Development of a Data/Text Analytics Tool to Enhance Quality and Efficiency of Bioequivalence Assessment

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Outline

- Background
- Aims
- Tool Development
- A Quick Look
- Current Status and Future Plan

Background

- Enhancing the quality and efficiency of bioequivalence (BE) assessment will facilitate generic drug approvals.
- The BE assessment process includes:

Straightforward information retrieval (labor-intensive works, e.g., data preparation)	**Information retrieval based on sematic understanding** (different expressions for the same meaning)	**Information summarization** (generating summary paragraphs)	**Inferencing/reasoning** (e.g., comments, and conclusion)

Background

- Current advances in artificial intelligence (AI) - especially data analytics techniques like text analysis and natural language processing (NLP) - offer great promise in developing tools to enhance the BE assessment process.

- The OGD under the Center for Drug Evaluation and Research (CDER) is developing a data/text analytics tool - **Bioequivalence Assessment Mate (BEAM)** - to address the need for more efficient, consistent, and high-quality BE assessments.

Aims of Developing the *BE Assessment Mate* (BEAM)

Near-term (pilot)

- Aim: Streamlining labor-intensive assessment works

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Long-term (under planning)

- Aim: Generating draft comments and conclusions

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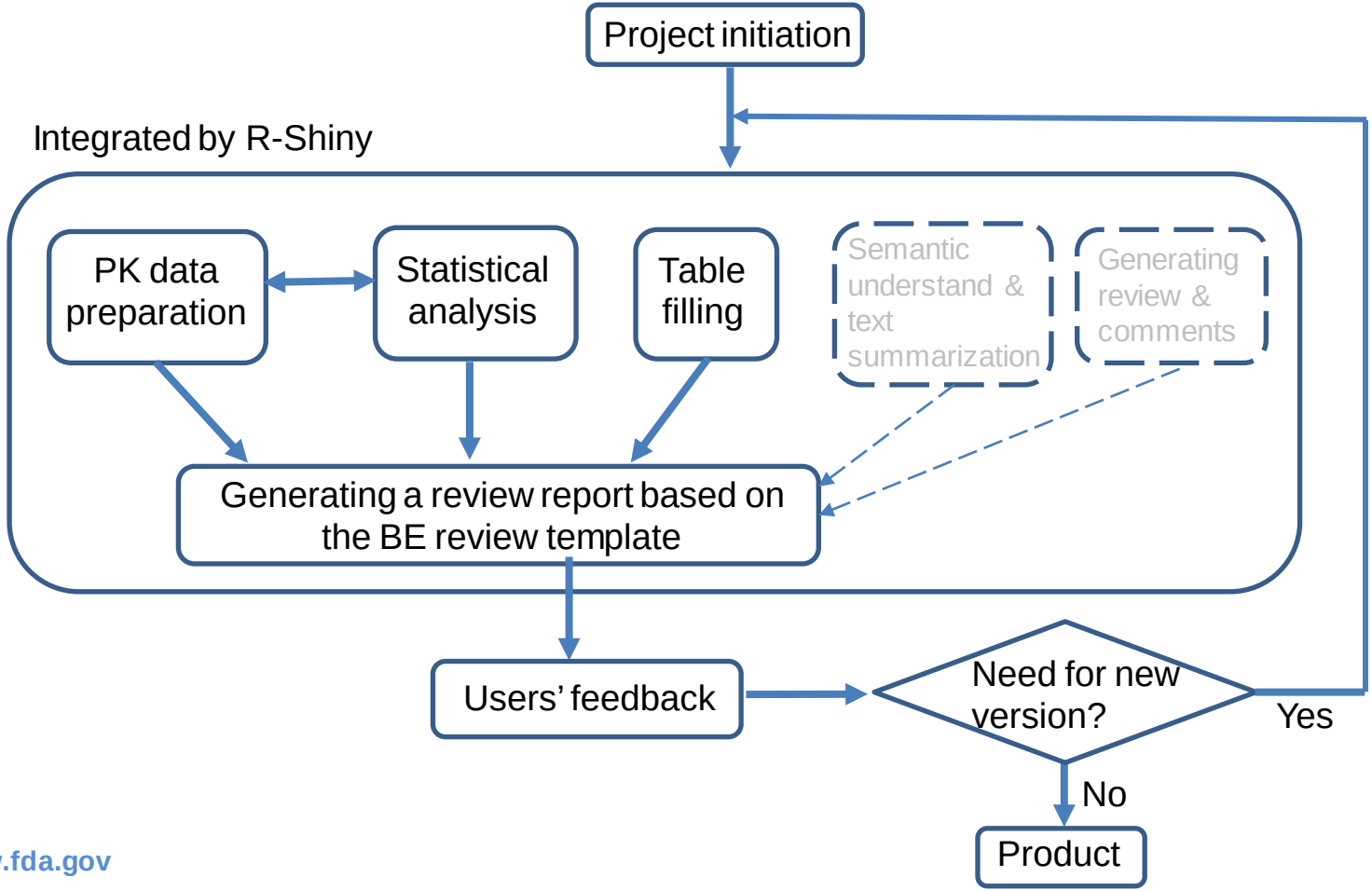
In this presentation, we mainly focus on the development of the near-term BEAM tool.

Focus of pilot: ANDAs with 2x2 crossover pharmacokinetic (PK) studies

- Fasting, Fed, Sprinkle
- AUC_t, AUC_i, C_{max}

Developing BEAM (near-term)



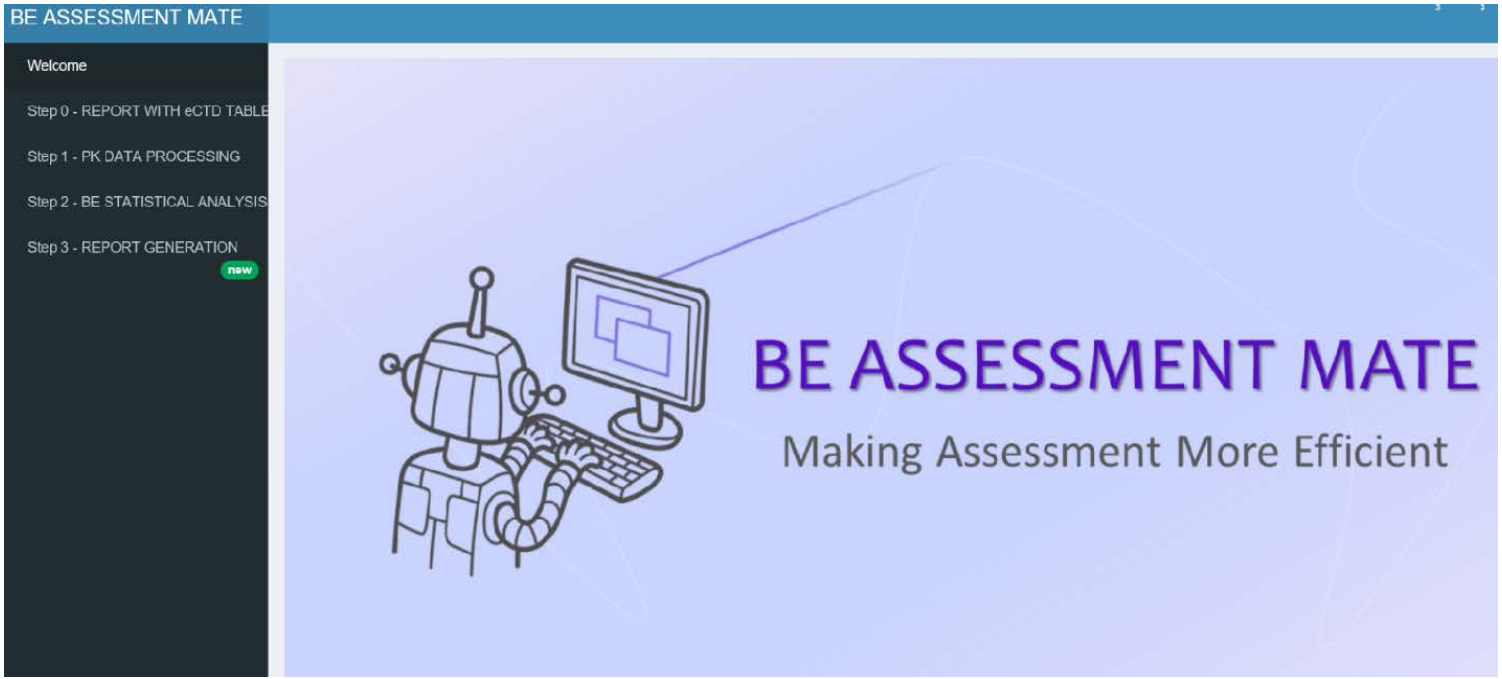
BEAM Feature Overview

- User-friendly interface by R-Shiny
- A few clicks to finish
  - PK data processing
  - BE statistical analysis
  - BE review report generation
- Documents with all the individual time-concentration plots and the mean plots
- Flexible for different review styles

- Able to process ANDAs with
  - Multiple analytes
  - Truncated area under the curve (AUC)
  - Multiple strengths
  - Need to recalculate PK metrics
  - Baseline corrected/adjusted
  - Different study designs (e.g., replicate or parallel)
  - Pharmacodynamic (PD) endpoint
  - Clinical endpoint
  - In vitro study

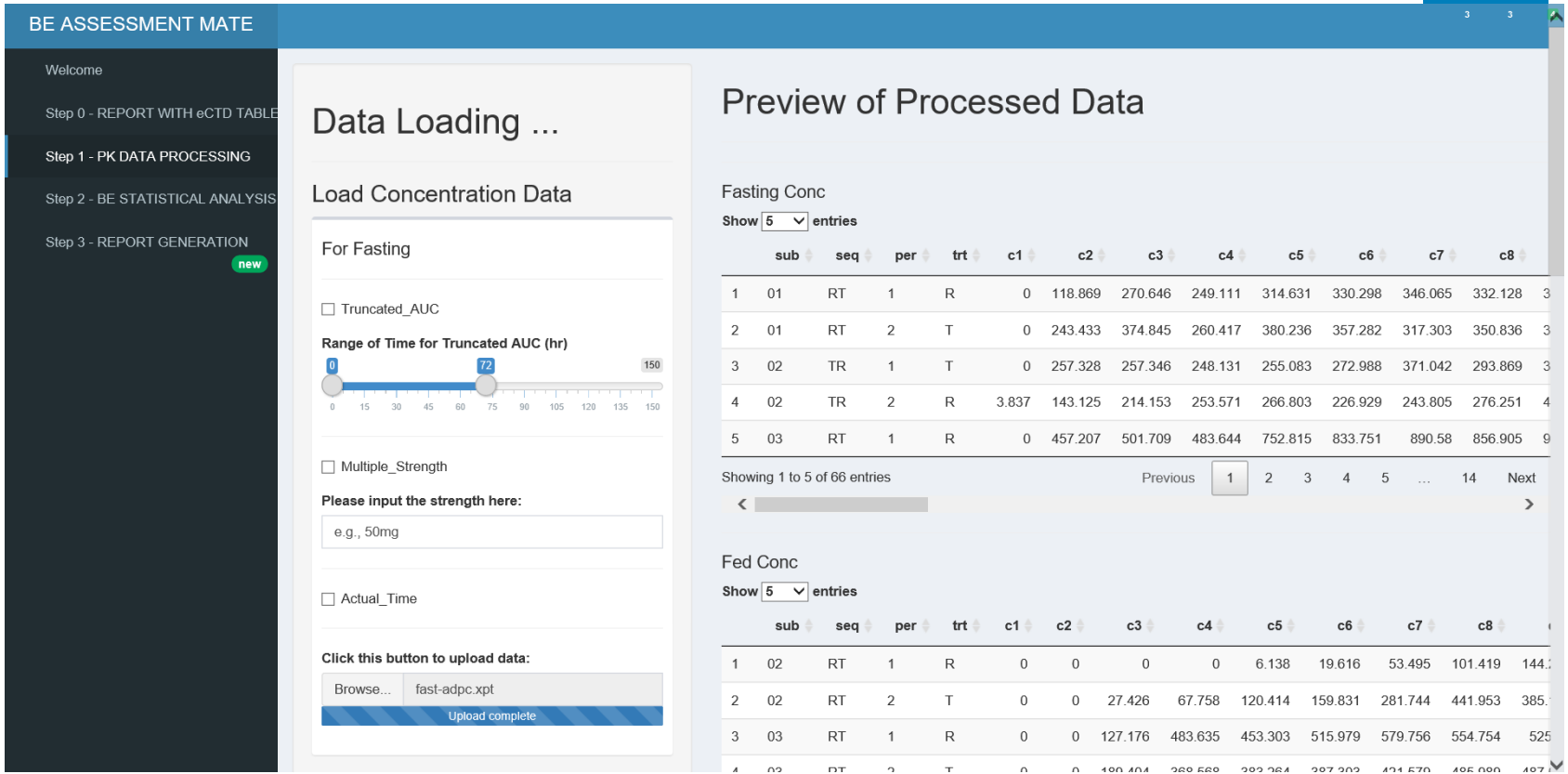
A Quick Look at the BEAM Tool

Start **BE ASSESSMENT MATE**



Welcome Page

Step 1 – PK DATA PROCESSING



Step 2 – BE STATISTICAL ANALYSIS

Step 0 - REPORT WITH eCTD TABLE

Step 1 - PK DATA PROCESSING

Step 2 - BE STATISTICAL ANALYSIS

Step 3 - REPORT GENERATION new

BE Statistical Analysis

Type of Analysis

- (•) Using Firm-Supplied KE and PK Data
- ( ) Using Firm-Supplied KE but Recalculating PK Data
- ( ) Recalculating KE and PK Data

Go4Fasting

START

Go4Fed

START

Go4Sprinkle

START

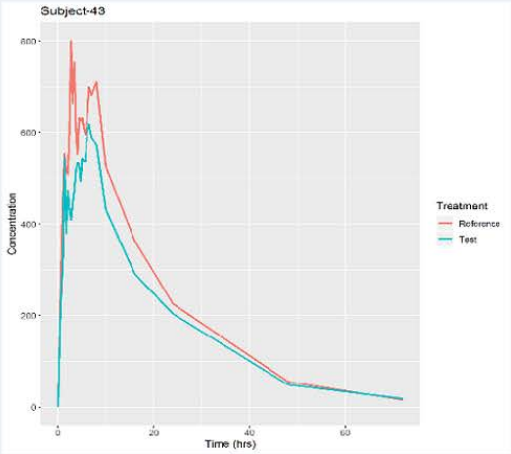
Generate Statistical Analysis Report

START

Time-Concentration Plot of A Random Subject

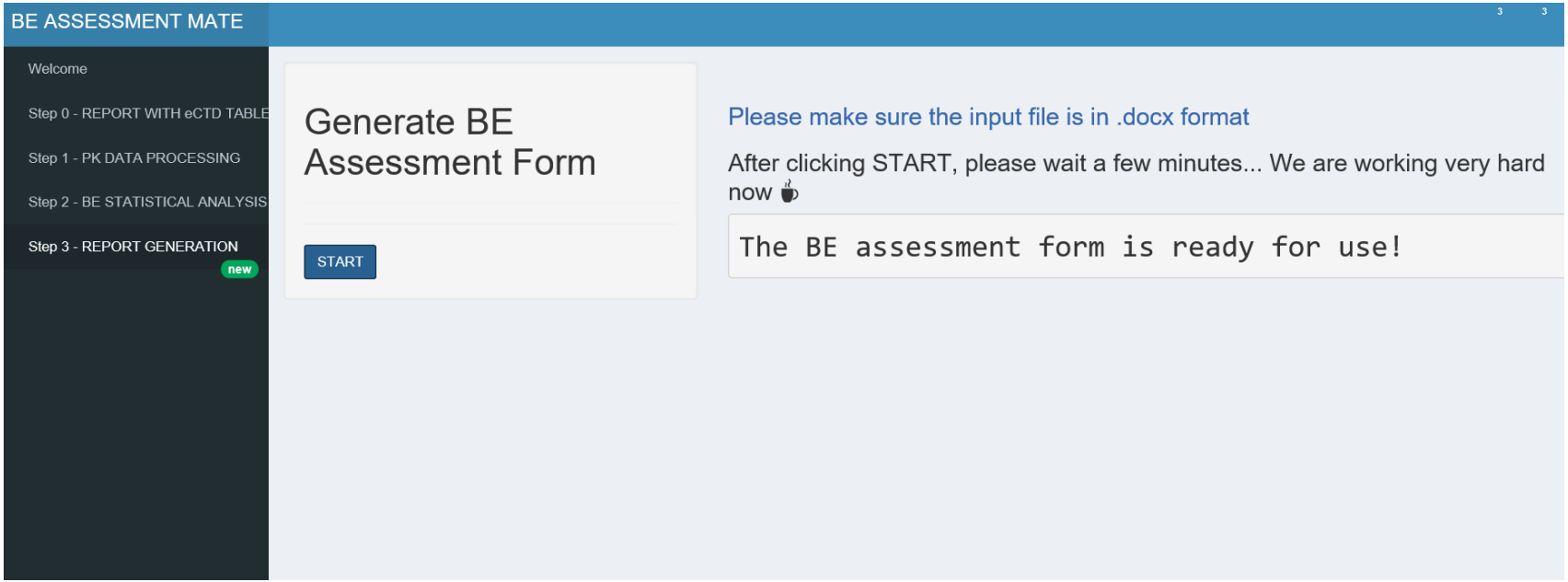
Note: TimeConcPlot_*.docx in the working folder will contain the mean plots and all the individual plots.

Fasting



Fed

Step 3 – REPORT GENERATION



Current Status

- We held 4 training sessions for the pilot version of the tool.
  - BE reviewers participated and used BEAM for an assigned ANDA assessment.
  - We are collecting and analyzing all the feedback from reviewers.

- More than 100 ANDAs have been used to test the tool by the development team.

- We are working with the Office of Computational Sciences in the Office of Translational Sciences in CDER to develop the web-based BEAM.

Next Steps

Mid-term (in development)

- Aim: Utilizing NLP to realize semantic information retrieval and text summarization; Web-based application

Long-term (under planning)

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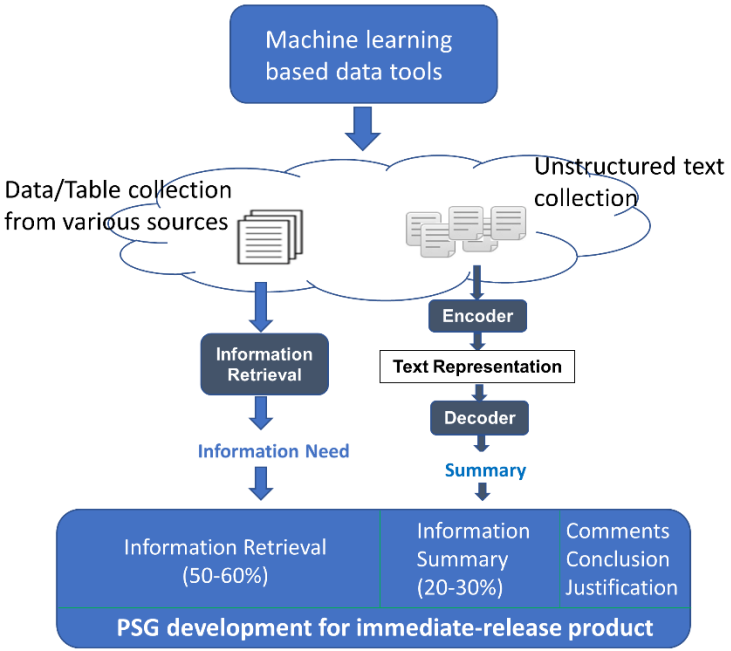
Progress on NLP

- Developing Tools based on Text Analysis and Machine Learning to Facilitate Product-Specific Guidance Development (75F40119C10106)
  - The state-of-the-art Bidirectional Encoder Representations from Transformers (BERT) model was utilized for the NLP application.
  - An NLP pipeline was developed to extract drug product information from drug labeling with minimal human intervention.
  - A manuscript is under review by *Frontiers in Research Metrics and Analytics, section Text-mining and Literature-based Discovery.*
  - An example on the next page



PSG: Product-Specific Guidance

https://www.fda.gov/drugs/generic-drugs/science-research

An example of identifying food effect information from drug labeling, **without keyword "food effect"**

NDA 205832

Absorption

Nintedanib reached maximum plasma concentrations approximately 2 to 4 hours after oral administration as a soft gelatin capsule under fed conditions. The absolute bioavailability of a 100 mg dose was 4.7% (90% CI: 3.62 to 6.08) in healthy volunteers. Absorption and bioavailability are decreased by transporter effects and substantial first-pass metabolism.

After food intake, nintedanib exposure increased by approximately 20% compared to administration under fasted conditions (90% CI: 95.3% to 152.5%) and absorption was delayed (median t_{max} fasted: 2.00 hours; fed: 3.98 hours), irrespective of the food type.

NDA 210491

Absorption

After a single dose in healthy subjects in the fed state, tezacaftor was absorbed with a median (range) time to maximum concentration (t_{max}) of approximately 4 hours (2 to 6 hours). The median (range) t_{max} of ivacaftor was approximately 6 hours (3 to 10 hours) in the fed state.

When a single dose of tezacaftor/ivacaftor was administered with fat-containing foods, tezacaftor exposure was similar and ivacaftor exposure was approximately 3 times higher than when taken in a fasting state.

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=da1c9f37-779e-4682-816f-93d0faa4cfc9
https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=302ae804-37db-44fd-ac2f-3dbdeda9aa4b

BEAM Project Team

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