

Modernizing the New Drug Regulatory Program in FDA/CDER

November 7, 2018

Lilliam Rosario, Ph.D.

Director, Office of Computational Science, Center for Drug
Evaluation and Research, Food and Drug Administration



Disclaimer

The views and opinions presented here represent those of the speakers and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.

Agenda

- FDA is Modernizing Drug Review Process
- OCS Supports Regulatory Review Decisions by:

- Enabling access to validated and usable standardized study data



Data

- Providing tools and systems to support analysis



Analytics and
Systems

- Delivering targeted services that create efficiencies and effectiveness



Services

FDA IS MODERNIZING DRUG REVIEW PROCESS

FDA Proposes Modernization to Support New Drug Development

- Aim is to **“maintain and advance FDA’s global leadership, and better support our deeply committed staff”**¹
- Focus on drug development and collaborations needed to ensure that the development and assessment of novel candidate drugs have appropriate input from external scientists, expert physicians, and patient communities



¹ Janet Woodcock, M.D., Director of the FDA’s Center for Drug Evaluation and Research

<https://blogs.fda.gov/fdavoices/index.php/2018/06/fda-proposes-process-modernization-to-support-new-drug-development/>

Posted on June 4, 2018 by FDA Voice

Proposed Changes to CDER's New Drug Regulatory Program

Proposal Includes

Changes in regulatory and review process

Organizational restructuring

Strengthening of support structures

- Personnel
- Information Technology

Janet Woodcock, M.D., Director of the FDA's Center for Drug Evaluation and Research

<https://blogs.fda.gov/fdavoices/index.php/2018/06/fda-proposes-process-modernization-to-support-new-drug-development/>

Posted on June 4, 2018 by FDA Voice

Highlights of the Proposal to Modernize New Drug Review

- **Recruiting** the best and brightest individuals from many disciplines
- Enhancing focus on **multidisciplinary teams**
- Prioritizing **operational excellence**
- Improving **knowledge management**
- Emphasizing the importance of **safety** across a drug's lifecycle
- Incorporating the **patient voice**

Modernization to Support New Drug Development

- CDER/FDA system is effective and we can always improve
 - CDER approved 46 novel drugs in 2017
 - 100% reviewed on time – fulfilling Prescription Drug User Fee Act
- Both science and technology are rapidly changing and we need to keep up
- **Aim is to generate efficiencies** so CDER/FDA can build **stronger external collaboration capabilities and enhanced support** for the scientific, clinical, and technological innovation

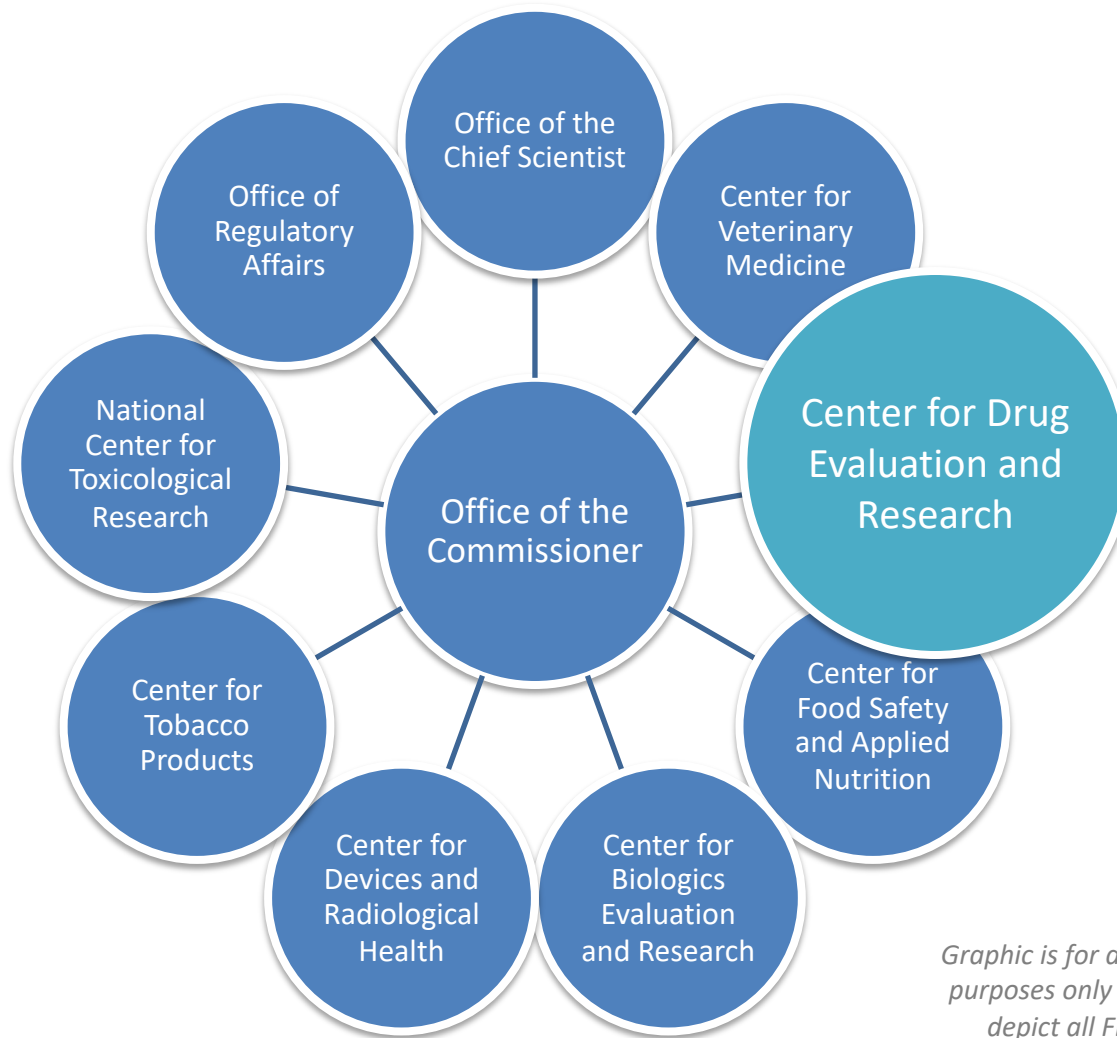
Janet Woodcock, M.D., Director of the FDA's Center for Drug Evaluation and Research

<https://blogs.fda.gov/fdavoices/index.php/2018/06/fda-proposes-process-modernization-to-support-new-drug-development/>

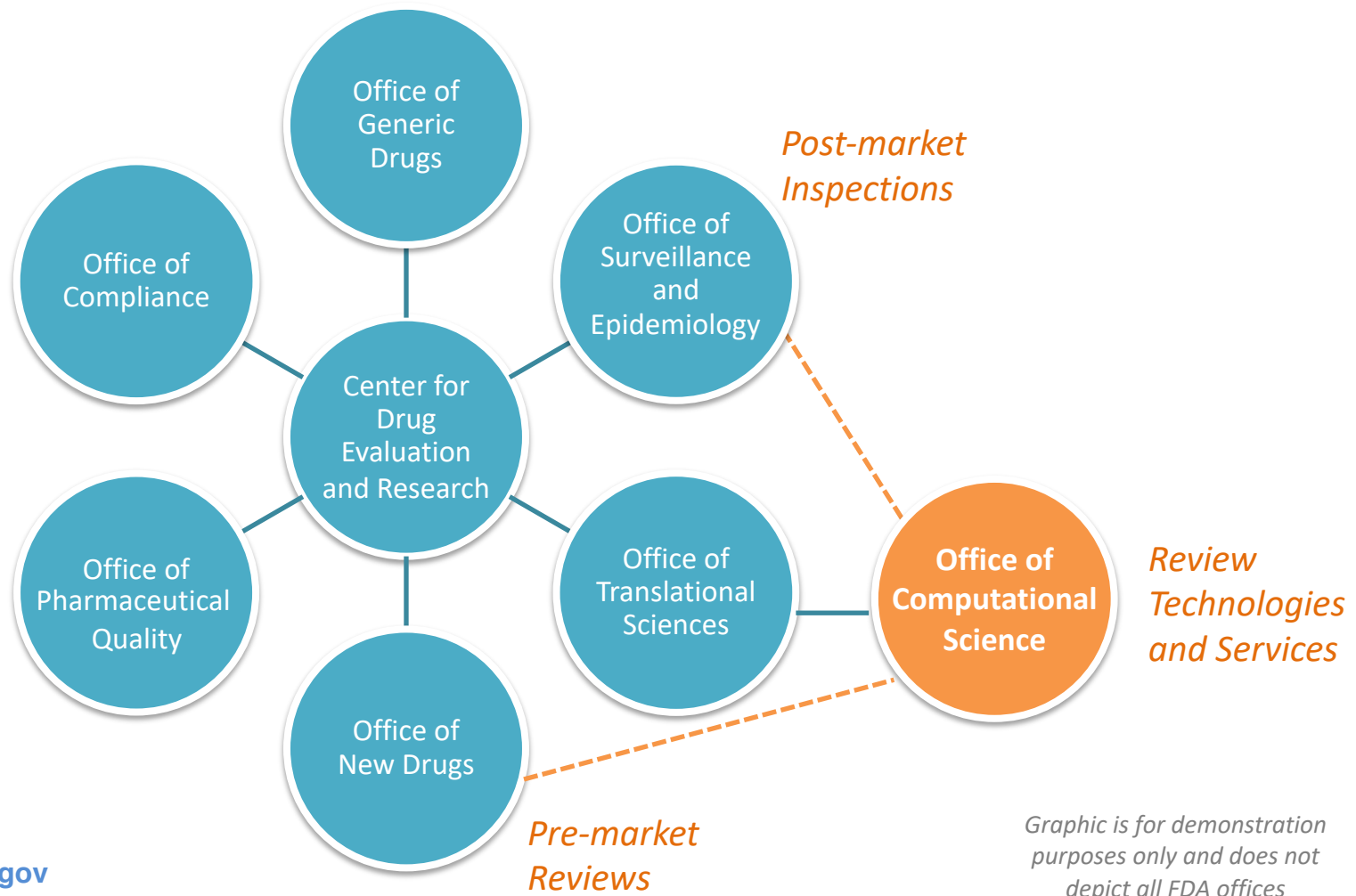
Posted on June 4, 2018 by FDA Voice

OFFICE OF COMPUTATIONAL SCIENCE SUPPORTS REGULATORY REVIEW AND THE NEW DRUG MODERNIZATION

Where We Are



Where We Are: CDER Review Offices



Who We Are



Our Vision

Drive the modernization of CDER's scientific review process through the implementation of tools, services, and training to enable reviewers to apply their expertise to information



Our Mission

To provide CDER reviewers innovative and reliable solutions that improve and strengthen the scientific review process by integrating data, tools, and training

OCS Provides Access to Standardized Data, Services, and Technologies to Support Regulatory Review



Data



Services



**Analytics
and
Systems**



**Research
and
Review**



FDA REQUIRES ELECTRONIC STANDARDIZED STUDY DATA

FDA Requires Standardized Electronic Submissions and Study Data

eCTD Guidance

Binding Guidance – Requires that content be submitted to the Agency electronically in the format specified in the guidance.



FDA *binding guidance and deadlines* for electronic submissions

eStudy Guidance

Binding Guidance— Requires that studies are compliant with the standards outlined in the FDA Data Standards Catalog



FDA *binding guidance and deadlines* for submission of standardized study data

Data Standards Catalog

Lists supported and/or required standards.



Lists *what* data standards are supported and required by FDA in electronic submissions

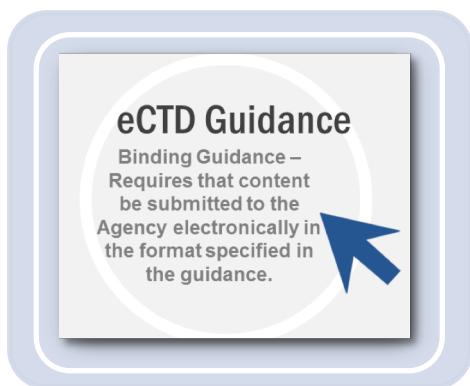
Tech Conformance Guide

How to submit standardized study data



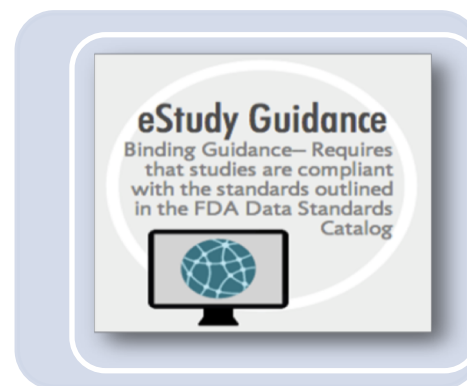
Describes *how* industry should submit standardized study data in NDAs, BLAs, INDs and ANDAs

FDA Requires Standardized Electronic Submissions and Study Data



FDA binding guidance and deadlines for electronic submissions

May 5th, 2016:
NDAs, ANDAs,
BLAs, DMFs
Dec 17, 2017:
Commercial INDs



FDA binding guidance and deadlines for submission of standardized study data

Dec 17, 2016:
NDAs, ANDAs,
BLAs, DMFs
Dec 17, 2017:
Commercial INDs

FDA Accepts Study Data using the Standards, Formats, and Terminologies Described in the FDA Data Standards Catalog



Lists *what* data standards are supported and required by FDA in electronic submissions

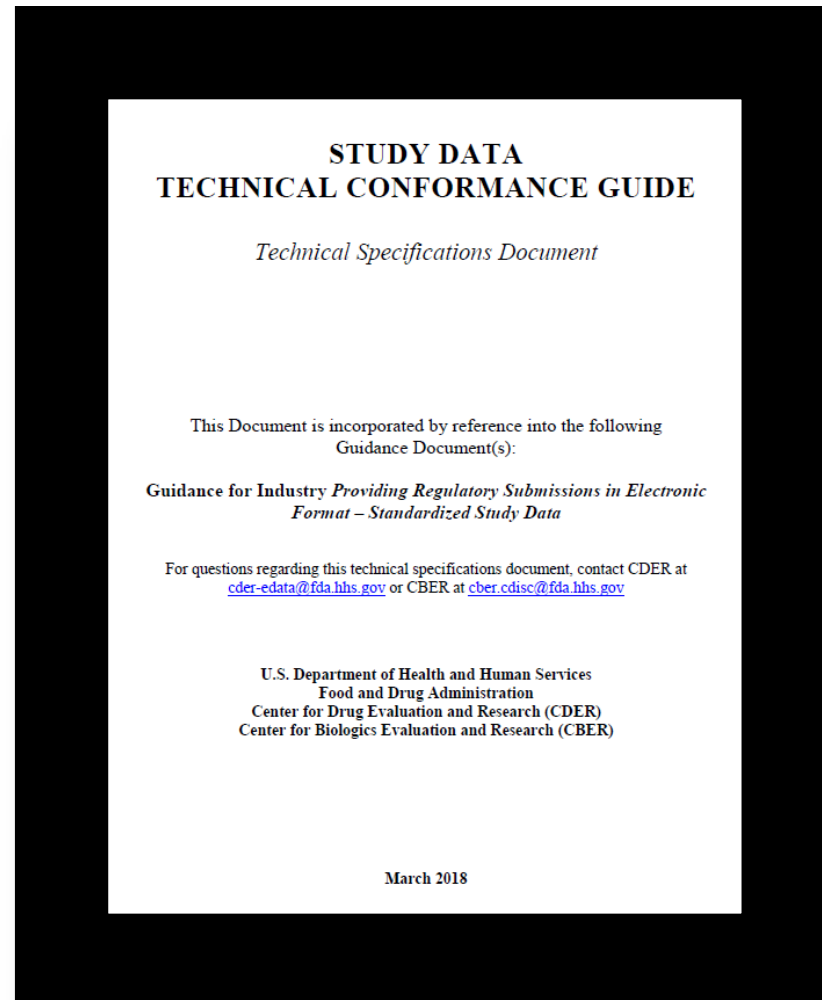
v5.1 (08-2-2018)

Data Exchange Standard	Exchange Format	Standards Development Organization (SDO)	Supported Version	Supported Implementation Guide Version	FDA Center(s)	Date Support Begins (MM/DD/YYYY)
Study Data Tabulation Model (SDTM)	XPT	Clinical Data Interchange Standards Consortium (CDISC)	1.1	3.1.1	CDER, CBER	Ongoing
SDTM	XPT	CDISC	1.2	3.1.2	CDER, CBER	10/30/2009
SDTM	XPT	CDISC	1.2	Version 3.1.2 Amendment 1	CDER, CBER	08/07/2013
SDTM	XPT	CDISC	1.3	3.1.3	CDER, CBER	12/01/2012
SDTM	XPT	CDISC	1.4	3.2	CDER, CBER	08/17/2015
Analysis Data Model (ADaM)	XPT	CDISC	2.1	1.0	CDER, CBER	Ongoing
ADaM	XPT	CDISC	2.1	1.1	CDER, CBER	03/15/2018
Standard for Exchange of Nonclinical Data (SEND)	XPT	CDISC	1.2	3.0	CDER	06/13/2011
SEND	XPT	CDISC	1.5	3.1	CDER	08/21/2017
Define	XML	CDISC	1.0	N/A	CDER, CBER	Ongoing
Define	XML	CDISC	2.0	N/A	CDER, CBER	08/07/2013

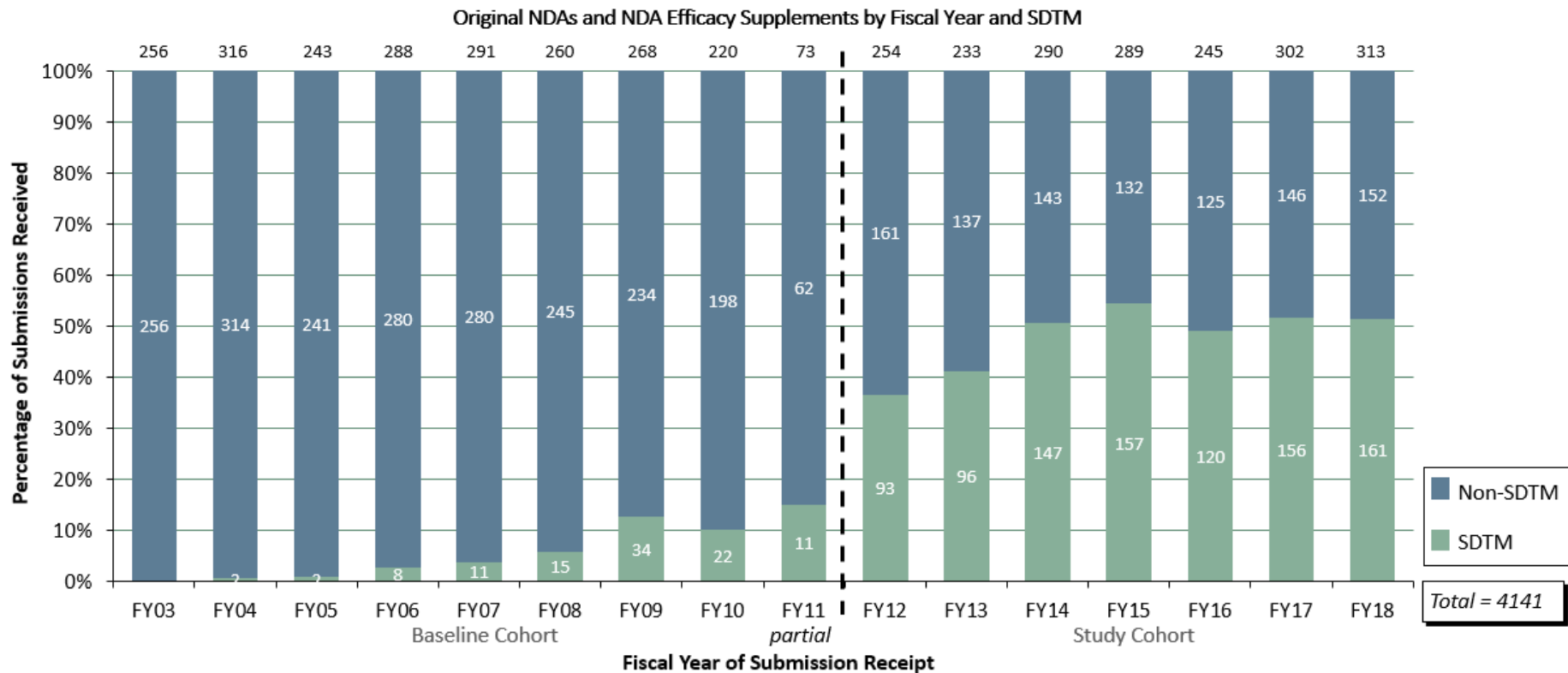
TCG provides technical specifications and general considerations on how to submit standardized electronic study data.



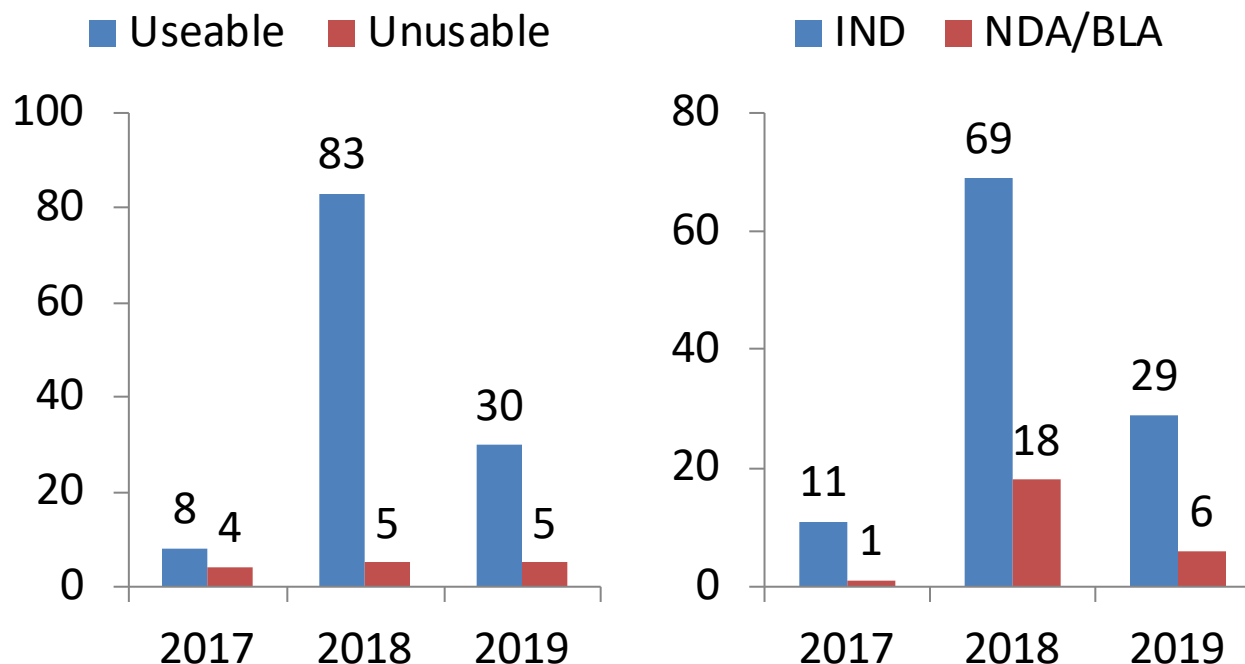
Describes *how* industry should submit standardized study data in NDAs, BLAs, INDs and ANDAs



Submission of Standardized Clinical Study Data: 51% of Original NDAs and efficacy supplement submissions contained SDTM data (FY18)



Submission of Standardized Nonclinical Study Data is Increasing



The types of studies included Repeat-Dose Toxicity, Single-Dose Toxicity, and Carcinogenicity.
 FDA has received 130 submissions with SEND data during FY17 thru beginning of FY19.

Validation Activities help ensure study data are compliant, useful, and will support meaningful review

- Validation activities occur at different times
 - Submission receipt
 - Beginning of the regulatory review





FDA Published Technical Rejection Criteria for Study Data

- The FDA may refuse to file (RTF) for NDAs and BLAs, or refuse to receive (RTR) for ANDAs, an electronic submission that does not have study data in conformance to the required standards specified in the FDA Data Standards Catalog.
- FDA published “Technical Rejection Criteria for Study Data” to specify the criteria for validation



Deadlines:
Dec 17, 2016:
NDAs, ANDAs,
BLAs, DMFs
Dec 17, 2017:
Commercial INDs

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM523539.pdf>



FDA Assessed Rate of Compliance for Requirement to Submit Standardized Study Data

- Conformance to requirement was assessed in sample of study data
 - Received between *12/18/2016 to 3/31/2018* for **NDA, BLA, and ANDA** Submissions
 - Received between *12/18/2017 to 3/31/2018* for Commercial **IND** Submissions
- Technical Rejection Criteria used to validate conformance
 - Two high-level errors
 - 1734 – A Trial Summary (TS.xpt) dataset must be present (supplies study start date and determines if standardized, electronic format is required)
 - 1736 – Demographics Domain (DM.xpt) and Define.xml or ADSL and Define.xml must be present for each qualifying study
 - Two medium-level errors
 - 1735 – Correct STF file must be used
 - 1737 – Only one dataset should be submitted as New



Less than 70% study data in sample were received with non-critical errors



	All	NDA	ANDA	BLA	Comm. IND
Total Number of Submissions	85,493	24,837	38,346	7,601	14,709
Total Number of Submissions with Study Data	3,221	1,126	1,446	473	176
Total Number Submissions with Critical Errors	1,032	302	551	138	41
Error 1734 (Absence of TS.xpt dataset)	968	290	506	137	35
Error 1736 * (Absence of DM.xpt and Define.xml or ADSL and Define.xml Demographics)	84	14	63	1	6
Error Rate (% among submissions with Study Data)	32.04%	26.82%	38.11%	29.18%	23.30%

* Error 1736 validation is not performed if a study has Error 1734

- NDA, BLA, and ANDA submissions received from 12/18/2016 to 3/31/2018
- Commercial IND submissions received from 12/18/2017 to 3/31/2018



Only ~ 50% study data in original NDAs were received with non-critical errors



	All	Original Submission	Efficacy Supplement	Rolling Submission
Total Number of Submissions with Study Data	1,126	142	92	25
Total Number Submissions with Critical Errors	302	74	28	10
Error 1734 (Absence of TS.xpt dataset)	290	68	28	10
Error 1736 * (Absence of DM.xpt and Define.xml or ADSL and Define.xml Demographics)	14	8	0	0
Error Rate (% among submissions with Study Data)	26.82%	52.11%	30.43%	40.00%

- NDA, BLA, and ANDA submissions received from 12/18/2016 to 3/31/2018
- Commercial IND submissions received from 12/18/2017 to 3/31/2018



About 80% nonclinical study data in sample were received with non-critical errors

	All	NDA	BLA	Comm. IND
Total Number of Submissions with xpt files	2,509	1,486	591	432
Original Submissions with m4 Study Data	59	12	3	44
Original Submissions with 1734 Error (Absence of TS.xpt dataset)	10	3	1	6
Original Submissions with 1736 Error (Absence of DM.xpt and Define.xml or ADSL and Define.xml Demographics)	1	0	0	1
Original Submissions with Critical Error (1734 /1736)	11	3	1	7
Critical Errors Rate for m4 Study Data	18.64%	25.00%	33.33%	15.94%

- NDA, BLA, and ANDA submissions received from 12/18/2016 to 8/31/2018
- Commercial IND submissions received from 12/18/2017 to 8/31/2018



Assessment Findings

- If FDA applied published technical rejection criteria to assess compliance to the requirement to submit standardized study data,
 - only ~3/4 of applications would pass validation
 - ~1/4 of applications would report high error
 - Identified errors are easily identified and correctable.
- To date, FDA has not rejected any submission containing errors as reflected in this analysis.
- FDA plans to use technical rejection criteria to identify applications that are not fulfilling the requirement.



TIP



To avoid validation errors, it is important for sponsors and applicants to understand the requirements specified in guidance and recommendations for submitting study data in the Study Data Technical Conformance Guide.



Validation Activities help ensure study data are compliant, useful, and will support meaningful review

- Validation activities occur at different times
 - Submission receipt
 - Beginning of the regulatory review

Validation Activities at Beginning of the Regulatory Review

- After an application has been successfully submitted, OCS provides data quality assessments
- OCS uses FDA Validator
 - To assess data quality
 - Conformance to the standard
 - Reviewability
 - To create reports for quality assessments and services



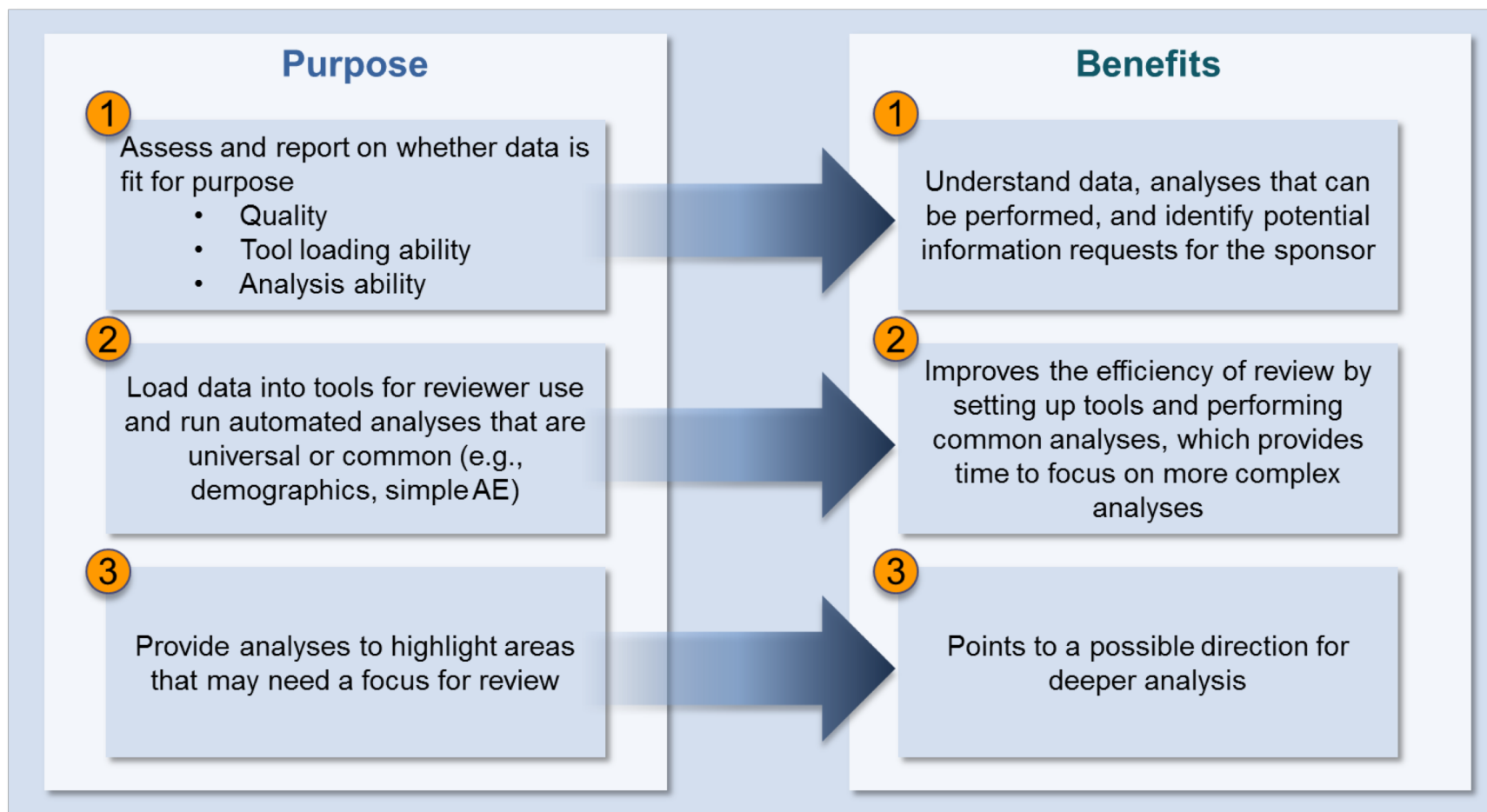


OCS SERVICES

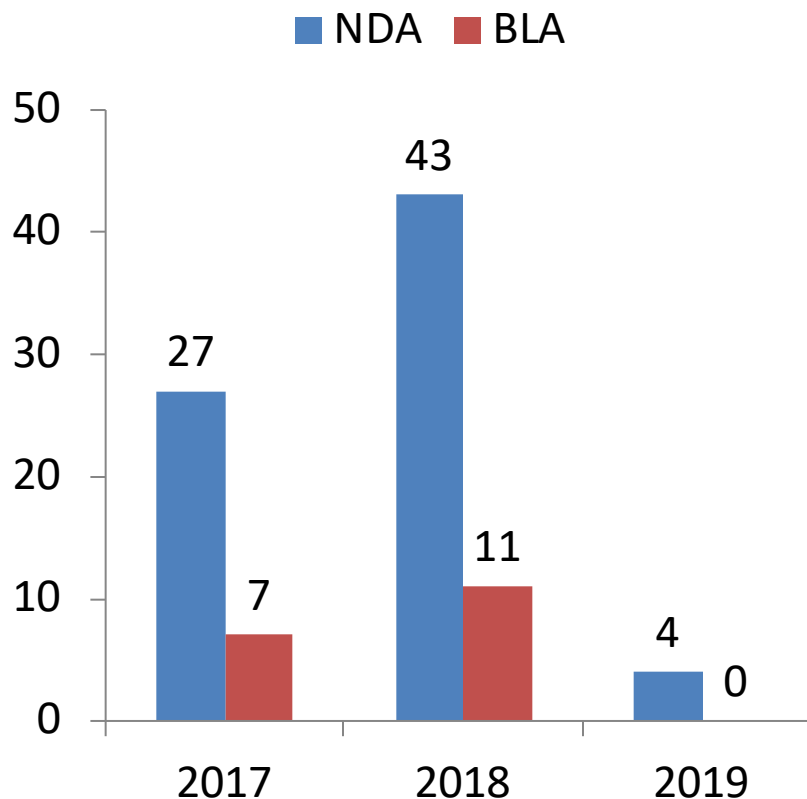


OCS SERVICES

Benefits of JumpStart Service



JumpStart Services Support Clinical Safety Review

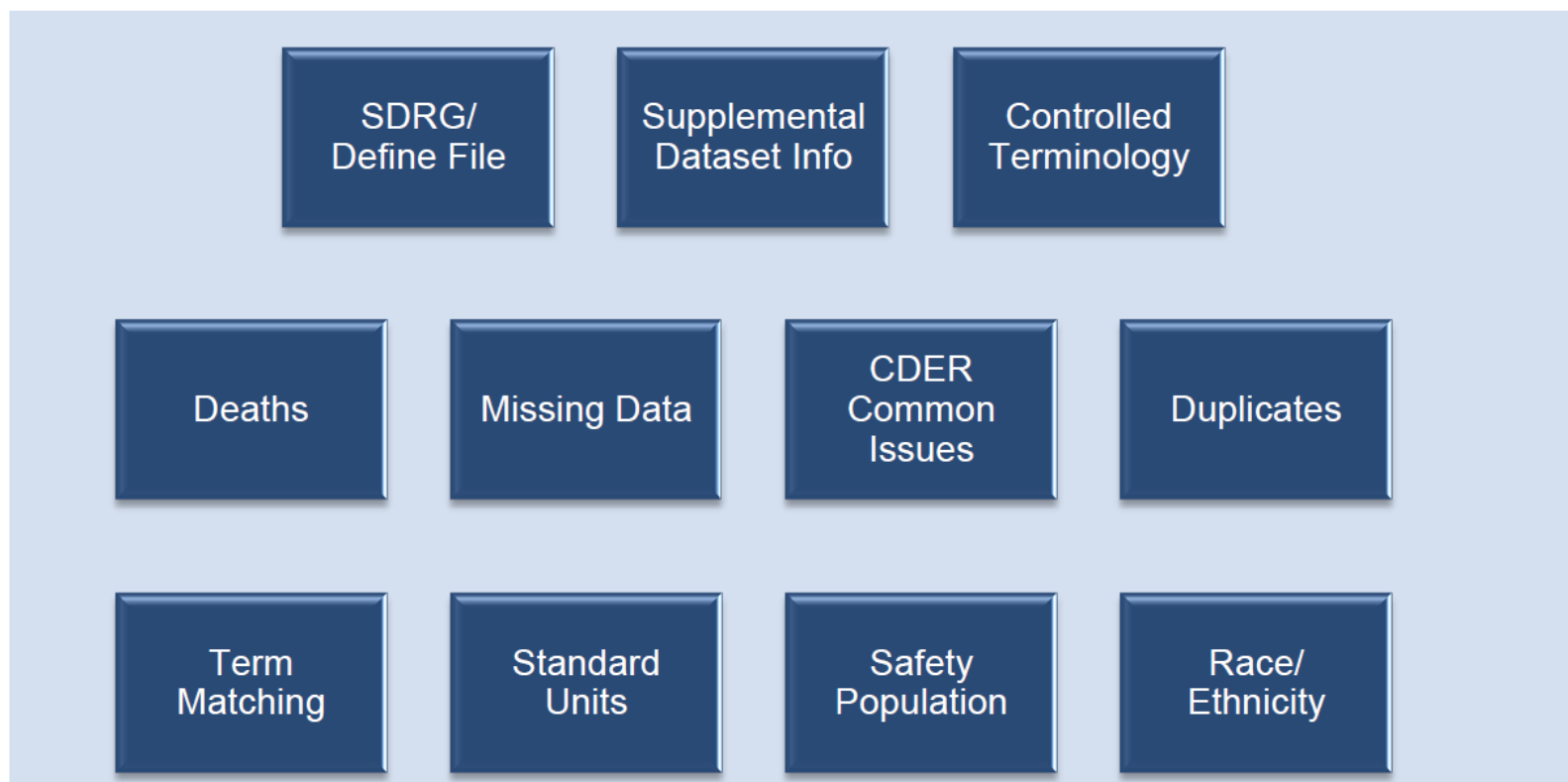


OCS Provides Data Quality Assessments for Clinical Data



- OCS provides Data Fitness assessments as part of the JumpStart Services
 - Completed 43 JumpStart services FY 2018 that included a Data Fitness Assessment
 - Expected to complete up to 120 Data Fitness assessments in FY 2019
- Created Core DataFit reports to expand reach
 - CoreDF Reports contain, on average, 68% of Data Fitness findings presented to reviewers during the JumpStart Service
 - Delivered 35 CoreDF Reports to reviewers, including desk-side services, across 13 reviewer divisions
 - Plan to deliver in FY 2019 to all Original NDAs and BLAs
 - Future: All Applications and Submissions with study data

Data Fitness Assessments for Clinical Study Data





Core DF Assessments for Clinical Study Data

Application: Pilots
Study: 900172

Generated: 2018-05-21T15:25:20
[Data Standards Training](#)

Safety and Efficacy of the Xanomeline Transdermal Therapeutic System (TTS) in Patients with Mild to Moderate Alzheimers Disease.

Summary	Findings
Standards / Dictionaries	Adverse Events
SDTM-IG 3.1.2	36 (92.3%) of serious adverse events are not flagged as serious
SDTM-CT 2017-09-29	473 (39.7%) of events are missing end time-point
MedDRA 8.0	230 (19.3%) of adverse events are potential duplicates
Subjects / Actual Arms	Disposition
306 - Subjects	No significant findings
86 - Placebo (28.1%)	Supplemental Info
52 - Screen Failure (17.0%)	No significant findings
72 - Xanomeline High Dose (23.5%)	Terminology
96 - Xanomeline Low Dose (31.4%)	No significant findings
Datasets	Laboratory
22 - Total Datasets	2,041 (3.5%) of observations are missing Reference Range Upper Limit in Standard Units (LBSTNRHI)
0 - Custom Datasets	318 (0.6%) of Standard Units (LBSTRESU) are missing when Standard Results (LBSTRESC) are provided
4 - Suppqal Datasets	Vital Signs
	No significant findings
	Demographics
	No significant findings
Reports	Exposure
Deaths	No significant findings
Death Summary	Other
Death Details	EPOCH variable was not provided
Death Reconciliation	Study day (AEDY) variable is missing when the Study Date/Time (AEDTC) variable is provided
Adverse Events	1 (0.4%) of subjects are missing baseline test results in LB
Adverse Events Coding Quality	Study day (CMDY) variable is missing when the Study Date/Time (CMDTC) variable is provided
Disposition	234 (100.0%) of RELREC domain records reference non-existent data in related domain
Disposition Coding Quality	64,403 (100.0%) of SUPPLB domain records reference non-existent data in related domain
Supplemental Info	Study day (DSDY) variable is missing when the Study Date/Time (DSDTC) variable is provided
Supplemental Contents	
Laboratory	
Upper Limit Normal Summary	

Pilot: Use of Clinical Data Specialist Role within Regulatory Review

Challenge:

- There are time limitations to analyze and review submission data
- Clinical reviewers are skilled medical therapists, not data scientists

Approach:

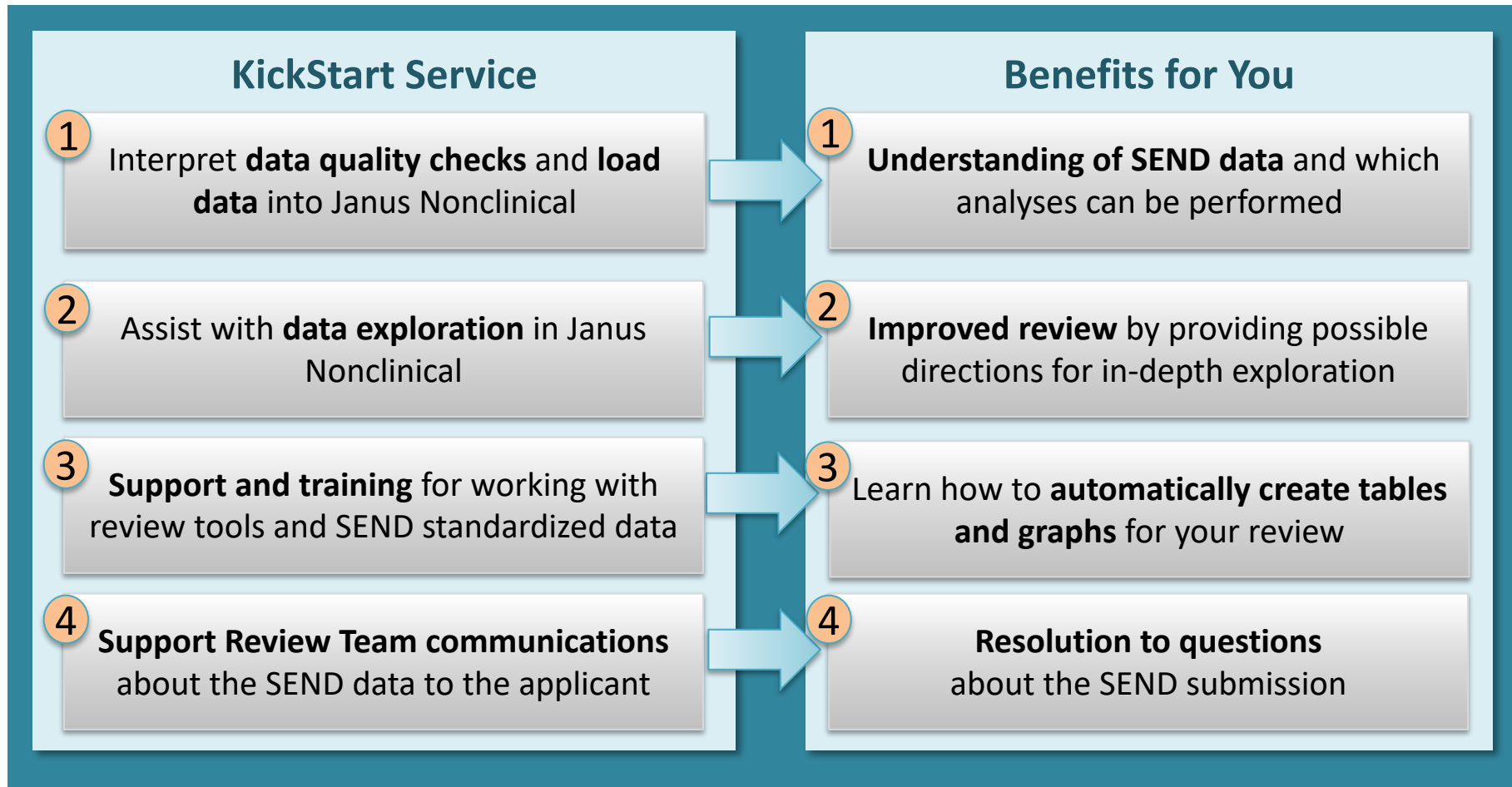
- OCS piloted using CDS to assist clinical reviewers with
 - data quality assessments
 - Safety analysis support throughout lifecycle of review

Results:

- CDS provides data management, data integration, and analysis support while clinical reviewer focuses on clinical meaning and implications
- CDS role develops algorithms to address specific safety concern that can then be re-used providing consistency when evaluating this type of safety concern
- OCS develops reusable analysis and code focused on specific therapeutic areas and/or clinical outcomes of interest to improve the efficiency of clinical review



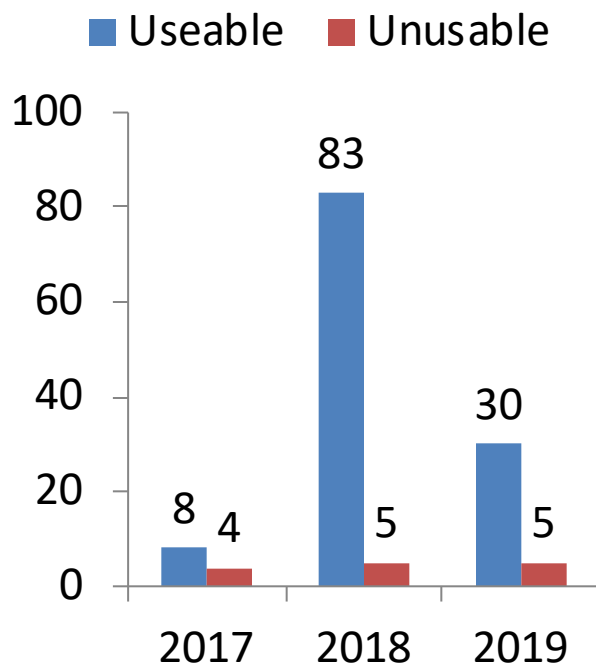
Benefits of KickStart Service



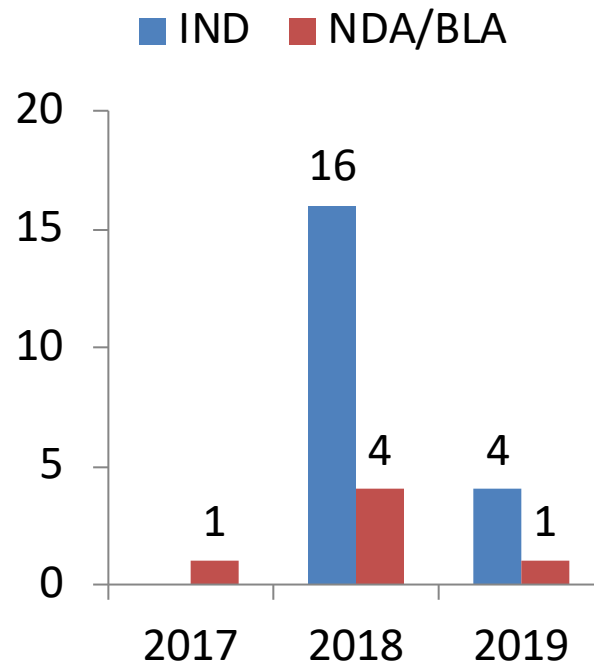
KickStart Services Support Nonclinical Review



Useable SEND



KickStart Services*



*Application must meet the following criteria:

- Study loaded into Janus Nonclinical
- Reviewer submits service request form
- Reviewer has not received a KickStart service



OCS Provides Data Quality Assessments for Nonclinical Data

- OCS provides Data Fitness assessments as part of the KickStart Service
 - Performs data quality checks for conformance and usability
 - loads into analytical environment
- Plan to automated Data Quality Reports for SEND data



ANALYTICS AND SYSTEMS



ANALYTICS AND SYSTEMS



OCS Analysis Toolbox

Offers a catalog of analytical tools or scripts that inform, facilitate, and support the review of study data



Simple Analyses

- Scripts or macros comprising small programs or a series of programs
- Analyses that answer a simple question or perform a simple function, such as showing population counts by arm variables and population flags

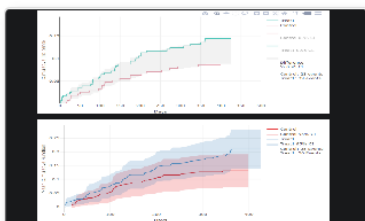


Complex Analyses

- “Guided” macros for more complex analyses
- Tool interfaces that facilitate dataset and parameter selection, such as selection of subgroups, filters, variables, and calculations, to produce the desired outputs



OCS Analysis Toolbox



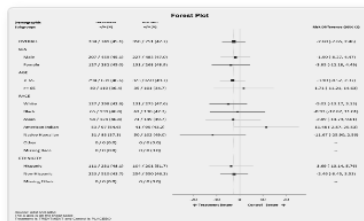
AE Temporal Tool

Longitudinal analysis of adverse events through Kaplan-Meier and Mean Cumulative Function

[User Guide](#)

[Start Setup](#)

AE Temporal Characterization Tool: conducts time to first event and time to recurrent event analysis for safety endpoints of interest



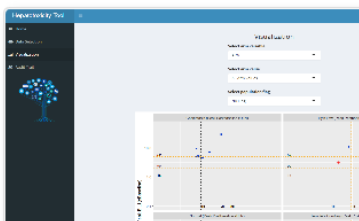
Demographic Tool

Performs demographic subgroup analysis through a web app

[User Guide](#)

[Start Setup](#)

Demographic Tool: provides targeted descriptive statistics and safety endpoint analysis for demographic subgroups



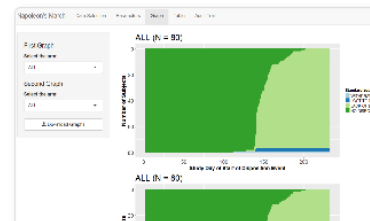
Hepatotoxicity Tool

Examine drug-induced liver injury through composite visualization

[User Guide](#)

[Start Setup](#)

Hepatotoxicity Tool: designed to complement standard Hy's Law analysis by providing drug induced liver injury analysis for subjects with underlying liver injury



Napoleon's March

Longitudinal visualization of disposition categories

[User Guide](#)

[Start Setup](#)

Napoleon's March: designed to analyze subject study disposition longitudinally



Adverse Event Temporal Characterization Tool



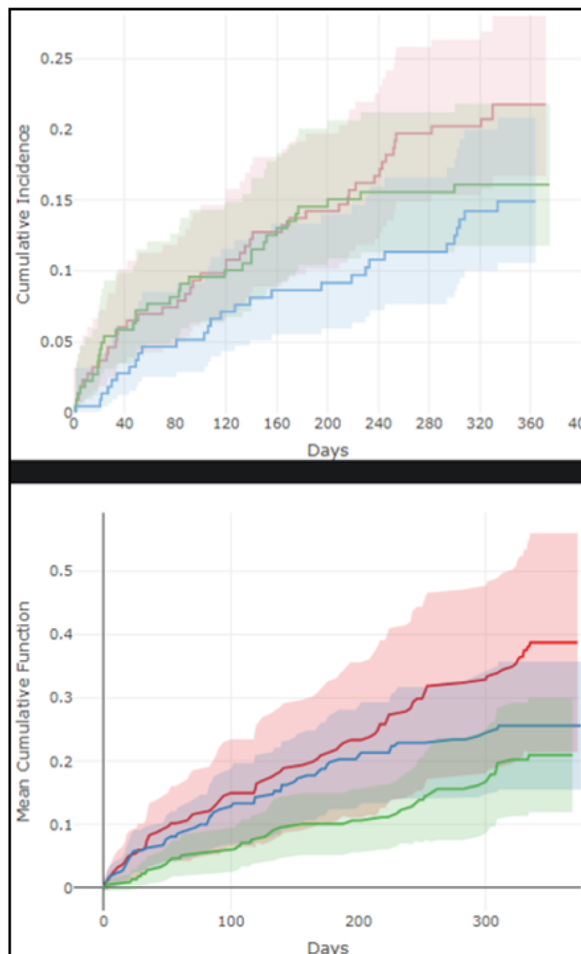
KM and MCF Analysis

Kaplan Meier (KM) Estimator:

- used to estimate survival function from lifetime data
- allows estimation of survival over time
- analyze any event of interest

Mean Cumulative Function (MCF):

- analysis of recurrent event data, where each population unit can be described by a cumulative history function for the cumulative number of events
- staircase function depicts the cumulative number of recurrences of an event



R Markdown generates HTML report that can be shared, keeping all the interactivity of the output but without the need of R or the source data!



R Markdown Report

Audit Trail	
Below is the audit trail information for the session you ran.	
Analysis Parameters	
Arm Variable:	TRT01A
Treatment Start Date Variable:	TRTSDT
Treatment End Date Variable:	TRTEDT
Number of days added to study lag:	0
Population Flag Variable:	SAPPL
Adverse Event Start Date Variable:	AE01DTC
Adverse Event Criteria:	AE00BYE including: Nervous system disorders
Session Information	
Tool Build Date:	2019-03-07
R Version:	3.4.1 (2017-06-30)
R Packages:	shiny, rmarkdown, dplyr, RAdapt, plotly, rmd, rms, Rstan, rstanarm, ggplot2, Formula, lattice, survival, shiny, stats, graphics, gDevices, utils, classes, methods, base



Hepatotoxicity Tool



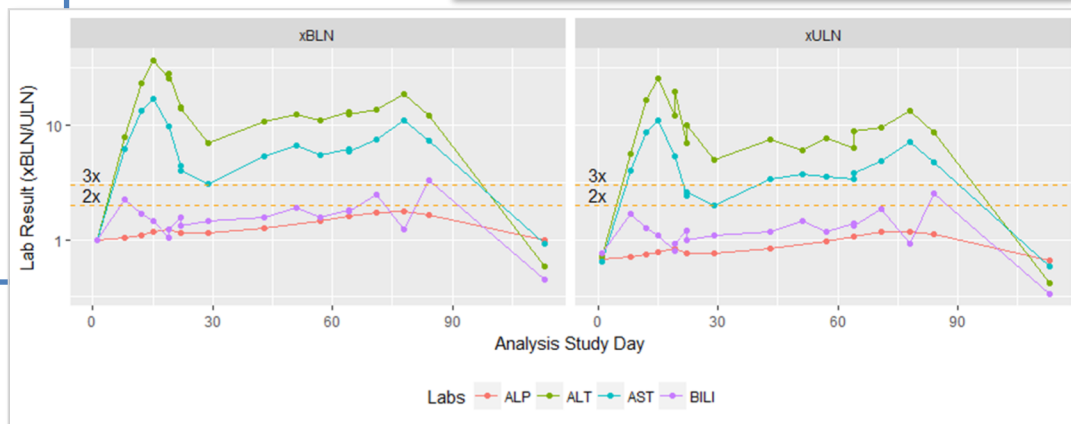
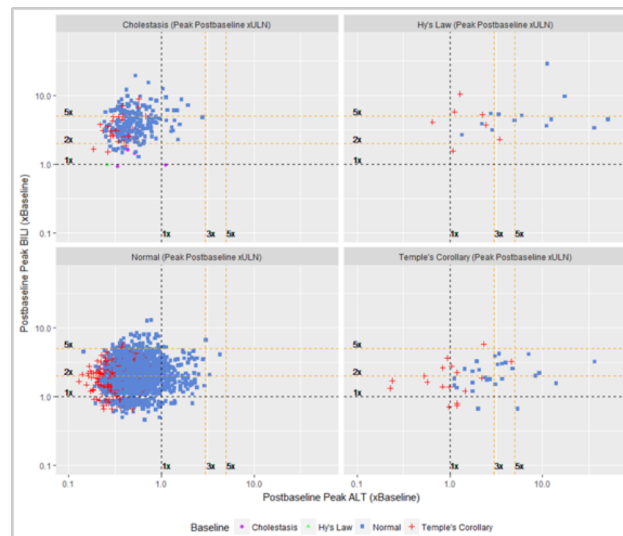
Use Case:

Subjects with elevated liver enzyme test results at baseline (e.g., subjects with Chronic Hepatitis C)

Solution:

Composite visualization that includes pre-treatment and on-treatment prevalence of:

- ALT and BILI in terms of Hy's Law candidate laboratory Upper Limit Normal thresholds
- magnitude of these elevations normalized by respective baseline test results





Kidney Function Tool

- Provides tool to assess the impact of a drug on kidney function (i.e., renal impairment)
- Analysis Components:
 - Provides clinical reviewers with information on:
 - Development of marked abnormality in serum creatinine
 - Shifts in estimated glomerular filtration rate (eGFR)
 - Changes in albumin/creatinine ratio
 - Shifts in albuminuria (e.g., normal to microalbuminuria)

Data **Parameters** **Analysis** **Audit Trail**

Subject Level Data

Browse... adsl.sas7bdat
Upload complete

Lab Data

Browse... adlb.sas7bdat
Upload complete

Converting the subject level dataset... done!
Converting the lab dataset... done!
Data looks good... let's proceed to parameter selection.

Data **Parameters** **Analysis** **Audit Trail**

Select the arm variables...

STUDYID

Select the endpoint...

Week 52 or EOT/EW

Select the variables for subset...

SAFFL

Select

Select the value to include for SAFFL.

Y

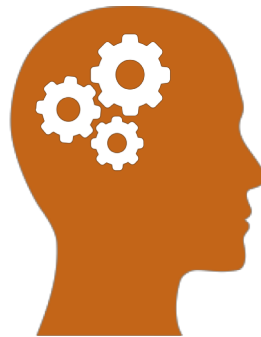
Generate

Data **Parameters** **Analysis** **Audit Trail**

Laboratory Changes and Downward Shifts (N = 757)

Serum creatinine, mg/dL (Baseline): Mean, median ± SD	0.86, 0.85 ± 0.17
Serum creatinine, mg/dL (Baseline to Week 52 or EOT/EW): Mean, median ± SD	0.02, 0.03 ± 0.1
Marked abnormality in SCr (developed change from Baseline >2.5 mg/dL)	0/757 (0)
eGFR, mL/min/1.73 m ² (Baseline): Mean, median ± SD	86.86, 86 ± 19.04
eGFR, mL/min/1.73 m ² (Baseline to Week 52 or EOT/EW): Mean, median ± SD	-1.8, -1.9 ± 10.9
Downward shifts in eGFR (Baseline to Week 52 or EOT/EW)	
Mild to moderate renal impairment (>60 mL/min/1.73 m ² to <60 mL/min/1.73 m ²)	26/712 (3.6%)
Moderate to severe renal impairment (>30 - <60 mL/min/1.73 m ² to <30 mL/min/1.73 m ²)	1/44 (2.27)
ACR, mg/g (Baseline): Mean, median ± SD	28.65, 6.3 ± 128.64
ACR, mg/g (Baseline to Week 52 or EOT/EW): Mean, median ± SD	3.37, 0.66 ± 158.4
Downward shifts in ACR (Baseline to Week 52 or EOT/EW)	
Normo- to microalbuminuria (<30 mg/g to >=30 mg/g)	25/646 (3.87)
Normo- to macroalbuminuria (<30 mg/g to >300 mg/g)	0/646 (0)
Micro- to macroalbuminuria (>=30 - <300 mg/g to >300 mg/g)	2/69 (2.9)

Download Report



RESEARCH AND REVIEW

Safety Assessments and Signal Detection



Drug Induced Liver Injury (DILI) Research

Challenge:

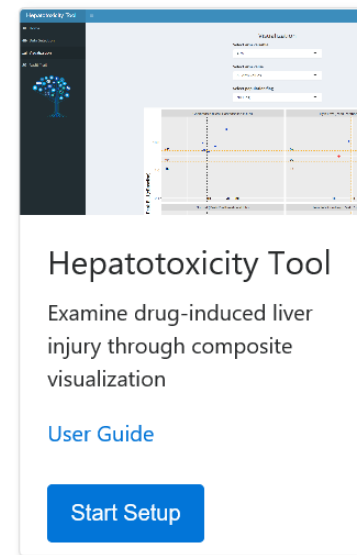
- There are no tools to identify DILI in subjects with liver disease who exhibit baseline pre treatment liver test values that exceed normal limits. A rise in liver test values above normal limits predicts fatal DILI when accompanied by liver dysfunction (Hy's law).
- In patients with liver disease, a rise in liver test values over baseline while on treatment can represent liver disease progression or DILI.

Approach:

- Compared the variability in liver test markers in clinical trials of healthy volunteers to patients with liver disease
- Developed a hepatotoxicity tool to visualize the change in liver tests from baseline and complement current DILI screening with Hy's Law analyses.

Results:

- The Hepatotoxicity Tool complements Hy's law analysis with a visualization of the change over baseline test values
- Provides reviewers a screening tool for DILI in treatment trials for liver disease



Machine Learning

Challenge:

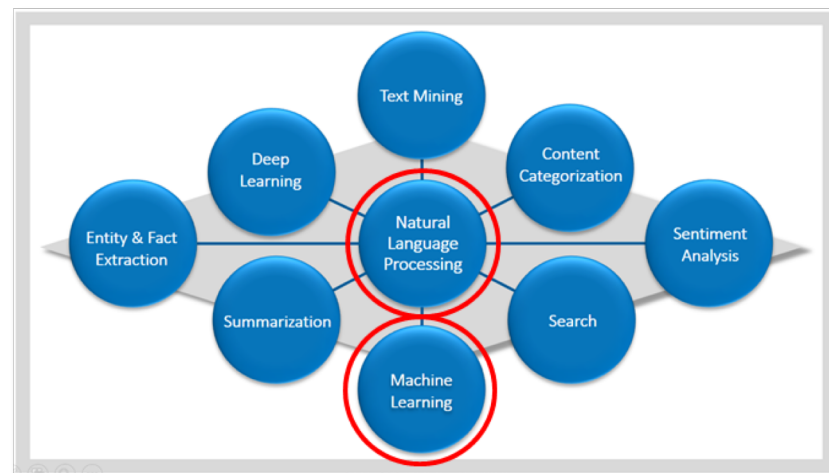
- Adverse event data includes text that provides context.
- Manual review of text is limiting and time-consuming.

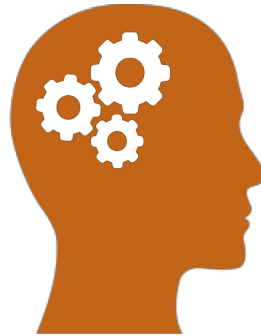
Approach:

- Test automated/semi-automated processing of text data using of statistical, machine learning, and linguistic techniques
- Generate structured data from unstructured, then apply modeling techniques

Results:

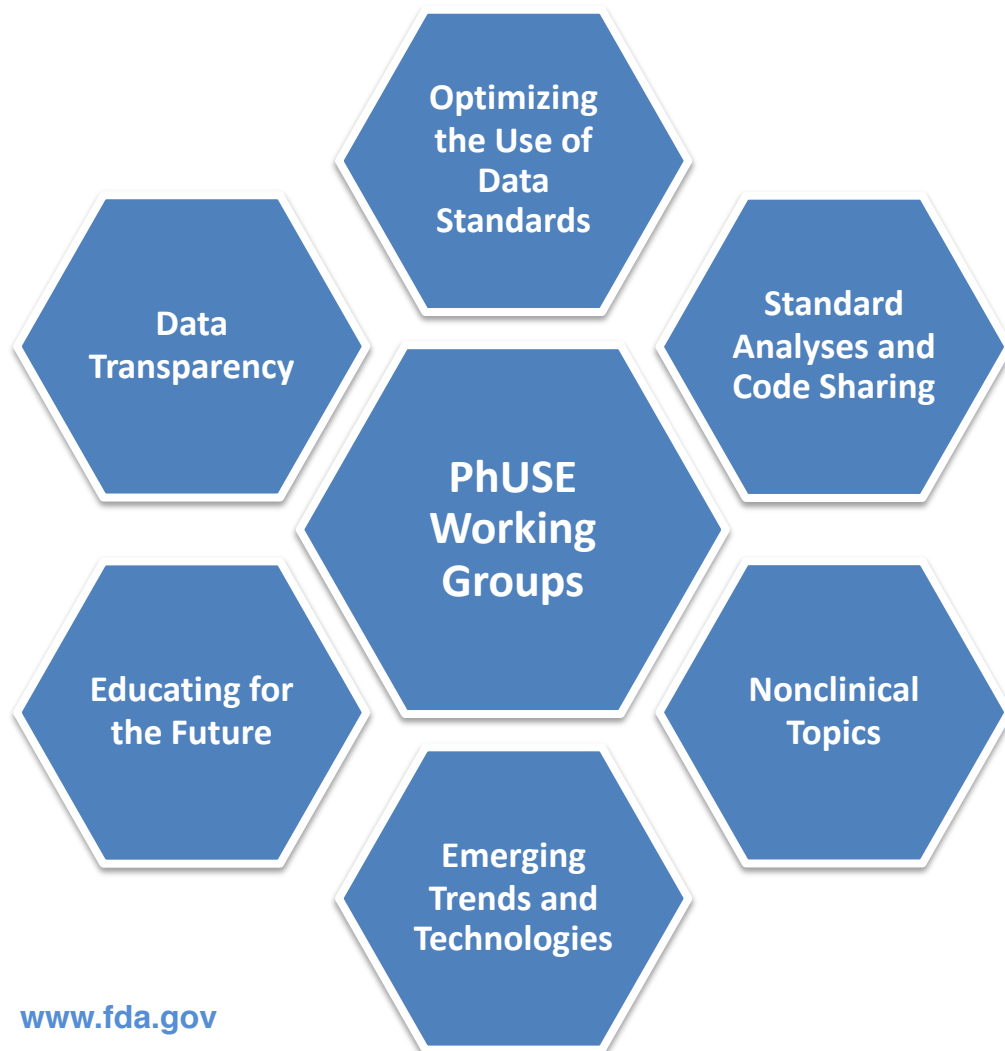
- Uncovered **relationships** between these drugs and hepatic failure
- Offered information on **drug combinations** related to hepatic failure
- Clarified factors that can **predict** a greater degree of hepatic failure from serious events (death) versus less serious (treatable) events
- Assisted with **rating the impact** of using these drugs on patients





RESEARCH COLLABORATIONS

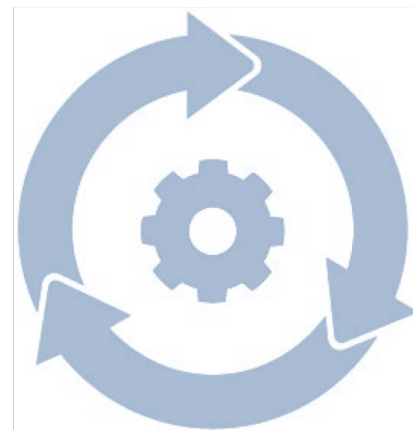
Current Collaborations: PhUSE



OCS collaborates with **Pharmaceutical Users Software Exchange** ([PhUSE](#)) in the Computational Science Symposium (CSS) and associated [working groups](#)

Modernization to Support New Drug Review

- Recruiting the best and brightest individuals from many disciplines
- Enhancing our focus on multidisciplinary teams
- Prioritizing operational excellence
- Improving knowledge management
- Emphasizing the importance of safety across a drug's lifecycle
- Incorporating the patient voice



Janet Woodcock, M.D., Director of the FDA's Center for Drug Evaluation and Research

<https://blogs.fda.gov/fdavoices/index.php/2018/06/fda-proposes-process-modernization-to-support-new-drug-development/>

Posted on June 4, 2018 by FDA Voice



**Office of Computational Science
10903 New Hampshire Avenue
Silver Spring, MD 20993**

Phone: 240-402-0401

Fax: 301-796-9907

Email: OCSServiceDesk@fda.hhs.gov

[Intranet Site](#) | [Internet Site](#)