An Automated AI Tool for the Analyses of Phase I, II, III Clinical Trials to Identify Pharmacokinetics Anomaly

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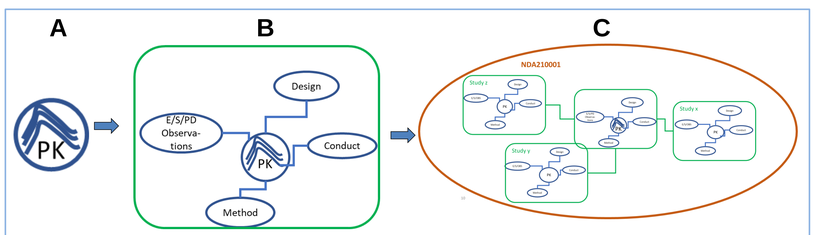
BACKGROUND and OBJECTIVE

An NDA/BLA submission consists of different clinical pharmacology studies containing Pharmacokinetics (PK) data such as dose adjustment, drug-drug interaction (DDI), pivotal bioequivalence (BE), special populations, etc. By analyzing different PK parameters (e.g., AUC, Cmax) of individual study, different anomalies related to PK can be identified in the "study level". Another critical analysis can be conducted by combining all the studies to identify PK anomalies in the "submission level". The goal of this project is to develop an automated review tool that can handle different designs such as crossover, parallel, sequential, multiple-cohort, and nested during analyses of individual study. Also, the tool should accomplish a meta-analysis of the entire submission using all the available studies to identify PK anomalies present in the submission level.



Figures 1:Towards big data A) PK data, B) Study information C) NDA containing different studies

METHODS

Tasks involved in the automation

- Data mapping: Identify the required variables from EDR
- Study design: Determine the specific randomization scheme and patient assignment
- Data management: Create datasets for analyses
- Code authoring: Generate relevant SAS codes to perform analyses
- Perform analyses and organize outputs

AI Features involved in the system

- Has a memory (knowledgebase & archive)
- Autonomously performs new tasks not encounter previously (e.g., brand new NMEs)
- Interactively provides feedbacks to and receives instructions from human users
- Dynamically optimize users experiences (auto-author, run-time efficiency, workflow adjustment, initial guess of everything)

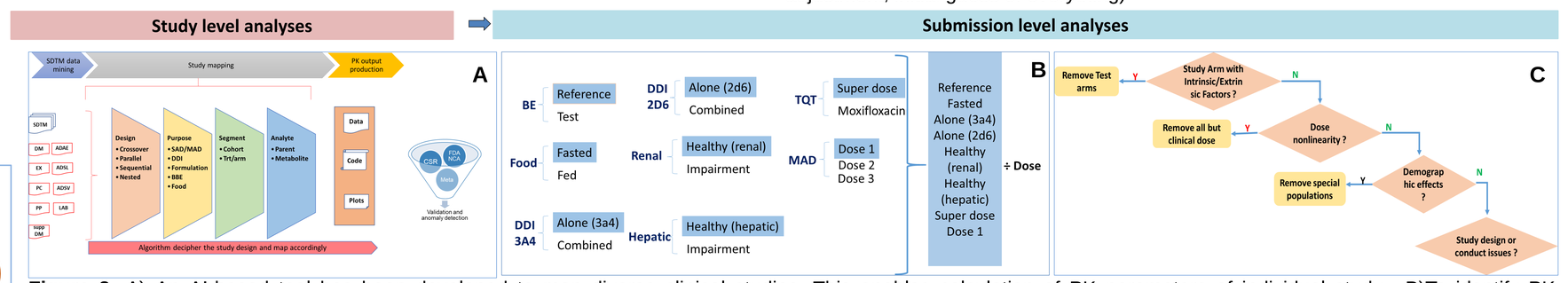


Figure 2: A) An AI-based tool has been developed to map diverse clinical studies. This enables calculation of PK parameters of individual study. B)To identify PK anomalies, only reference arms of different studies are considered and normalized by the dose. C) Then, a decision tree-based method is applied before conducting a meta-analysis.

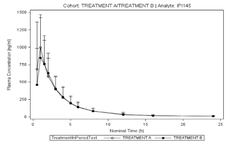
Total 116 computations tasks codified in SAS macros (28Procedures, 35 macros, 58 sub macros), >2500 AI actions to automate the 116 tasks using C#, Javasripts: 52 models, >2500 VS objects.(https://github.com/FDA/PKView)

RESULTS and DISCUSSONS

Study level Anomaly detection

Firm/FDA Ratio to detect discrepancy

A: Map and visualize the Time-Concentration profile from PC



Figures 3: Time-Concentration PK Profile

B: Map Firm's PK data and generate summary statistics from PP

Table Title: Summary table of PK parameters from different visits

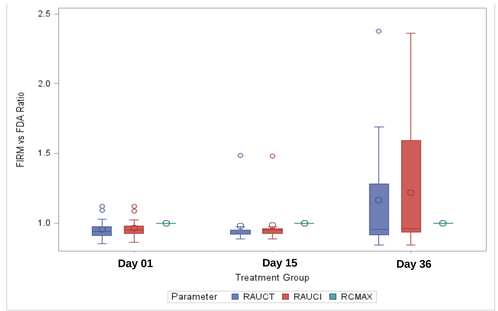
	Day 01			Day 15			Day 36	
Parameter Short Name	N	Mean (STD)	Geo. Mean (CV%)	N	Mean (STD)	Geo. Mean (CV%)	N	Mean (STD)	Geo. Mean (CV%)
AUCIFO	14	1290.37 (1154.88)	994.68 [76.32]	12	1355.91 (1493.12)	946.16 [92.78]	10	1251.76 (1269.09)	884.14 [96.49]
AUCLST	16	1160.44 (1115.9)	850.94 [88.71]	13	1260.35 (1445.27)	854.19 [98.33]	12	1206.35 (1159.45)	889.03 [88.11]
CMAX	16	381.94 (176.32)	347.99 [45.73]	13	377.69 (204.9)	335.97 [50.76]	12	373.75 (218.74)	317.01 [65.18]

C: PK parameters calculated by FDA using NCA

FDA NCA

Firm NCA

D: Firm/FDA Ratio to detect discrepancy



Figures 4: Box plot of FIRM/FDA ratio

Statistical-sensitivity analyses

-Statistical analysis: 90%CI using Forest plot.

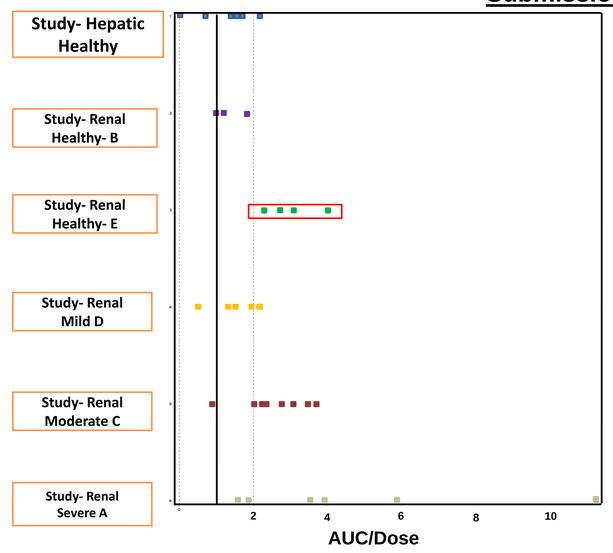
-Sensitivity analyses:

- AUCinf calculation: To check whether AUCinf/AUClast> 120%
- PK parameters outliers: 2 x SD
- Point analysis of per subject start time
- Between-treatment of PK parameters : scatter plots

Anomaly: Eight (8) subjects showed large FIRM/FDA ratios on AUC's of omeprazole due to insufficient 'length of sampling time'.

Impact: Further analysis by the review team revealed that some of the "missing data values" for the early absorption phase were BLOQ for omeprazole.

Submission level Anomaly detection



Included studies: Renal and Hepatic studies were considered in this particular analyses.

Anomaly:

- In the Renal Impairment study of this submission, both Group B and E are healthy subjects but the AUCs' are different by ~2 fold between the two groups in either parent drug or the 3 active metabolites.
- This indicates that the two reference arms AUCs do not represent the typical distribution in healthy populations, and the resulting comparisons between renal impaired vs healthy are not reliable.
- Further investigations found that if creatinine clearance values are considered of each subject in the original control group (E; red box), these subjects should be categorized as mild renal impairment instead of "healthy control".
- Impact: Reanalysis of the study results was conducted which improved the reliability of the study and no dose adjustment for renal was recommended in the label.

Figures 5: Example of submission level anomaly. The red box indicates - the study containing potential anomaly.

CONCLUSIONS

The tool has helped in the QBR review process, to formulate the critical questions for mid-cycle meetings, and often to modify the final label. The tool has improved efficiency of OCP reviewers by decreasing the analyses time.

ACKNOWLEDGEMENTS

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