



U.S. FOOD & DRUG
ADMINISTRATION

Data-Driven CDER Regulatory Review: Now and Future

2020



FDA Disclaimer

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

- ❖ **Guidance and Standards**
- ❖ **Compliance and Validation**
- ❖ **Data Exchange**
- ❖ **Review Aids**
- ❖ **Journey to Future**

- ❖ Reviewing regulatory submission in a timely manner is critical for FDA's review process (e.g. Reviewers have 30 days to review an IND application)
- ❖ When sponsors submit data to the FDA in a reliable and accessible format, it improves efficiency and consistency of review decisions
- ❖ Data standards (eCTD, CDISC, etc.) enable FDA to streamline the review process:
 - Reduce time for reviewers to locate and identify study data
 - Reduce the burden on sponsors and reviewers from IRs (Information Requests)
 - Reduce review time by enabling the use of COTS reviewer's tools such as JReview, JMP Clinical, etc. to automate review analyses
 - Support data driven decisions by applying data mining and data analytic techniques

“The agreement to assemble all the Quality, Safety and Efficacy information in a common format (called CTD - Common Technical Document) has revolutionized the regulatory review processes, led to harmonized electronic submission that, in turn, enabled implementation of good review practices. For industries, it has eliminated the need to reformat the information for submission to the different ICH regulatory authorities.”

Source: <https://www.ich.org/products/ctd.html>

STANDARDS AND GUIDANCE

[“eCTD Guidance”](#) - *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*

- ❖ Updated February 2020 (Revision 7)
- ❖ Type III DMF added to exemption section
- ❖ New section on waivers to address types of submissions that may qualify for a long-term or short-term waiver from the eCTD requirement and the instructions on how to submit a request

Electronic Common Technical Document (eCTD)

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The eCTD is the standard format for submitting applications, amendments, supplements, and reports to FDA’s Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).

Important Dates

Reminder: Per [Providing Regulatory Submissions In Electronic Format — Standardized Study Data, Guidance for Industry](#), electronic submission of standardized study data is required for NDA, BLA, ANDA, and Commercial IND. FDA plans to implement eCTD validation checks when submissions contain content under modules 4 and 5 beginning **September 15, 2021**. Submissions which fail this validation will be subject to rejection. Please see the [Technical Rejection Criteria for Study Data](#) and the [eCTD Validation Criteria](#) (error code 1734, 1735, 1736, 1789) for details.

After the dates listed below, eCTD requirements for submissions to CDER and CBER will go into effect and submissions that do not use eCTD will not be filed or

Quick Links

- [NDA to BLA eCTD Transition Instruction to Industry](#) (PDF - 90 KB)
- [eCTD Guidance \(Final, Rev 7\)](#) (PDF -11 KB)
- [eCTD Submission Standards](#) (PDF - 91KB)
- [FDA Data Standards Catalog](#)
- [eCTD Technical Conformance Guide](#) (PDF - 303KB)
- [Drug Master Files \(DMFs\)](#)
- [Technical Rejection Criteria for Study Data Information](#)
- [eCTD Submission Types and Sub-Types](#) (PDF - 630 KB)

Notices

- [FDA announces effective date for study data information](#) **NEW**

[“Study Data Guidance”](#) - *Providing Regulatory Submissions in Electronic Format -- Standardized Study Data*

❖ Sponsors must conform to standards in the FDA Data Standards Catalog:

- ❑ NDA, BLA, ANDA studies that started after December 17th, 2016
- ❑ Commercial IND studies started after December 17th, 2017

For more information on how to submit and what will be validated, see the documents below:

- ❖ [Technical Rejection Criteria for Study Data](#) – Latest update October 2019
- ❖ [Study Data Technical Conformance Guide](#) – Latest update October 2019
- ❖ [Study Data for Submission to CDER and CBER website](#)

Study Data for Submission to CDER and CBER

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Data standards enable FDA to modernize and streamline the review process. They also enable more consistent use of analysis tools to better view drug data and highlight areas of concern.

Study data standards describe a standard way to exchange clinical and nonclinical research data between computer systems. These standards provide a consistent general framework for organizing study data, including templates for datasets, standard names for variables, and standard ways of doing calculations with common variables.

FDA is instituting new requirements for data standards that will apply to most study data submitted to FDA’s Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).

Beginning after the dates specified below, FDA may refuse to file for New Drug Applications (NDAs) and Biologics License Applications (BLAs) or refuse to receive for Abbreviated NDAs (ANDAs) any electronic submission whose study data do not conform to the required standards specified in the [FDA Data Standards Catalog](#). See the [Technical Rejection Criteria for Study Data \(PDF\)](#) for more information. FDA conducted an analysis of study data conformance on submissions received during a

Stay Connected

If you have study data questions for CDER, please contact the CDER eDATA Team at cdere-data@fda.hhs.gov.

For electronic submissions, contact the CDER Electronic Submission (ESUB) Support Team at esub@fda.hhs.gov.

If you have study data questions for CBER, please contact CBER-edata@fda.hhs.gov.

For electronic submissions, contact CBER ESUB at esubprep@fda.hhs.gov.

EXAMPLE OF FUTURE STANDARDS WORK

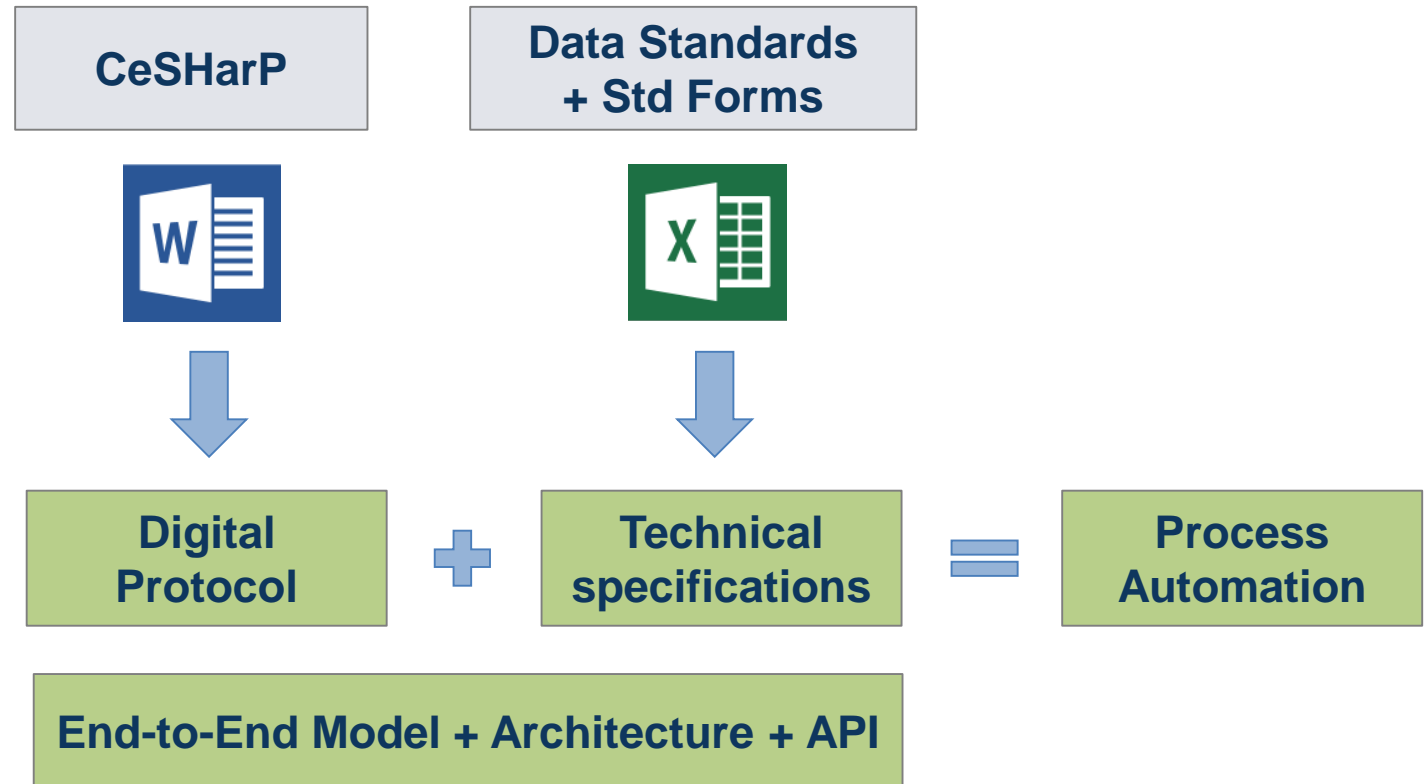
- ❖ Clinical protocol is an important document that describes the processes and procedures directing the conduct and analysis of a clinical study.
- ❖ Lack of harmonization leads to inconsistent quality of protocols, and different Format and core content of study protocols makes interpretation difficult
- ❖ Truly electronic protocol, not just electronic paper
- ❖ Human readable as well as machine readable
- ❖ We Like a Structured, Harmonized Version...
 1. Information always in the same place, means the same thing across Sponsors
 2. Makes review process faster, more efficient
 3. Eases searching through data

ICH M11 Clinical Electronic Structure Harmonized Protocol (CeSHarP):

A new harmonized guideline on the clinical protocol that specifies a comprehensive organization with standardized content (including both required and optional components).

Deliverables:

- ❖ Guideline: Describes Purpose, Scope, Design Principles & Framework for Content & Technology Innovation
- ❖ A template to include identification of headers, common text and a set of data fields and terminologies which will be the basis for efficiencies in data exchange
- ❖ A technical specification that uses an open, non-proprietary standard to enable electronic exchange of clinical protocol information



COMPLIANCE AND VALIDATION



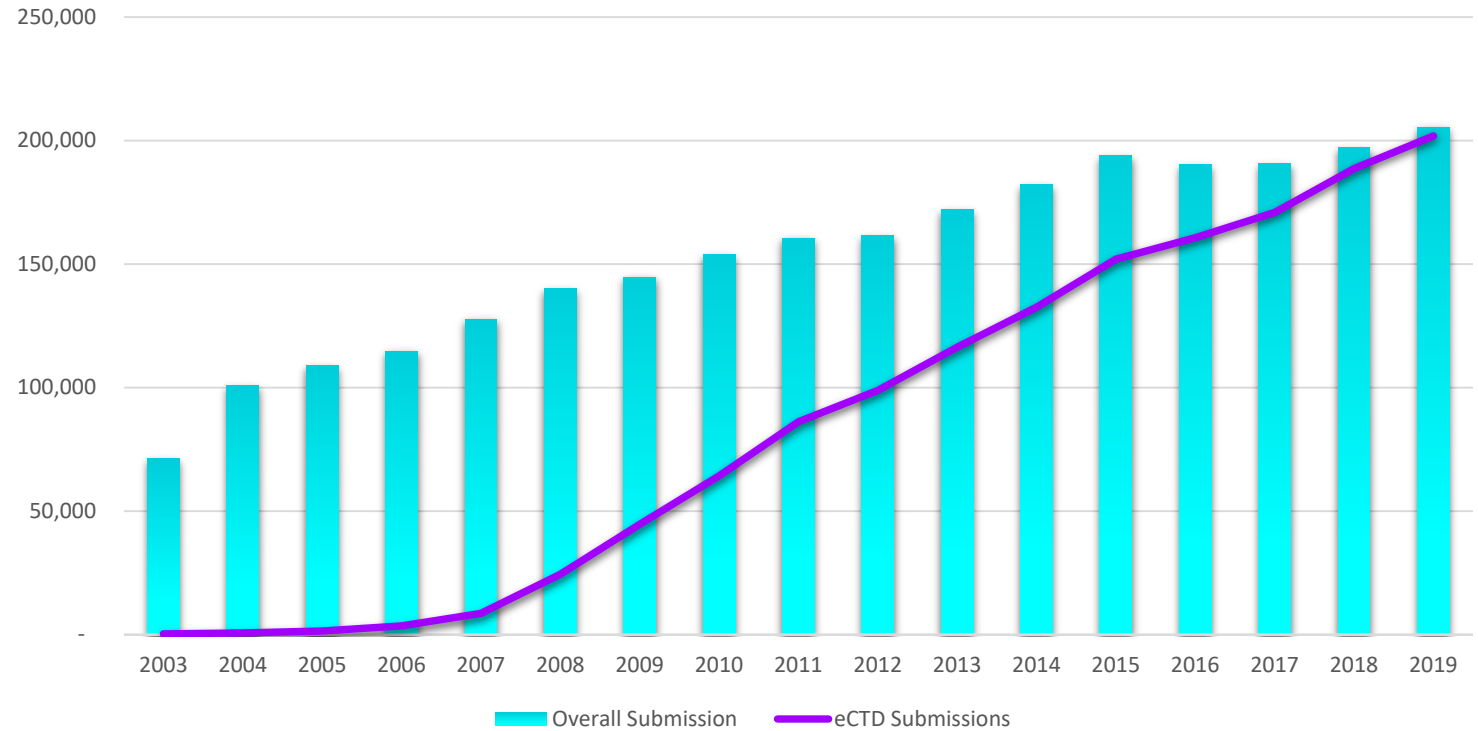
TRANSITION TO ELECTRONIC SUBMISSIONS



In FY19, CDER received approximately 205,000* electronic submissions via ESG. Nearly 202,000 were in eCTD.



Comparison: Overall Electronic Submissions vs. eCTD Submissions



*excludes Research IND, DMF Type III, and Promotional/Advertising

Automate process to identify Submission Category

Process:

1. Determine Submission Category based on structured data in eCTD sequence
2. Route to Review Division based on Submission Category

Benefit:

1. Reviewers see submission sooner
2. Reduced manual data entry

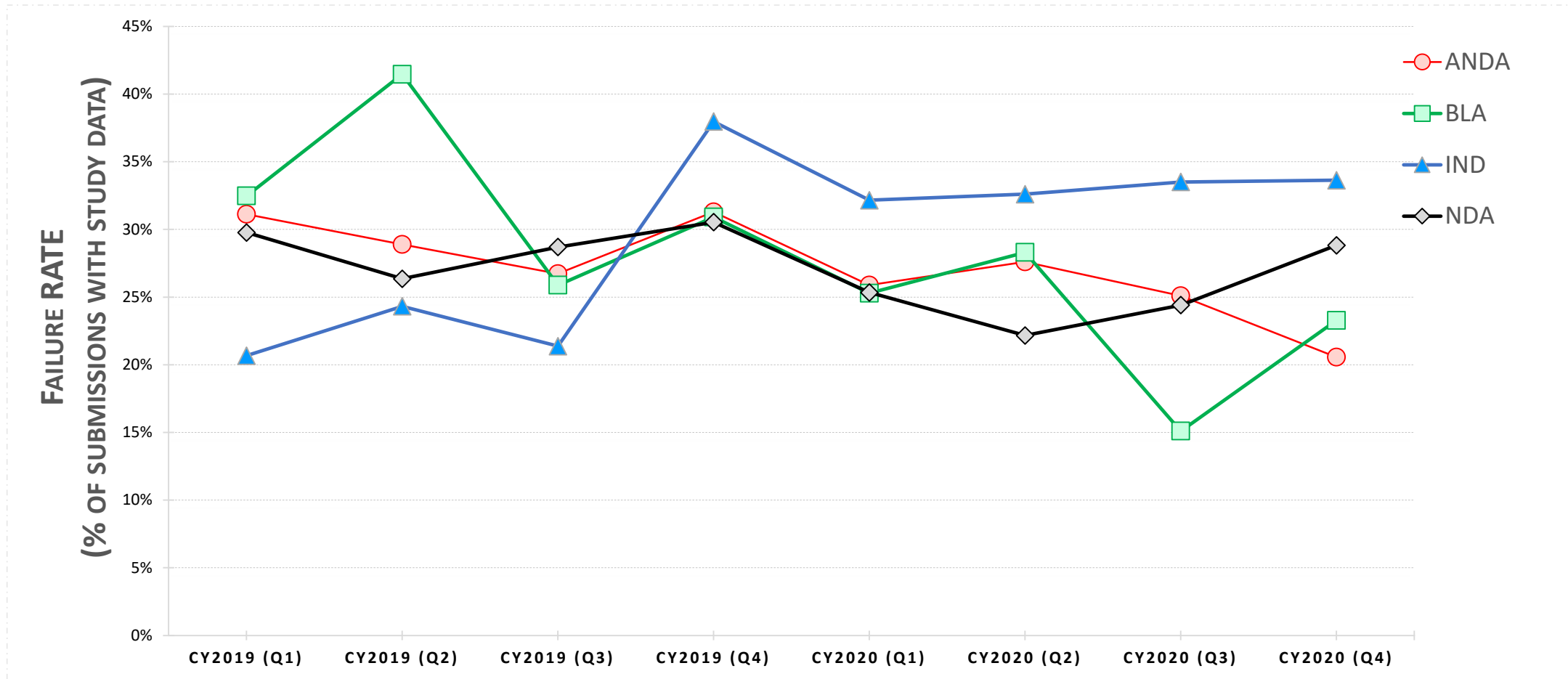


Document Room continues to process submissions where category cannot be determined automatically and submissions which contain high validation errors

CDER STUDY DATA TRC CONFORMANCE (CY19/CY20)



The conformance rate to Study Data Technical Rejection Criteria is still less than ideal.



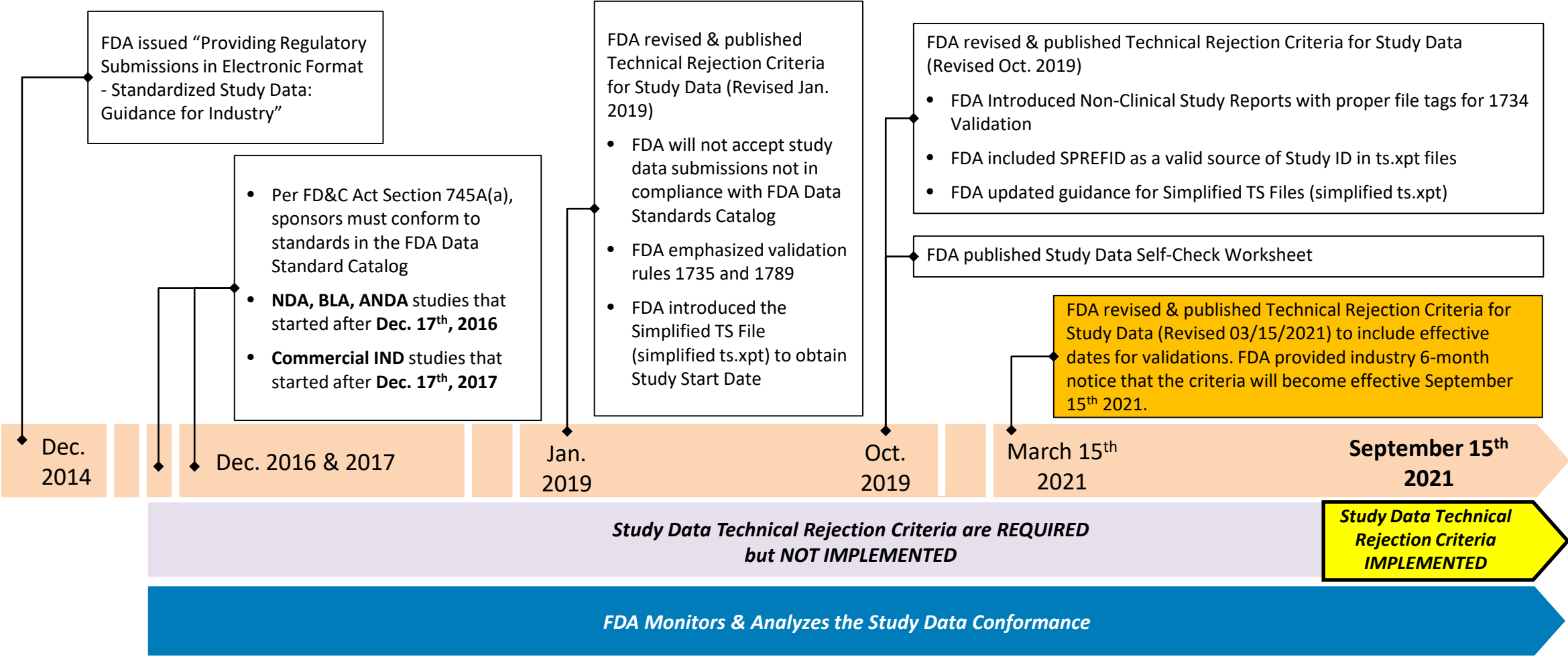
Notes:

- 1) CY2019 and CY2020 analysis was conducted according to the TRC (Revised Oct. 2019)
- 2) Analysis includes NDA, BLA, ANDA and Commercial IND Sequence received by CDER between 1/1/2019 and 12/31/2020
- 3) Validation of error 1736 is not performed if a study has error 1734
- 4) M4 Definition of Study Data - .xpt files and/or a Study Report tagged as pre-clinical-study-report, legacy-clinical-study-report, or study-report-body present in eCTD module 4
- 5) M5 Definition of Study Data - .xpt files present in eCTD module 5

UPCOMING STUDY DATA TRC ENFORCEMENT



September 15th 2021: The eCTD validations listed in the Technical Rejection Criteria become effective. FDA will reject submissions that fail these validations.



DATA EXCHANGE



ELECTRONIC SUBMISSION PATHS TO CDER

CDER NextGen (CDER Only except for DDT)

- Drug Shortage Notifications
- Non-eCTD submission to DMF Type III, Research IND
- Non-eCTD submission to application granted eCTD Waiver
- Pre-ANDA Meetings
- GDUFA II Program User Fees
- Controlled Correspondence
- Drug Development Tools (DDT)
- Request an Application Number
- Non-eCTD submission of Medical Gas, Promotional Material, EUA, or Presubmission correspondence

ESG (All Centers)

- eCTD submission to NDA, BLA, ANDA, IND, DMF applications
- Non-eCTD submission to DMF Type III, Research IND
- Non-eCTD submission to application granted eCTD Waiver
- E2B Postmarket Safety Reports (submitting to FAERS)
- SPL Submissions

CDER Direct (CDER Only), SPL Submissions

- NDC Labeler Code Requests
- Product Listing and Reporting
- Establishment Registrations and annual updates
- GDUFA Facility Self-ID Product Listing
- 503 Outsourcing Facility – registration and product reporting
- Wholesale Drug Distributors and Third Party Logistic Providers (WDD/3PL)

ELECTRONIC SUBMISSION PATHS TO CDER



- ❖ Urgent Need: Minimize the need to physically receive and process paper; reduce touch time and speed access to reviewers
- ❖ Solution: Cloud-based CDER NextGen Portal
 - ✓ receive related Research INDs
 - ✓ an alternative submission capability for submissions not required to

Step 1. Once you land on the Portal homepage, click **FDA Alternative Submission**.

- ## Submission Types
- DMF Type III
 - eCTD Waived Submission
 - ANDA
 - BLA
 - DMF Type II, IV, V
 - IND
 - NDA
 - Emergency Use Authorization
 - Emergency Use Authorization Request
 - Emergency Use Authorization Subsequent Submission
 - Marketing and Advertising
 - Medical Gas
 - Pre-Submission
 - BLA
 - IND
 - NDA

SUBMIT RESEARCH IND VIA CDER NEXTGEN PORTAL

APPLICATION BUILDER

- Application / Submission
- Company and Contact
- Product
- Nonclinical Studies
- Clinical Studies
- Upload Documents
- Review & Submit

Application Builder
A convenient and logical way to complete your submissions

Need Help?

The [Help Center](#) is available to answer all your Research IND related questions.

Help Center
Easily accessible support when making your submission

Research IND

Application / Submission Details

Submission Type

Find detailed information about the submission types on the FDA 1571 instructions.

* This submission contains the following

Initial

IND Number

Provide the IND number if it was previously assigned. If an IND number has not been assigned, leave the field blank. For IND numbers less than six digits, the IND number should be preceded using zeros (i.e., for IND 12345 enter 012345).

* IND Number

Request IND Number

IND Serial Number

IND submission should be consecutively numbered. The initial IND should be numbered 'Serial number: 0000.' The next submission (e.g., amendment, report, or correspondence) should be numbered 'Serial Number: 0001.' Subsequent submissions should be numbered consecutively in the order in which they are submitted.

* IND Serial Number

Select all that apply:

Emergency Research Exception From Informed Consent Requirements

Charge Request

Expanded Access Use 21 CFR 312.300

Please visit the [Expanded Access page](#) for more information about Individual Patients.

Individual Patient, Non-Emergency 21 CFR 312.310

Intermediate Size Patient Population 21 CFR 312.315

Individual Patient, Emergency 21 CFR 312.310(d)

Treatment IND or Protocol 21 CFR 312.320

Referenced Applications

List Numbers of all Investigational New Drug Applications (21 CFR Part 312), New Drug Applications (21 CFR Part 314), Drug Master Files (21 CFR Part 314.420), and Biologics License Applications (21 CFR Part 601) referred to in this application.

Add Application +

Save and Close

Save

Next

Navigation Pane

Transition between pages easily with buttons on each page

STUDY DATA SUBMISSION USING PORTAL



APPLICATION BUILDER

- Application / Submission
- Company and Contact
- Product
- Nonclinical Studies
- Clinical Studies**
- Upload Documents
- Review & Submit

Need Help?

The [Help Center](#) is available to answer all your Research IND related questions.

CDER NextGen Portal

Add Clinical Study

*Study ID:

*Study Title:

Phases of Clinical Investigation:

Other (specify):

*Study Type:

Other (specify):

*Has the study started? Yes No

Does this submission contain clinical study data and/or protocol information? Yes No

We encourage Research IND Investigators to provide the National Clinical Trial (NCT) number for their studies.

Please provide the National Clinical Trial (NCT) number:

Enter Numbers Only:

*Are any cross references associated with this study? Yes No

CDER NextGen Portal

Add Clinical Study

*Please upload unique file names and refrain from uploading files with same names.

Investigator's Brochure -

Described In 21 CFR 312.23(a)(5). File uploads must be less than 45MB and one of the following file types: xls,xlsx, doc, docx, ppt, pptx, pdf, sas

Or drop files

Search uploaded documents:

- Investigator's Brochure**
- Form FDA 3674 Certification of Compliance
- Informed Consent
- Study Protocol
- Study Report
- Dataset
- Previous Human Experience
- Form FDA 1572 and Investigator CVs
- Other Documents

Adding study related Protocol, Report, Datasets, etc.

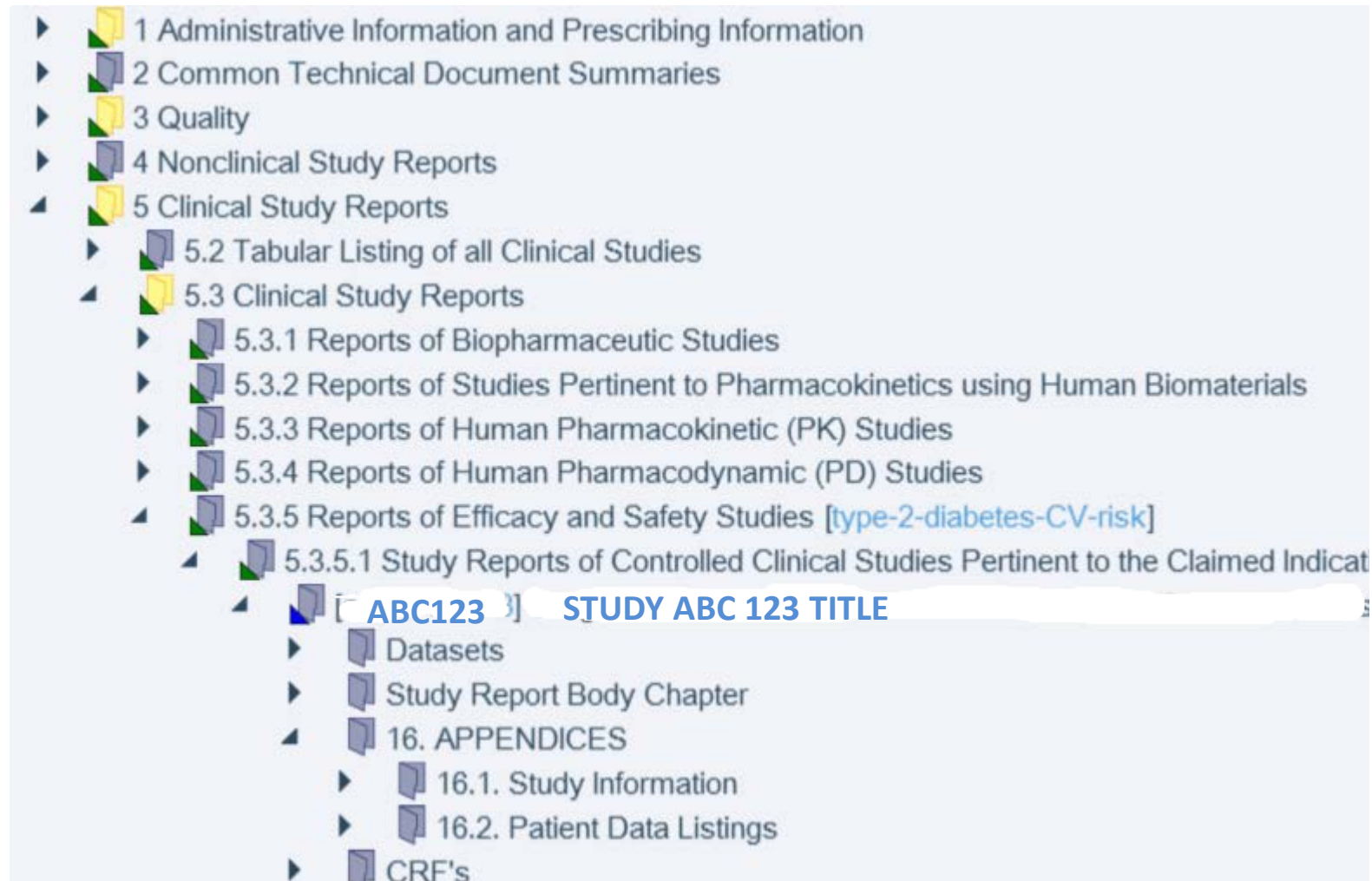
REVIEW AIDS



REVIEW ECTD SUBMISSION



FDA uses LORENZ docuBridge to support review of eCTD submissions



REVIEW ECTD SUBMISSION

FDA also utilizes multiple tools and systems to support analysis:

The collage features several software interfaces:

- Janus Nonclinical Review (Preprod):** A table showing organ/tissue findings for 'Janus' across different dosages and sexes. The table includes columns for Organ/Tissue, Finding, Result Modifier, Severity, and various dosage groups (e.g., 001-0, 001-200, 001-500).
- JMP Clinical:** A line graph titled 'Average Measurements Across Analysis Visit' showing ALT Blood (U/L) over time. The y-axis ranges from 0 to 180 U/L. The graph shows a significant spike in ALT levels around the 10th visit.
- OCS Data Central:** A search interface for locating data, with a search bar and a table of results showing columns like Sequence, Study ID, Data Standard, Number of Subjects, Last Modified, Program Submission?, EDR Source Location, and Data Central Location.
- CoreDF:** A data quality report titled 'Potential Data Quality Issues' with sections for Demographics, Disposition, Exposure, Adverse Events, and Laboratory. It lists specific issues such as '38 (5.0%) of RACE values not found in CDISC code list' and '240 (5.1%) of laboratory test results are potential duplicates'.
- Analysis Studio:** A data analysis tool showing a list of parameters and a scatter plot of data points.
- JMP:** A table listing various parameters and their corresponding values, such as 'PAIN ABDOMINAL', 'HEADACHE', 'URINE DISCOLOR', etc.

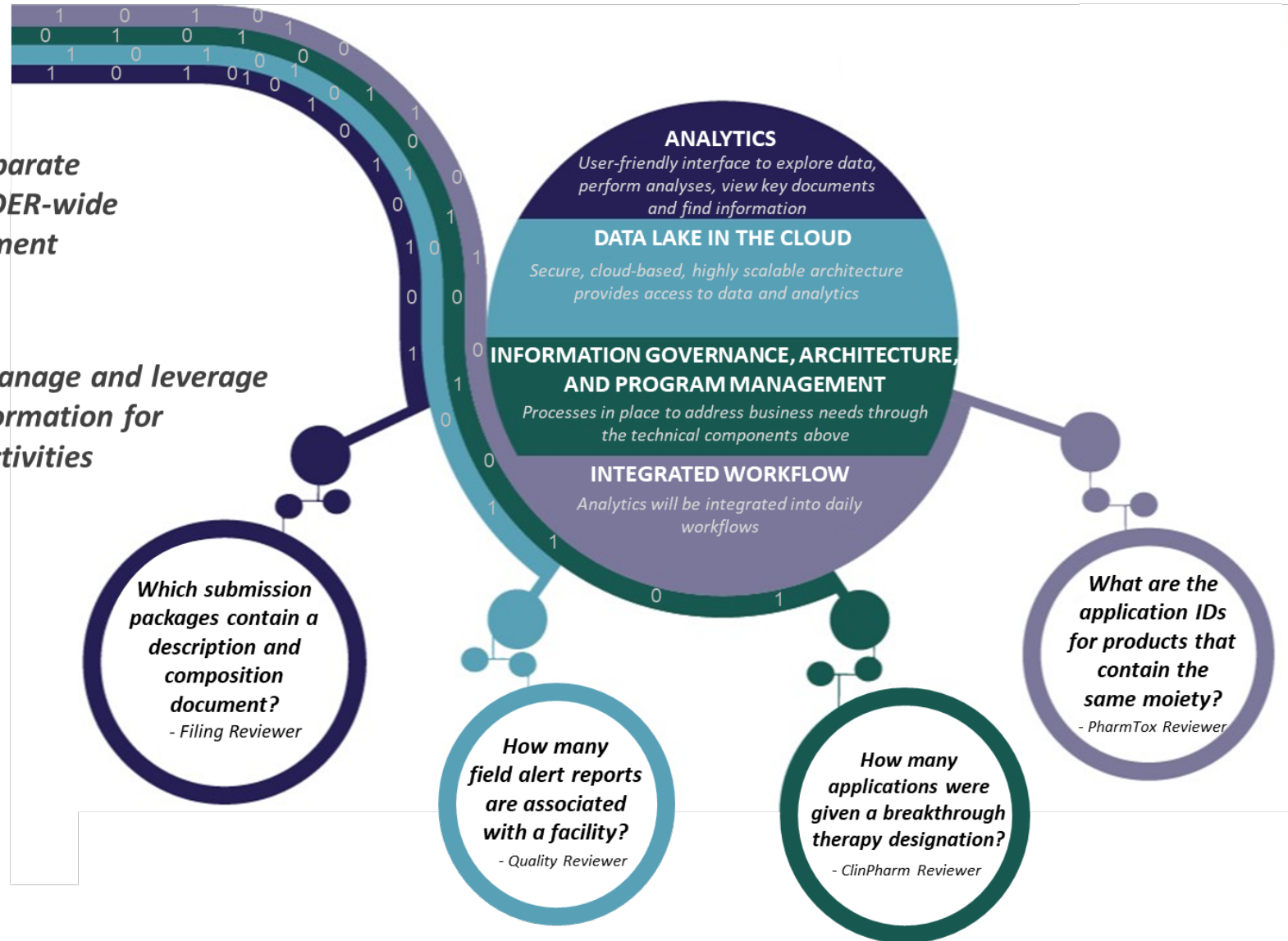
Two icons are overlaid on the collage: a wrench and screwdriver icon on the left, and a hand holding a bar chart icon on the right.

SHIFT TOWARDS A CLOUD-BASED DATA ENVIRONMENT



Bringing together disparate data sources into a CDER-wide Information Management Platform...

...to better manage and leverage available information for regulatory activities



JOURNEY TO FUTURE



POTENTIAL FOR REGULATORY DOSSIERS IN THE FUTURE



From Submit to Collaborate

The next generation of regulatory submission capabilities should move from a transactional **submit and review** model to an environment where regulatory policy & technology support **information sharing, communication and consistency**.

From Documents to Data

To advance beyond today's document-based construct, we need to shift towards **data-based** dossiers. This is **continuously structurally validated** to ensure compliance and data sets are **supplemented** by documents. These data should **seamlessly flow** to existing **CDER Informatics systems** to ensure full data lifecycle connectivity.

From Regulator-specific to multi-Regulator

The future should allow sponsor data sets for the same product to be made available to **multiple regulators** and eliminate duplicative submissions to multiple authorities. Regulators should have the ability to **collaborate with each other** and the sponsor to **increase** the **value** of the dossier.

From Fixed Formats to more Dynamic Standards

As the complexity of data changes going forward (e.g., RWE/RWD), the platform should have the ability to incorporate **new data standards** and apply these to data sets included in dossiers. Data should be able to be **validated against data standards** to ensure that the reviewer sees the complete picture.

SOME INTERESTING INITIATIVES

Real-time Oncology Review (RTOR)

Announced to the public in Fall 2018

Aims to explore a more efficient review process to ensure that safe and effective treatments are available to patients as early as possible – once clinical trial results are available but before the information is formally submitted.

This is an example of a shift from a **sponsor/regulator** submission mindset to a **collaborative dossier mindset**.

Project Orbis

Started in September 2019

Provides a framework for concurrent submission and review of oncology products among international partners (US, Australia, Canada, Singapore, Switzerland).

This is an example of **collaboration** among international regulators.

Digital IND Safety Reporting Program

Implemented in 2019

Provides a digital framework for electronic submissions of IND Safety Reports using ICH E2B data standards¹ for adverse event reports, moving away from paper and pdf reviews and tracking.

Both pre-market and post-market safety information is visualized, analyzed, and tracked in the same system. This is an example of **moving from digital documents to digitalized**, actionable information.

OneSource

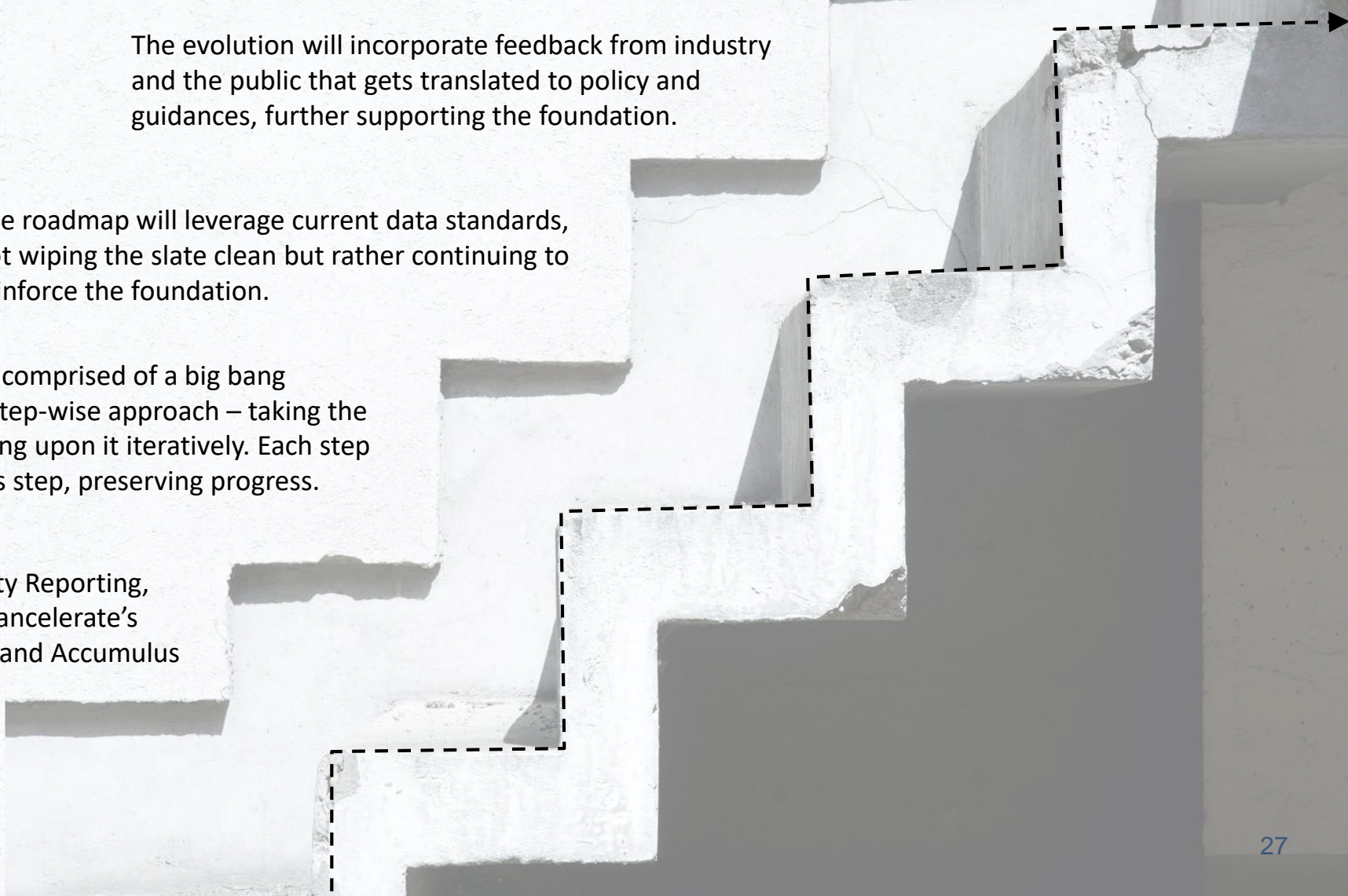
Initial pilot concluded October 2019

In the context of the I-SPY breast cancer trials, this automates flow of structured EHR data (or RWD) into external systems. Leverages HL7, CDISC and IHE data standards for capture and transmission of clinical data, avoiding source data verification, reducing burden on healthcare providers and research staff, and improving data quality.

This use case is focused on moving from fixed forms (like CRFs) to **dynamic data standards** and on incorporating new data standards to **accommodate RWD and RWE**.

IT'S A JOURNEY

The Roadmap to the Future will Require Iteration, Agility and Collaboration



The evolution will incorporate feedback from industry and the public that gets translated to policy and guidances, further supporting the foundation.

The roadmap will leverage current data standards, not wiping the slate clean but rather continuing to reinforce the foundation.

The journey will not be comprised of a big bang approach but rather a step-wise approach – taking the current state and building upon it iteratively. Each step protects to the previous step, preserving progress.

Internal projects like Orbis and Digital IND Safety Reporting, and external projects and collaborations like Trancelerate's DataCelerate and Common Protocol Template, and Accumulus can serve as next steps in the journey.

Thank You!

