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.
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
ELECTRONIC SUBMISSION GUIDANCE

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

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.

* Excludes promotional/advertising
“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 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!

<table>
<thead>
<tr>
<th>Error</th>
<th>Description (Reference to FDA Technical Rejection Criteria For Study Data Oct. 2019 version)</th>
<th>Severity Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1734</td>
<td>A Trial Summary (TS) dataset (ts.xpt) with information on study start date (SSD) must be present for each study in required sections*</td>
<td>High</td>
</tr>
<tr>
<td>1735</td>
<td>Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*</td>
<td>High</td>
</tr>
</tbody>
</table>
| 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

- 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

### Error Description

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

### 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

<table>
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<td>1734</td>
<td>Trial Summary (TS) dataset (ts.xpt) with information on study start date must be present for required sections*</td>
</tr>
</tbody>
</table>

- **91% of 1734 errors are due to missing ts.xpt files**
- **70% of those errors are in the repeat dose toxicology eCTD section**

1,569 Non-clinical Studies with Error 1734

- **1,432 Non-clinical Studies Missing ts.xpt**
  - Studies with study data or reports: 1,432
  - Studies with only study reports: 1,388
  - Studies with only study data: 45

**Toxicology Sections**

- 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 studies

| Error 1734 | 1,569 |
| Missing ts.xpt | 1,432 |

1734 Error and Simplified TS File Expectation

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

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)
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:

<table>
<thead>
<tr>
<th>STUDYID</th>
<th>TSPARMCD</th>
<th>TSVAL</th>
<th>TSVALNF</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Study ID in STF File</td>
<td>• STSTDTC for a nonclinical study</td>
<td>• Format: yyyy-mm-dd</td>
<td>• Left blank when study start date is provided in TSVAL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Left blank when study start date is not available or irrelevant</td>
<td>• “NA”</td>
</tr>
</tbody>
</table>

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/) 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)
WHEN WILL STUDY DATA TRC BE EFFECTIVE?

- Public Notice
- Provide warning message as part of 3rd acknowledgement
- Enforcement 6 months after the Public Notice
SUBMIT TO CDER VIA NextGen PORTAL
The CDER NextGen Portal is a cloud-based system that has enabled a transformation in the way CDER and industry work together.
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.

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<th>Mar</th>
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SUPPORT FOR YOUR ELECTRONIC SUBMISSION

- eCTD and General Electronic Submission Questions – esub@fda.hhs.gov
- Study Data Submissions – edata@fda.hhs.gov
- CDER NextGen Portal Submissions – edmsupport@fda.hhs.gov
ACKNOWLEDGMENTS

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