R submission Pilots to FDA

By the R consortium R submission Working Group

Presenter:
Ning Leng, People and Product Lead, Product Development Data Sciences,
Roche-Genentech *(we are hiring! Data Scientist - Software Engineering Specialty)*

Background

Regulatory Submissions to the Health Authorities

- To support the market approval of a treatment, sponsors will submit a comprehensive package of materials to health authorities (HA) to evaluate a product's efficacy and safety
    - Include analysis reports, data sets and software programs
- In addition to reviewing reports, HA reviewers also reproduce key analysis results
    - Review submitted data/code, independent programming
- Proprietary software has been widely used, due to reproducibility and quality considerations
    - In recent years, there are increasing interests in adopting open-source software

The R Consortium R Submission Working Group:

A cross industry collaboration to improve open-source language usage in the regulatory setting

Open-source language based submission to FDA:

The Challenges

Reproducibility

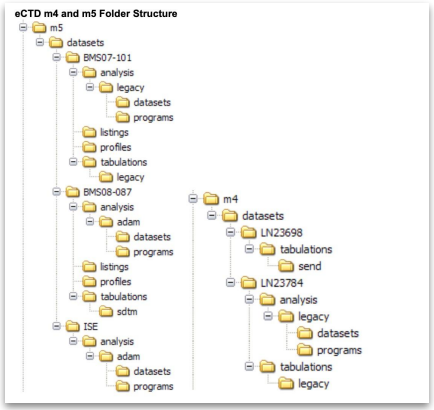
e.g. ensure reviewers access to the same package versions (health authority reviewer may not have access to the container technology)

Submission of R packages with private information (R packages that cannot be put in public domain)

Technical challenge: FDA esubmission gateway does not allow for compressed files for security reasons (such as rpkg.tar.gz)

Fit into the well-established FDA required file structure

And ensure relevant information are easily findable by the reviewers



Pilot 1 Submission to FDA: Project Scope

Key evaluation aspects:

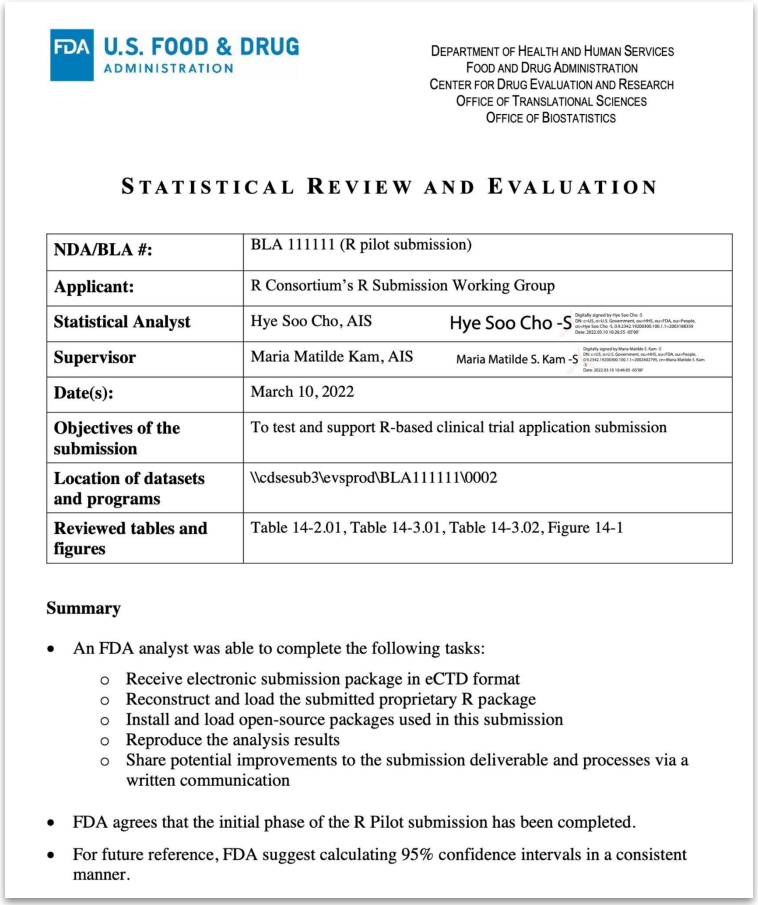
- For Submitter
  - Submission of a proprietary R package (`pilot1wrappers`, converted to txt format via pkglite)
  - Preparation of R-based submission materials (Reviewer's Guide, etc.)
- For FDA staff
  - Reproduce analysis results by reconstructing submitted proprietary package (`pilot1wrappers`) / retrieving open source packages with certain version
  - Provide feedbacks and/or review comments

Data and analysis scope:

- Data from CDISC pilot 1 - publicly available, simulated data
  - Data generation script out of the scope of this pilot
- 4 outputs - 3 tables, 1 figure
  - This pilot will provide R scripts for output generation and a proprietary R package which contains analysis wrappers

Pilot 1 Submission to FDA:

A successful open pilot that showcased using R in FDA submission



U.S. FOOD & DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

NDA/BLA #:	BLA 111111 (R pilot submission)
Applicant:	R Consortium's R Submission Working Group
Statistical Analyst	Hye Soo Cho, AIS Hye Soo Cho -S
Supervisor	Maria Matilde Kam, AIS Maria Matilde S. Kam -S
Date(s):	March 10, 2022
Objectives of the submission	To test and support R-based clinical trial application submission
Location of datasets and programs	\\cdsesub3\evsprod\BLA111111\0002
Reviewed tables and figures	Table 14-2.01, Table 14-3.01, Table 14-3.02, Figure 14-1

Summary

- An FDA analyst was able to complete the following tasks:
  - Receive electronic submission package in eCTD format
  - Reconstruct and load the submitted proprietary R package
  - Install and load open-source packages used in this submission
  - Reproduce the analysis results
  - Share potential improvements to the submission deliverable and processes via a written communication
- FDA agrees that the initial phase of the R Pilot submission has been completed.
- For future reference, FDA suggest calculating 95% confidence intervals in a consistent manner.

- https://github.com/RConsortium/submissions-pilot1-to-fda
  - Final submission folder for Pilot 1 - following eCTD required folder structure

The Submission pilot 1 execution team
Ning Leng, Heng Wang (Roche)
Mike Stakehouse, Eli Miller (Atorus)
Yilong Zhang, Peikun Wu (Merck)

Next Steps

- Pilot 2: shiny based pilot submission to FDA
- Pilot 1 extensions: pilots to additional agencies (Japan-PMDA, HTAs)

Our webpage: https://rconsortium.github.io/submissions-wg/

All materials are open to the public

Anyone is welcome to join the working groups! (info@r-consortium.org)

Additional Working Groups

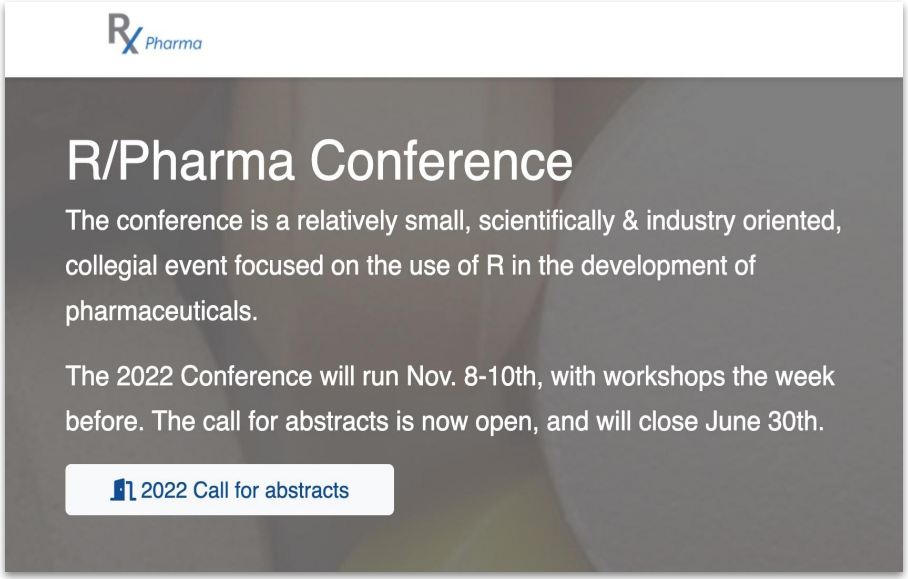
- R validation hub
  - Assess quality of open source software packages and validation
- R tables for regulatory reporting working group
  - Easier generation of tables fulfilling regulatory requirements:
- Pharmaverse
  - Cross industry collaborations to co-create a regulatory reporting toolsuite

Upcoming Events

R Adoption Series: Using R in regulatory review

July 13 (Wed), 11-12:30 EST
Meeting length: 1.5 hr

- Opening (5min)
  - Coline Zeballos, R consortium/Roche
- Presentation: Achieving Regulatory Approval Using R (25min)
  - Tae Hyun Jung, FDA
- Presentation: Review experience of the R consortium R submission pilot 1 (20min)
  - Hye Soo Cho, FDA
- Panel discussion (40min)
  - Moderator: Ning Leng, R consortium/Roche
  - Panelists: Paul Schuette, FDA; Hye Soo Cho, FDA; and Tae Hyun Jung. FDA



Thank you!