Challenges in Processing PK Data from ANDA Submissions for BE Assessment and Current Perspectives on Updating the PK Data Standard

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Outline

- Background
- Challenge and issue
- Current solutions
  - BE Assessment Mate (BEAM) – an automation tool to mitigate the issue.
- Updating PK data standard

Background

- Dating back to 2015 and earlier, generic drug applicants followed a simple format to prepare and submit PK data in ANDAs.

PK Concentration data

Subject ID	Sequence	Period	Treatment	Concentrations (1-n)	Time (1-n)
1	2	1	1	0…83.3	0…120
1	2	2	2	0…94.4	0…120
2	1	1	2	0…155.2	0…120

PK parameter data

Subject ID	Sequence	Period	Treatment	AUCt	AUCi	Cmax	Tmax
1	2	1	1	2577.78	2878.63	174.1	3.677
1	2	2	2	2734.63	2575.78	137.2	3.373
2	1	1	2	3677.39	3875.4	277.6	1.7

Background

- As the CDISC (Clinical Data Interchange Standards Consortium) was implemented[1-3], potential ambiguities existed for generic drug applicants to prepare PK data.
  - Inconsistent variables were used to report data
  - Data entry can be random, even wrong:
    - Drug name was used to fill out the variable of treatment, instead of using “T or R”
    - Text description were mixed in the reported time points and/or data values
    - And more random errors
  - Critical information were missing

1. Providing Regulatory Submissions In Electronic Format — Standardized Study Data Guidance for Industry
2. ANDA Submissions — Content and Format Guidance for Industry
3. STUDY DATA TECHNICAL CONFORMANCE GUIDE - Guidance for Industry Providing Regulatory Submissions in Electronic Format – Standardized Study Data

Challenges and Issues

- Due to the ambiguities, applicants used their own interpretations to prepare PK data, which leads to:
  - Inconsistent PK data
  - Wrong use of variables or data entries
  - Missing information
  - OGD reviewers need to manually clean/curate submitted data (4-6 hours)
  - IR may be issued to delay the review process

Current solutions

- BE reviewers can manually clean up submitted PK datasets for the downstream analysis (time consuming)

- **BEAM (BE Assessment Mate)** – a BE assessment tool developed to facilitate the good-quality and efficient BE assessment by streamlining labor-intensive work in BE assessment

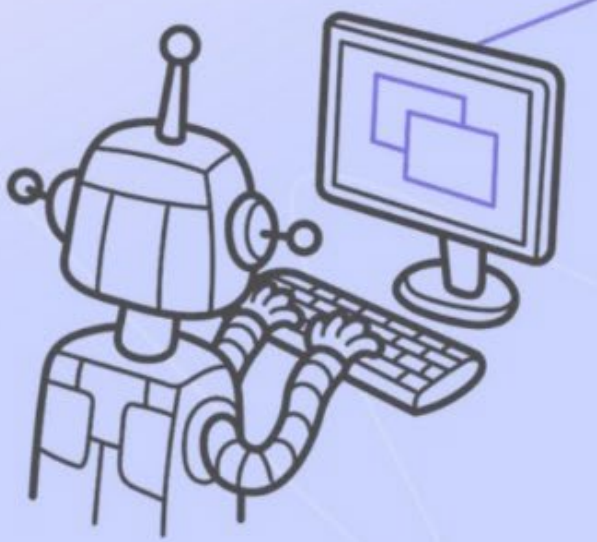
Step 0
- REPORT WITH eCTD TABLE

Step 1
- PK DATA PROCESSING

Step 2
- BE STATISTICAL ANALYSIS

Step 3
- REPORT GENERATION

Step 4
-Publish to GDSA BE



BE ASSESSMENT MATE

Making Assessment More Efficient

What is **BEAM**?

BEAM was developed to streamline the labor-intensive work during PK/BE data analysis to facilitate high-quality and efficient regulatory assessments.

BEAM's core functions

PK data processing 1

Benefit:

- BE reviewers often need a few hours to make the submitted PK data executable for downstream analysis
- With BEAM, this effort can be done within a few clicks

Routine BE statistical analysis 2

Benefit:

- BE reviewers click a few buttons to complete BE statistical analysis
- Flexible for different analysis needs (e.g., recalculating PK parameters)

Review documents generation 3

Benefit:

- One click to auto-populate the BE review template from the submitted eCTD information tables and BE statistical analysis report
- ~70% tables/figures in the template can be auto-populated.

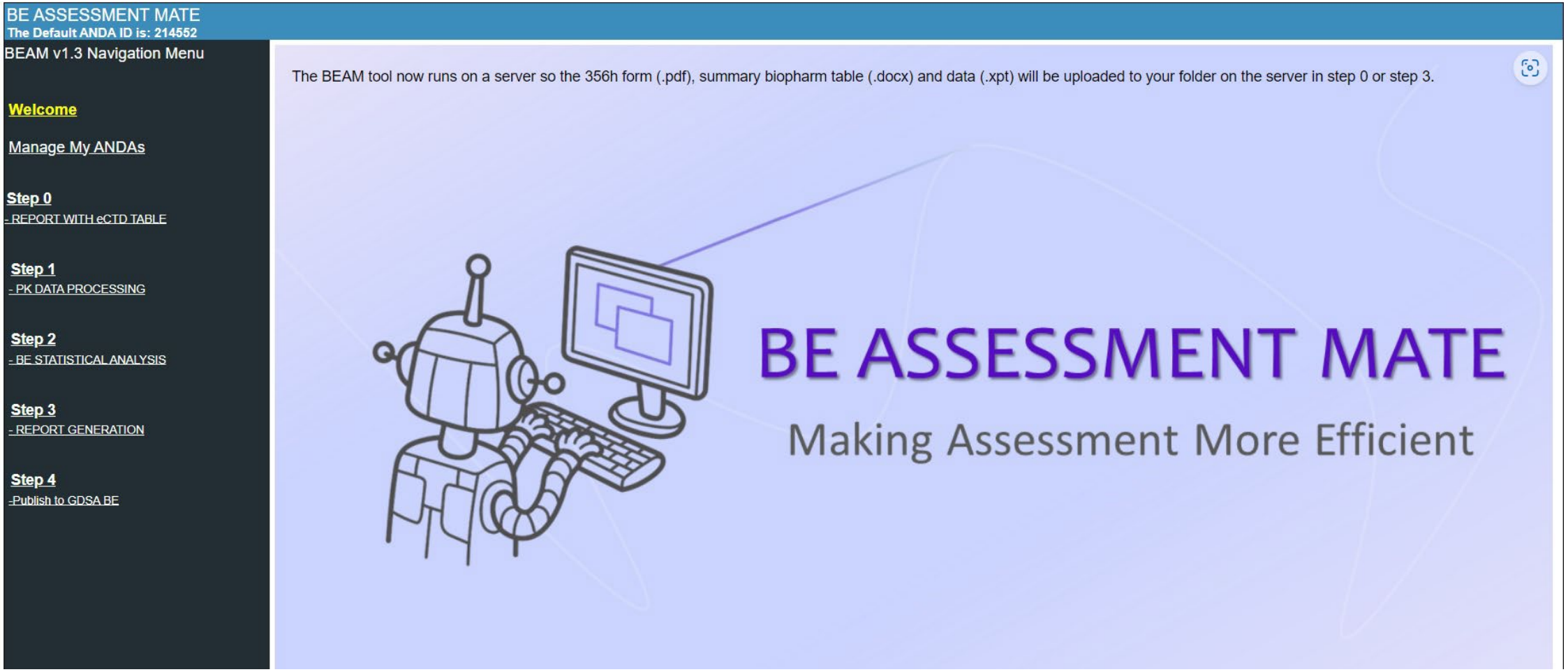
Integration 4

Benefit:

- Data engine to supply data for internal BE information management system
- Enterprise-level solution to host other BE review tools
- Improving business intelligence for the BE assessment process

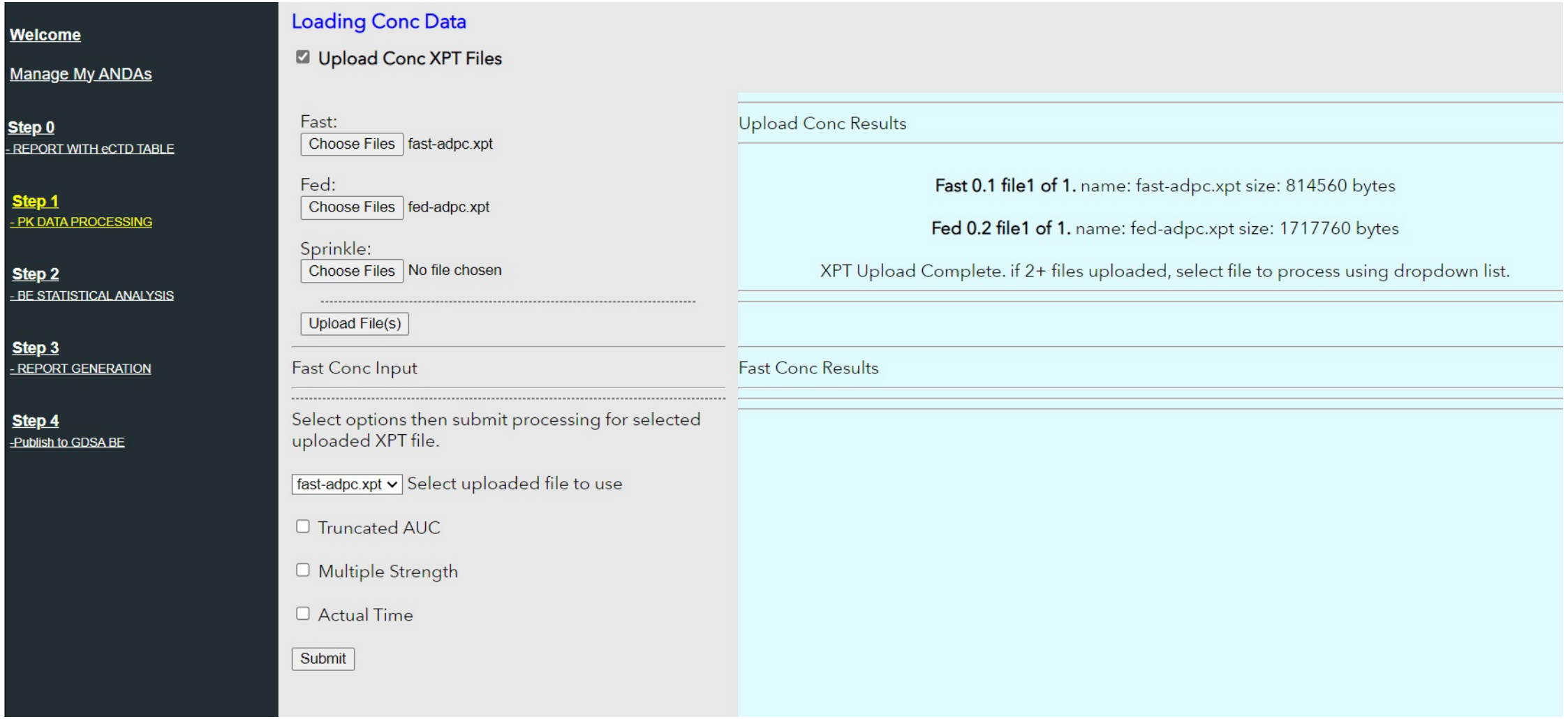
A Quick Look at the BEAM Tool

Start **BEAM**

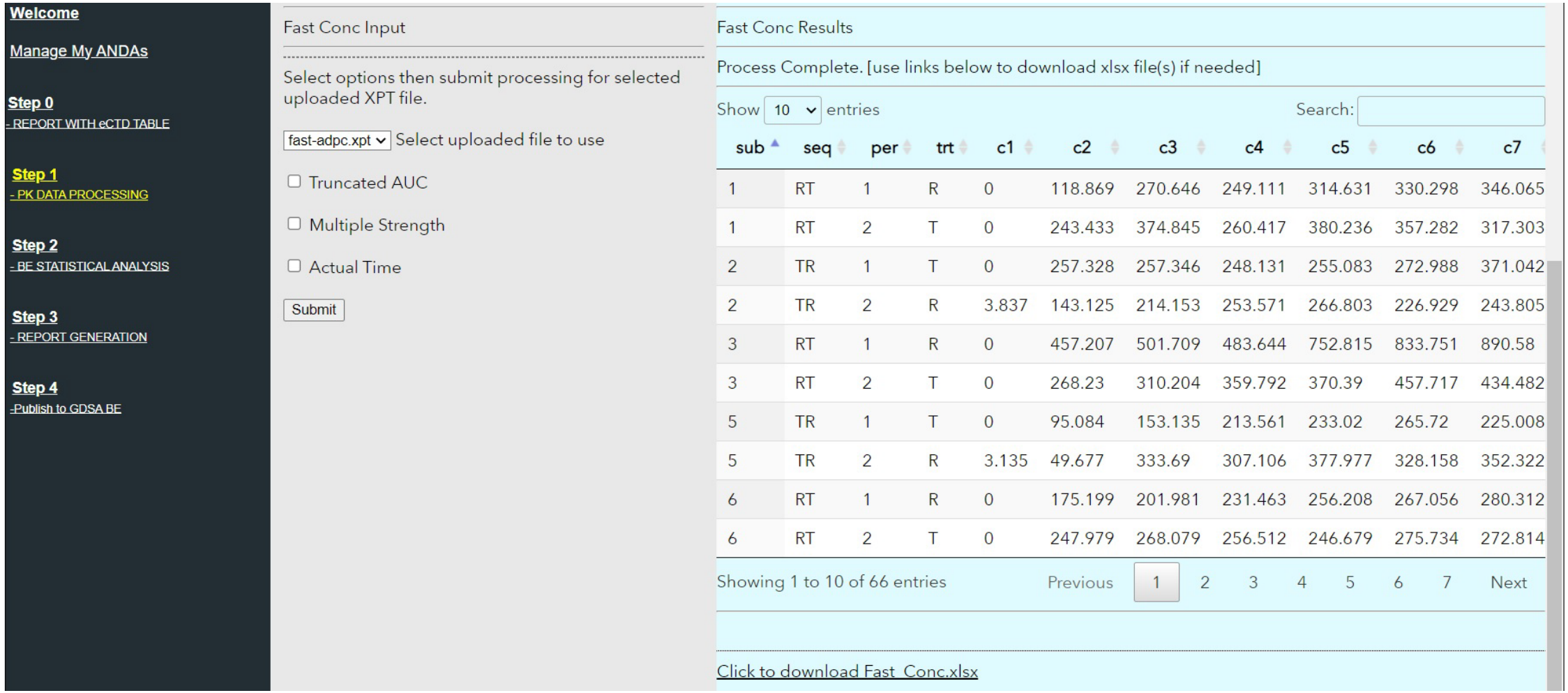


Welcome Page

Step 1 – PK DATA PROCESSING



Step 1 – PK DATA PROCESSING



sub	seq	per	trt	c1	c2	c3	c4	c5	c6	c7
1	RT	1	R	0	118.869	270.646	249.111	314.631	330.298	346.065
1	RT	2	T	0	243.433	374.845	260.417	380.236	357.282	317.303
2	TR	1	T	0	257.328	257.346	248.131	255.083	272.988	371.042
2	TR	2	R	3.837	143.125	214.153	253.571	266.803	226.929	243.805
3	RT	1	R	0	457.207	501.709	483.644	752.815	833.751	890.58
3	RT	2	T	0	268.23	310.204	359.792	370.39	457.717	434.482
5	TR	1	T	0	95.084	153.135	213.561	233.02	265.72	225.008
5	TR	2	R	3.135	49.677	333.69	307.106	377.977	328.158	352.322
6	RT	1	R	0	175.199	201.981	231.463	256.208	267.056	280.312
6	RT	2	T	0	247.979	268.079	256.512	246.679	275.734	272.814

Step 2 – BE STATISTICAL ANALYSIS

Welcome

Manage My ANDAs

Step 0
- REPORT WITH eCTD TABLE

Step 1
- PK DATA PROCESSING

Step 2
- BE STATISTICAL ANALYSIS

Step 3
- REPORT GENERATION

Step 4
-Publish to GDSA BE

☑ **Change Type of Analysis**
- ◉ Using Firm-Supplied KE and PK Data
- ○ Using Firm-Supplied KE but Recalculating PK Data
- ○ Recalculating KE and PK Data

☐ **Upload the Modified XLSX files from Step 1 if needed (optional)**

Go4Fasting

Completed

Go4Fed

Start

Go4Sprinkle

Start

Generate Statistical Analysis Report

☐ *Check to run Report without rerunning Go4 steps*

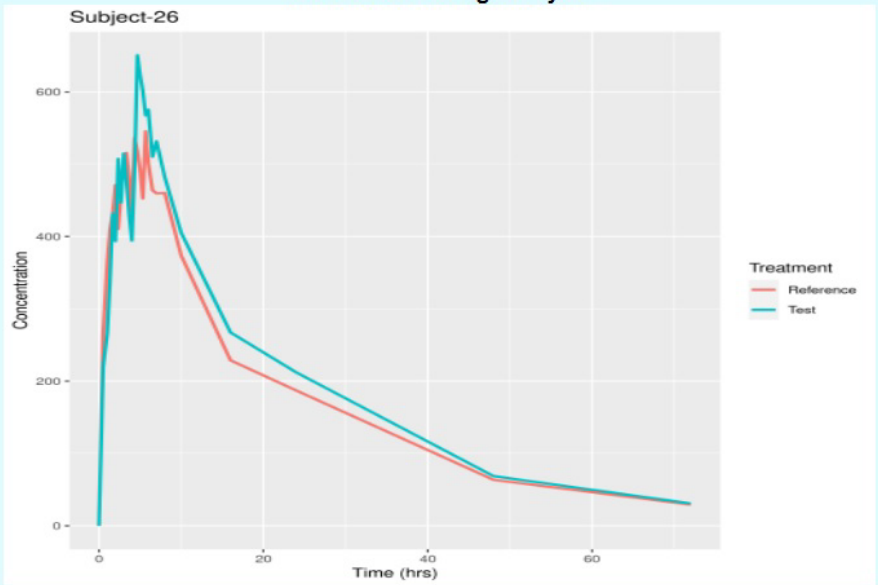
Start

Default ANDA Set.

Time Concentration Plot of A Random Subject

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

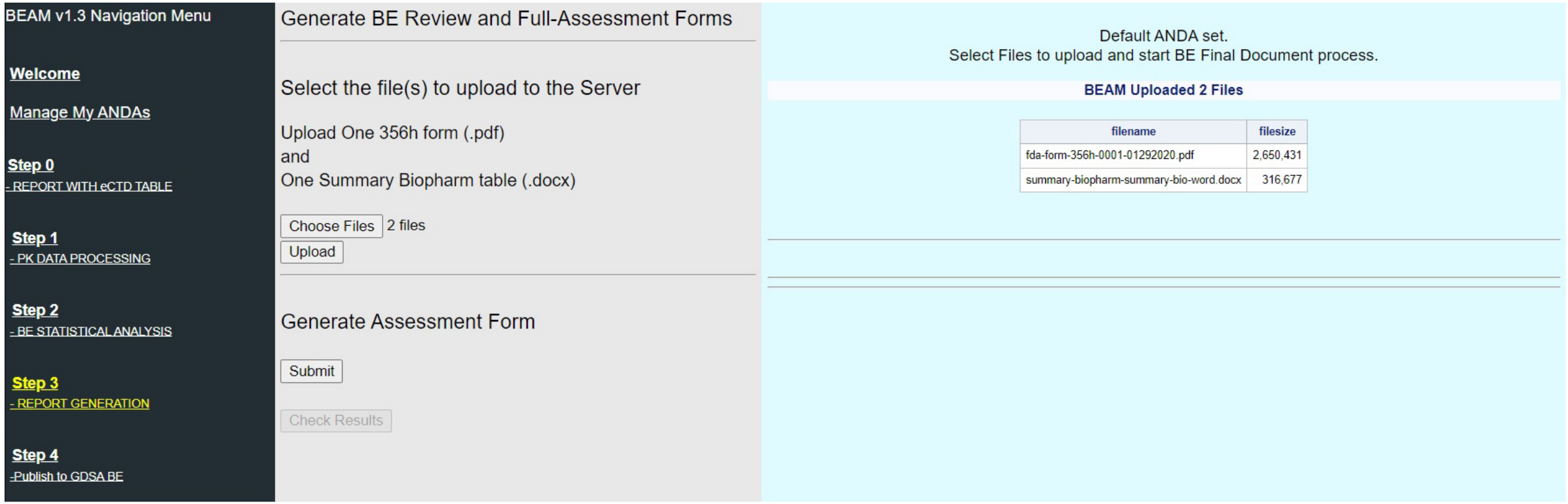
Results of Fasting Analysis



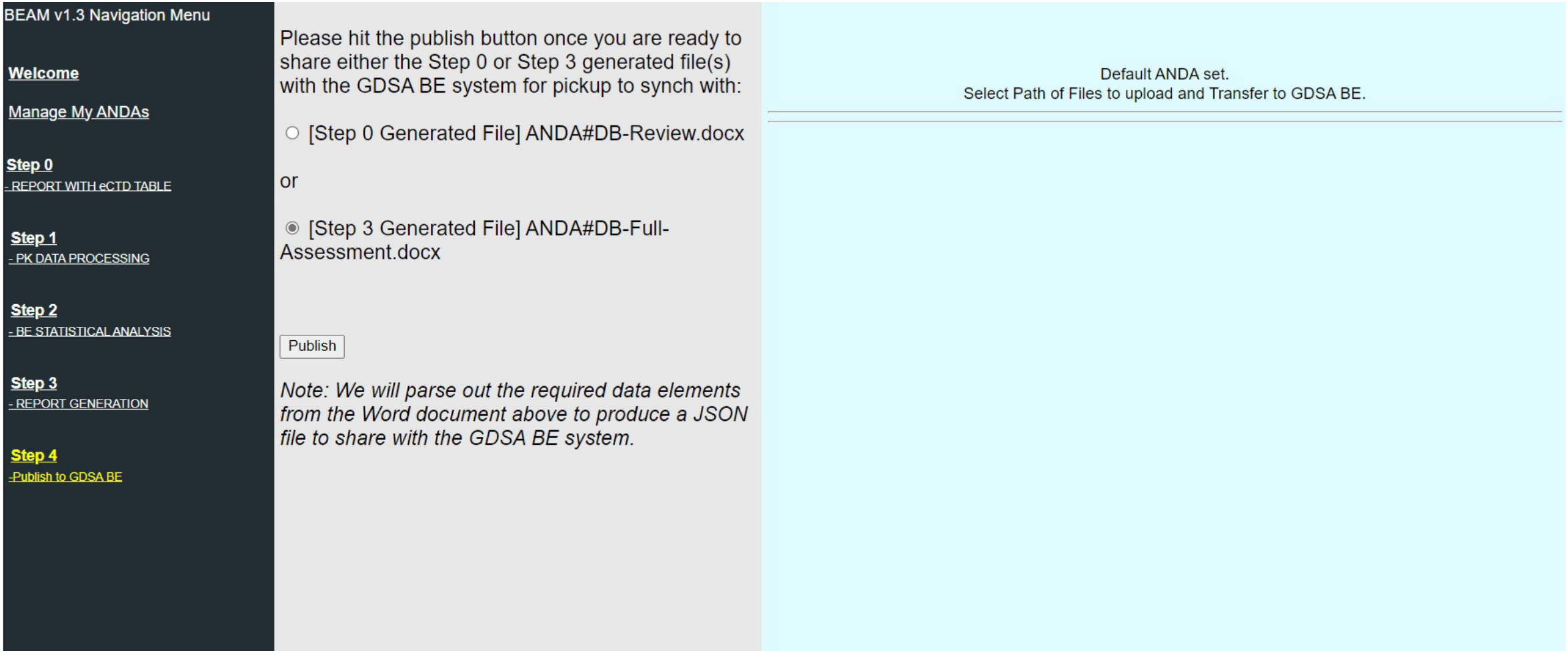
Click to download example fasting png
Click to download TimeConcPlot_Fasting.docx

Click to download _Fasting_plot_.png
Click to download _Fasting_Datasets_sas.doc
Click to download _Fasting_stat_sas.doc
Click to download _Fasting_table_sas.doc

Step 3 – REPORT GENERATION



Step 4 – Publish to **GDSA BE**



Resolving the issue at the source

- The functions of PK data processing in the BEAM tool were developed by studying hundreds in-house ANDAs.
- However, there are still issues for some new ANDA submissions, for new variations or errors are not fully predictable due to the nature of human error involved in this issue.
- Updating PK data standards by providing more instructive guideline would address the issue at the source.
  - STUDY DATA TECHNICAL CONFORMANCE GUIDE - Guidance for Industry Providing Regulatory Submissions in Electronic Format – Standardized Study Data

Discussion

- Does your agency experience similar PK data-related issues? If so, what are your experience and suggestions on how to handle it?
- Could you share any experience/suggestion about updating data standard?

Thank you for your attention!