

## 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.**

# PRESENTER

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## Ethan Chen

Director, Division of Data Management Services and Solutions, Office of Business Informatics | CDER | US FDA

Ethan Chen provides overall leadership to CDER in streamlining electronic and traditional submissions and delivering solutions to enable rapid adoption of emerging electronic data standards. Since joining the FDA in 2012, Mr. Chen has led several critical initiatives as the CDER Informatics Architect, including Data Management and Business Intelligence programs. While leading the CDER Division of Data Management Service and Solution, Ethan had successfully implemented the eCTD electronic submission mandate.

# Electronic Submissions Update

## - From eCTD to CDISC Implementation and Beyond

PharmaSUG Single Day Event – October 22-23, 2020

# AGENDA

- ❖ Electronic Submissions to FDA
- ❖ Study Data Conformance Analysis, Resources and Tools
- ❖ Submit to CDER via NextGen Collaboration Portal

# ELECTRONIC SUBMISSIONS TO FDA

# PURPOSE OF ECTD AND STUDY DATA REQUIREMENTS

- ❖ Reviewing study data 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 timeliness of review decisions
- ❖ CDISC Standards 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 commercial off the shelf 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>

Per FD&C Act Section 745A(a), drug application sponsors must use the standards defined in the FDA Data Standards Catalog starting 24 months after the issuance of final guidance for a specific submission type.

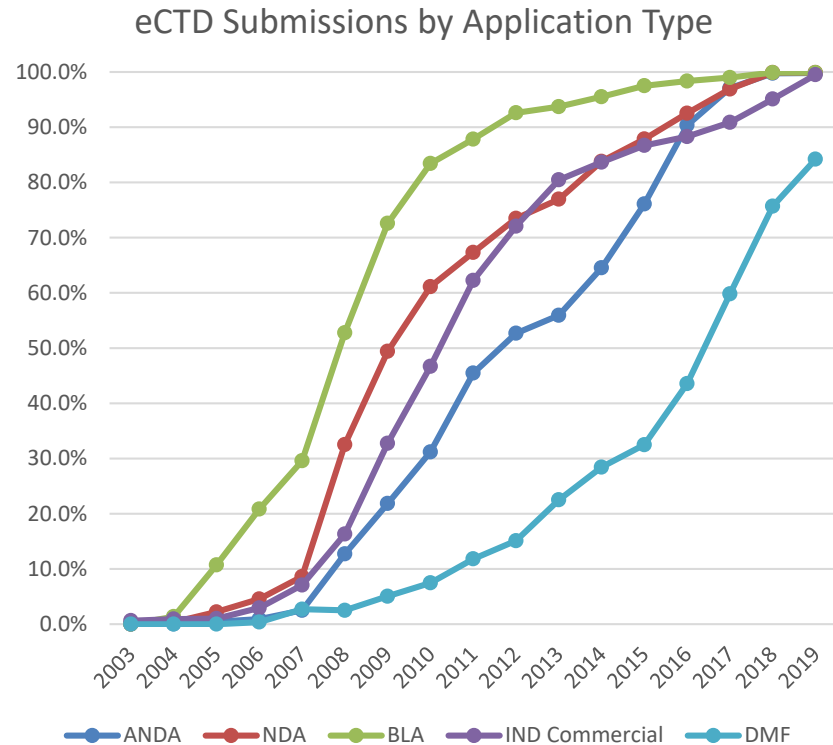
**[“eCTD Guidance”](#)** - *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*

- ❖ 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

# CURRENT STATE: RECEIVED SUBMISSIONS

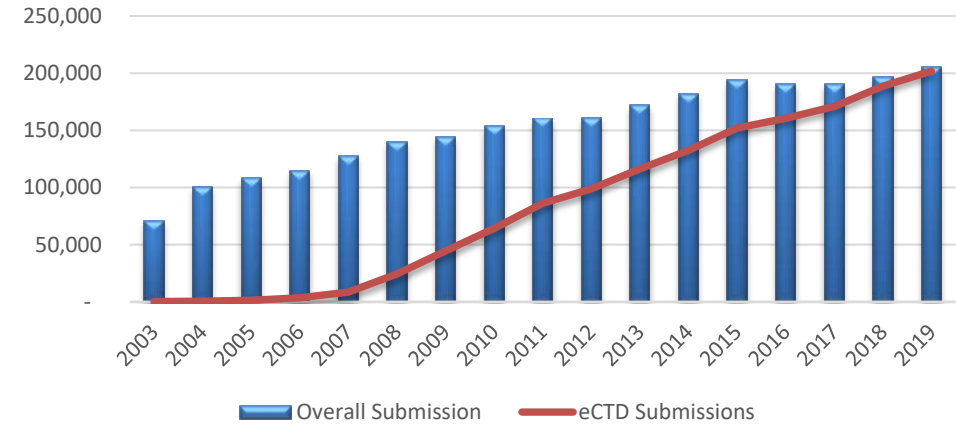


CDER received approximately 205,000\* electronic submissions via ESG in FY19. Nearly 202,000 were in eCTD.



\* Excludes promotional/advertising

Comparison: Overall Submissions vs. eCTD Submissions



In FY19, 99% of the regulatory submissions (specific to Commercial INDs, NDAs, ANDAs, BLAs, DMFs Type II, IV and V) were submitted in eCTD format



## **“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

### ❖ **FDA uses eCTD validations (1734, 1735, 1736, 1789)** to confirm Sponsors are conforming to the FDA Data Standards Catalog. This subset of eCTD validations are described in detail in the Technical Rejection Criteria for Study Data

## **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 July 2020
- ❖ [Study Data for Submission to CDER and CBER website](#)

# STUDY DATA TECHNICAL CONFORMANCE GUIDE VS. TECHNICAL REJECTION CRITERIA FOR STUDY DATA



- ❖ Study Data Technical Conformance Guide provides technical recommendations for submitting study data according to CDISC standards
- ❖ **Technical Rejection Criteria for Study Data provides the conditions under which FDA will not accept submissions with study data!**

Error	Description (Reference to FDA Technical Rejection Criteria For Study Data <u>Oct. 2019 version</u> )	Severity Level
1734	A Trial Summary (TS) dataset (ts.xpt) with information on study start date (SSD) must be present for each study in required sections*	High
1735	Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*	High
1736	For SEND data, a DM dataset and define.xml must be submitted in required sections* For SDTM data, a DM dataset and define.xml must be submitted in required sections* For ADaM data, an ADSL dataset and define.xml must be submitted in required sections*	High
1789	Study files must be referenced in a Study Tagging File (STF). STFs are not required for 4.3 Literature references, 5.2 Tabular listings, 5.4 Literature references, and 5.3.6 Postmarketing reports	High

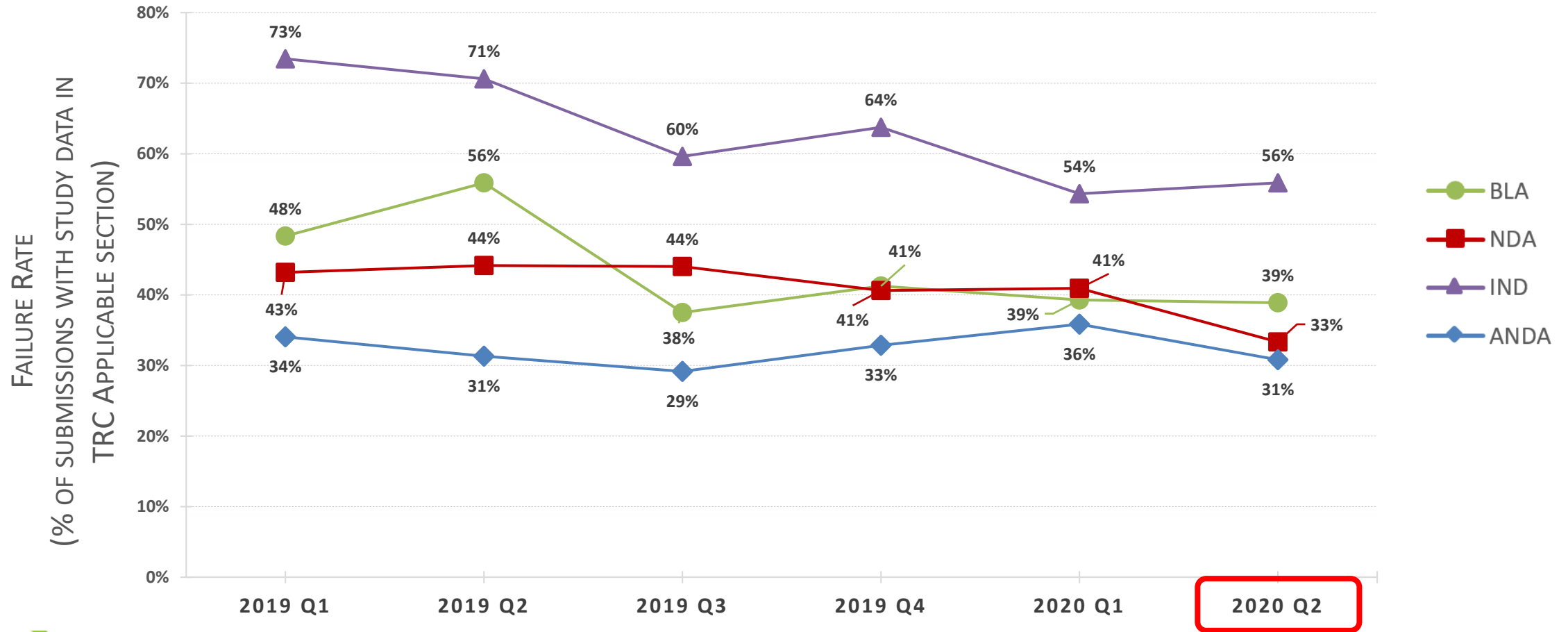
\* Refer to the latest Technical Rejection Criteria for Study Data for more details

# **STUDY DATA CONFORMANCE ANALYSIS, TOOLS AND RESOURCES**

# QUARTERLY TREND: 1734 & 1736 FAILURE RATE



Analysis includes NDA, BLA, ANDA and commercial IND submissions received by CDER between 1/1/2019 and 6/30/2020

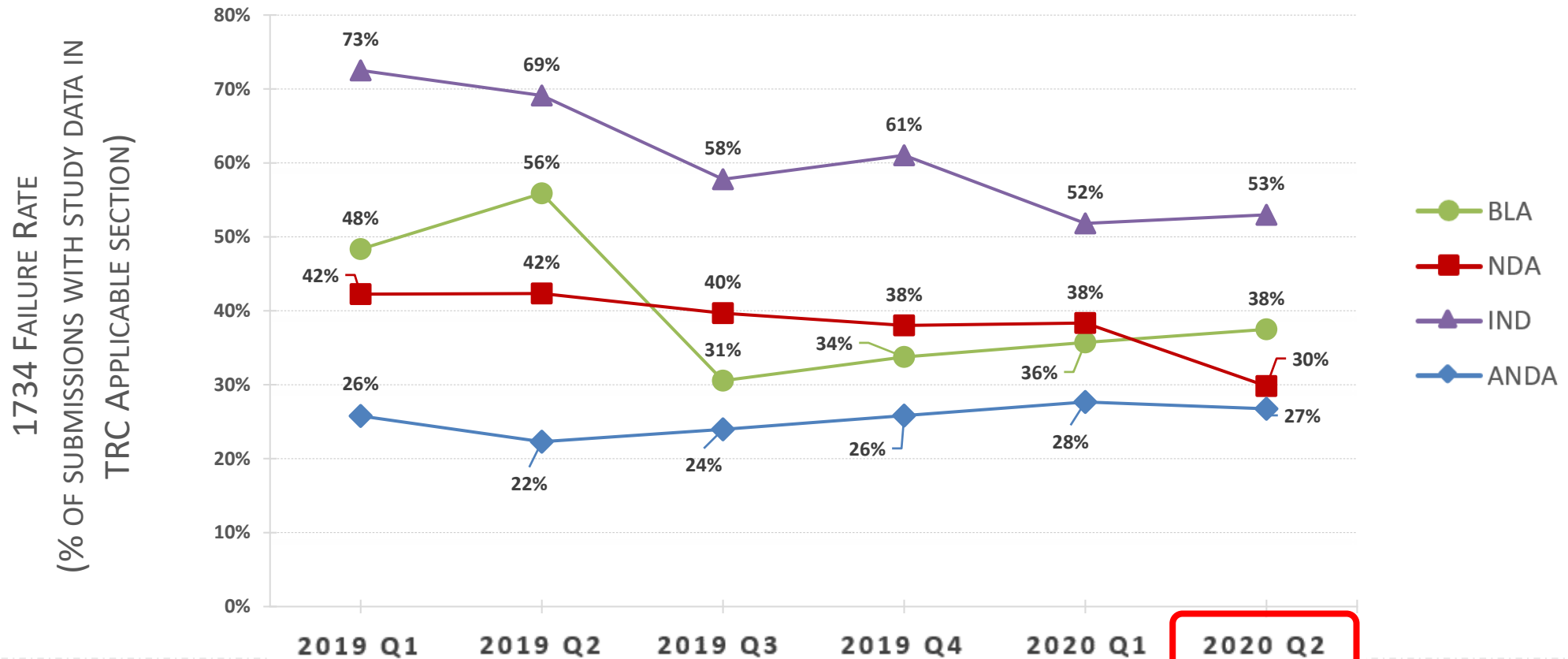


**Notes:**

- 1) Submissions with multiple studies can report both 1734 and 1736 failures
- 2) 1736 is not analyzed if the study fails 1734
- 3) Analysis is conducted according to the revised TRC (Revised Oct. 2019)

# QUARTERLY TREND: 1734 FAILURE RATE

- ❖ IND applications show the greatest decrease in the 1734 failure rate over the time period (CY2019 Q1 through CY2020 Q2)
- ❖ Compared to other application types, NDAs show the most significant decline between CY2020 Q1 and Q2
- ❖ NDA decline attributed to a lower number of M4 (non-clinical) missing ts.xpt detected and a slightly higher number of simplified ts.xpt identified



**Notes:**

- 1) Analysis includes ANDA, BLA, NDA and commercial IND submissions received by CDER between 3/1/2020 and 6/30/2020
- 2) Analysis is conducted according to the revised TRC (Revised Oct. 2019)

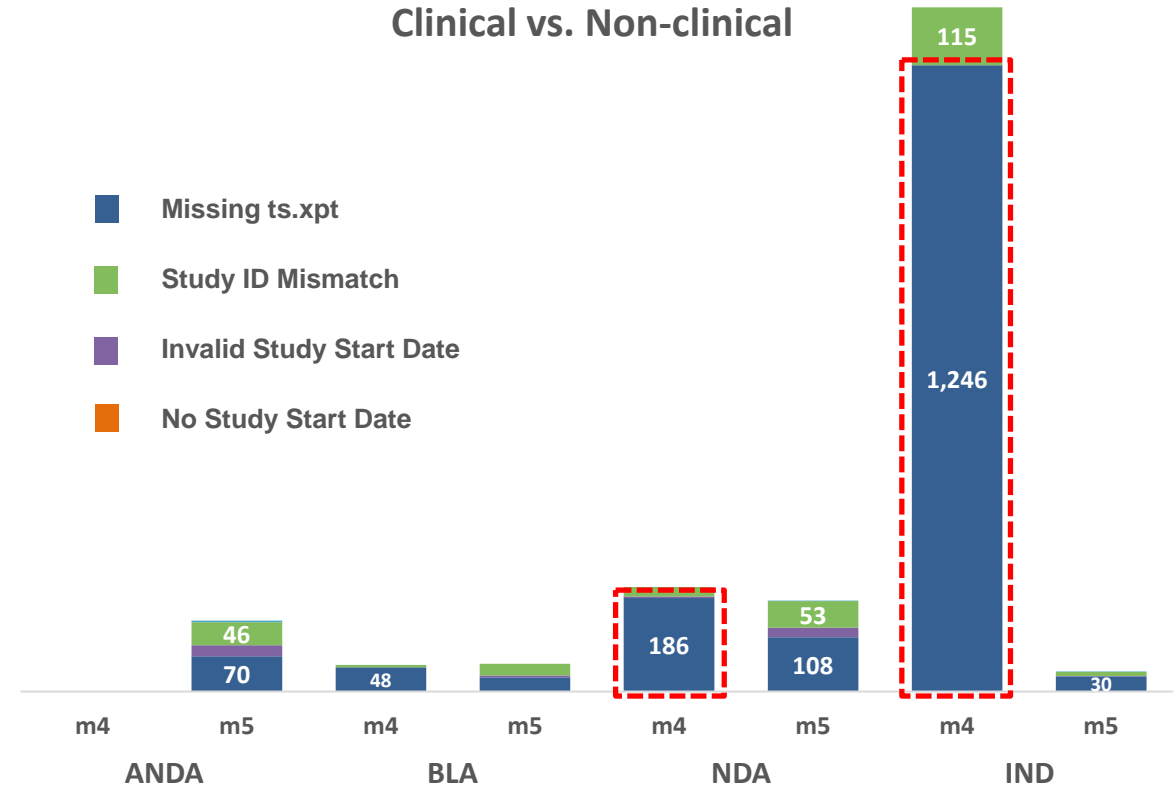
# ERROR REASONS FOR VALIDATION RULE 1734



Error	Description
<b>1734</b>	Trial Summary (TS) dataset (ts.xpt) with information on study start date must be present for required sections*

- ❖ Submitting a simplified ts.xpt with non-clinical studies will greatly reduce the 1734 error rate
- ❖ Common error reasons for all application types:
  - A missing ts.xpt file
  - Study ID Mismatch between TS and STF files

1734 Error Reasons Q1 – Q2 2020  
Clinical vs. Non-clinical



**Notes:**

\* Refer to the latest Technical Rejection Criteria for Study Data for more details

- 1) Analysis includes ANDA, BLA, NDA and commercial IND submissions received by CDER between 1/1/2020 and 6/30/2020
- 2) Analysis is conducted according to the revised TRC (Revised Oct. 2019)

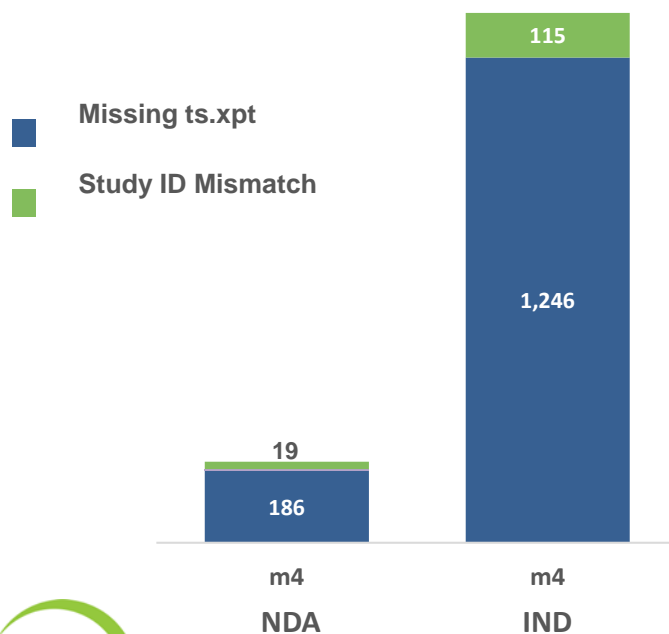
# ERROR REASONS FOR VALIDATION RULE 1734



Error	Description
<b>1734</b>	Trial Summary (TS) dataset (ts.xpt) with information on study start date must be present for required sections*

❖ **91% of 1734 errors are due to missing ts.xpt files**

1,569 Non-clinical Studies with Error 1734



❖ **70% of those errors are in the repeat dose toxicology eCTD section**

1,432 Non-clinical Studies Missing ts.xpt

	Count
<b>Studies with study data or reports</b>	<b>1,432</b>
Studies with only study reports	1,388
Studies with only study data	45

Toxicology Sections	Count
<b>Studies with study data or reports</b>	<b>1,432</b>
Repeat dose toxicology (m4.2.3.2)	997
Single dose toxicology (m4.2.3.1)	271
Carcinogenicity (m4.2.3.4)	114
Other	50

**Notes:**

- \* Refer to the latest Technical Rejection Criteria for Study Data for more details
- 1) Analysis includes ANDA, BLA, NDA and commercial IND submissions received by CDER between 1/1/2020 and 6/30/2020
- 2) Analysis is conducted according to the revised TRC (Revised Oct. 2019)

# SIMPLIFIED TS FILE EXPECTATION

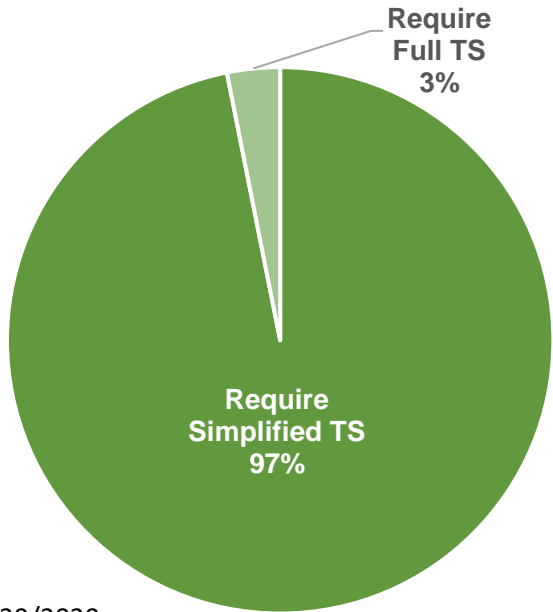
- ❖ 97% of non-clinical studies which fail 1734 can be corrected by submitting a simplified ts.xpt file
- ❖ Submitting a simplified ts.xpt with a study report does not replace the requirement to submit a full ts.xpt with SEND study data

## 1734 Errors for NDA and IND Non-Clinical studies

Total Number of Studies with Study Data and/or Study Reports in the TRC Applicable Sections	3,041
Error 1734	1,569
Missing ts.xpt	1,432

1734 Error and Simplified TS File Expectation

	Total	IND m4	NDA m4
1734 Error Missing ts.xpt	1,432	1,246	186
Require Simplified TS	<b>1,388</b>	1,208	180
Require Full TS	45	39	6



**Notes:**

- 1) Analysis includes ANDA, BLA, NDA and commercial IND submissions received by CDER between 1/1/2020 and 6/30/2020
- 2) Analysis is conducted according to the revised TRC (Revised Oct. 2019)



# SIMPLIFIED TRIAL SUMMARY FILE (TS.XPT)

- ❖ A Simplified ts.xpt file would be expected in cases in which a non-clinical study report submitted is not required to include accompanying SEND datasets
- ❖ **Simplified ts.xpt:**
  - ❖ Sponsors should submit a dataset named ‘ts.xpt’ with four variables: STUDYID, TSPARMCD, TSVAL, and TSVALNF. Exempted non-clinical studies should submit a simplified ts.xpt file with TSVALNF value as “NA”
- ❖ **Example of Simplified ts.xpt Dataset:**

STUDYID	TSPARMCD	TSVAL	TSVALNF
<ul style="list-style-type: none"> <li>• Study ID in STF File</li> </ul>	<ul style="list-style-type: none"> <li>• STSTDTC for a nonclinical study</li> </ul>	<ul style="list-style-type: none"> <li>• Format: yyyy-mm-dd</li> <li>• Left blank when study start date is not available or irrelevant</li> </ul>	<ul style="list-style-type: none"> <li>• Left blank when study start date is provided in TSVAL</li> <li>• “NA”</li> </ul>

**References:**

FDA Study Data Technical Conformance Guide (Section 8 and Appendices C Version 4.4, Oct 2019)  
 FDA Study Data Technical Rejection Criteria (Revised Oct. 2019)

# HOW TO IDENTIFY AND CREATE A SIMPLIFIED TS.XPT

- ❖ **Sponsors should submit a simplified ts.xpt even if datasets are not submitted for a non-clinical study**
- ❖ To understand if a simplified ts.xpt file is required, please review the TRC Self-Check Worksheet
- ❖ FDA has created a step-by-step [Simplified ts.xpt Creation Guide](#) on how to create a simplified ts.xpt using free and open source tools such as R or Python
- ❖ There is also a utility ([https://geotiger.shinyapps.io/07\\_genTS/](https://geotiger.shinyapps.io/07_genTS/)) created by the PhUSE Standard Analyses & Code Sharing working group to assist in generating a simplified ts.xpt file

# FDA TOOLS: STUDY DATA SELF-CHECK WORKSHEET & INSTRUCTIONS

- ❖ Technical Rejection Criteria for Study Data (Oct 2019)
- ❖ Technical Rejection Criteria Self-Check Worksheet (Nov 2019)
- ❖ Technical Rejection Criteria Self-Check Worksheet Instructions (Nov 2019)
- ❖ Guide to create Simplified TS using free and open source software ( R and Python)

The screenshot shows a webpage titled "Study Data for Submission to CDER and CBER" under the "Study Data Standards Resources" section. The page includes social media sharing options (Facebook, Twitter, LinkedIn, Email, Print) and a "Sign up for email updates" link. The main content discusses data standards, their benefits for modernizing the review process, and provides contact information for CDER and CBER. It also mentions that FDA is instituting new requirements for data standards that will apply to most study data submitted to CDER and CBER. A "Stay Connected" sidebar provides contact details for CDER eDATA and CBER ESUB teams.

Study Data Standards Resources / Study Data for Submission to CDER and CBER

## Study Data for Submission to CDER and CBER

Share Tweet LinkedIn Email Print

[Sign up for email updates.](#)

**Study Data Standards Resources**

- Study Data for Submission to CDER and CBER

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 specified time period and developed a presentation on the overall conformance results. [Study Data Conformance \(PDF\)](#) To assist sponsors when submitting study data FDA has created the [Technical Rejection Criteria Self-Check Worksheet \(PDF\)](#) and [Worksheet Instructions \(PDF\)](#).

CDER and CBER strongly encourage Investigational New Drug (IND) sponsors and NDA applicants to consider the implementation and use of study data standards as early as

**Stay Connected**

If you have study data questions for CDER, please contact the CDER eDATA Team at [cdere-data@fda.hhs.gov](mailto:cdere-data@fda.hhs.gov).

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

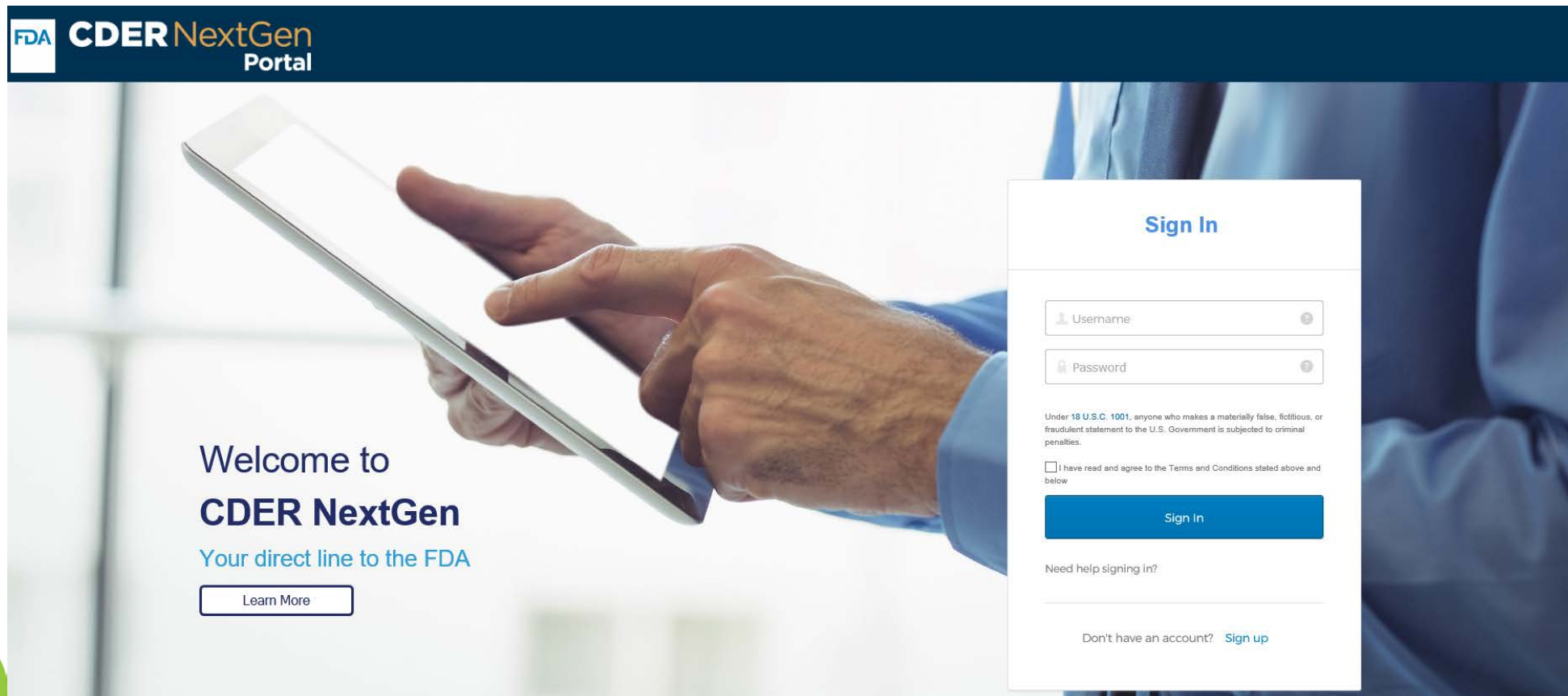
# WHEN WILL STUDY DATA TRC BE EFFECTIVE?



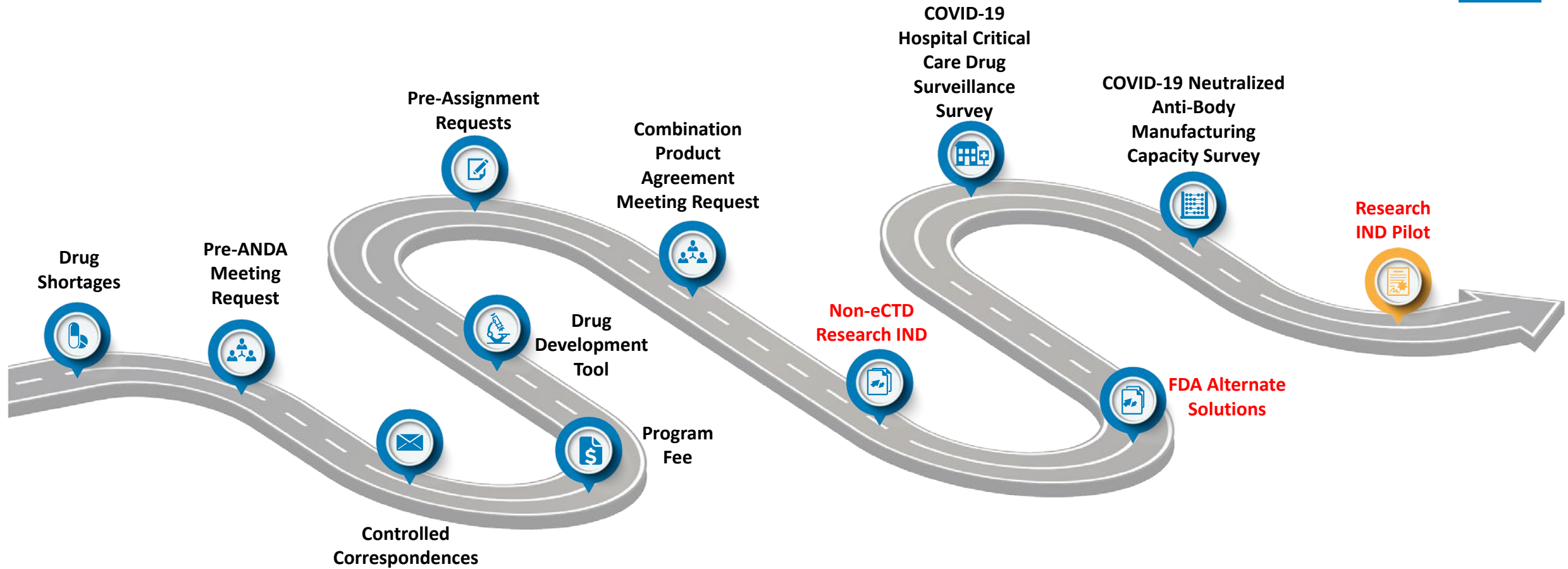
**SUBMIT TO CDER VIA NextGen PORTAL**

# WHAT IS CDER NextGen PORTAL

The CDER NextGen **Portal** is a **cloud-based** system that has enabled a transformation in the way CDER and industry work together.



# CDER NextGen PORTAL PATHWAY



# ELECTRONIC SUBMISSION PATHS TO CDER

## 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 Post-market 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)

## CDER NextGen (CDER Only except for DDT)

- Request an Application Number
- 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)
- Non-eCTD submission of Medical Gas, Promotional Material, EUA, or Pre-submission Correspondence
- COVID-19 Hospital Critical Care Drug Surveillance Survey
- COVID-19 Neutralized Anti-Body Manufacturing Capacity Survey



## WHAT IS RESEARCH IND IN CDER NextGen?

**What's New:** FDA recently added a new event in the CDER NextGen Portal for Research IND submissions

**Target Audience:** Sponsors who currently submit Research INDs in paper (non-eCTD)\*

**Benefits of Submitting via CDER NextGen Portal:**

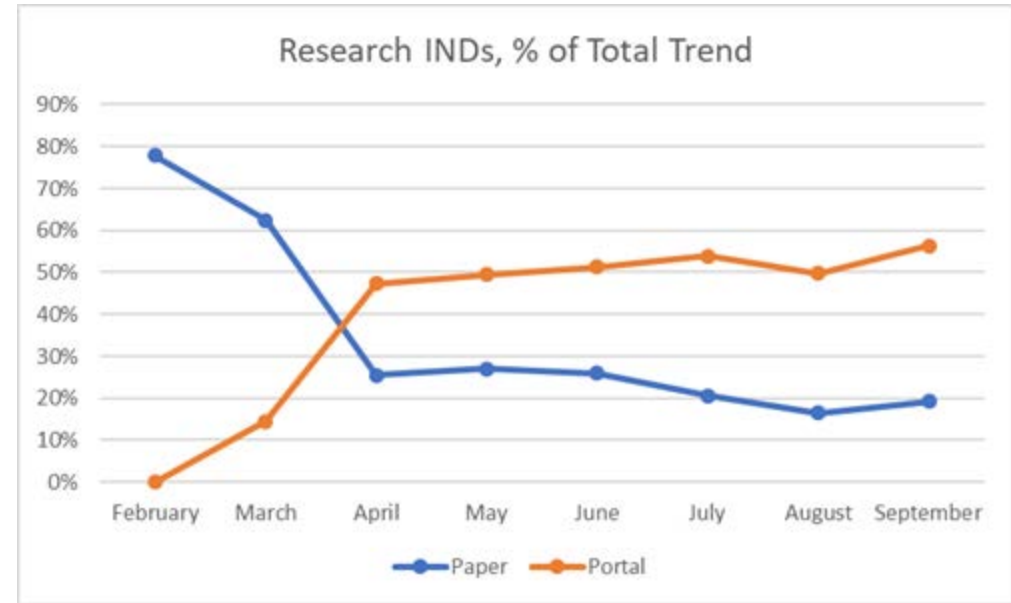
<https://www.fda.gov/media/136301/download>

\*This is for Research INDs only. Commercial INDs must be in eCTD and may not use the CDER NextGen Portal unless granted an eCTD waiver. See *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications Guidance for Industry* ([eCTD Guidance](#)) for more information.

# RESEARCH IND SUBMISSION TREND



Paper Submission of Research INDs dropped from 78% to 19% after the release of CDER NextGen **Portal** solution in March. The solution improved timely access to documents.



2020	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep
<b>Paper</b>	78%	62%	26%	27%	26%	21%	16%	19%
<b>Portal</b>	0%	15%	47%	50%	51%	54%	50%	56%
<b>Gateway</b>	22%	23%	27%	23%	23%	26%	34%	24%
<b>Total</b>	100%	100%	100%	100%	100%	100%	100%	100%

# SUPPORT FOR YOUR ELECTRONIC SUBMISSION

- ❖ eCTD and General Electronic Submission Questions – [esub@fda.hhs.gov](mailto:esub@fda.hhs.gov)
- ❖ Study Data Submissions – [edata@fda.hhs.gov](mailto:edata@fda.hhs.gov)
- ❖ CDER NextGen Portal Submissions – [edmsupport@fda.hhs.gov](mailto:edmsupport@fda.hhs.gov)



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*Thank  
You*