R Validation Hub

Andy Nicholls (GSK)

Matthias Trampisch (Boehringer Ingelheim)

Sumesh Kalappurakal (J&J)

Agenda

- The R Validation Hub

- Background

- R package risk assessment

- Adoption roadmap

Mission statement

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.

Who are we?

- Initiated by PSI AIMS SIG
- Now an R Consortium Working Group
- Executive Committee
  - Andy Nicholls (GSK)
  - Lyn Taylor (Phastar)
  - Joe Rickert (RStudio / R Consortium)
  - Juliane Manitz (Merck KGaA)
  - Yilong Zhang (MSD)
  - Doug Kelkhoff (Genentech)
  - Keaven Anderson (MSD)
- ~100 members
- >50 organisations

- Streams
  - Metrics (riskmetric R package)
    - MSD
    - Genentech
    - Merck KGaA
    - RHO
    - Atorus Research
    - GSK
    - Biogen
  - Testing
    - GSK
    - MSD
  - Comms

See https://www.pharmar.org/about/

Resources

- Keep up to date at https://www.pharmar.org/
  - Blog posts
  - Presentations
  - White paper
- Tools available on GitHub
  - Riskmetric R Package
  - Risk Assessment App [coming soon]
- Mailing list

Contact us at psi.aims.r.validation@gmail.com.

Validation Hub   ABOUT US ▾   BLOG   REGULATIONS   VALIDATION ▾   RESOURCES ▾   CONTACT US

WHITE PAPER

PLEASE SEE OUR WHITE PAPER, TITLED "A RISK-BASED APPROACH FOR ASSESSING R PACKAGE ACCURACY WITHIN A VALIDATED INFRASTRUCTURE."

Background

High Level Definitions

- **Verification**. Mainly testing to ensuring that the results are correct
- **Qualification**. Ensuring that a product works under specific conditions
- **Validation**. A process to ensure that software meets predetermined specification/quality attributes

- Examples
  - We would typically **validate**
    - an environment such as an SCE
    - an application, eg a Shiny app
  - We **qualify**
    - that SAS behaves as expected when installed in our environment
  - We **verify**
    - the results of an analysis by double programming
    - that if I call a function/macro with specific parameters then I get the expected result (unit testing)

Regulations

- FDA: "…statistical software is not explicitly discussed in [21 CFR Part 11]"

- ICH: "…software used should be reliable, and documentation of appropriate software testing procedures should be available"

**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

What is R?
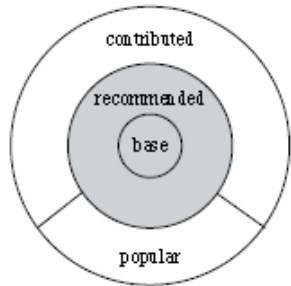
- "R" can refer to:

  - A base product owned by the R Foundation, **Core R**
    - Well-established base functionality

  - Contributed packages (libraries of code) from the community
    - Many different owners
    - Varying degrees of quality
    - Many are essential to make good use of R (eg tidyverse)

Figure: German, D.M. & Adams, Bram & Hassan, Ahmed E.. (2013). The Evolution of the R Software Ecosystem. Proceedings of the Euromicro Conference on Software Maintenance and Reengineering, CSMR. 243-252. 10.1109/CSMR.2013.33.

Core R vs SAS

- R is proposed to be used in the same way that we currently use SAS

- SAS is generally a *trusted* vendor

  - We trust their SDLC

  - We also trust their installation tests

  - We trust that the underlying procedures do what they're supposed to

- The R Foundation provide the following documents outlining the processes they follow to ensure a quality product

  - 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

- Core R is a reliable alternative to SAS

Contributed R Packages

- Effective use of R requires the functionality contained with R contributed packages

    - A typical installation may include 100s of additional packages of code

- R packages can be written by multiple authors

- Some could be considered reliable/trusted sources, some not

- The R Validation Hub are not aiming to 'validate' packages

- Packages will typically be used to develop bespoke code

- AND (as with SAS) all code will be subject to existing SOPs

- BUT we still need to establish a process that reduces risk
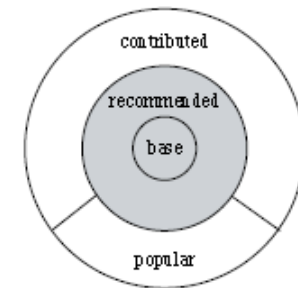
However, there may be some value in validating statistical methods in some packages

R Package Risk Assessment

R Package Risk Assessment

- It is unrealistic (impossible?) to audit every R package author / maintainer

- How can we establish trust?

  1. Retrofit a "validation" by writing our own requirements and tests

     - Not necessarily a 1 to 1 mapping between us and the author

     - Fails to acknowledge the benefits of open source community review

     - Generally not what is done for closed source solutions

  2. Develop a **risk-based methodology** for assessing accuracy

     - Makes use of what we already know

       - Availability of maintenance practice – a 'virtual audit'

       - Community usage / user testing

     - Effort is focussed on high-risk areas

White Paper

A Risk-based Approach for Assessing R package Accuracy within a Validated Infrastructure

Andy Nicholls, *Statistics Director, Head of Statistical Data Sciences, GSK*

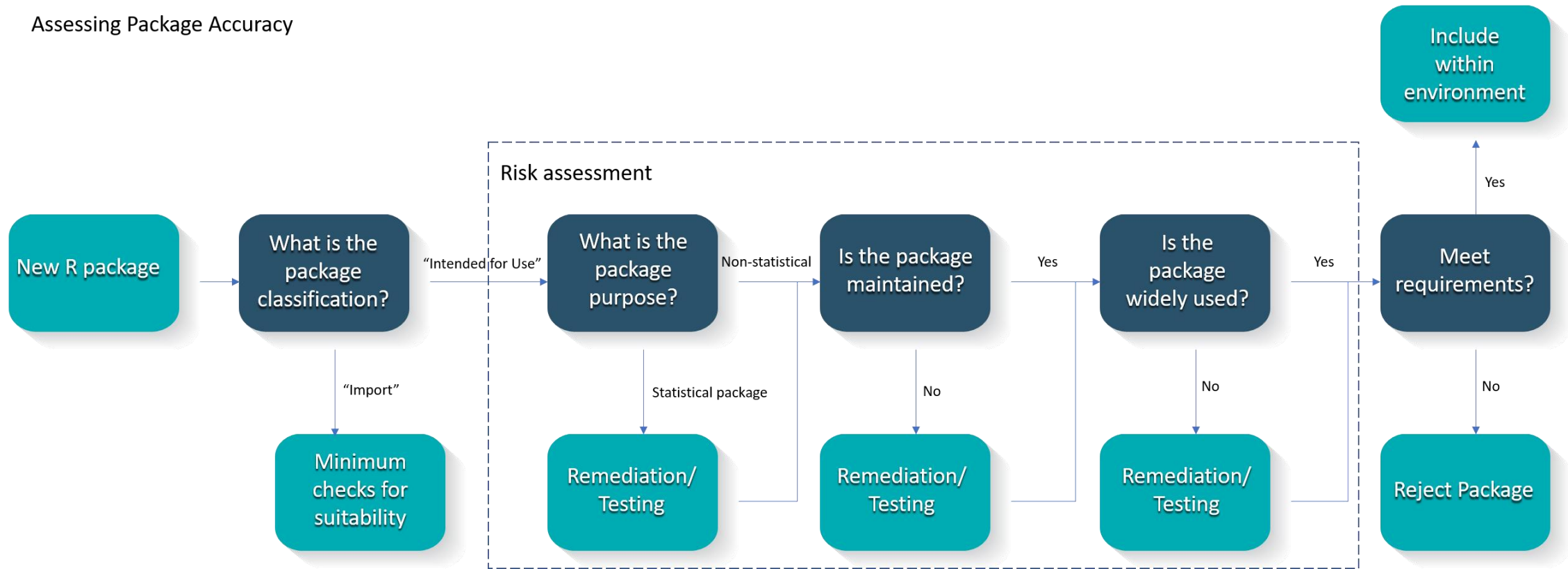**Paulo R. Bargo,** *Director Scientific Computing, Statistics & Decision Sciences, Janssen R&D*

John Sims, *Director, Analytical Systems Architect & Data Science - Pfizer Vaccine Research*

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

23-Jan-2020
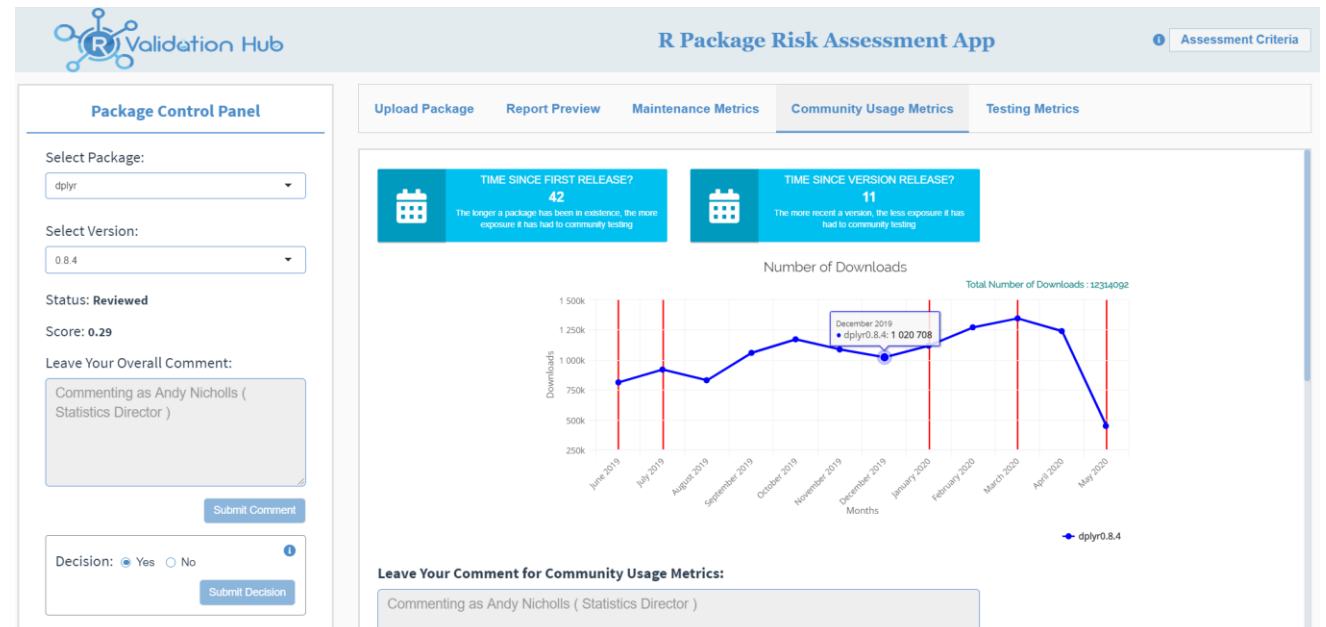
1. Scope and Background

R Package Risk Assessment Workflow

Assessing Package Accuracy

Conducting a Risk Assessment

- Collaborative effort to generate an R package, riskmetric

- Working with Fission Labs on a tool to allow for additional comments to be added before generating **package risk reports**

  - Funded by R Consortium grant
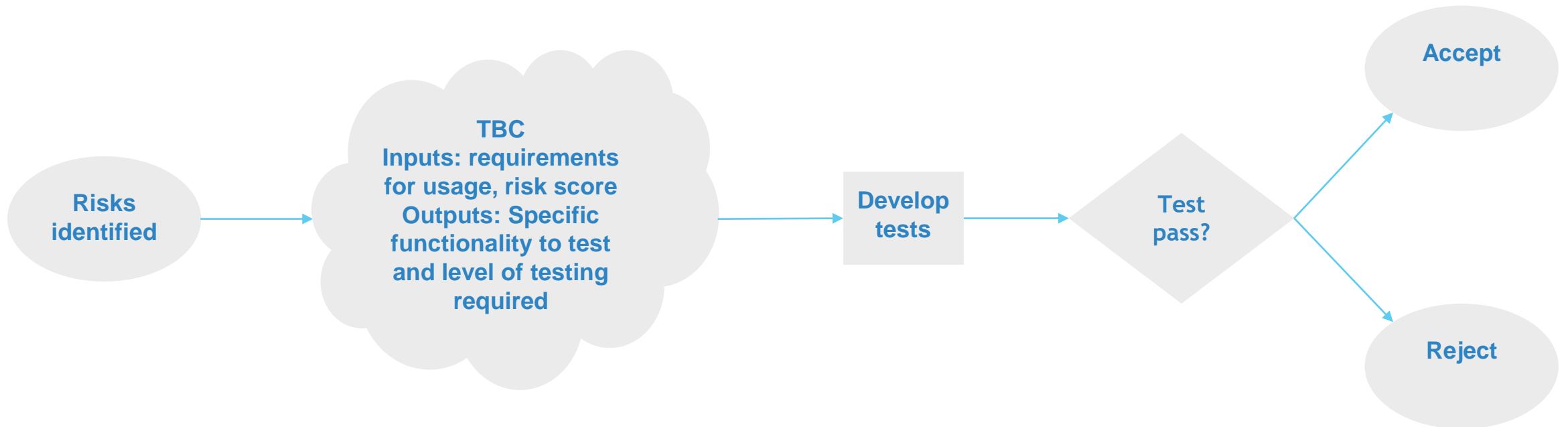
  - Estimated v1.0 July 2020

Screenshot from prototype app, currently in development

Testing

- Current strategy being developed by GSK/MSD

- The risk assessment would **not** negate the need for testing

- Qualification tests will be required regardless of risk

    - GSK already has a base suite of tests to build upon

- Higher risk packages will require tests to verify package accuracy

- The strategy is yet to be developed

- A *very* high level outline is provided on the following slide

- R has established test frameworks that facilitate test-requirement traceability

- **Reminder:** The R Validation Hub's aims is not to 'validate' packages but help reduce the risk when generating submission and other GxP output

Scaled Testing for Accuracy

Risks identified

TBC
Inputs: requirements for usage, risk score
Outputs: Specific functionality to test and level of testing required

Develop tests

Test pass?

Accept

Reject

R Adoption Roadmap

The Wider Landscape

- ValidR appears to be the most popular route to using R for regulatory work

- Companies increasingly looking at R Validation Hub as a viable alternative
  - Biogen and GSK recently committed members to riskmetric development team

- Conversations ongoing with FDA to endorse the approach
  - Tomas Drgon speaking with FDA's Scientific Computing Board
  - A TransCelerate workstream is focussed on regulatory engagement

- A TransCelerate project is currently working on a similar risk-based strategy
  - "Modernization of Analytics"
  - Targeting broader framework including closed source
  - Currently thinking influenced by R Validation Hub's white paper

Options: Using R for GxP Output Generation

ValidR

Pros
- Established processes
- Low resource requirement
- Relatively quick start

Cons
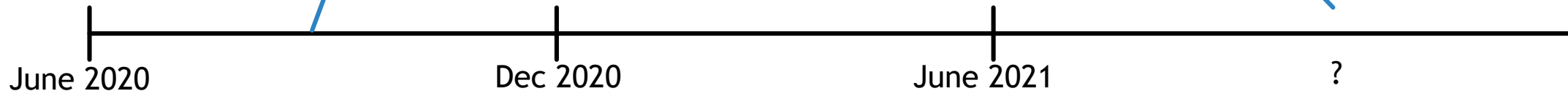- Low flexibility
- Tied to 3rd party
- Older R releases

Full validation

Pros
- Confidence that R is OK to use

Cons
- Possibly not required
- Extremely costly

June 2020   Dec 2020   June 2021   ?

Risk-based

Pros
- Flexibility
- Lower long-term costs

Cons
- Requires internal resource investment
- Long-term maintenance
- Difficult to convince QA?

R Validation Hub Roadmap

1. Process and Communication

   ✔ Publish website   ← **Jan 2019**

   ✔ Agree high level process   ← **Jun 2019**

   ✔ Tools (riskmetric, app) at pilot implementation stage   ← **Aug 2019**

   ✔ Develop white paper   ← **Jan 2020**

2. Validation / Qualification Suite

   • CRAN release of riskmetric package   ← **Jul 2020**

   • Release risk assessment app v1   ← **Aug 2020**

   • Centralised risk assessment app and DB   ← **June 2021?**

   • Share test suite

   • *Build test execution tool*   ← **??**

   • *Provide an example deployment*
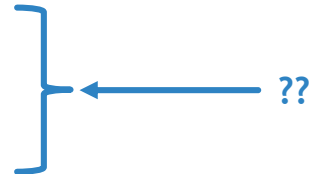
3. Repository

   • Build Pharma R Repository

Accelerating the R Validation Hub Work

- *Current* target for implementable system: June 2021

- Opportunity to accelerate development via headcount working on open source tools

  - Additional metrics for riskmetric package (current team of ~8 people working mainly out of hours)

  - Associated improvements to risk assessment app (current development ends July 2020)

  - Development of test framework and test (starting up, GSK/MSD leading initiation)

- With dedicated resource, an implementable system is possible before end 2020…

Implementing the R Validation Hubs Framework
Draft GSK estimate

- Assumptions
  - Acceptance of process from QA group!
  - An initial installation of 80-100 R packages
  - Imports excluded
  - Availability of risk assessment tooling from R Validation Hub
- Requirements
  - 2x Business FTE @100% for 6-9 months to:
    - Review/QC metrics
    - Develop framework for requirements to testing
    - Implement framework
  - 0.5x Tech FTE to assist in automating the tests
  - Additional oversight / QA to ensure compliance

Discussion