21 April 2021

INDUSTRY CONSIDERATIONS IN DIVERSIFYING THE STATISTICAL TOOL SETS USED TO SUPPORT FDA SUBMISSIONS

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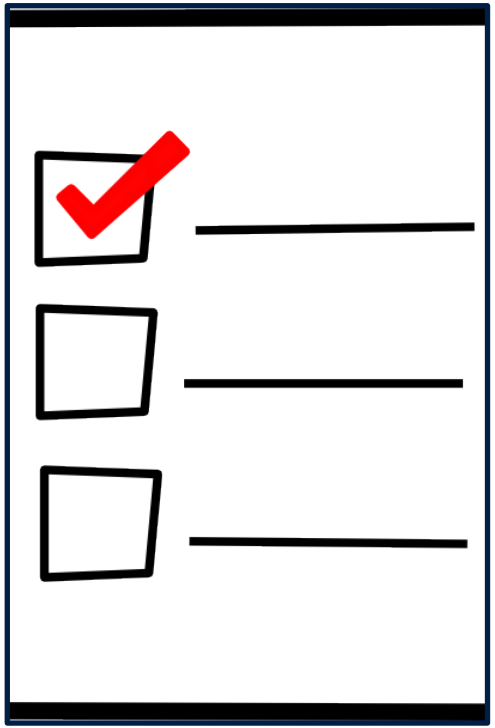
OUTLINE OF PRESENTATION

- Sequence of questions when considering moving to open source:
  - Why would we change?
  - Can we change?
    - R Foundation views
    - FDA view
  - How would we change?

- Conclusion



WHY CHANGE?

- Training inefficiencies
  - Recent graduates have more exposure to and experience with open-source solutions (e.g., R) than with proprietary solutions (e.g., SAS)
  - Training new employees on legacy systems could be wasteful if those legacy systems are soon to be retired/replaced

- Cost considerations
  - Hard to justify cost of proprietary software when open-source solution with comparable functionality is readily available
  - Excess reliance on a single solution puts us in a poor negotiating position
  - When we started moving towards open source, our existing contract with SAS scaled linearly with the number of desktop installations
    - Use of server or cloud solutions was not widespread

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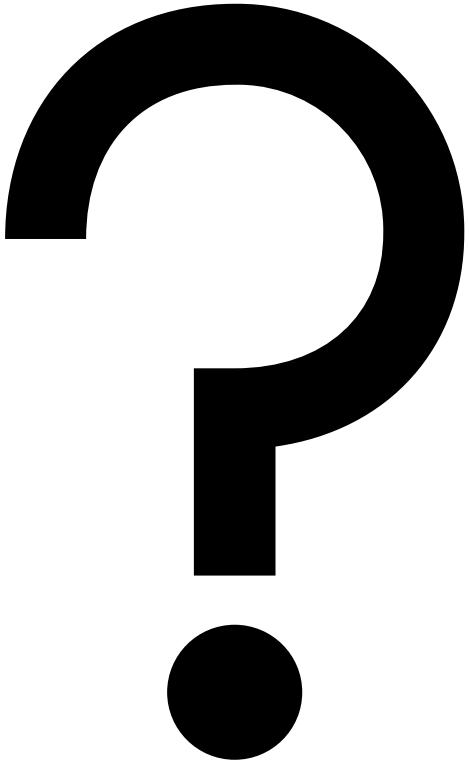
CAN WE CHANGE?

- Most frequent topic that comes up concerns compliance
- Often couched in terms of compliance with 21 CFR Part 11
  - This section focuses on electronic records and electronic signatures
- Issue has been raised many times
  - A few resources have been put together on the topic by the R Foundation



R PROJECT VIEWS ON COMPLIANCE AND VALIDATION

r-project.org/certification.html

[Home]

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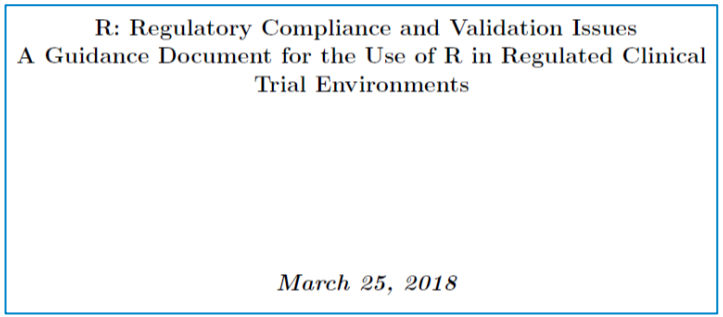
CRAN

Certification

- R: Regulatory Compliance and Validation Issues: A guidance document for the use of R in regulated clinical trial environments.
- R: Software Development Life Cycle: A description of R's development, testing, release and maintenance processes (contentwise, this is a **subset** of the regulatory compliance document above).



R: Regulatory Compliance and Validation Issues
A Guidance Document for the Use of R in Regulated Clinical Trial Environments

March 25, 2018

It is important to note that there is a significant obligation on the part of the end-user's organization to define, create, implement and enforce R installation, validation and utilization related Standard Operating Procedures (SOPs) within the end-user's environment. These SOPs should define appropriate and reasonable quality control processes to manage end-user related risk within the applicable operating framework. The details and content of any such SOPs are beyond the scope of this document.

The term "validation" is interpreted in different ways in different fields. The FDA clearly defined the term in guidance[3] and it should be noted that validation is more than a verification or testing exercise.

Validation is defined by the FDA as: "Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes."[4]

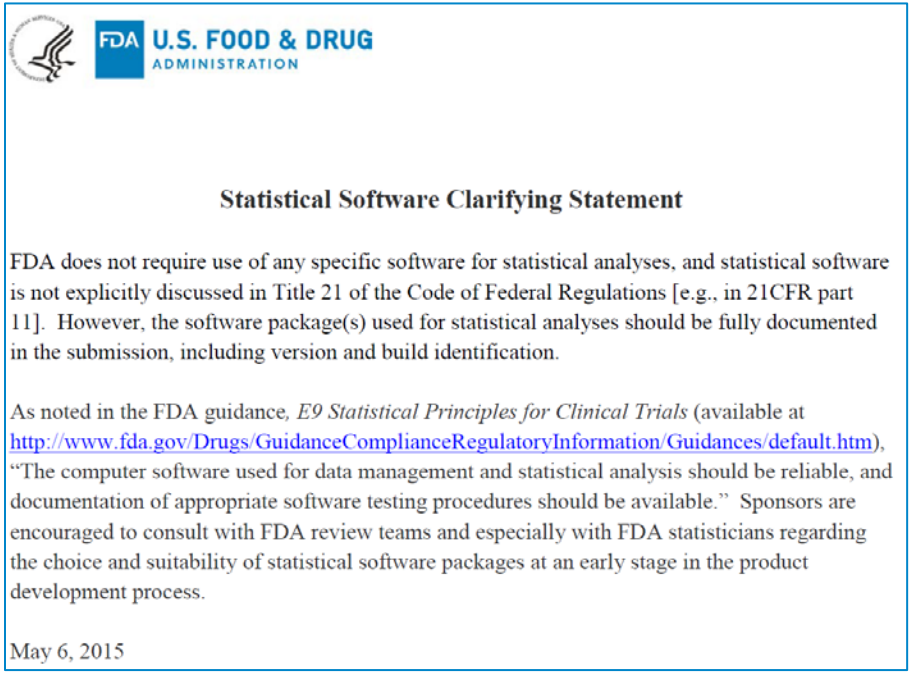
The FDA explains that validation encompasses the overall program and is designed to assure quality and consistency for a process/product throughout its lifecycle. In contrast, verification is an activity performed during and/or between phases of the overall lifecycle. Software testing is one form of verification.

Qualification can be seen as a phase of verification and/or testing within an overall validation program.

The purpose of this document is to demonstrate that R, when used in a qualified fashion, can support the appropriate regulatory requirements for validated systems, thus ensuring that resulting electronic *records* are "trustworthy, reliable and generally equivalent to paper records."

RELEVANT STATEMENT FROM FDA

- The uninitiated may feel that only commercial statistical software systems could be accepted by FDA
- FDA has clearly stated that this is not the case
- Language such as that shown to the right can be helpful in convincing non-specialists that other options are viable
  - "Thanks again Ted, looks like we have a green light. It's time we entered the 21st century and get rid of the Model T."



FDA U.S. FOOD & DRUG ADMINISTRATION

Statistical Software Clarifying Statement

FDA does not require use of any specific software for statistical analyses, and statistical software is not explicitly discussed in Title 21 of the Code of Federal Regulations [e.g., in 21CFR part 11]. However, the software package(s) used for statistical analyses should be fully documented in the submission, including version and build identification.

As noted in the FDA guidance, *E9 Statistical Principles for Clinical Trials* (available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm), "The computer software used for data management and statistical analysis should be reliable, and documentation of appropriate software testing procedures should be available." Sponsors are encouraged to consult with FDA review teams and especially with FDA statisticians regarding the choice and suitability of statistical software packages at an early stage in the product development process.

May 6, 2015

HOW WOULD WE CHANGE?
PLAN

- Dispersed funding and governance structure meant that corporate-wide edicts were not viable
  - Encouragement rather than orders
- Privacy and data access concerns arose in a similar time frame
- Aligned on plan to move from desktop SAS, to server SAS, and then to server R

HOW WOULD WE CHANGE?
REALITY

- Newer rounds of contract negotiations with SAS include a flat fee for any SAS usage (desktop or server) up to a certain number of users
  - No benefit within the life of the contract for not utilizing all available licenses
  - As cost was a major driver, less buy-in for change when no immediate cost benefit
- Strong internal resistance (programmers and statisticians) from experienced practitioners
  - Pushed for new hires to use new tools; delay on movement away from SAS for tenured colleagues
    - Maintain intellectual capital of expert users
  - Certain tasks (e.g., working with device data) work well in SAS; haven't yet developed competitive alternative
    - If a newer hire needs to perform these tasks, end up using SAS
- Still proceeding with set up of R server solutions, but uphill battle for wide voluntary adoption

CONCLUSION

- Cost (in various forms) was the biggest driver for considering change
  - Delayed nature of cost benefits has reduced interest in changing away from SAS
- Compliance fears about using open-source software were raised, but not found to be major hurdle
  - Larger issue was ensuring validation of novel R code in a high-profile project (Tarek's discussion)
- Biggest challenge to date has been large, mature team that is change averse
  - "Institutional inertia"
  - May have additional opportunity to change minds with future roll-out of SAS Viya

THANK YOU!

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