Best Practice for Interactive Analysis for Submission – A PHUSE White Paper

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Introduction

Can sponsors provide interactive visualization tools as part of the submission to move away from the **"digitized paper"[1]?** What is the best practice for interactive analysis in order to ensure compliance in a regulatory setting? Formed in 2017, the PHUSE Data Visualization project **aimed to explore and assess the benefits and technical feasibility of providing interactive analysis as a reviewing aid to the FDA.** We learned from industry practices and discussed various approaches on how to embed interactive tools as part of the eCTD process. We also conducted two proof of concept projects and one pilot with real submission for an html interactive display and a Docker R Shiny approach. This white paper intends to provide recommendations based on our learnings and invite everyone to collectively explore the best way to leverage emerging technologies to advance how we consume and share data.

Paradigm Shift: digitized paper – Interactive Analysis*

Effective interactions, fast drug approval, more novel medicine to patients

Sponsors

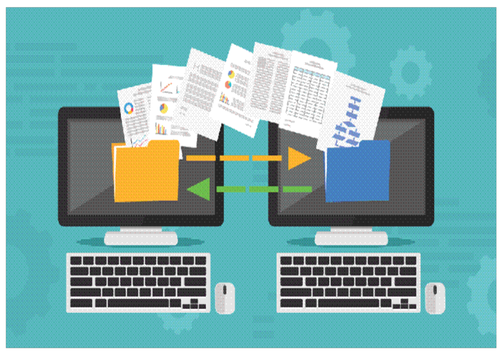
- Leverage agility of interactive data visualization and automated analysis for quick insights and guided analysis
- Streamline process from exploratory to decision-making and filing

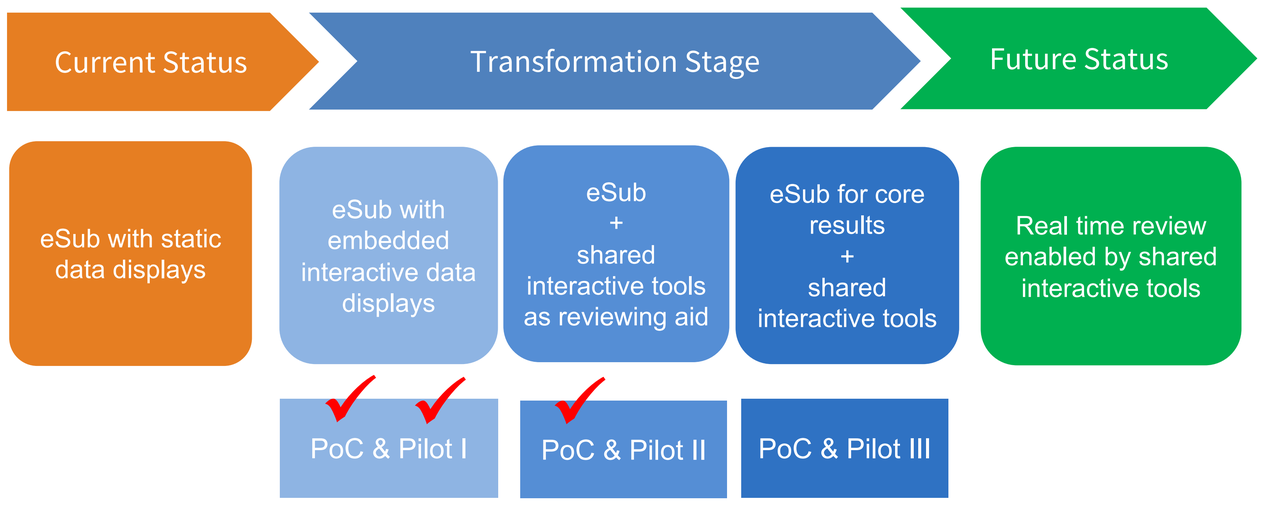
FDA

- Perform effective review of the submitted data and analysis
- Conduct additional exploratory analysis as needed

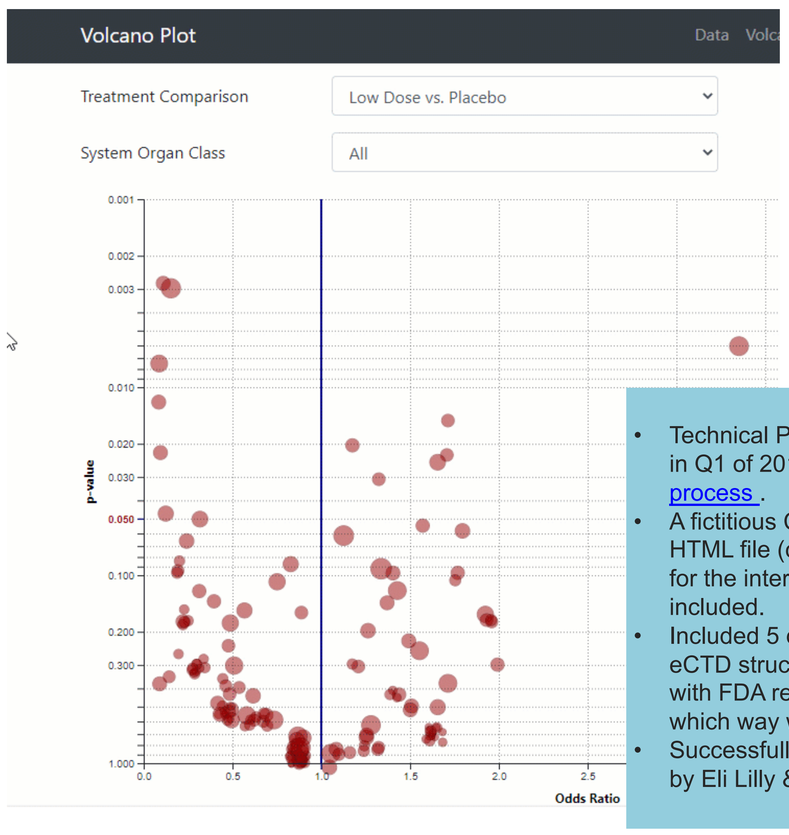
***Interactive analysis:** analysis and visualization outputs created using interactive tools such as Spotfire, R Shiny, Javascript etc.*

Interactive Analysis Roadmap





PoC I & Pilot I: HTML submission

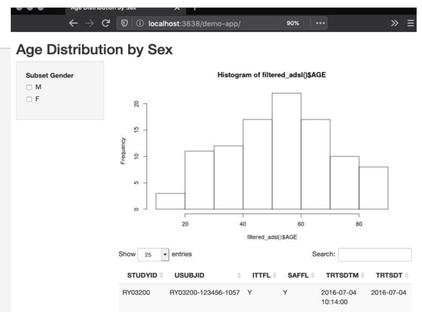


- Technical PoC was successfully completed in Q1 of 2019 using the sample submission process .
- A fictitious CSR with a hyperlink to an HTML file (containing CSS and javascript) for the interactive volcano plot was included.
- Included 5 different ways of populating the eCTD structure with the HTML file. Met with FDA reviewer remotely to determine which way was optimal.
- Successfully included in two submissions by Eli Lilly & Co in 2019 and 2020.

PoC II: Docker Containerization

Figure 1: How Docker files fit into eCTD structure

Figure 2: Launched Shiny app within a container



- The technical PoC was successfully submitted to the FDA by Genentech in Dec 2019
- Used Docker as the container to package a simple Shiny application in R (see figure 2) to explore how to submit an open-source based interactive visualization tool with the FDA via containerization approach.
- Encountered an issue related to FDA security concern during the initial PoC when installing R package library in a local drive.
- A second iteration is in progress by
  - redesigning to install R package library within the container to avoid security issue, and
  - restructuring to improve workflow for shared package library among multiple interfaces including analytical and visualization portals

Learning from PoC Projects

- **PoC projects** offer the ability to assess technical feasibility to share interactive displays with Healthcare Authorities (HA) with no risk
- **How to modernize the eCTD process?**
  - ✓ The HTML submission could be improved if eCTD requirement allowed additional file tags such as "data visualization".
  - ✓ The eCTD could be relaxed to allow uppercase letters for file extension. This will allow submitting R packages using ".R" file extension (instead of .r) per R coding best practice.
- **Learned to optimize how to populate the eCTD backbone for HTML submission**
- **Early collaboration with FDA staff is critical for Docker approach**
  - ✓ How to design the submission package requires close collaboration with FDA staff
  - ✓ FDA needs specialized knowledge on Docker to set up the app on a virtual machine

Conclusions

- The positive feedback from FDA on HTML submission are very encouraging. The reviewer acknowledged that the interactive volcano plot enabled the reviewer to see patterns and outliers that might have been overlooked with the standard static output.
- The interactive analysis signifies a new platform for data review and data analysis in clinical trial. We hope our technical exploration on sharing mechanism with the FDA will pave a way to support data exchange freely in the future.

Next Steps

- Consider piloting the Docker with Shiny application for a real submission assuming the Docker PoC goes successfully
- Consider other approaches on how to share interactive analysis with the HA (see LINK for more details). For example,
  - ✓ submitting an interactive tool as an R package;
  - ✓ using a third party server/cloud. Connect with other industry initiatives such as Accumulus project[2] to explore a cloud-based solution for sharing interactive analysis with HAs
- Call for more participation from sponsors and HAs, particularly EMA & PMDA.
- The whitepaper is a work in progress and is aimed to be published in Q4.

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Genentech PoC team: Nilesh Narayan, Doug Kelkhoff, Xiangyun Wang

References:

[1]Reliance on Digitized Paper is Slowing Drug Development – US FDA's Woodcock
[2]The Last Days Of PDFs: Industry Works To Solve Its US FDA Application Problem