GUF CDISC

Octobre 2019, Rennes

Implémentation du CDISC pour la PK: du SEND au ADaM en passant par le SDTM

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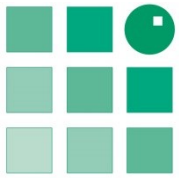
Content disclaimer

The content of this presentation is aiming at exchanging feedbacks and experiences on implementation of CDISC for PK analyses and represent conventions and examples taken by the authors, so these should not be considered as official recommendations.



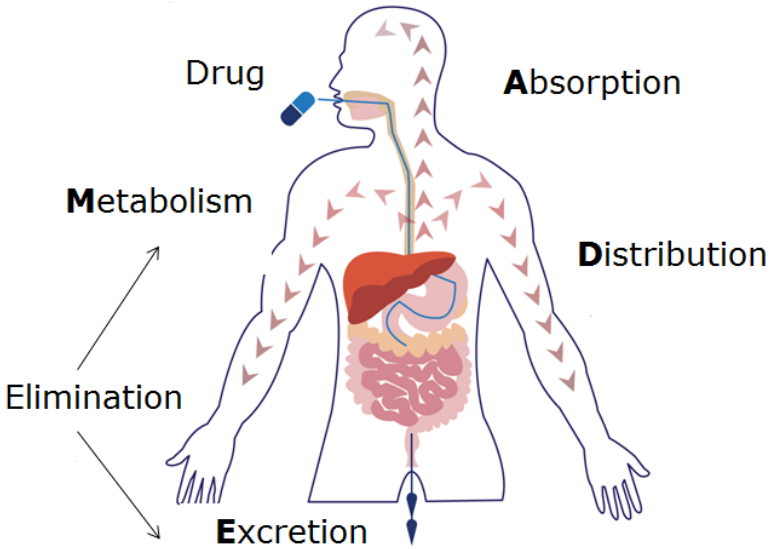
Agenda

- Introduction
- Process SDTM/ADaM
  - Controlled terminologies
  - RELREC
  - Significant digits
  - ADaM parameters
  - Analysis Result Metadata
  - ADNCA
  - PK/QTc analyses
- Process SEND
  - Sparse sampling
  - PK satellites
  - Differences with the SDTM IG

What is pharmacokinetics ?

- Pharmacokinetics is the study of what happens to a drug in the body, from administration until elimination from the body.

- Model ADME (Absorption, Distribution, Metabolism and Excretion) is generally used to describe the process of the drug-body interaction.



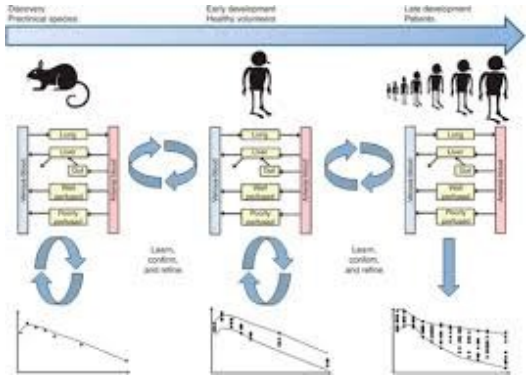
Parameters derivation methods

Simple mathematical equations allowing descriptive approach of phenomena

- **Non-compartmental analysis (NCA) ~** 90% of current PK analysis
  - Diversity of applications in clinical studies: SAD/MAD, Hepatic impairment, DDI, Food-effect, Bioequivalence…
  - Following FDA and EMEA guidelines, the statistical analysis should be based on the non-compartmental parameters (AUC, C_{max}, T_{max}…)

Mathematical models to describe dynamic phenomena

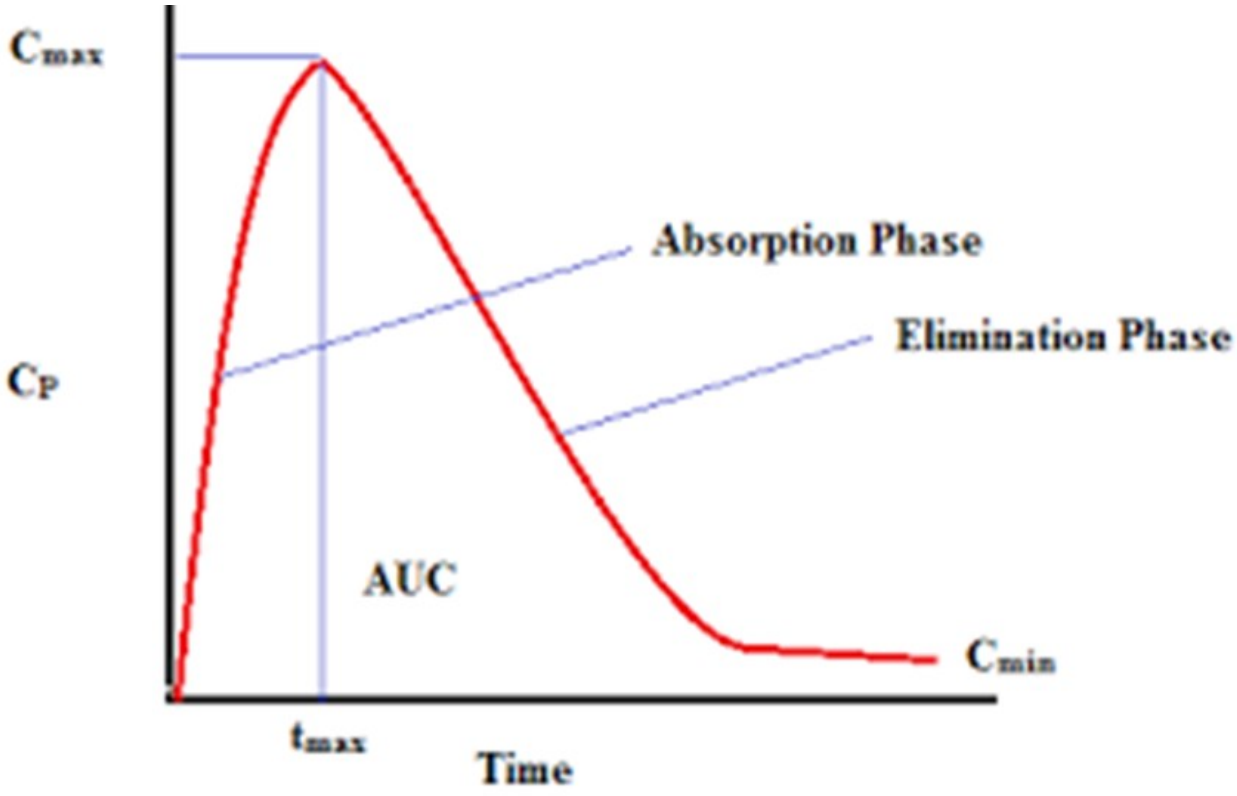
- **Compartmental analysis (**for mechanism understanding)
  - For example: to describe a bi-phasic profile
  - Modeling of PK profile to adjust PK parameters (select a model, weighting…)
- **Pharmacokinetic-Pharmacodynamic**
- *Population pharmacokinetic*
- *Physiologically-based pharmacokinetic model (PB-PK)*



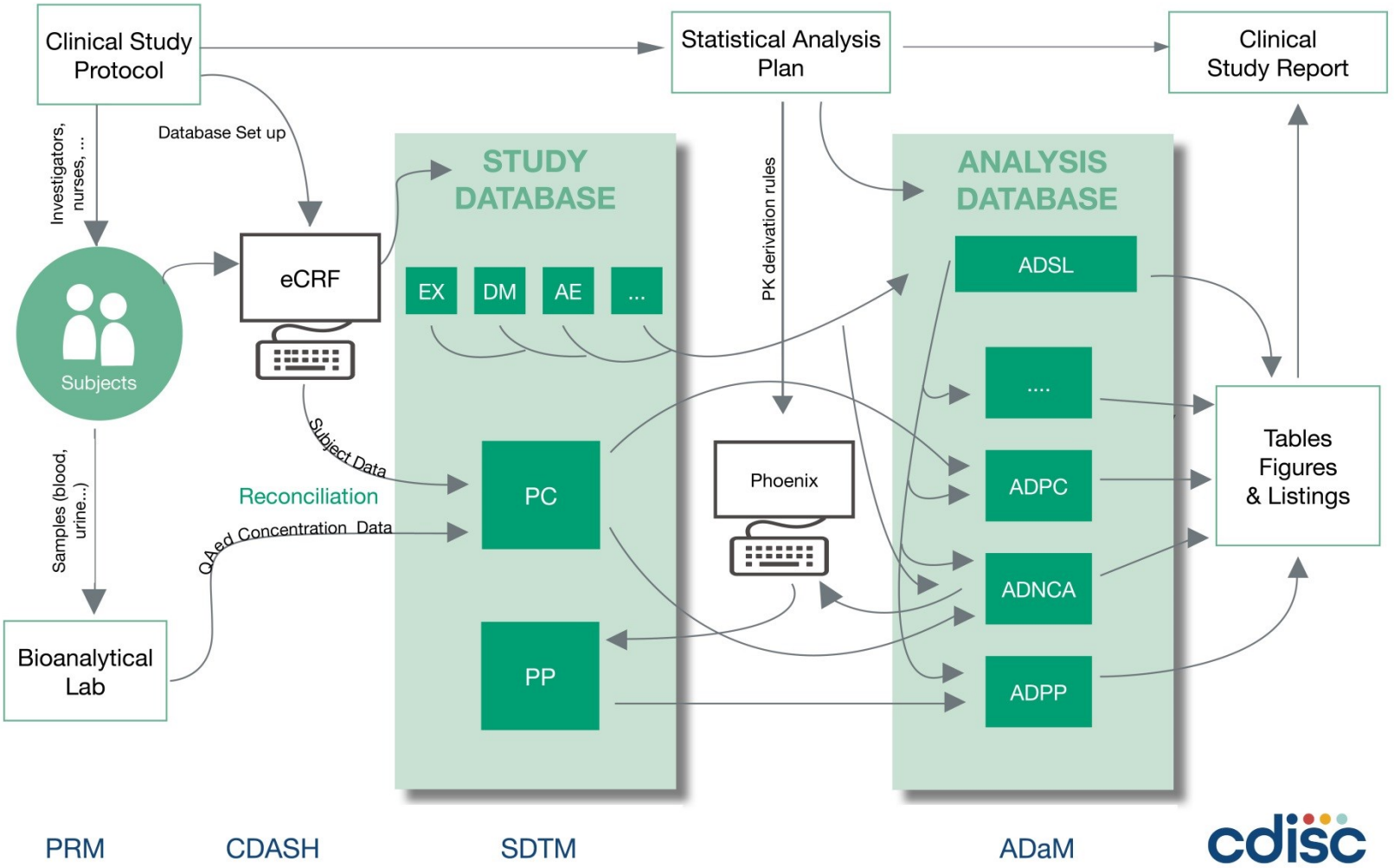
Main PK parameters

⇒ Study of concentrations as a function of time

Main PK parameters: tmax , Cmax, AUC



SDTM/ADaM process

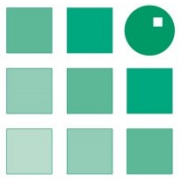


Controlled terminologies (1)

- PK parameters

Code	Codelist Name	CDISC Submission Value	NCI Preferred Term
C85565	PK Parameters	AUC to Last Nonzero Conc	Area Under the Curve From Dosing to Last Concentration
C85818	PK Parameters	Half-Life Lambda z	Terminal Half Life
C85652	PK Parameters	Lambda z	Lambda Z
C70918	PK Parameters	Max Conc	Cmax
C70919	PK Parameters	Time of CMAX	Tmax

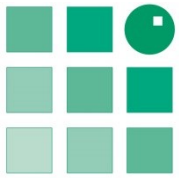
- PCORRES expected to be as transferred by the lab (e.g. “BLQ”, “<LLOQ”, “<0.25”)
- No convention for PCSTRESC, but “BLQ” expected by the FDA.



Controlled terminologies (2)

- UNIT used in PC domain
- PKUNIT used in PP domain

- But difference: original unit ng/mL should be mapped to ug/L according to UNIT codelist in PCORRESU
- Although ng/mL used in PP domain according to CT PKUNIT

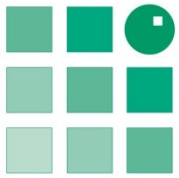


RELREC

- Relationships between PC and PP domains using PCGRPID and PPGRPID

STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
BTLSTD001	PC		PCGRPID		MANY	A
BTLSTD001	PP		PPGRPID		MANY	A

- Issue when the database lock is delayed for PK domains (when bioanalysis results are provided later), since RELREC also used for other domains (like AE and CM).

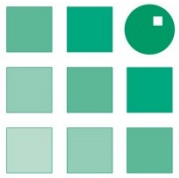


Significant digits

- No official rule, depending on sponsor (application or not, and differing definitions)

- Managed with --ORRES and --STRESC/--STRESN

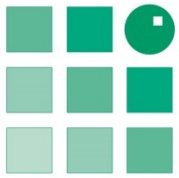
PPGRPID	PPTESTCD	PPTEST	PPORRES	PPORRESU	PPSTRESC	PPSTRESN	PPSTRESU
D1	AUCLST	AUC to Last Nonzero Conc	13.5759	h*ng/mL	13.6	13.6	h*ng/mL
D1	TMAX	Time of CMAX	0.5	h	0.500	0.5	h
D1	CMAX	Max Conc	5.78	ng/mL	5.78	5.78	ng/mL
D1	LAMZ	Lambda z	0.122733	/h	0.123	0.123	/h
D1	LAMZHL	Half-Life Lambda z	5.64761	h	5.65	5.65	h



ADaM parameters (1)

Suggestion: deriving PARAM using NCI preferred terms

SUBJID	PARCAT1	PARCAT1N	PARAMN	PARAM	PARAMCD	PPTEST	NCI Preferred Term
00011001	PARENT	1	1	**Parent - Area Under the Curve From Dosing to Last Concentration (h*ng/mL)**	PAUCLST	AUC to Last Nonzero Conc	Area Under the Curve From Dosing to Last Concentration
00011001	PARENT	1	2	**Parent - Cmax (ng/mL)**	PCMAX	Max Conc	Cmax
00011001	PARENT	1	3	**Parent - Tmax (h)**	PTMAX	Time of CMAX	Tmax
00011001	PARENT	1	4	**Parent - Terminal Half Life (h)**	PLAMZHL	Half-Life Lambda z	Terminal Half Life
00011001	PARENT	1	5	**Parent - Lambda Z (/h)**	PLAMZ	Lambda z	Lambda Z
00011001	METABOLITE	2	1	**Metabolite - Area Under the Curve From Dosing to Last Concentration (h*ng/mL)**	MAUCLST	AUC to Last Nonzero Conc	Area Under the Curve From Dosing to Last Concentration
00011001	METABOLITE	2	2	**Metabolite - Cmax (ng/mL)**	MCMAX	Max Conc	Cmax
00011001	METABOLITE	2	3	**Metabolite - Tmax (h)**	MTMAX	Time of CMAX	Tmax
00011001	METABOLITE	2	4	**Metabolite - Terminal Half Life (h)**	MLAMZHL	Half-Life Lambda z	Terminal Half Life
00011001	METABOLITE	2	5	**Metabolite - Lambda Z (/h)**	MLAMZ	Lambda z	Lambda Z



ADaM parameters (2)

Addition of the Log transformed parameter in ADPP as recommended in the ADaM IG

CDISC ADaM Implementation Guide Version 1.1

3.3.4 Analysis Parameter Variables for BDS Datasets

Table 3.3.4.1 Analysis Parameter Variables for BDS Datasets

Variable Name	Variable Label	Type	Codelist/ Controlled Terms	Core	CDISC Notes
PARAM	Parameter	Char		Req	The description of the analysis parameter. Examples include: "Supine Systolic Blood Pressure (mm Hg)", "Log10 (Weight (kg))", "Time to First Hypertension Event (Days)", "Estimated Tumor Growth Rate", etc. PARAM should be sufficient to describe unambiguously the contents of AVAL and/or AVALC. PARAM must include all descriptive and qualifying information relevant to the analysis purpose of the parameter.

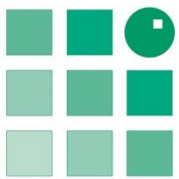
SUBJID	PKSFL	PARAMN	PARAM	PARAMCD	AVAL
00011001	Y	1	Parent - Cmax (ng/mL)	PCMAX	13.5
00011001	Y	2	**Log (Parent - Cmax (ng/mL))**	LPCMAX	1.13
00011001	Y	3	Parent - Area Under the Curve From Dosing to Last Concentration (h*ng/mL)	PAUCLST	5.78
00011001	Y	4	**Log (Parent - Area Under the Curve From Dosing to Last Concentration (h*ng/mL))**	LPAUCLST	0.762

Analysis Result Metadata

Table 14.2.2.4.1

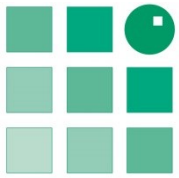
Display	**APPENDIX 14.2 [page=23] Analysis of the Treatment B effect on Treatment A for Cmax and AUC0-last - Pharmacokinetic Set**
Analysis Result	**Analysis of variance (ANOVA) using log-transformed data for Cmax and AUC0-last comparing Test (Treatment A under co-administration with Treatment B) versus Reference (Treatment A administered alone) treatments**
Analysis Parameter(s)	PARAMCD IN ("LAUCLST" (Log (Area Under the Curve From Dosing to Last Concentration (h*ng/mL))) , "LCMAX" (Log (Cmax (ng/mL))))
Analysis Variable(s)	AVAL (Analysis Value)
Analysis Reason	SPECIFIED IN SAP
Analysis Purpose	PRIMARY OUTCOME MEASURE
Data References (incl. Selection Criteria)	ADPP [PKSFL = "Y" and PARAMCD IN ("LAUCLST", "LCMAX")]
Documentation	Used PROC MIXED in SAS for the evaluation of the effect of Treatment B on Treatment A Statistical Analysis Plan

Programming Statements	[SAS EG version 7.1 and SAS server version 9.4]
	`proc mixed data=ADPP method=REML;`
	` by PARAMCD;`
	` class TRTAN USUBJID;`
	` model AVAL = TRTAN / solution cl alpha=0.10 ddfm=kr;`
	` random USUBJID;`
	` lsmeans TRTAN / cl alpha=0.10;`
	` estimate 'Test versus Reference' TRTAN -1 1 / cl alpha=0.10 e;`
	`run;`
	…



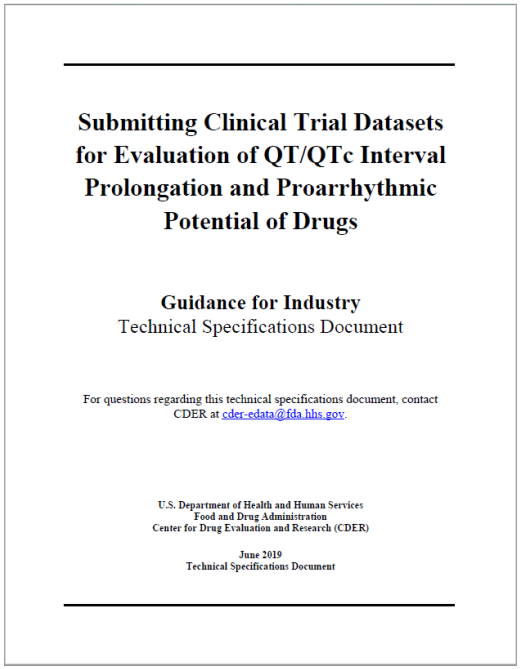
ADNCA

- New FDA guideline expected in 2020
- Soon to come non-compartmental analysis (NCA) ADaM dataset
- To fill a gap between SDTM and ADaM standards to produce a standard dataset for PK parameters derivation
- Provided to the PK scientist for calculation of PK parameters (NCA and compartmental, but not for population PK modelling)
- Including data for concentration, dosing, actual times, flags for exclusion of records and subjects, AEs impacting PK (e.g. vomiting and nausea)
- Following flexible ADaM Basic Data Structure (BDS)



PK/QTc analyses

- QT/QTc interval prolongation studies with time-matched PK concentrations
- FDA Technical Specifications Document (June 2019)



Submitting Clinical Trial Datasets for Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential of Drugs

Guidance for Industry
Technical Specifications Document

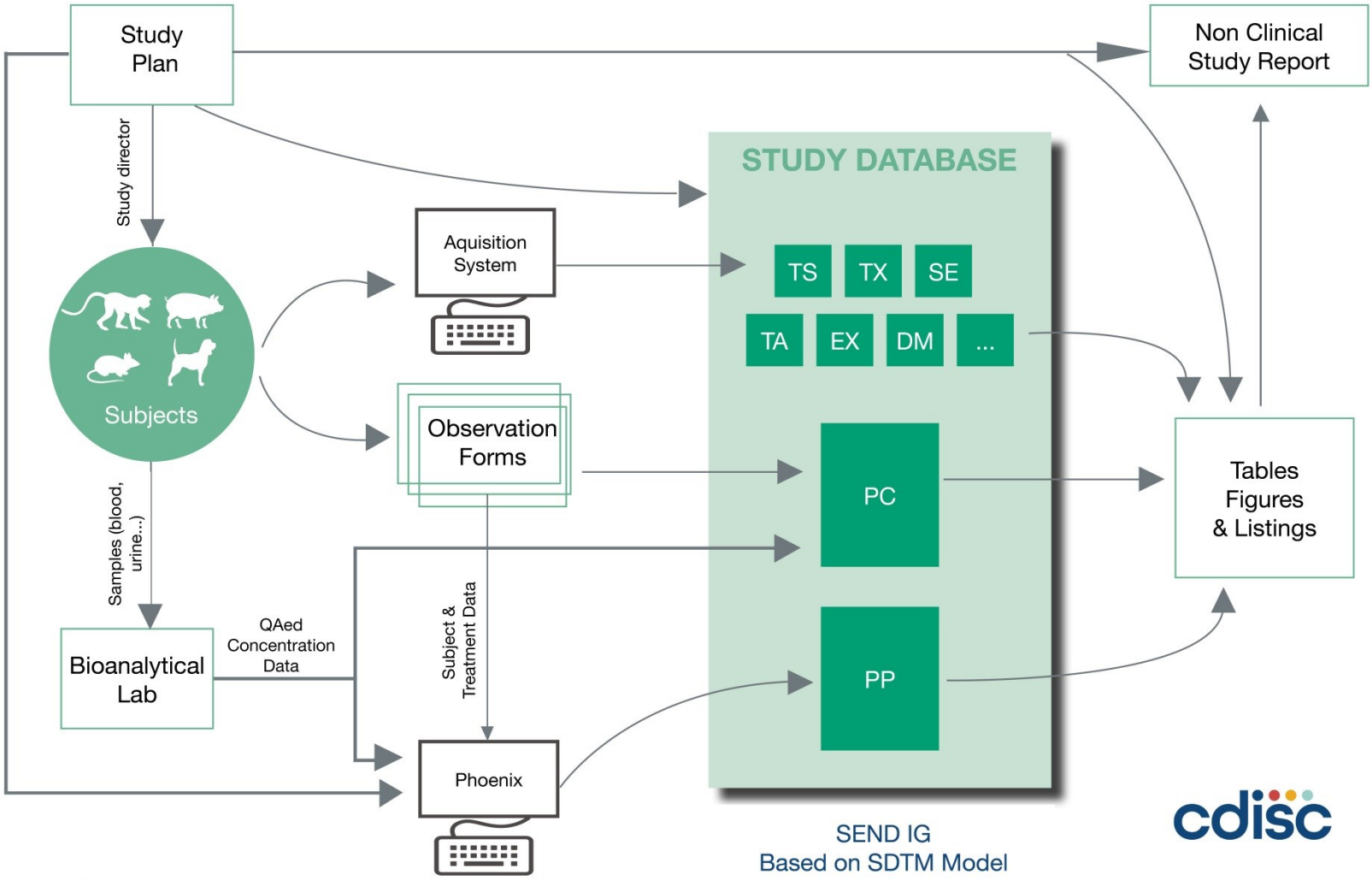
For questions regarding this technical specifications document, contact CDER at cder-edata@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

June 2019
Technical Specifications Document

- EG data consideration in derivation of ADPC variables (consistent coding e.g. matching ATPT)
- Addition of variables in ADEG
  - to identify matching timepoints and analysable records for concentration/QTc analysis
  - to derive comparator corrected change from baseline
- No creation of ADS with PC and EG data

SEND process



Sparse sampling

- Not possible to take excessive blood sample on animals (limited to 10% of total volume)
- Blood samples from different animals in the same treatment groups are pooled together.
- POOLDEF domain should be included and POOLID variable should be present in PC and PP domains.

Group	Animal no.	Predose	1h	2h	3h	4h	5h
1	1	x		x		x	
1	2		x		x		x

POOLDEF

STUDYID	POOLID	USUBJID
BTLSTD001	POOL01	001
BTLSTD001	POOL01	002

PP

USUBJID	POOLID	PPGRPID	PPTESTCD	PPTEST	PPCAT
	POOL01	GRP1	AUCLST	AUC to Last Nonzero Conc	DRUGA
	POOL01	GRP1	TMAX	Time of CMAX	DRUGA
	POOL01	GRP1	CMAX	Max Conc	DRUGA

PC

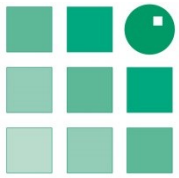
USUBJID	PCGRPID	PCTESTCD	PCTEST	PCORRES	PCORRESU	PCTPT	PCTPTNUM
001	GRP1	DRUGA	Drug A	BLQ	ng/mL	PREDOSE	0
001	GRP1	DRUGA	Drug A	169.525	ng/mL	2 HOURS POST DOSE	2
001	GRP1	DRUGA	Drug A	4.961	ng/mL	4 HOURS POST DOSE	4
002	GRP1	DRUGA	Drug A	87.81	ng/mL	1 HOUR POST DOSE	1
002	GRP1	DRUGA	Drug A	48.138	ng/mL	3 HOURS POST DOSE	3
002	GRP1	DRUGA	Drug A	2.295	ng/mL	5 HOURS POST DOSE	5

PK satellites

- In order not to disturb the animals during the experiments, PK is performed separately
  - After the experiment following a wash-out period
  - With different animals in parallel

- Specification in TX domain

SETCD	SET	TXPARMCD	TXPARM	TXVAL
TRTATK	Drug A, TK	ARMCD	Arm Code	1
TRTATK	Drug A, TK	GRPLBL	Group Label	Drug A
TRTATK	Drug A, TK	SETLBL	Set Label	Drug A, TK
TRTATK	Drug A, TK	TKDESC	Toxicokinetic Description	TK
TRTA	Drug A, Non-TK	ARMCD	Arm Code	1
TRTA	Drug A, Non-TK	GRPLBL	Group Label	Drug A
TRTA	Drug A, Non-TK	SETLBL	Set Label	Drug A, Non-TK
TRTA	Drug A, Non-TK	TKDESC	Toxicokinetic Description	NON-TK



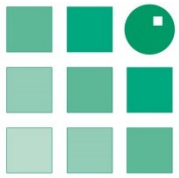
Differences with SDTM (1)

- Trial design sets should described subjects with PK as this is more traumatic for animals and could impact the study results.

  ⇒ Addition of TX domain

- Animals could be assessed in groups and these need to be identified in the database

  ⇒ Addition of POOLDEF domain (with relationships in RELREC)



Differences with SDTM (2)

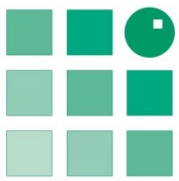
- Variables not used for human studies:

  --EXCLFL, --NOMDY, --NOMLBL, --REASEX, --USCHFL, --DTHREL, and FETUSID.

- Different labels in PCDY, PCGRPID, PCNAM, PCORRES, PCORRESU, PCREASND, PCREFID, PCSTRESC, PCSTRESN, PCSTRESU, PCTEST, PCTESTCD, VISITDY, PPENINT, PPGRPID, PPORRES, PPORRESU, PPREASND, PPSTINT, PPSTRESC, PPSTRESN and PPSTRESU.

- Different controlled terminologies expected:

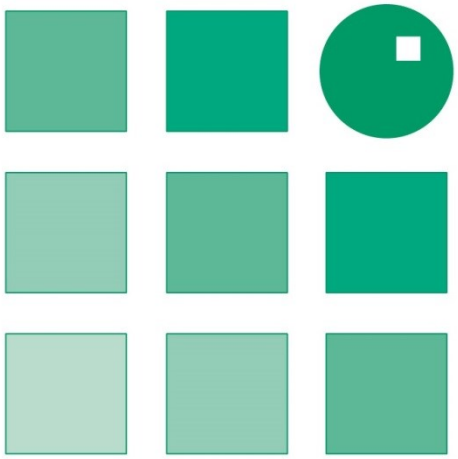
Domain	Name	SDTM IG 3.2	SEND IG 3.1
PC	PCMETHOD	(METHOD)	
PC	PCORRESU	(UNIT)	(PKUNIT)
PC	PCSPCCND	(SPECCOND)	
PC	PCSPEC	(SPECTYPE)	(SPEC)
PC	PCSTRESU	(UNIT)	(PKUNIT)
PP	PPSPEC	(SPECTYPE)	(SPEC)



Conclusion

Do you have any experience
to share in the implementation
of CDISC for PK analyses?

Questions ?



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