

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	AU Ct	AU Ci	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 implemented¹⁻³, 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

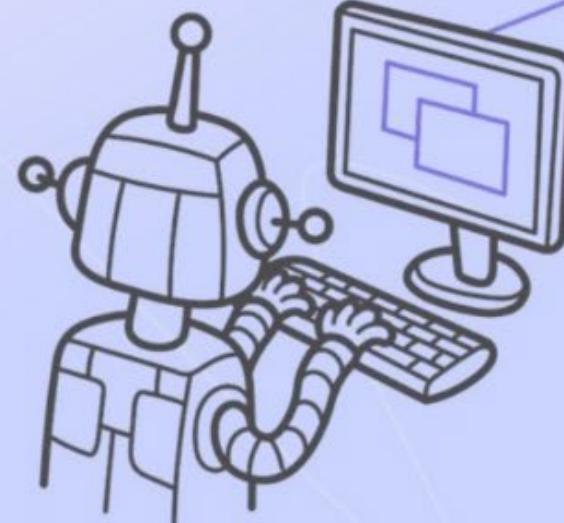
- BE STATISTICAL ANALYSIS

Step 3

- REPORT GENERATION

Step 4

- Publish to GDSA BE

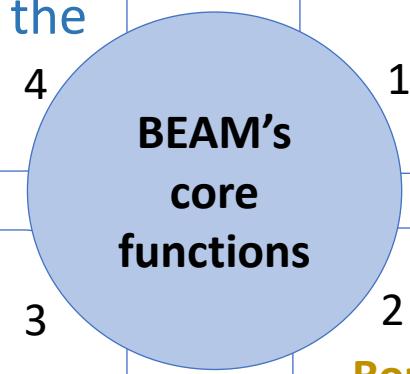


BE ASSESSMENT MATE

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

4
1
3
2

Integration

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

PK data processing

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

Review documents generation

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.

Routine BE statistical analysis

Benefit:

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

A Quick Look at the BEAM Tool

Start BEAM

BE ASSESSMENT MATE
The Default ANDA ID is: 214552

BEAM v1.3 Navigation Menu

[**Welcome**](#)

[Manage My ANDAs](#)

Step 0
[- REPORT WITH eCTD TABLE](#)

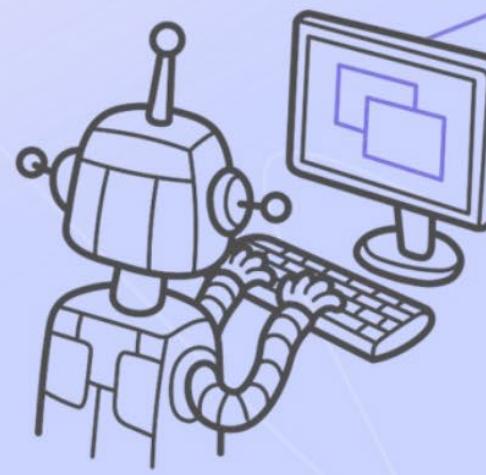
Step 1
[- PK DATA PROCESSING](#)

Step 2
[- BE STATISTICAL ANALYSIS](#)

Step 3
[- REPORT GENERATION](#)

Step 4
[- Publish to GDSA BE](#)

The BEAM tool now runs on a server so the 356h form (.pdf), summary biopharm table (.docx) and data (.xpt) will be uploaded to your folder on the server in step 0 or step 3.



BE ASSESSMENT MATE
Making Assessment More Efficient

Welcome Page

Step 1 – PK DATA PROCESSING

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](#)

Loading Conc Data

Upload Conc XPT Files

Fast:
 fast-adpc.xpt

Fed:
 fed-adpc.xpt

Sprinkle:
 No file chosen

Fast Conc Input

Select options then submit processing for selected uploaded XPT file.

Select uploaded file to use

Truncated AUC

Multiple Strength

Actual Time

Upload Conc Results

Fast 0.1 file1 of 1. name: fast-adpc.xpt size: 814560 bytes

Fed 0.2 file1 of 1. name: fed-adpc.xpt size: 1717760 bytes

XPT Upload Complete. if 2+ files uploaded, select file to process using dropdown list.

Fast Conc Results

Step 1 – PK DATA PROCESSING

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

Fast Conc Input

Select options then submit processing for selected uploaded XPT file.

fast-adpc.xpt ▾ Select uploaded file to use

Truncated AUC

Multiple Strength

Actual Time

Submit

Fast Conc Results

Process Complete. [use links below to download xlsx file(s) if needed]

Show 10 entries Search:

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

Showing 1 to 10 of 66 entries

Previous [1](#) [2](#) [3](#) [4](#) [5](#) [6](#) [7](#) Next

[Click to download Fast_Conc.xlsx](#)

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

- 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

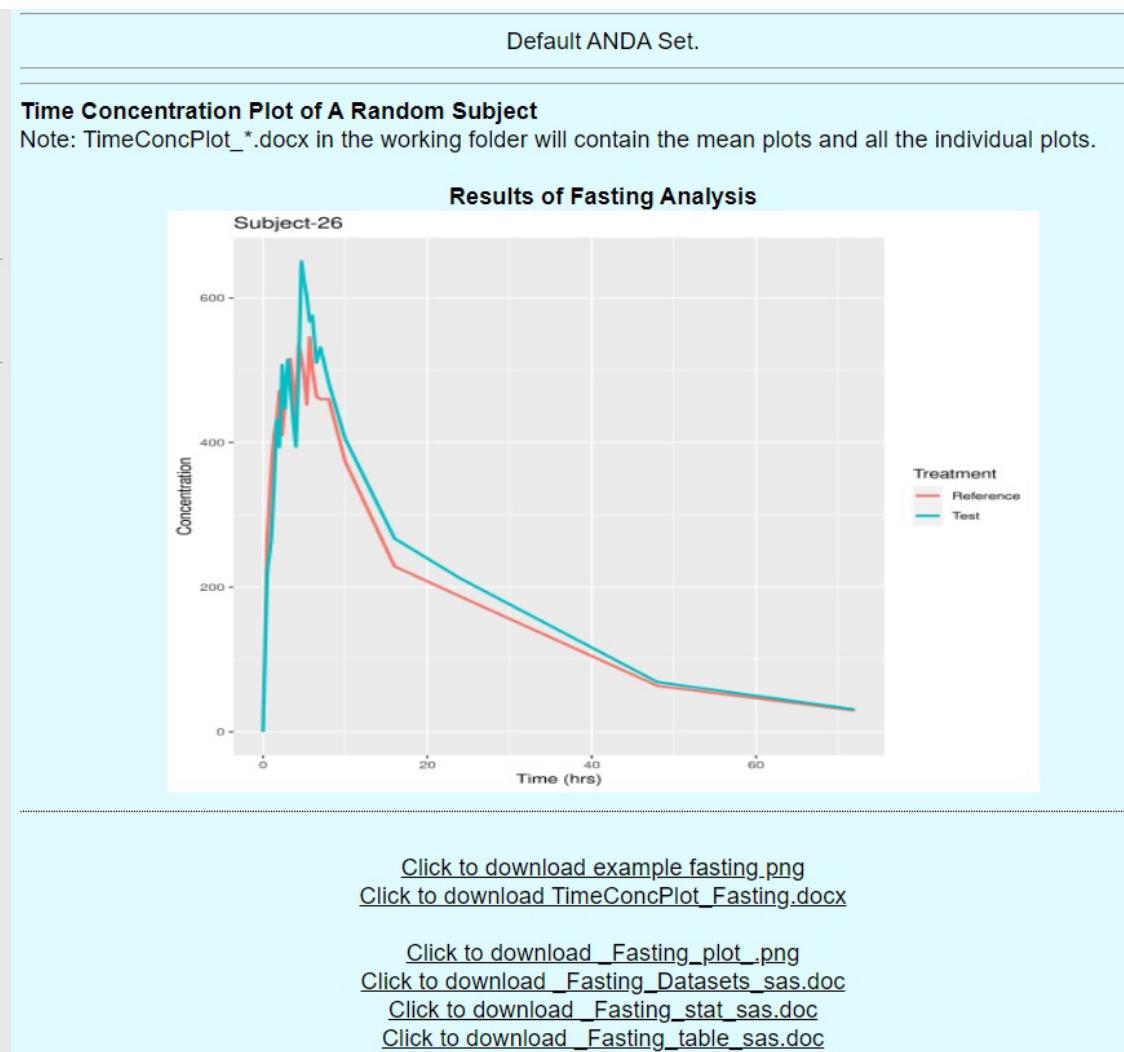
Go4Fed
Start

Go4Sprinkle
Start

Generate Statistical Analysis Report

Check to run Report without rerunning Go4 steps

Start



Step 3 – REPORT GENERATION

BEAM v1.3 Navigation Menu

[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](#)

Generate BE Review and Full-Assessment Forms

Select the file(s) to upload to the Server

Upload One 356h form (.pdf)
and
One Summary Biopharm table (.docx)

2 files

Generate Assessment Form

Default ANDA set.
Select Files to upload and start BE Final Document process.

BEAM Uploaded 2 Files

filename	filesize
fda-form-356h-0001-01292020.pdf	2,650,431
summary-biopharm-summary-bio-word.docx	316,677

Step 4 – Publish to GDSA BE

BEAM v1.3 Navigation Menu

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

Please hit the publish button once you are ready to share either the Step 0 or Step 3 generated file(s) with the GDSA BE system for pickup to synch with:

- [Step 0 Generated File] ANDA#DB-Review.docx

or

- [Step 3 Generated File] ANDA#DB-Full-Assessment.docx

Publish

Note: We will parse out the required data elements from the Word document above to produce a JSON file to share with the GDSA BE system.

Default ANDA set.

Select Path of Files to upload and Transfer 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!