

R Adoption Series

Review Experience with R based Submissions

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.



Outline

- 1. What is Important to FDA?
- 2. R based Submission
- 3. Findings / Issues
- 4. Recommendations



What is Important to FDA? (In R based Submissions)



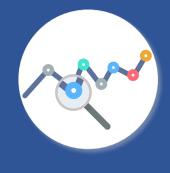
Conformance



Reproducibility



Traceability





Conformance

Follow <u>FDA application</u> <u>submission guidance and</u> meet requirements

- Study Data Technical Conformance Guide – Technical Specifications Documents
- CDISC
- Electronic Common Technical Document format (eCTD)
- Etc.

Reproducibility

Obtain consistent results using the same data

Traceability

Enable the understanding of the data's lineage and/or the relationship between an element and its predecessor(s)



R based Submissions



R Submission Working Group Pilot Project

Pilot 1 (completed)

 To test an R-language based submission package can meet the needs and expectations of the FDA

Pilot 2 (completed)

 To test a Shiny application created with the R-language can be bundled into a submission package and transferred to FDA

Pilot 3 (Reviewing)

 To re-test the pilot 1 with ADaM datasets generated using R



Application Review

Clinical Trial Submission

- There have been a few SAS and R hybrid submissions.
- There have been some challenges in replicating the sponsor's computational environment.



Findings / Issues



R versions / R packages

- Different versions of R may not perform as desired.
- Switching between R versions in RStudio can be problematic.
- 'renv' package can create reproducible environments and manage package dependencies; however, it might not be ideal.



Different Environments

- Different operating systems (Linux vs. Windows)
 - Different operating system may cause some differences.
 - In the Pilot review, some file names and file paths had to be changed.
- Warning messages may appear differently.
- In the 'renv' set up, the reviewer may need to select different options to proceed.



Flexibility

- R offers greater flexibility.
 - Multiple ways to calculate values
 - Diverse packages
 - Different default settings for functions and representing missing data
- Shiny app's interactive features could be inappropriately used to enable p-hacking and for cherry picking.



Recommendations



For Future R based Submission,

- Let FDA know at the design stage.
- Use CRAN or a curated repository for sourcing packages.
- Use standard packages and minimize dependency on sponsor developed packages.
- Provide thorough documentation and detailed comments.



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