Implementation of Risk Assessment for R packages: Learnings and Reflection

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on behalf of the R Validation Hub, an R Consortium-funded ISC Working Group

R Validation Hub

Abstract

This contribution has the aim to reflect on the implementation of risk-based approaches to assess R package accuracy within a validated infrastructure. The discussion reflects thinking of the R Validation Hub working group, which is a cross-industry initiative funded by the R Consortium. Our mission is to enable the use of R by the bio-pharmaceutical industry in a regulatory setting, where the output may be used in submissions to regulatory agencies. In early 2020, the R validation Hub has published a white paper which addresses concerns raised by statisticians, statistical programmers, informatics teams, executive leadership, quality assurance teams and others within the pharmaceutical industry about the use of R and selected R packages as a primary tool for statistical analysis for regulatory submission work. In the meanwhile, the R consortium has successfully submitted a fully R-based test package to FDA and various companies have implemented the concept of risk-based R package validation into their standard processes. We will present our learnings from those applied case studies. We highlight which aspects were easy to implement into practice and where difficulties occurred. We also review how new developments in the `riskmetric` R package and shiny app can help with the recent learnings.

Validation Hub

What is the R validation Hub?

- started by the PSI AIMS Special Interest Group

- R Consortium Working Group

- approx. 100 members; > 50 organizations

Mission: R Validation Hub is a cross-industry initiative whose mission is to enable the use of R by the Bio-Pharmaceutical Industry in a regulatory setting, where the output may be used in submissions to regulatory agencies.

Validation Hub

Resources / Achievements

Website www.pharmaR.org

- Blog posts

- Presentations

- White paper

- Case Studies

Tools available on GitHub / CRAN

- R Package [riskmetric](): provides a number of metrics to help quantify R package quality; led by Doug Kelkhoff (Roche)

- [Risk Assessment App](): Shiny Application for riskmetric package; led by Marly Gotti (Biogen)

Validation Hub

White Paper

- Provides arguments that there is minimal risk in using Core R for regulatory analysis and reporting

- Suggests a pipeline for risk-based assessment of contributed R packages based on

  - Intended use

  - Type of implemented method

  - Maintenance quality

  - Community usage

  - Remediation and testing

https://www.pharmar.org/white-paper/
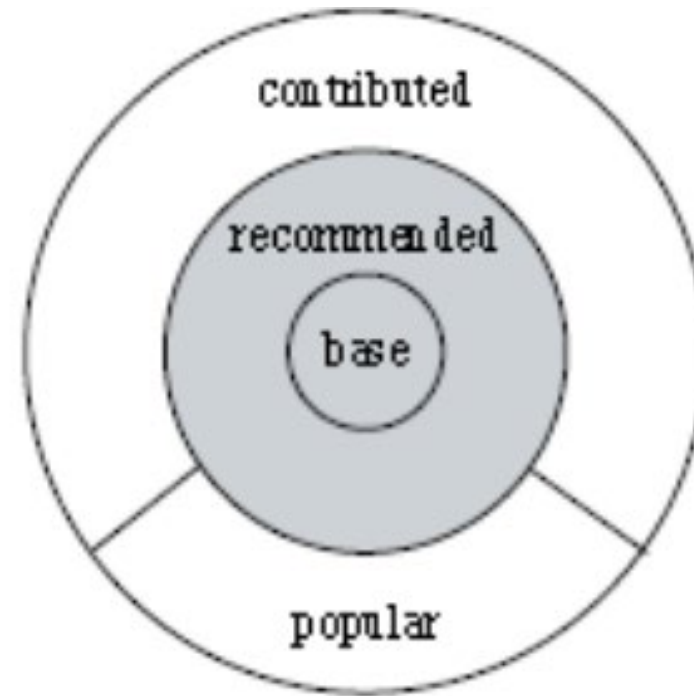
R package riskmetric

```
library(riskmetric)
pkg_tbl <- pkg_ref(c("riskmetric", "utils", "ggplot2",
                      "Hmisc", "survminer", "coxrobust"))
res <- pkg_tbl %>%
  pkg_assess() %>%
  pkg_score() %>%
  mutate(risk = summarize_scores(.))
```

package	version	license	export_help	has_vignettes	has_bug_reports_url	bugs_status	has_news
riskmetric	0.1.0.9001	NA	1	0	1	0.5667	0
utils	3.6.2	NA	0.996	1	0	0	0
ggplot2	3.2.1	NA	1	1	1	0.6333	1
Hmisc	4.3.1	NA	1	0	0	0	0
survminer	0.4.6	NA	1	1	1	0.2333	1
coxrobust	1.0	0	0	0	0	0	0

Validation Hub

https://cran.r-project.org/web/packages/riskmetric

Risk Assessment App

The shiny application has the following functionalities:

- inherits the advantages of the shiny R package (no R programming knowledge is needed to use the application),

- allows users to provide feedback on the risk calculated by riskmetric,

- gathers information on community and maintenance metrics of the package,

- has embedded authorized personnel that can perform risk assessments and modify metric weights depending on the user access level,

- stores historical comments and final decisions,

- contains a reporting tool that allows users to share the assessment insights with other reviewers as either a Word Document or an HTML file.

https://github.com/pharmaR/risk_assessment

Case Studies

- Several pharma companies participated a case series sharing different experiences on building a GxP framework with R

- All implementations follow the risk validation process for R packages as outlined in the white paper

  - Different weights were assigned to the testing coverage and various suggested maintenance metrics

  - Different risk remediation strategies have been applied

- Common challenges included

  - Ensuring R package reviewers have the right technical expertise

  - Finding appropriate test data and sharing test cases

https://github.com/pharmaR/case_studies

Partner Initiatives

- ## R Tables for Regulatory Submissions Working Group
  - Create tables that meet the requirements of FDA submission document standards

- ## R Submission Pilot WG
  - Focus on IT and platform challenges to make "all R" regulatory submissions

- ## Clinical Statistical Reporting in a Multilingual World
  - Seeks to provide a framework for assessing the fundamental differences for a particular statistical analysis across languages

- ## R/Pharma
  - Annual conference focus on the use of R in clinical drug development

Summary

The R validation hub helped to:

- Establish open-source mentality of sharing within biopharmaceutical industry
- Provide tools for risk-based assessment of R packages
- Supports a framework in which R can be used for regulatory submissions

Further Information

- Website: www.pharmaR.org
- White paper: https://github.com/pharmaR/white_paper
- GitHub Repo: https://github.com/pharmaR

Thank you to anyone who has contributed to the R validation Hub and its partner initiatives. If you want to get more involved, contact us!