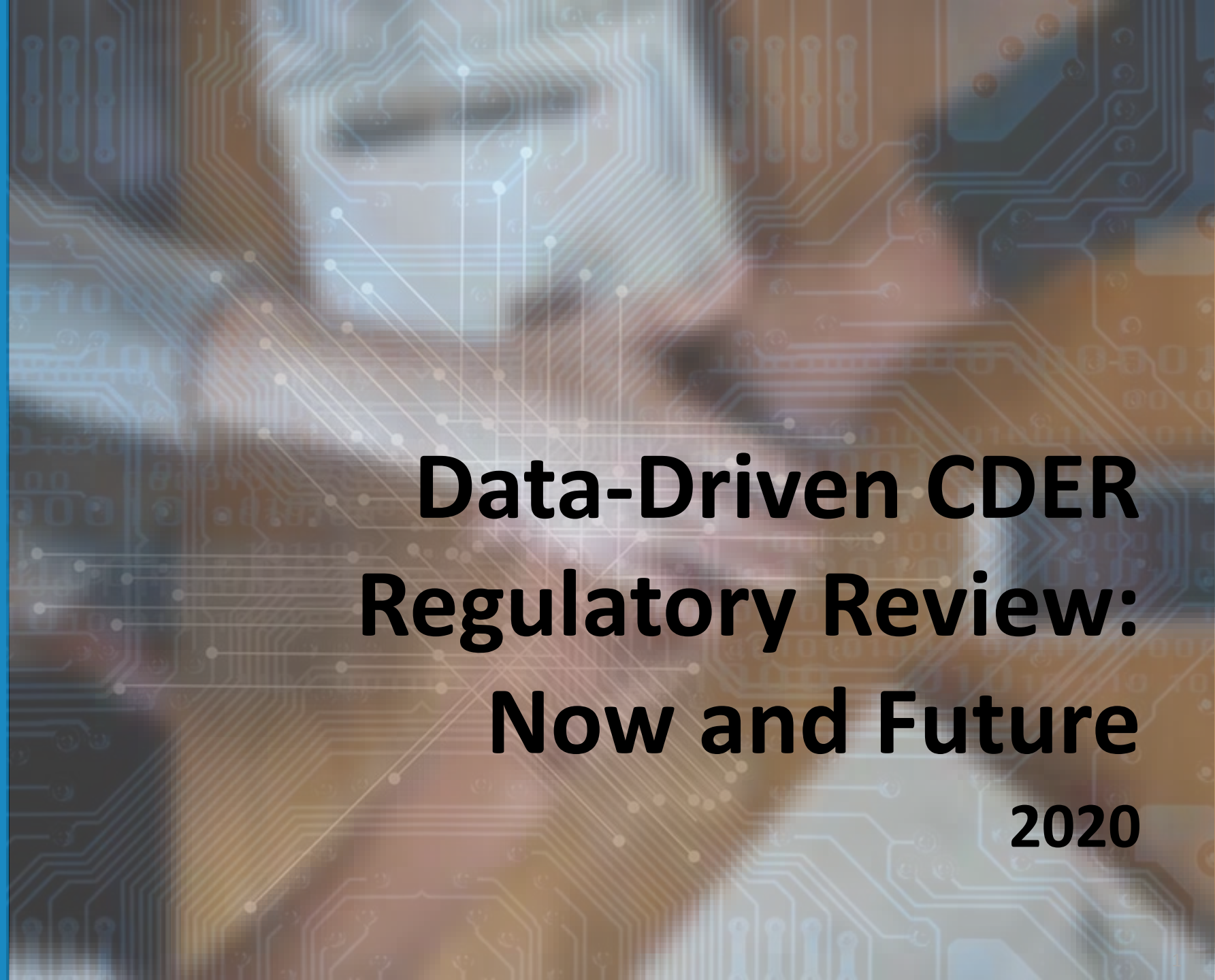
U.S. FOOD & DRUG ADMINISTRATION



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.

AGENDA

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

DATA-DRIVEN REGULATORY REVIEW PROCESS

- 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."

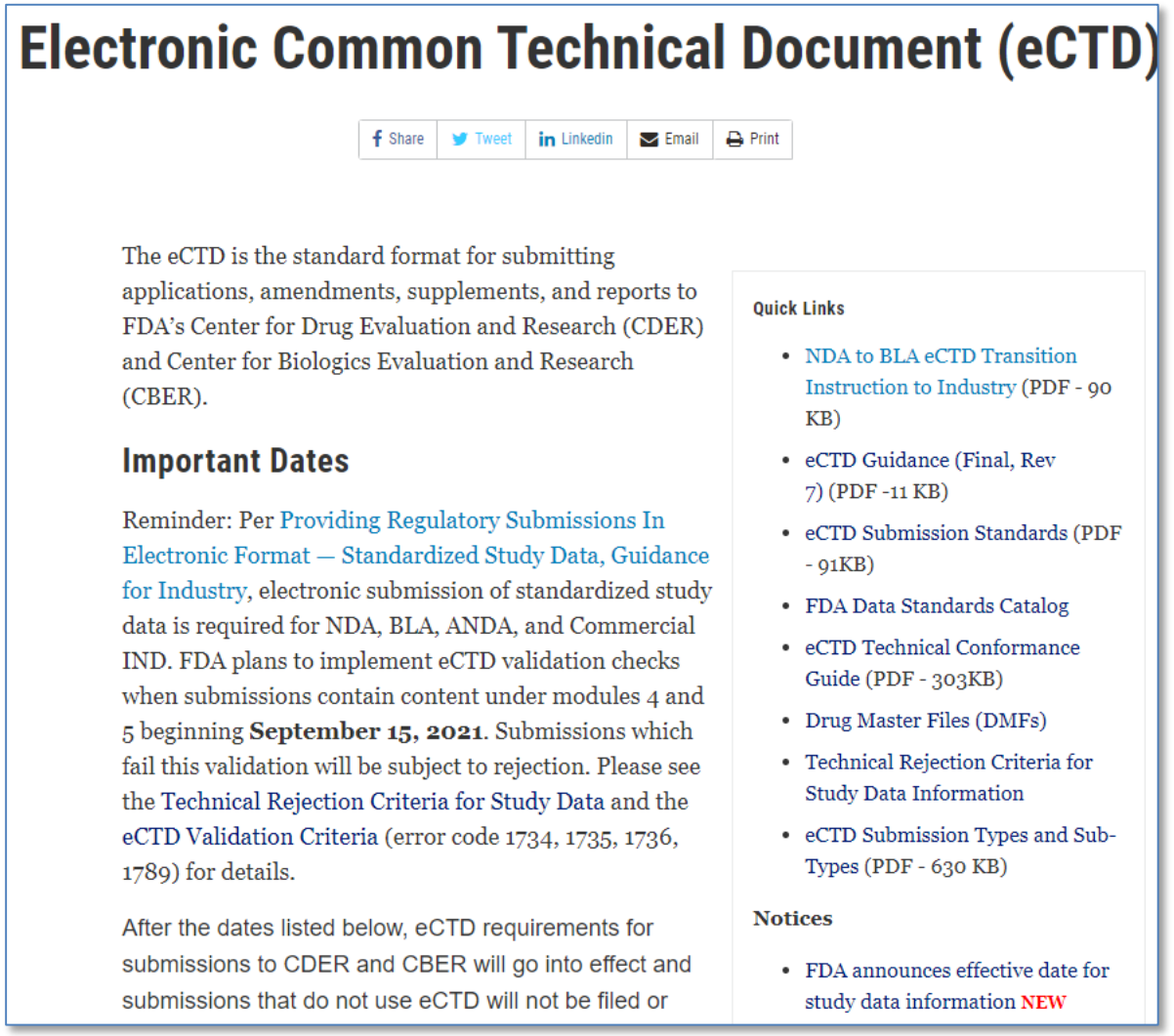
Source: https://www.ich.org/products/ctd.html

STANDARDS AND GUIDANCE

FDA ELECTRONIC SUBMISSION 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

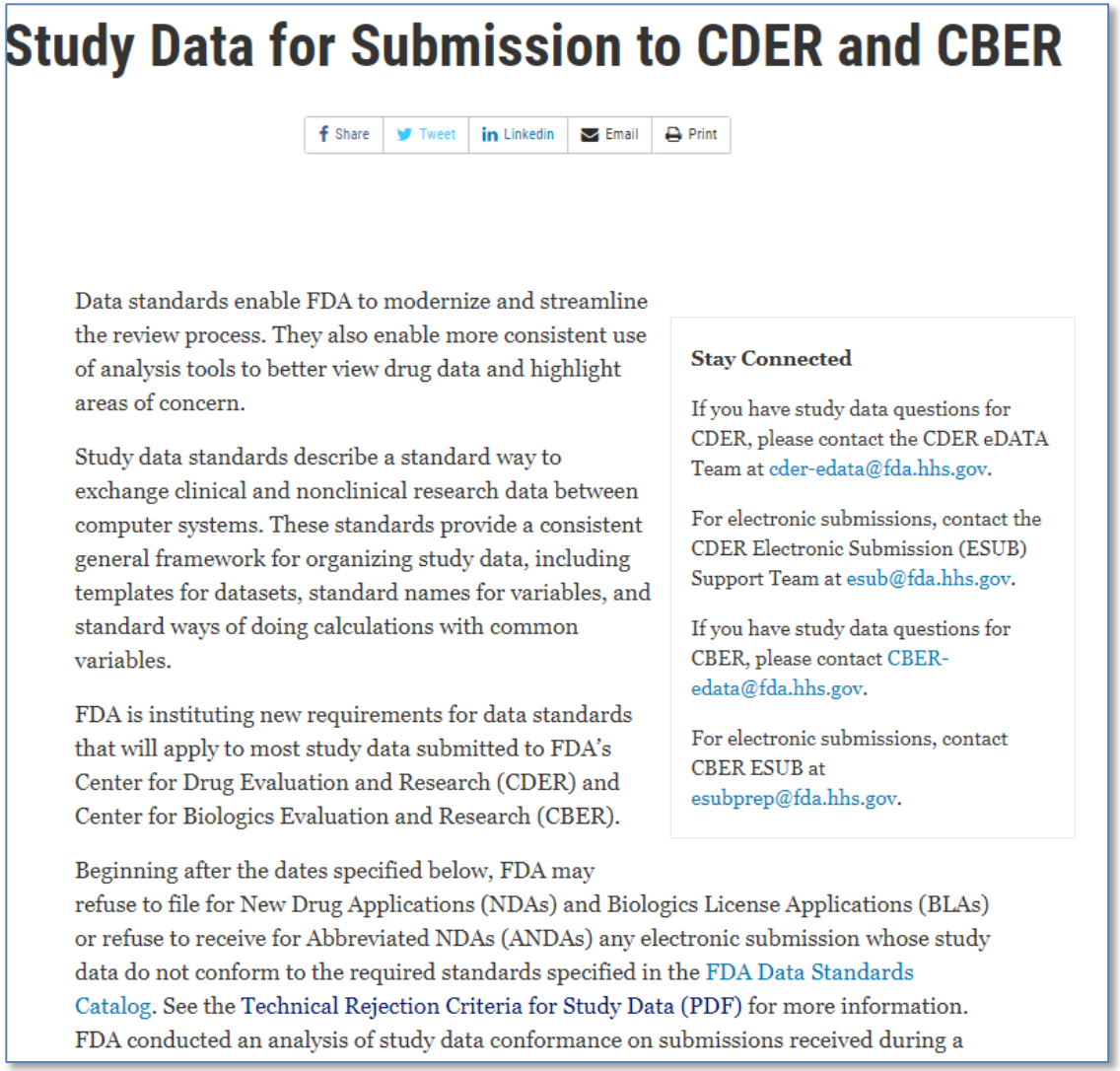
FDA STUDY DATA GUIDANCE

"**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).

Stay Connected

If you have study data questions for CDER, please contact the CDER eDATA Team at cder-edata@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.

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

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

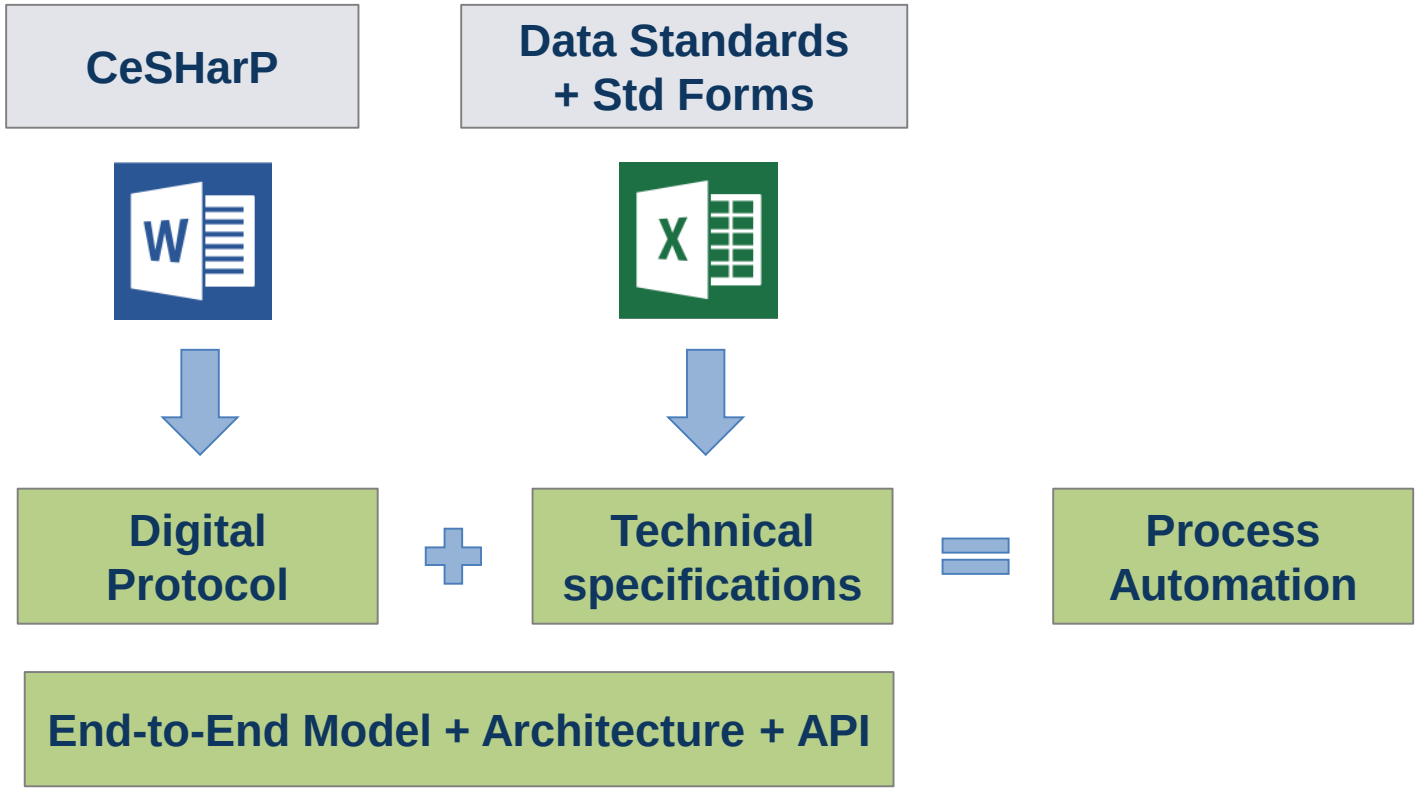
ICH M11 CeSHarP

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:

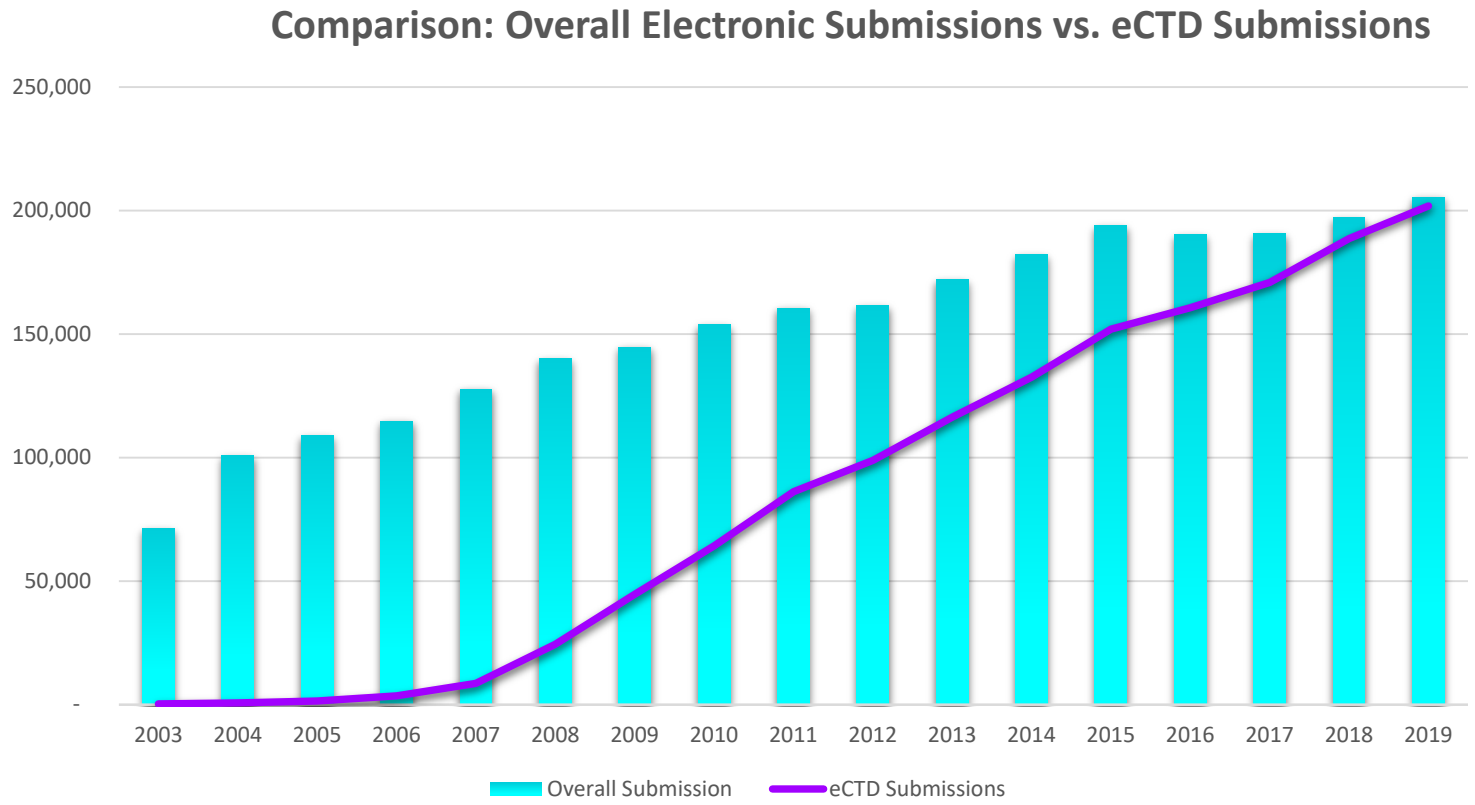
- Guideline: Describes Purpose, Scope, Design Principles & Framework for Content & Technology Innovation
- A template to include identification of headers, common text and a set of data fields and terminologies which will be the basis for efficiencies in data exchange
- A technical specification that 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.



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

CDER SUBMISSION PROCESSING – A LOOK UNDER THE HOOD

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

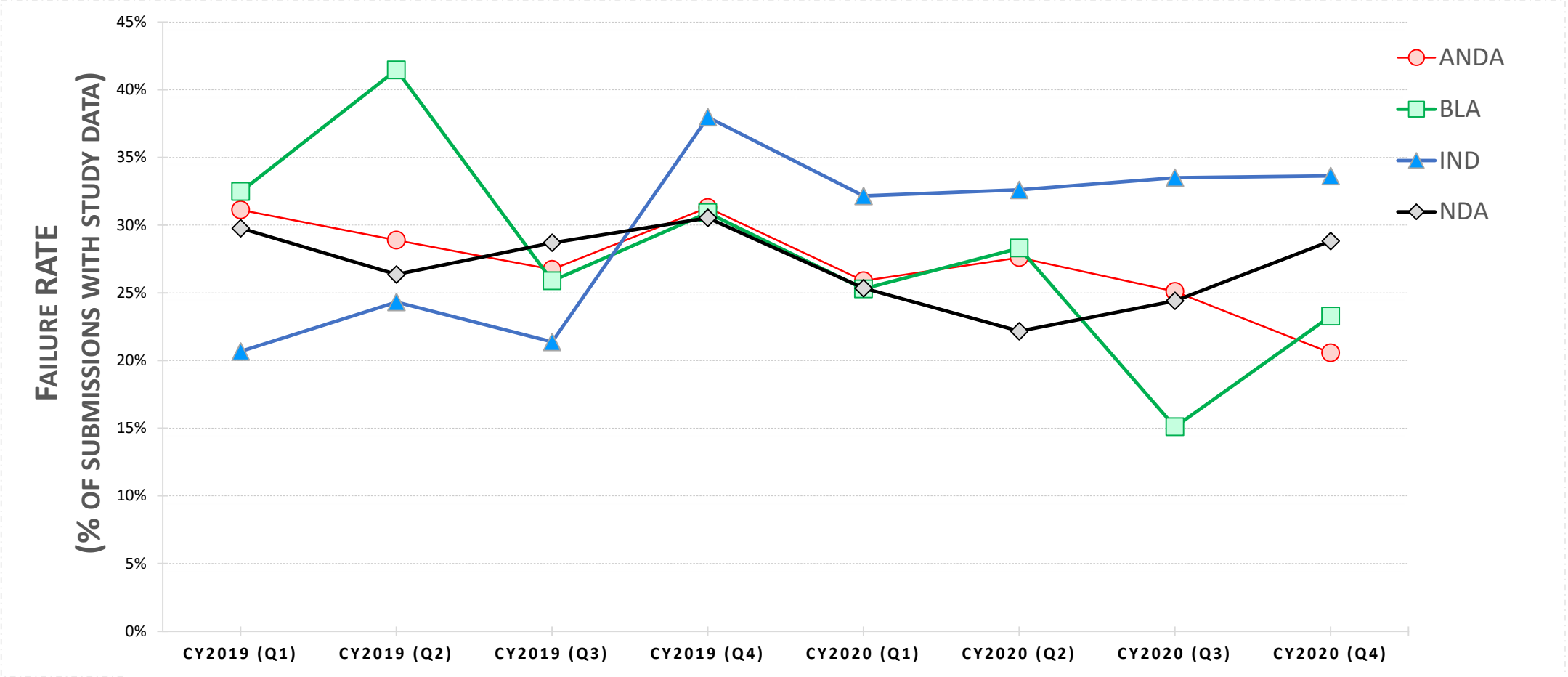
Benefit:

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.

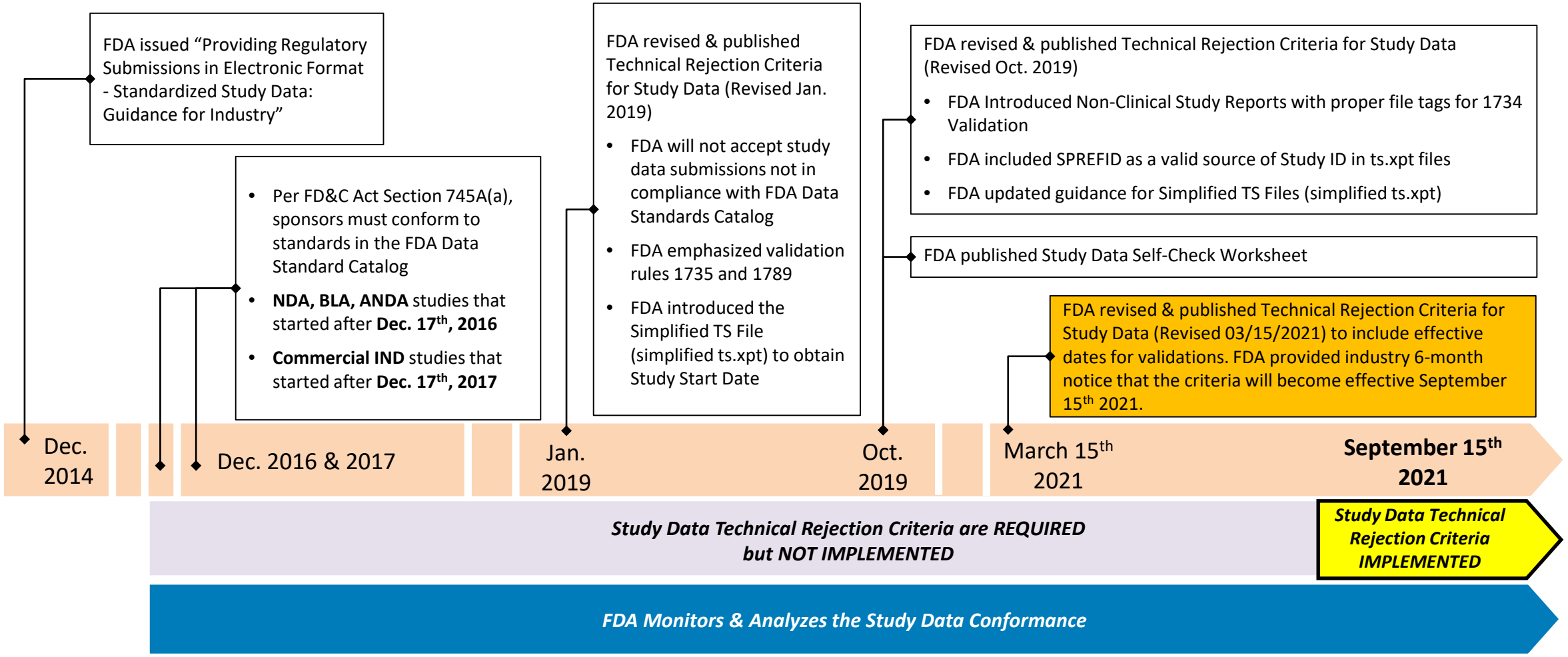


Notes:

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)

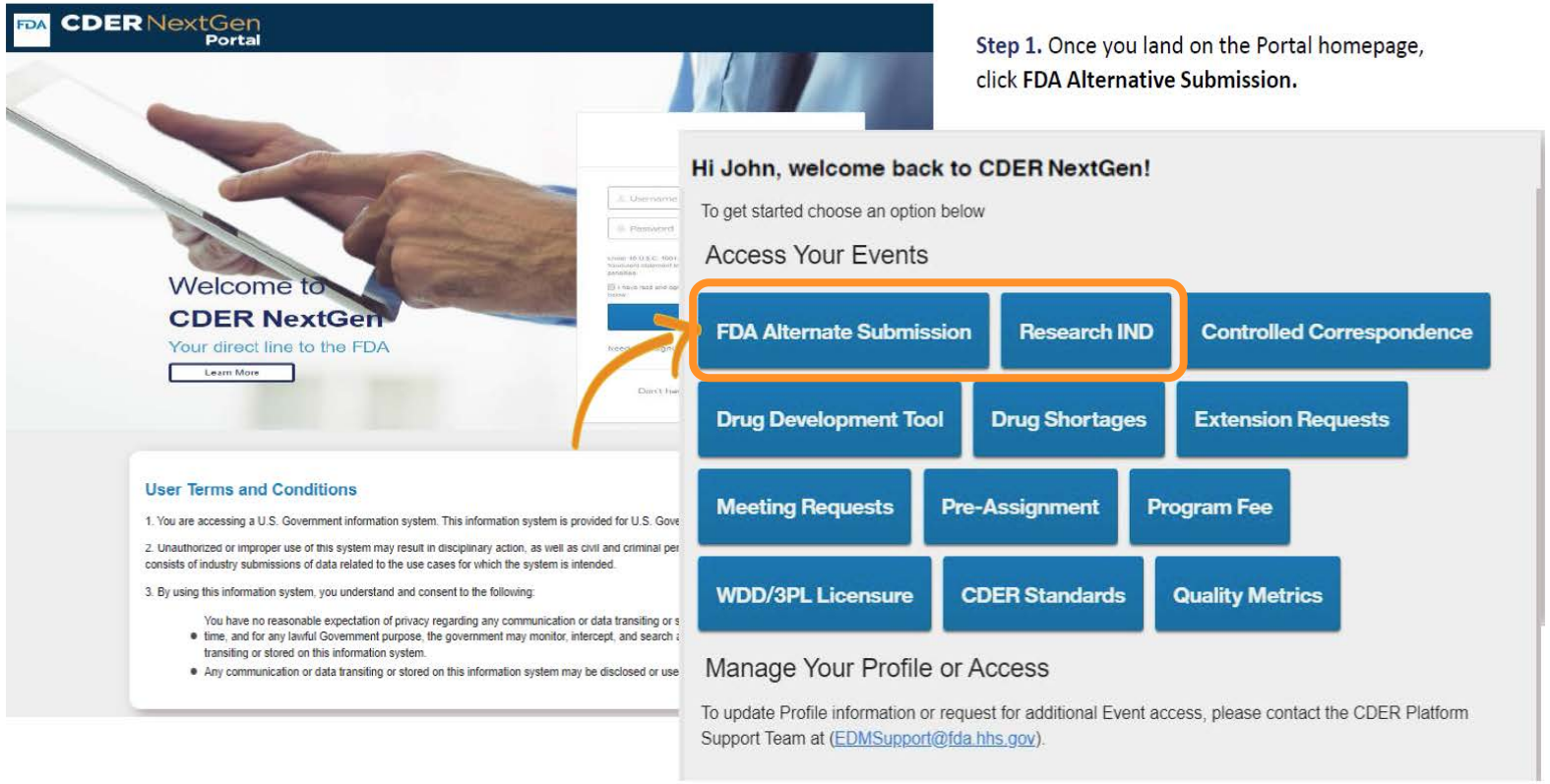
- eCTD submission to NDA, BLA, ANDA, IND, DMF applications
- Non-eCTD submission to DMF Type III, Research IND
- Non-eCTD submission to application granted eCTD Waiver
- E2B Postmarket Safety Reports (submitting to FAERS)
- SPL Submissions

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



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

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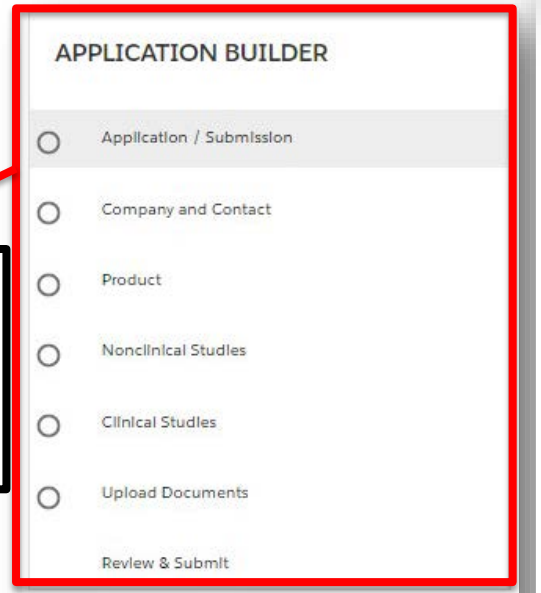
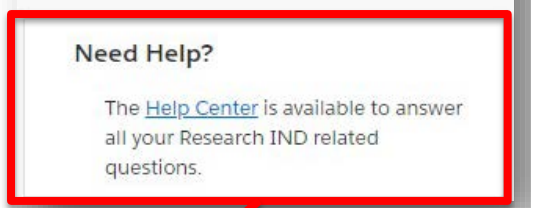
SUBMIT RESEARCH IND VIA CDER NEXTGEN PORTAL



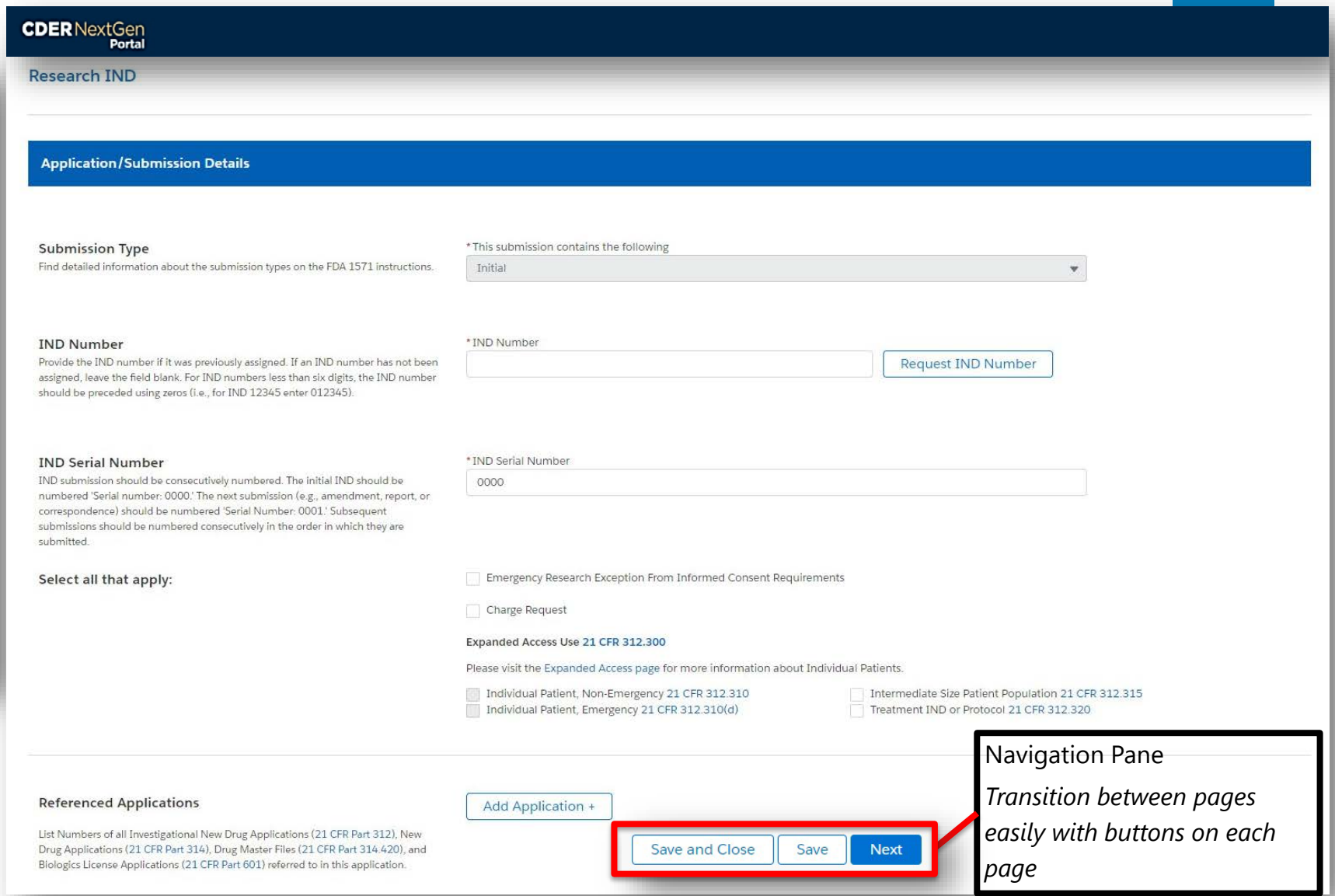
Application Builder

A convenient and logical way to complete your submissions



Help Center

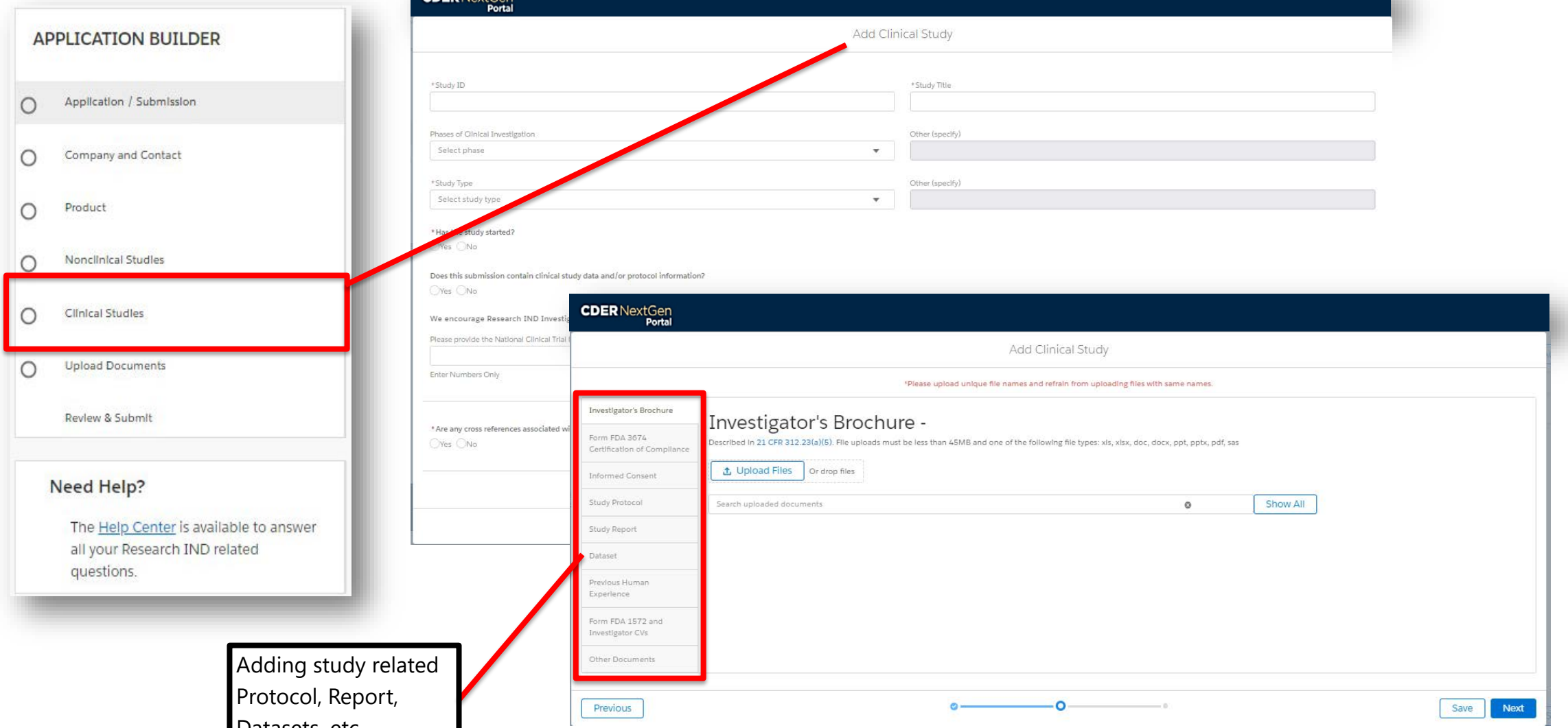
Easily accessible support when making your submission



Navigation Pane

Transition between pages easily with buttons on each page

STUDY DATA SUBMISSION USING PORTAL

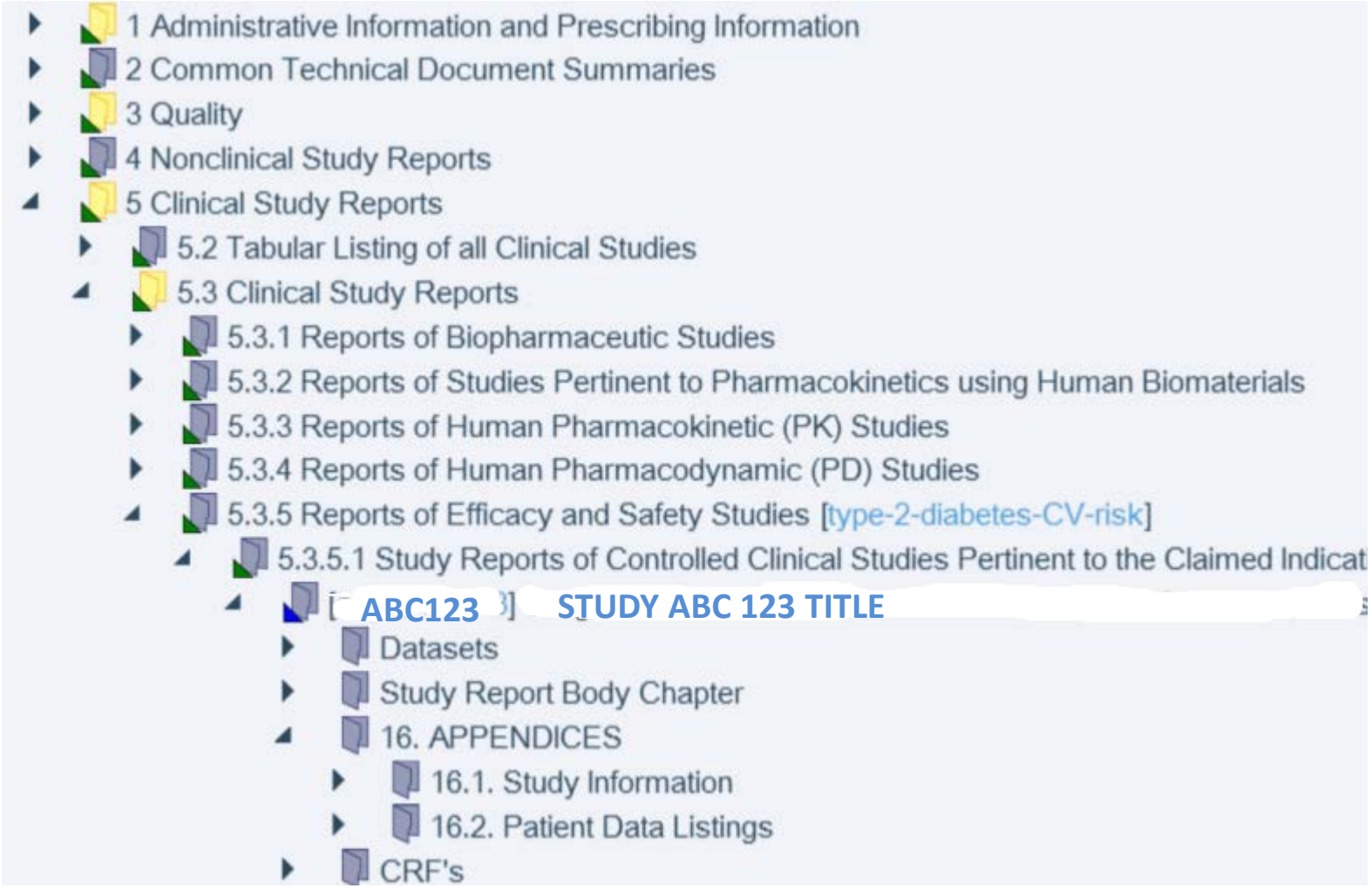


Adding study related Protocol, Report, Datasets, etc.

REVIEW AIDS

REVIEW ECTD SUBMISSION

FDA uses LORENZ docuBridge to support review of eCTD submissions



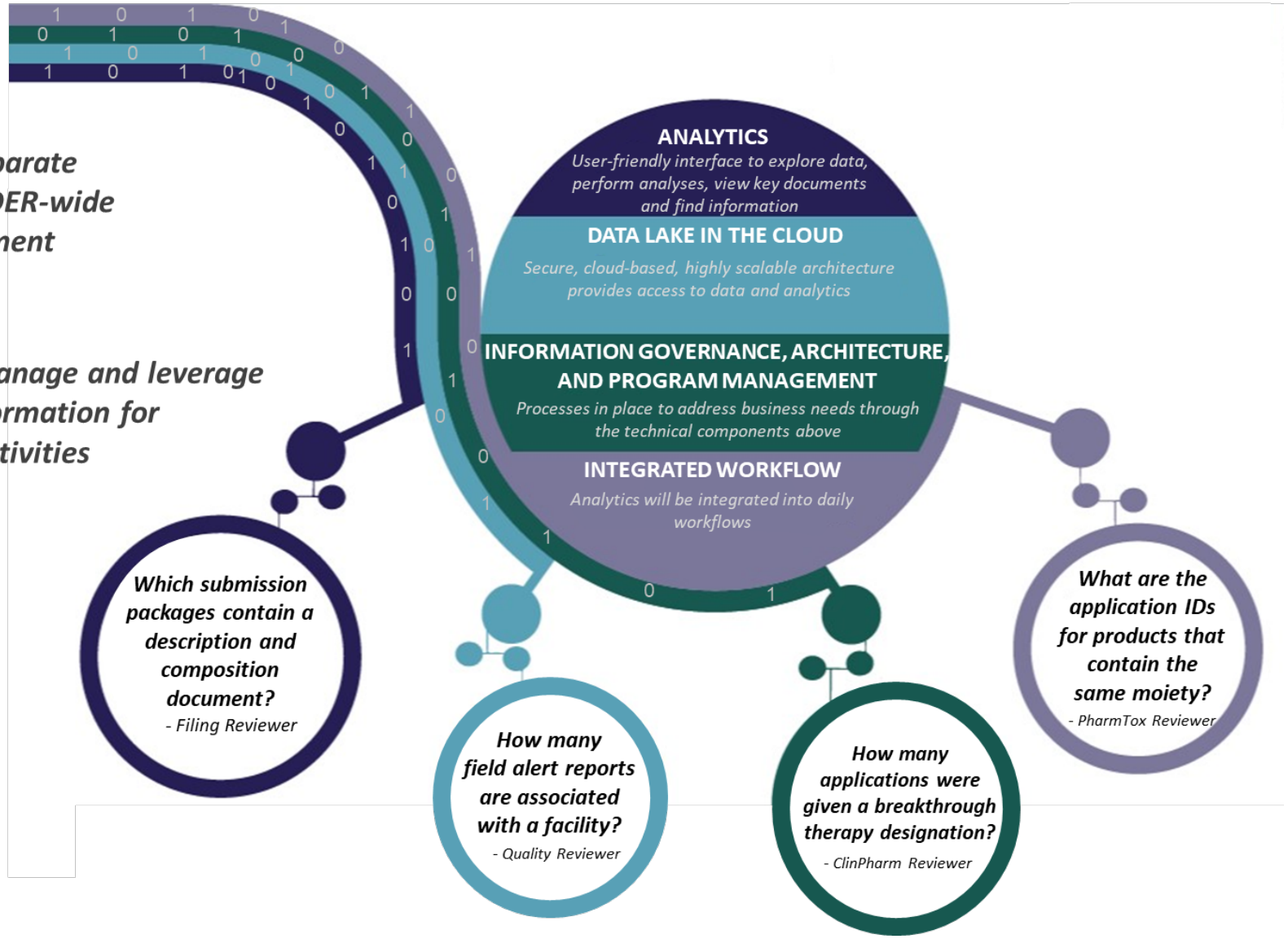
REVIEW ECTD SUBMISSION

FDA also utilizes multiple tools and systems to support analysis:

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



JOUNEY 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 standards[1] 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 JOUNEY

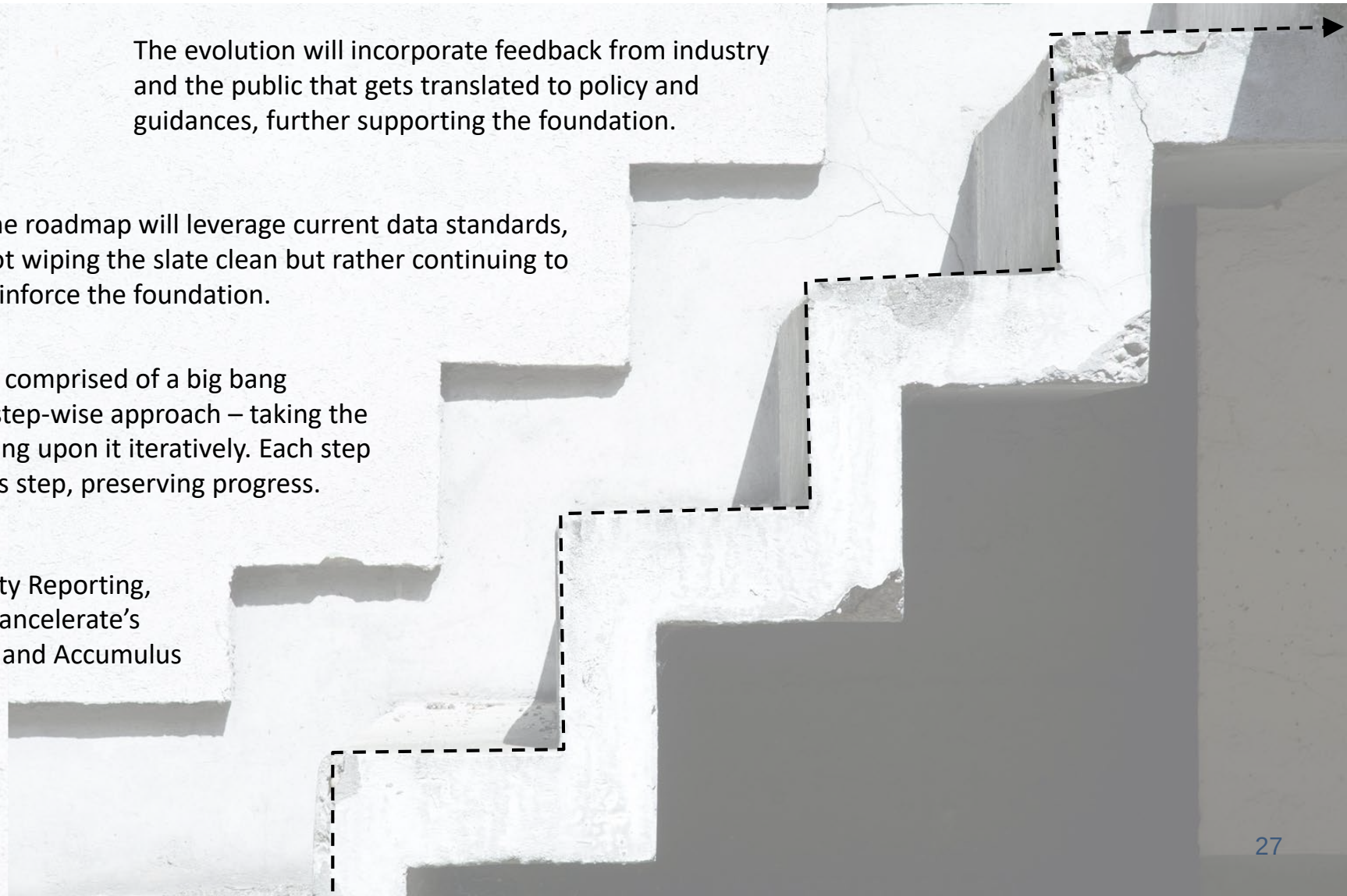
The Roadmap to the Future will Require Iteration, Agility and Collaboration

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!