industry.[15] However, other software packages such as R and Python are sometimes used.[15]

R Programs

R is an open-source programming language that is sometimes used in the pharmaceutical industry, particularly for graphics and simulations.[15,16,17,18] The process for submitting R programs to the FDA and PMDA is essentially the same as submitting SAS programs.[1,6] All the FAQs and Best Practices in this paper apply to R programs.

- R programs should be submitted in ASCII text format with ".txt" file extensions to the FDA and with ".R" file extensions to the PMDA.
- R programs do not need to be directly executable on the FDA or PMDA computer systems.
- R packages should be provided, if they will help the reviewers understand the analyses.
- A program guide should be provided for R programs either in the ADaM Data Reviewers Guide or in a stand-alone document.
- Good Programming Practices should be followed when writing R programs. [19]

A larger question (that is outside the scope of this paper) is whether R meets the requirements for validation described in the FDA guidance documents Guidance for Industry - Computerized Systems Used in Clinical Investigations (2007) and FDA General Principles of Software Validation; Final Guidance for Industry and FDA Staff (2002). To learn more about the use of R for regulatory submissions, refer to the excellent paper "R: Regulatory Compliance and Validation Issues A Guidance Document for the Use of R in Regulated Clinical Trial Environments" written by the R Foundation for Statistical Computing.[18]

Other Languages

SAS and R are the most commonly used statistical analysis software packages used in the pharmaceutical industry.[15] But there are examples of other languages, such as Python, being used in the industry.[20,21] Also, some recruiters are now encouraging people to acquire R and Python programming skills to "guarantee your future career marketability" in data sciences.[22]

Just as with the R language, the process and principles for submitting programs in other languages to the FDA and PMDA are the same as SAS programs.[1,6] For example, Python scripts with a ".py" extension would need to be renamed to have a ".txt" extension before submitting them to the FDA.

BEST PRACTICES

This section lists a high-level recommended step-by-step process for submitting software programs to regulatory agencies, along with suggestions of best practices to ensure quality and efficiency.

RECOMMENDED PROCESS FOR SUBMISSION OF SOFTWARE PROGRAMS TO REGULATORY AGENCIES

1. Understand the requirements for submission of software programs
   The first step is to educate yourself on the requirements for submission of software programs using the guidance documents and resources listed in this paper.

2. Seek agreement with Regulatory Agencies as early as possible.[1,5,10]
   It is always best practice to consult with and seek agreement with regulatory agencies as early as possible for all aspects of submission data packages. For submission of software programs, sponsors should seek agreement on:

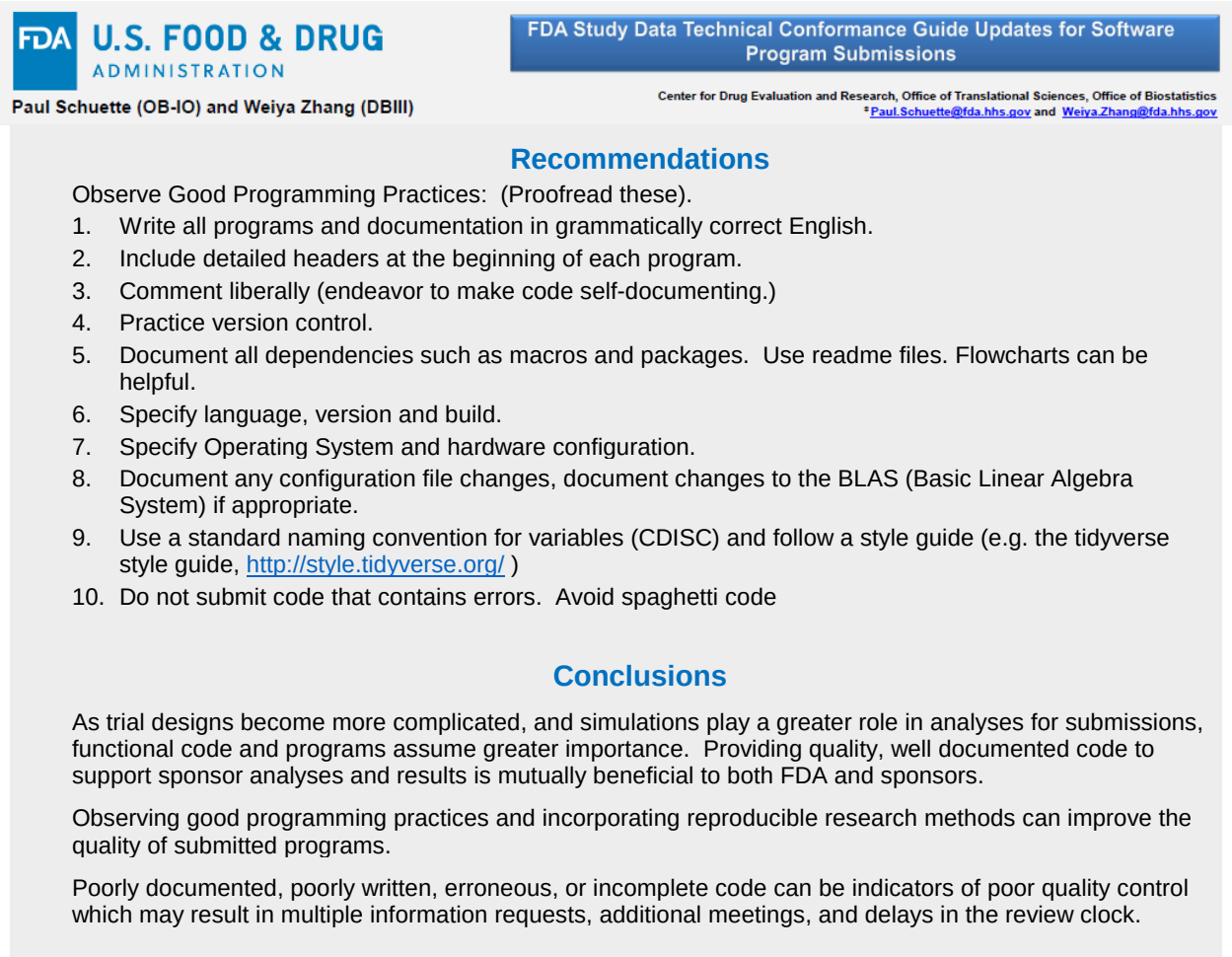
   - Use of a non-typical software package, if applicable, to ensure the regulatory agency agrees that the software package meets their requirements.[5]
   - Confirm in general which software programs will be submitted
   - Clarify whether the review team wants executable programs. The FDA and PMDA Technical Conformance Guides are clear that executable programs are not required. But occasionally, a review team requests these. So, it is best to confirm the specific expectations and requirements of the review team.

3. Build in quality for programs from the beginning – follow Good Programming Practices.[19]

   While preparing analyses for a submission, it is important to keep in mind that regulatory reviewers will likely read your software programs. So, it is best practice to make sure programs are readable, well-commented (both header comments and inline comments), and that they comply with Good Programming Practices.

   Information about Good Programming Practices is available at the PhUSE Wiki at http://www.phusewiki.org/wiki/index.php?title=Good_Programming_Practice.[19] The submission process will be much smoother and efficient if programs are written to follow Good Programming Practices from the beginning, rather than modifying them to comply with Good Programming Practices late in the submission process.

To reinforce the importance of following Good Programming Practices, here are excerpts from a poster titled "FDA Study Data Technical Conformance Guide Updates for Software Programs Submission" presented at 2018 PhUSE CSS from Paul Schuette and Weiya Zhang from the FDA.[23]



FDA U.S. FOOD & DRUG ADMINISTRATION

Paul Schuette (OB-IO) and Weiya Zhang (DBIII)

FDA Study Data Technical Conformance Guide Updates for Software Program Submissions

Center for Drug Evaluation and Research, Office of Translational Sciences, Office of Biostatistics

Paul.Schuette@fda.hhs.gov and Weiya.Zhang@fda.hhs.gov

Recommendations

Observe Good Programming Practices: (Proofread these).

1. Write all programs and documentation in grammatically correct English.
2. Include detailed headers at the beginning of each program.
3. Comment liberally (endeavor to make code self-documenting.)
4. Practice version control.
5. Document all dependencies such as macros and packages. Use readme files. Flowcharts can be helpful.
6. Specify language, version and build.
7. Specify Operating System and hardware configuration.
8. Document any configuration file changes, document changes to the BLAS (Basic Linear Algebra System) if appropriate.
9. Use a standard naming convention for variables (CDISC) and follow a style guide (e.g. the tidyverse style guide, http://style.tidyverse.org/)
10. Do not submit code that contains errors. Avoid spaghetti code

Conclusions

As trial designs become more complicated, and simulations play a greater role in analyses for submissions, functional code and programs assume greater importance. Providing quality, well documented code to support sponsor analyses and results is mutually beneficial to both FDA and sponsors.

Observing good programming practices and incorporating reproducible research methods can improve the quality of submitted programs.

Poorly documented, poorly written, erroneous, or incomplete code can be indicators of poor quality control which may result in multiple information requests, additional meetings, and delays in the review clock.

4. Plan which programs will be submitted, including standard macros and programs for the drug label and standard macros.

   - Include Programs for Product Label Information
     In 2018, the FDA updated the *Study Data Technical Conformance Guide* to add programs that generate prescribing information for the product label to the list of programs to be submitted ("Furthermore, sponsors should submit software programs used to generate additional information included in Section 14 CLINICAL STUDIES of the Prescribing Information.").[1] Drug labels typically contain AE summaries and PK analysis results from late phase Clinical Pharmacology studies (i.e. renal, hepatic, QTc, etc.). Drug labels may also contain additional information dependent on therapeutic area, indication, and the specific compound. Staff who prepare software programs for submission to the FDA must ensure that they consult with their submission team, so they correctly identify and submit programs for analyses included in the drug label.

   - Decide which standard macros to submit
     Review standard macros used by programs that create ADaM datasets, etc and decide which macros would add value to a regulatory reviewer.

5. Prepare documentation for the programs to help the regulatory agencies understand them
   See FAQ ***What type of documentation should be included with the programs?*** in the previous section of this paper for more information on the types of documentation that should be submitted.

6. For FDA submissions, convert program file extensions to ".txt". For PMDA submissions, do not change file extensions of programs.[1,6]

7. Load programs to the proper location in the eCTD. [1,6] The specific process for this step will vary by company.

CONCLUSION

At first glance, the task of submitting software programs to regulatory agencies seems like it should simple. But as this paper has demonstrated, there are nuances to this task, and it is necessary to properly plan and prepare for this step in the submission process.

REFERENCES

[1] US Food & Drug Administration. Oct. 2018. "Study Data Technical Conformance Guide V4.2. Accessed Nov. 15, 2018. https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM624623.pdf .

[2] US Food & Drug Administration. September 1998. "Guidance for Industry: E9 Statistical Principles for Clinical Trials". Accessed Dec. 15, 2018. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073137.pdf .

[3] US Food & Drug Administration. May 2007. "Guidance for Industry: Computerized Systems Used in Clinical Investigations". Accessed Dec. 12, 2018. http://academy.gmp-compliance.org/guidemgr/files/7359FNL.PDF .

[4] US Food & Drug Administration. Jan. 2002. "General Principles of Software Validation; Final Guidance for Industry and FDA Staff". Accessed Dec. 15, 2018. https://www.fda.gov/downloads/medicaldevices/.../ucm085371.pdf .

[5] US Food & Drug Administration. May 2015. "Statistical Software Clarifying Statement". Accessed Dec. 15, 2018. https://www.fda.gov/downloads/forindustry/datastandards/studydatastandards/ucm587506.pdf .

[6] Japan Pharmaceuticals and Medical Devices Agency. Aug. 2016 "Revision of Technical Conformance Guide on Electronic Study Data Submissions". Accessed Nov. 20, 2018. https://www.pmda.go.jp/files/000215100.pdf .

[7] Health Canada. Jan. 2018. "Notice – Mandatory use of the Electronic Common Technical Document (eCTD) format". Accessed Dec. 21, 2018. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/activities/announcements/notice-mandatory-use-electronic-common-technical-document-ectd-format.html .

[8] freyr Global Regulatory Solutions and Services. "eCTD Submissions – A quick look over the FDA & HC deadlines". Accessed Dec. 21, 2018. https://www.freyrsolutions.com/blog/ectd-submissions-a-quick-look-over-the-fda-hc-deadlines .

[9] US Food & Drug Administration. Nov. 2017. "Specifications for File Format Types Using eCTD Specifications." Accessed Dec. 15, 2018. https://www.fda.gov/downloads/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/ucm347471.pdf .

[10] Japan Pharmaceuticals and Medical Devices Agency. June 2014. "Basic Principles on Electronic Submission of Study Data for New Drug Applications. Accessed Dec. 17, 2018. https://www.pmda.go.jp/files/000153708.pdf .

[11] Japan Pharmaceuticals and Medical Devices Agency. April 2015. "Notification on Practical Operations of Electronic Study Data Submission". Accessed Dec. 17, 2018. https://www.pmda.go.jp/files/000206451.pdf .

[12] US Food & Drug Administration Center for Drug Evaluation and Research (CDER) eData Team. April 2018. Email correspondence with Maria Dalton.

[13] PhUSE Analysis Data Reviewer's Guide site on PhUSE Wiki. Jan 2015. "ADRG Package v1.1 2015-01-26". Accessed Dec. 21, 2018. https://www.phusewiki.org/wiki/index.php?title=Analysis_Data_Reviewer%27s_Guide .

[14] CDISC Analysis Data Model Team. Feb 12, 2016. "Analysis Data Model Implementation Guide V1.1".

[15] Manu Jeevan. Sept. 21, 2016. "R, Python or SAS: Which one should you learn first?". Accessed Dec. 21, 2108. https://www.edvancer.in/r-python-or-sas-which-one-should-you-learn-first/

[16] TechWorld. Aug. 20, 2014. "R programming language gaining ground on traditional statistics packages". Accessed Dec. 21, 2018. https://www.techworld.com/news/apps-wearables/r-programming-language-gaining-ground-on-traditional-statistics-packages-3538938/ .

[17] Yilong Zhang, Changhong Shi, Lei Xu, Zhen Zeng, Gregory Golm. March 2018. "R for SDTM and ADaM Data". Poster at 2018 PhUSE Computational Science Symposium. Accessed Dec. 22, 2018. https://www.phusewiki.org/docs/2018%20US%20CSS/posters/PP10.pdf .

[18] The R Foundation for Statistical Computing. March 25, 2018. "R: Regulatory Compliance and Validation Issues A Guidance Document for the Use of R in Regulated Clinical Trial Environments". Accessed Dec. 15, 2018. https://www.r-project.org/doc/R-FDA.pdf .

[19] PhUSE Steering Board for Good Programming Practice in Health and Life Sciences. March 2014. "Guidance on Good Programming Practice V1.1". Accessed Dec. 21, 2018. https://www.phusewiki.org/wiki/index.php?title=Good_Programming_Practice_Guidance .

[20] Python Software Foundation. "Python Success Stories". Accessed Dec. 18, 2018. https://www.python.org/about/success/astra/ .

[21] RxDataScience. "Top Use Cases for Machine Learning in Pharma". Accessed Dec. 21, 2018. https://www.rxdatascience.com/blog/top-use-cases-for-machine-learning-in-pharma .

[22] SmithHanley Associates LLC. July 26, 2018. "If R and Python are better, why do so many job ads still seek SAS?". Accessed Dec. 21, 2018. https://www.smithhanley.com/2018/07/26/r-python-better-job-ads-still-seek-sas/ .

[23] Paul Schuette and Weiya Zhang. March 2018. "FDA Study Data Technical Conformance Guide Updates for Software Programs Submission". Poster at 2018 PhUSE Computational Science Symposium. Accessed Nov. 17, 2018. http://www.phusewiki.org/docs/2018%20US%20CSS/posters/PP33.pdf .

ACKNOWLEDGMENTS

I would like to thank and acknowledge Warwick Benger, Miho Hashio, and Junko Urata at GSK who provided me with invaluable information about regulatory submissions. I am very grateful for their kind support and guidance.

I would also like to thank and acknowledge the members of the PhUSE CDISC Data Submissions FAQ Team for the advice and support they provide to members of the PhUSE community.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Maria Dalton
GlaxoSmithKline
1250 S. Collegeville Road
Collegeville, PA 19426-0989, USA
Work Phone: 610-917-7320
Email: maria.y.dalton@gsk.com

Brand and product names are trademarks of their respective companies.