

Roche's first end-to-end R journey to submission

Jingyuan Chen
Principal Data Scientist, Genentech

PHUSE US Connect
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Early Adopters Journey

Early Adopters - The Journey

PD Data Sciences: End users



Choosing the
right study

Consider study
Timelines



Upskilling

Motivation

Passion

Practice



Programming
strategy

First Line in R
Validation/QC in
SAS



Stakeholder
management

Health Authority
Collaborations

Learning Experience



Learning Curve

- Initially feels steep
- Increase in confidence, familiarity and delivery
- Second study reporting underway



Pharmaverse: Positive User Feedback

- Modular approach to the setup of ADaM programs using {admiral} provide clear transparency of the code and adaptability
- The documentation are easy to follow
- Template programs ensure quick and consistent starting point

The Programming Strategy

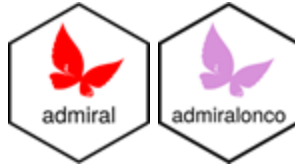
End-to-end in R submission - using primarily open source packages from pharmaverse



SDTM



ADaM



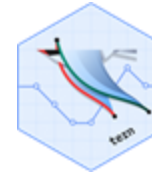
Proprietary



TLGs

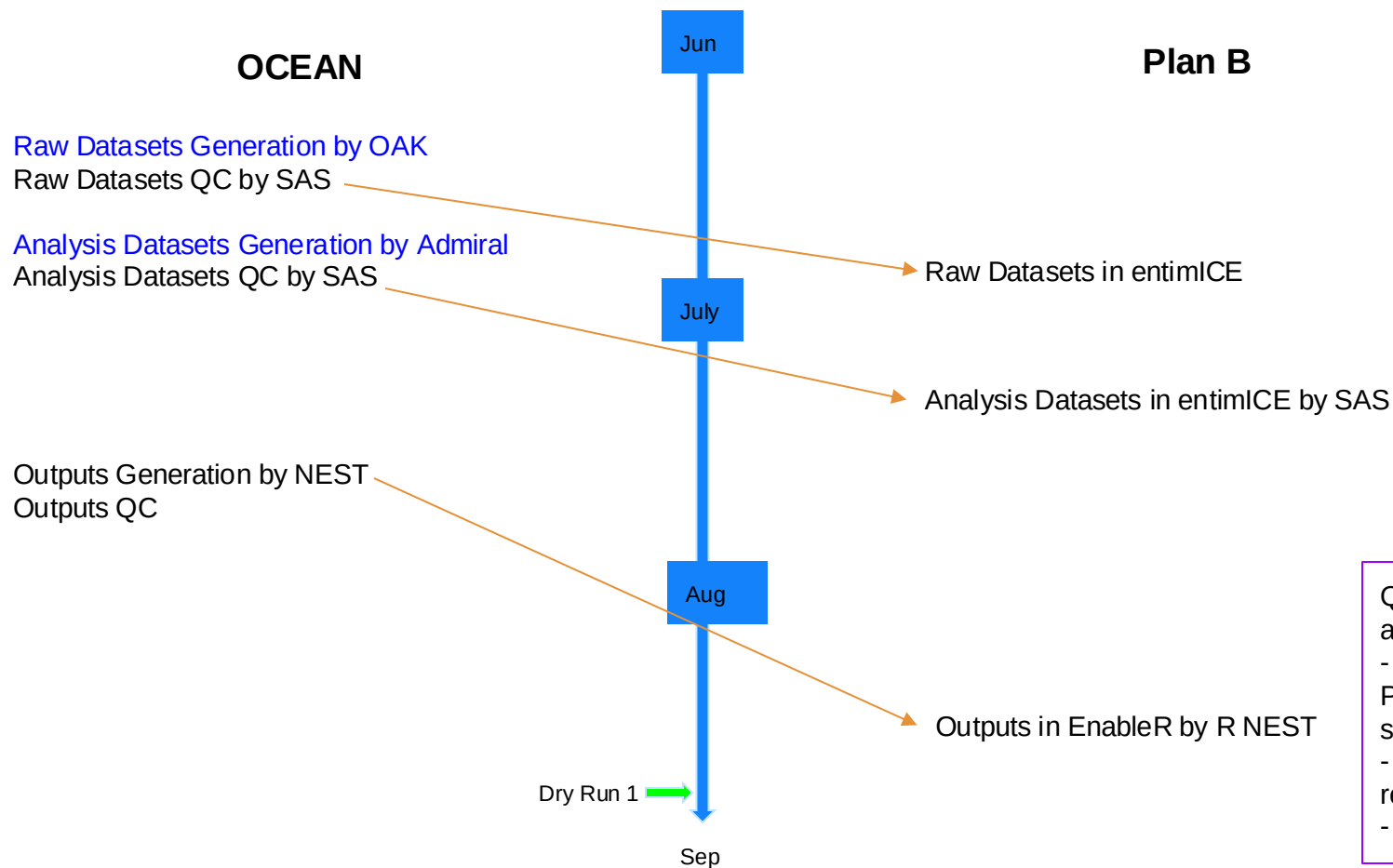


**Readable
code**



Risk Management & Convenience Global Filling Team

Risk Management & Back up Plan



QC would be missed at Dry Run 1

- Reference QC Programs from other studies
- Request additional resource
- adjust QC plan

Speed up Exploration and Reduce Formal Outputs

- Usage of Rshiny



Endpoint Tracking - PFS

Data Clinical Interpretation -
Stakeholders

Patent filings

Patient access

Health Authority Questions

Endpoint Tracking - OS

Pre- DBL*
During Review

DBL

Post Submission -

*DBL= DatabaseLock

The Regulatory Submissions Journey

Regulatory Submission Journey

- ❖ Global eSub- FDA, EMA, NMPA.
- ❖ How we prepare the eSUB module 5 with limited extra effort
- ❖ HA interactions prior submission, and related feedback during review period.

eSUB Contents for E2E R Study

SDTM Package:

- ☐ SDTM data in xpt format from **OAK**
- ☐ Define.xml
- ☐ SDRG
- ☐ aCRF

ADaM Package:

- ☐ ADaMs data in xpt format from **admiral (admiralroche)**
- ☐ Define.xml
- ☐ **Readable code** for ADaMs and Key outputs
- ☐ ADRG

Information for use of R

- ☐ **programTOC** :
 - R specific details
 - Package being used & version
 - Instruction to install R on windows and packages (both open and Proprietary)
- ☐ **Validation reports** for key R packages.

Internal Validation Process

- Broadly follow the process outlined by the [R Validation Hub's white paper](#)
- Internal R packages Validation process:
 - Autovalidate R is a process of documenting and upholding a set of R package quality expectations.
 - All validation processes are a balance among being thorough, actionable, and fast.
 - [[Roche's approach to software validation.](#)]



R/Pharma 2022 Day 2: Coline Zeballos & Doug Kelkhoff, Roche's approach to software validation



File of ProgramTOC discloses R Packages



Description of eSUB package



List of Analysis Dataset Programs



List of Output Programs



How to use the readable codes



Appendix: Instruction to execute analysis programs in R

File of ProgramTOC discloses R Packages

How to use the Readable code

Proprietary R Analysis Packages

Proprietary R Analysis Package	Package version	Description
<u>admiralroche</u>	0.3.0	Roche-specific extension of admiral. Provides Roche-specific functionality to facilitate ADaM programming using admiral.

Open-source R Analysis Packages

R Packages	Package version	Description
admiral	0.12.1	A toolbox for programming Clinical Data Interchange Standards Consortium (CDISC) compliant Analysis Data Model (ADaM) datasets in R. Analysis derivations are implemented in accordance with the "Analysis Data Model Implementation Guide" (CDISC Analysis Data Model Team, 2021, < https://www.cdisc.org/standards/foundational/adam/adamig-v1-3-release-package >).
<u>admiraldev</u>	0.5.0	Utility functions to check data, variables and conditions for functions used in 'admiral' and 'admiral' extension packages.



Examples in [R Consortium Submission Working Group](#):

File of ProgramTOC discloses R Packages

Appendix: Instruction to Execute Analysis Program in R

- 1 Install R
- 2 Define Working Directory
- 3 Specify R package repository
- 4 Install open-source R packages
- 5 Install Proprietary R packages
- 6 Update paths to source datasets and execute programs

Interactions with Health Authorities : FDA

Prior to Submission

June
2023

Briefing Package :

Propose to include R open source packages for readable code submission for the pivotal Study.

Aug
2023

FDA written response:

Agreement

Please provide appropriate justification and evidence of validation of the package or function used.

Interactions with Health Authorities: FDA

After Submission



- Technical Walkthrough Meeting
- Datasets & supporting documents in module 5
- List and location of the R documents
- Point out different defaults between R and SAS®



FDA Approval 6.5 months after submission.

No Technical Related Information Request Regarding R Submission.

Feedback from FDA After Approval



Use of R Software for eSub Packages



- The format of software programs submitted is acceptable.
- **Content** of software programs should be discussed in pre-filing interactions

EMA: EU Raw Data Pilot



- EU Raw Data Pilot Meeting
- Similar contents as FDA technical walkthrough
- More details regarding the contents of submitted datasets
- Example of connecting information from the submitted documents



No Technical Questions So Far

Interactions with NMPA



Already have some discussion about R submission via R consortium



Had some pre-consultation in other studies

Sponsor proposed to **include R open source packages for readable code submission** in briefing package

June 2023

June 2023

Open-ended responses during **consultation window** when consulted if R submission is acceptable

FDA written response that agreed and to provide appropriate justification **evidence of validation** of the package or function used.

Aug 2023

Sept 2023

Type III meeting was requested with more comprehensive supportive information

Database Lock

Nov 2023

Jan 2024

CDE written response that **consistent with FDA, no specific software** requirement for analyses. The analysis software and corresponding functions used should be **validated**.

Take Home Messages



- Health Authorities are open to the usage of R for submission.
- Communicate clearly and align with Health Authorities prior to submission.
- Practical plan within study team and make it happen.
- Disclose the usage of R in submitted package.
- Limited extra efforts to achieve R submission.

Doing now what patients need next