ELECTRONIC SUBMISSION OF PHARMACOMETRICS DATA SETS AND REPORTS FOR REGULATORY SUBMISSIONS

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Disclaimer

- **The opinions expressed in this presentation are the presenter's and do not necessarily reflect the official views of the United States Food and Drug Administration (FDA).**

Modeling and Simulation to Inform Drug Development Decision Making

- **Why**: Informs decision making and information gaps
- **What & When**: Types of analyses at various development milestones
- **How**: How to communicate modeling and simulation work to the agency

Problem Statement

- Many analyses are conducted to support key decision making during drug development
- Uncertainty on what to provide and how to provide it
- Incomplete submission of key decision making steps can create a disconnect between M&S findings and decision making
- Clarify expectations at different stages

Why Modeling and Simulation? (1)

- M&S approaches facilitate the integration of data from many sources and transform into simple figures and tables for informed decision making

PK

Efficacy

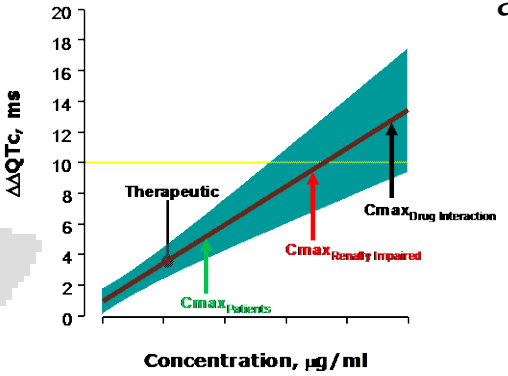
Safety

Covariate

Data Assembly

Analyses

Output



Decision and Action

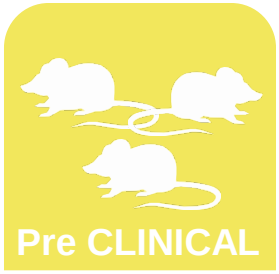
Translate M&S output into action

Why Modeling and Simulation? (2)

- Statement from Dr. Gottlieb – July 7th, 2017
  - How FDA Plans to Help Consumers Capitalize on Advances in Science
  - *"… **use of in silico tools in clinical trials for improving drug development and making regulation more efficient**."*
  - ***"Modeling and simulation play a critical role in organizing diverse data sets and exploring alternate study designs"***
  - ***"updated guidance on how aspects of these in silico tools can be advanced and incorporated into … drug development"***
  - Relevant throughout IND, NDA, and BLA reviews

https://blogs.fda.gov/fdavoice/index.php/2017/07/how-fda-plans-to-help-consumers-capitalize-on-advances-in-science/

Analyses and Questions Change Over Development

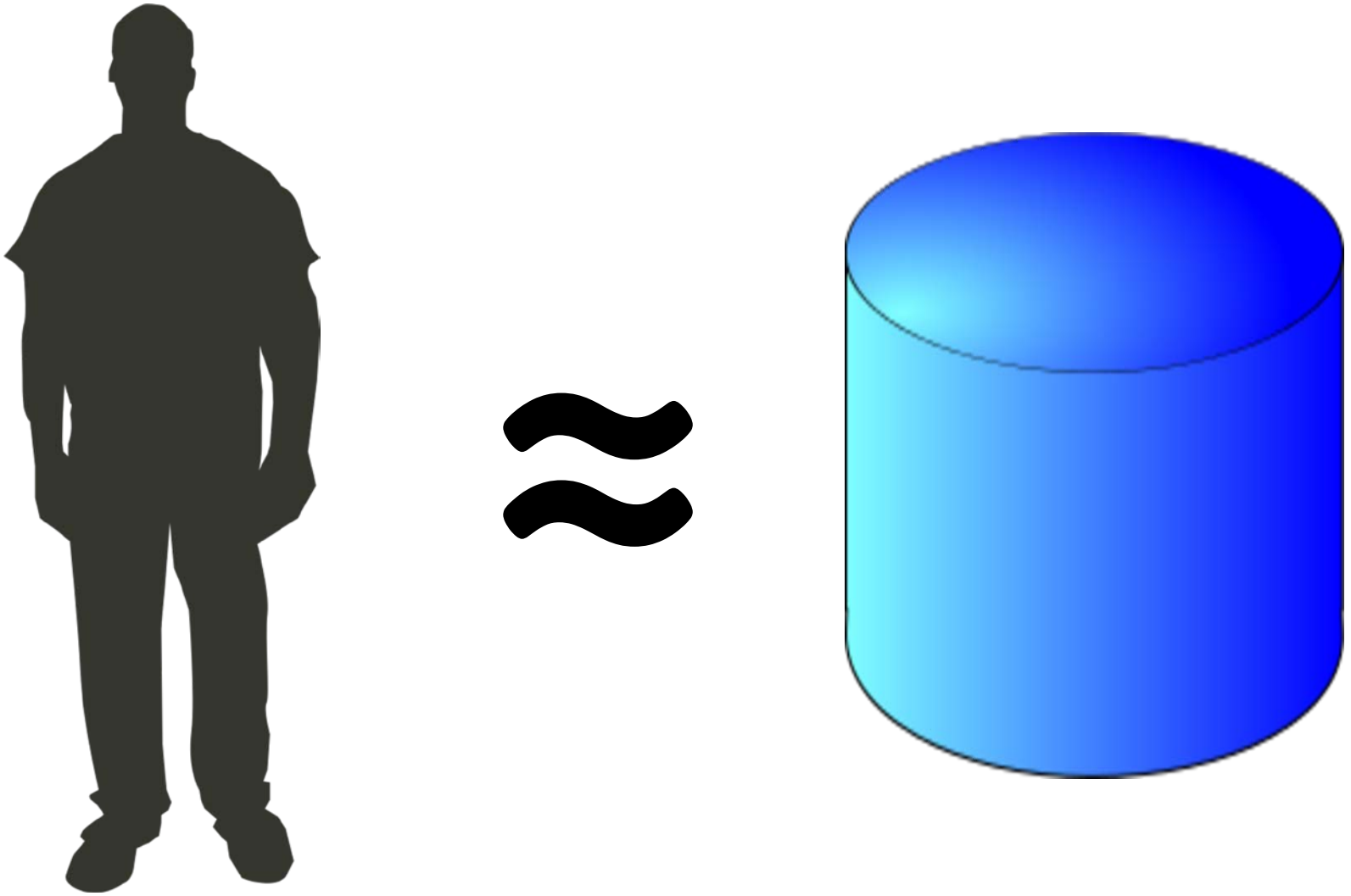


	Pre CLINICAL	PHASE I SAFETY	PHASE II EFFICACY	PHASE III POPULATION
Data Generated	In vitro PD Animal PK & PD	PK & PD Biomarkers Safety Prelim Efficacy	PK & PD Biomarkers Safety Efficacy	Safety & Efficacy PK
Analysis Tools	QSP Preclin PK-PD ER	PK-PD ER & DR: safety efficacy	Integrated ER and DR PopPK	ER and DR PopPK
Decisions	Target Selection Feasibility	Go-No Go Regimen selection	Go No-Go Phase 3 Dose Intrinsic/Extrinsic factors	Data driven dose modifications for safety and efficacy

QSP = Quantitative Systems Pharmacology, ER = Exposure-Response, DR = Dose-Response, PopPK = Population PK

Key Themes: Traceability

Key Themes: Assumptions



Key Themes: Application

Expectations with IND submissions

- General: Adequate information and justification to support
  - Dosing range/interval
  - Size-based vs fixed dosing
  - Population and trial design
  - Safety signals/concerns
  - Biomarkers that may be used to demonstrate effectiveness, select patients, decision making

- If modeling and simulation analyses serve an important component for decision making where feedback is sought, those results should be provided to the Agency
  - Separate reports to the IND

Expectations with EOP2 Meetings

- Items from previous slide are also applicable here as well as
  - To illustrate rationale for doses in Phase III
    - Justify the dose selection and number of doses → scientific rationale
  - To justify the need for (or lack thereof) of dose adjustments in patients

- Modeling results conducted to support these decisions should be included in the EOP2 package
  - Provide summary of rationale alongside the questions with hyperlinks to more detailed information elsewhere in the submission
  - More complete materials later in the package or as appendices or as separate documents in the submission

- EOP2 meeting is a critical step before embarking on a pivotal trial
  - Dose selection and taking multiple doses forward helps to best assess benefit:risk profile of a compound

Expectations with Pre-BLA/NDA Meetings

- Often an administrative meeting
  - Can be better utilized for outlining expectations on analyses

- Package should clearly highlight how modeling and simulations are being used to support decision making in their submission
  - Include what decisions are being supported by such analyses, how they plan to conduct the analysis, and any key assumptions
  - Some examples would include analyses to support:
    - Dosing based on intrinsic factors, such as renal and hepatic impairment
    - Dosing based on drug-drug interactions
    - Dosing in pediatrics
- Talk about analyses that have been/will be conducted

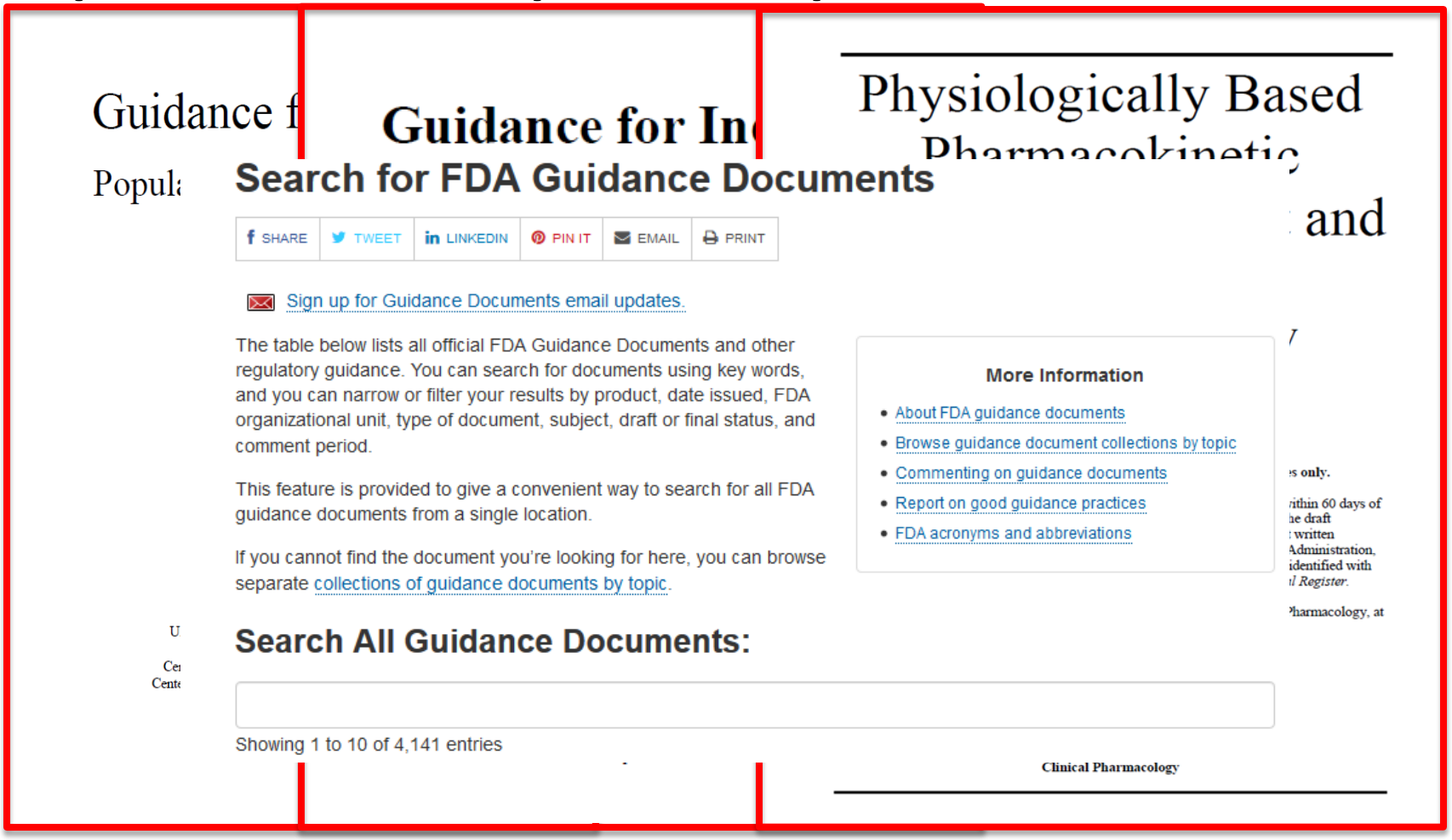
Expectations for a Marketing Application Submission

- All pre-BLA/NDA comments and questions should be addressed
- Main analysis reports should be included in Module 5
  - Population PK, exposure-response efficacy/safety, PBPK
- Modeling analyses to support decision making should also be included (with proper context) within Module 2, Summary of Clinical Pharmacology and within other summaries as appropriate
- Labeling that is supported by M&S should be clearly denoted in the annotated label

- The sponsor should **be as clear as possible where and how they are using modeling analyses to support decision making**.
  - focus review efforts
  - Clearer communications back to sponsors as review progresses

A Subset of Relevant Guidances

Population PK **Exposure-response** **PBPK**



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Physiologically Based

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http://www.fda.gov/downloads/Drugs/.../Guidances/UCM072137.pdf
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https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

Some Applications of Population PK

Drug Development

- Alternative Dosing Schemes in Clinical Studies
- Study Sample Size and Sampling Scheme
- Deriving Exposure-Metrics for Exposure-Response Analysis
- Dosing in Pediatric Patients

Drug Use

- Characterization of drug pharmacokinetics
- Specific populations
- Drug-Drug Interactions

Some Applications of Exposure-Response

Drug Development

- Link animal and human findings
- Provide evidence for mechanism of action (PoC)
- Provide evidence the mechanism leads to a short-term clinical outcome (PoC)
- Provide guidance for designing trials utilizing an informative dosing range

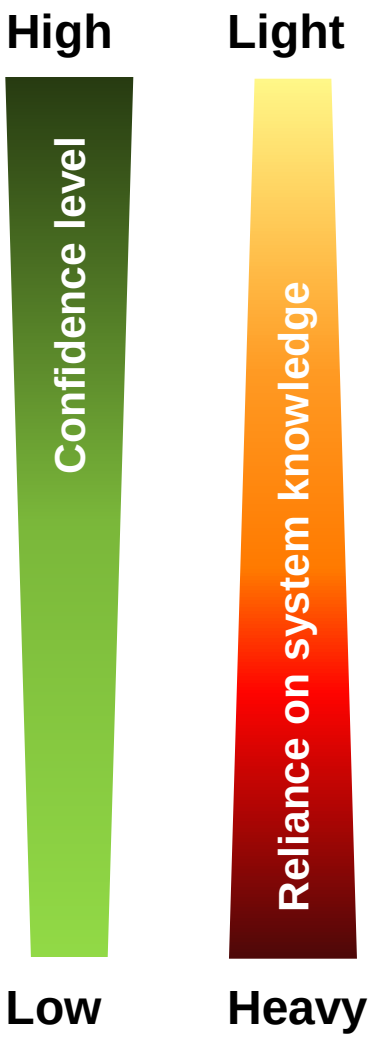
Determination of S&E

- Contribute to evidence of effectiveness
- Provide support for primary efficacy studies
- Support new target population, use in subpopulations, or alterations to the dosing regimen, form, or route of administration

PBPK applications: current status

	Applications	Status
Drug-drug Interactions	*Drug as enzyme substrate*	• *Substrate/inhibitor models verified with key clinical data can be used to simulate untested scenarios and support labeling*
	Drug as enzyme perpetrator	• *Use to confirm the lack of enzyme inhibition* • *Additional evidence needed to confirm predictive performance for positive interactions*
	Transporter-based	• *In vitro-in vivo extrapolation not mature* • *Complicated by transporter-enzyme interplay* • *Predictive performance yet to be demonstrated*
Specific populations	*Organ impairments (hepatic and renal)*	• *Predictive performance yet to be improved* • *System component needs an update*
	Pediatrics	• *Allometry is reasonable for PK down to 2 years old* • *Less than 2 years old ontogeny and maturation need to be considered*
Others with limited experiences	*Pregnancy, ethnicity, geriatrics, obesity, disease states* *Food effect, formulation change, PH effect (including DDIs on gastric PH)* *Tissue concentration*	

Wagner, CPT-PSP, 2015



Expectations with Population PK, Exposure-Response, and PBPK Reports

- Include a concise, top level summary of findings that can be interpreted by non-experts
- The report should follow best practices, list assumptions, and have appropriate documentation
- Data sets, analysis scripts, and define files should be included for all major modeling steps and analyses
- Analyses used to support decision making should be clearly denoted:
  - dosing in the general or special populations, any alterations to studied dosing, no-effect boundaries, labeling statements

Some Common Frustrations (1)

Dos

- Concise, top level summary of findings
- Denote analyses supporting decision making

- Data sets, analysis scripts, and define files should be included
- Flowchart on how data and scripts connect

Dont's

- Complicated, quantitative summary that does not explain how results are applied

- No clear description on how the datasets were assembled or how scripts fit together

Some Common Frustrations (2)

Dos

- Link subject IDs between clinical data and M&S analyses
- Translate population PK covariate effects to changes in exposure
- Translate ER covariate effects into changes in response
- Provide comparisons between observed and predicted results

Dont's

- Reports and analyses separate from rest of package
- Covariate effects shown only as changes in CL or V
- Covariate effects shown only as changes on PD parameters
- ER analyses provided but may not be directly relatable

Some Common Frustrations (3)

Dos

- Justification for covariate claims based on available data
- Stratification of VPC by relevant covariates

- Justification for dosing or dose adjustments based on totality of information
- Hyperlinks in the reports

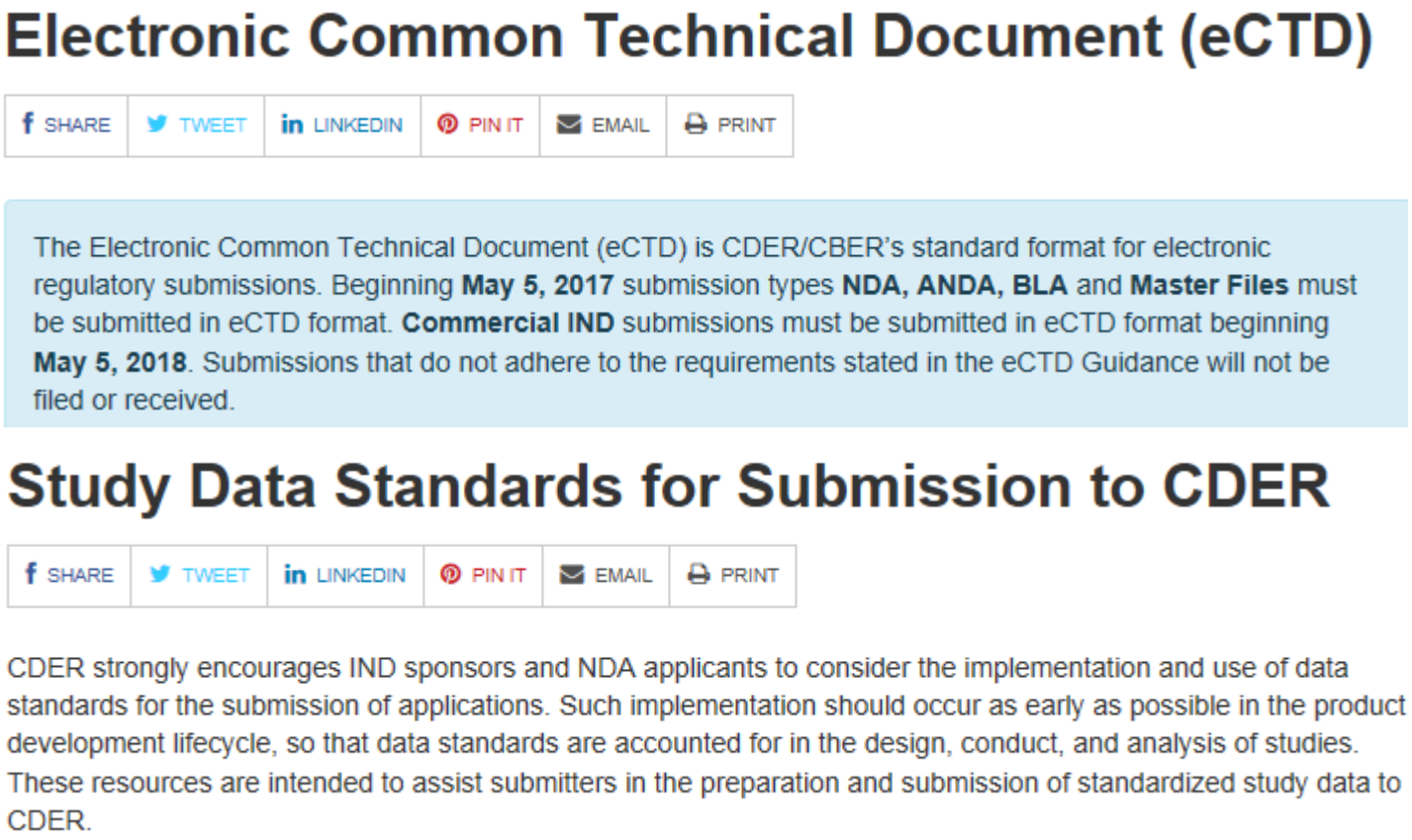
Dont's

- Covariate statements based on significance
- Diagnostics only showing all data on the same plot

- Need for dose adjustments based only on changes in exposure
- Stand-alone report

Data and Report Submission for Pharmacometric Analyses

- Information on format of materials and where it should be submitted



Electronic Common Technical Document (eCTD)

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The Electronic Common Technical Document (eCTD) is CDER/CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017** submission types **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will not be filed or received.

Study Data Standards for Submission to CDER

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CDER strongly encourages IND sponsors and NDA applicants to consider the implementation and use of data standards for the submission of applications. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. These resources are intended to assist submitters in the preparation and submission of standardized study data to CDER.

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm
http://http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm

Specifications for File Format Types Using eCTD Specifications

- Provides specifications for submitting file for mat types using eCTD specifications
- Accepted file types and the eCTD locations in which those file types should be provided

- Permits certain file types (.csv, .ctl, .sas, .r) in Modules 3 – 5 and allows for some PBPK types
  - Discuss plans for submission with the Agency if there are any question

https://www.fda.gov/downloads/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/ucm347471.pdf

Additional Links

- Guidance documents:
  - ICH-E4---Dose response
  - FDA's Exposure-response guidance
  - FDA's population PK guidance
  - FDA's evidence of effectiveness guidance
  - FDA's PBPK guidance
  - FDA's pediatric guidance

- Data submission:
  - http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm

- Manuscripts:
  - MID3: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4809625/
  - ISoP best practice for model evaluation: http://onlinelibrary.wiley.com/doi/10.1002/psp4.12161/epdf
  - Reporting Guidelines for PopPK Analyses: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4432104/

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Questions


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