Why We Should Care about eCTD in the Submission Process

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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.

Note: this training will be based on FDA submission, not other agencies

Agenda

- Why is “Standards in Submission” important?
- What Biometric needs to prepare for eSubmission
- Introduction of eCTD (Electronic Technical Document)
- Biometric Submission Package based on eCTD
- How can we validate eCTD – Specification for eCTD Validation Criteria
- Biometric Department Responsibilities for Submission
- Conclusion

Why September is important for me?

Offensive Lineman vs Biometric department?

As an offensive lineman, **my best game day** would be when my quarterback is always protected and **no one notices me for doing my job.**

Why is “Standard in Submission” important?

Standards as Required by FDA Data Standards Catalog

According to **FDA Data Standards Catalog**, all clinical trial studies starting after December 17th, 2016 with the exception of certain INDs will be **required** to have **CDISC compliant data**.
And after May 5th, 2017, all the submission files should follow **electronic common technical document (eCTD)**.

FDA Data Standards Catalog v6.0 (07-19-2019) - Supported and Required Standards

For full description of column headings, see Instr.& Column Descriptions tab

Use	Data Exchange Standard	Exchange Format	Standards Development Organization (SDO)	Supported Version	Supported Implementation Guide Version	FDA Center(s)	Date Support Begins (MM/DD/YYYY)	Date Support Ends (MM/DD/YYYY)	Date Requirement Begins (MM/DD/YYYY)	Date Requirement Ends	Statutory, Regulatory, or Guidance Authority	Information Sources
Regulatory Applications (IND, NDA, ANDA, BLA, master files)	Electronic Common Technical Document (eCTD)	Extensible Markup Language (XML)	International Council for Harmonisation (ICH)	3.2.2	M2 eCTD: Electronic Common Technical Document Specifications	CDER, CBER	06/01/2008		05/05/2017 [5] 05/05/2018 [6]		Regulatory Submissions in Electronic Format	Electronic Submissions-Electronic Comm Technical Document (eCTD)
Documents	PDF	PDF	Adobe	1.7	N/A	CBER, CDER, CDRH	11/20/2012					For CDRH only: eCopy Program for Med Device Submissions
Clinical and Non-Clinical study data sets - Transport	SAS (XPORT)	XPT	SAS	5	SAS Technical Support TS-140	CDER, CBER	Ongoing		12/17/2016 [1] 12/17/2017 [2]		Standardized Study Data	For CDER and CBER only: Technical Confo Guide
Sharing Structured Information	XML		W3C	1.0		CBER, CDER, CDRH	Ongoing					W3C - XML Technology
Analysis program files	ASCII		ANSI			CBER, CDER, CDRH	Ongoing					ANSI

Why is it Important?

Is it possible that FDA can reject your application if submission data do not meet FDA requirements?

YES

What Biometric needs to prepare for eSubmission

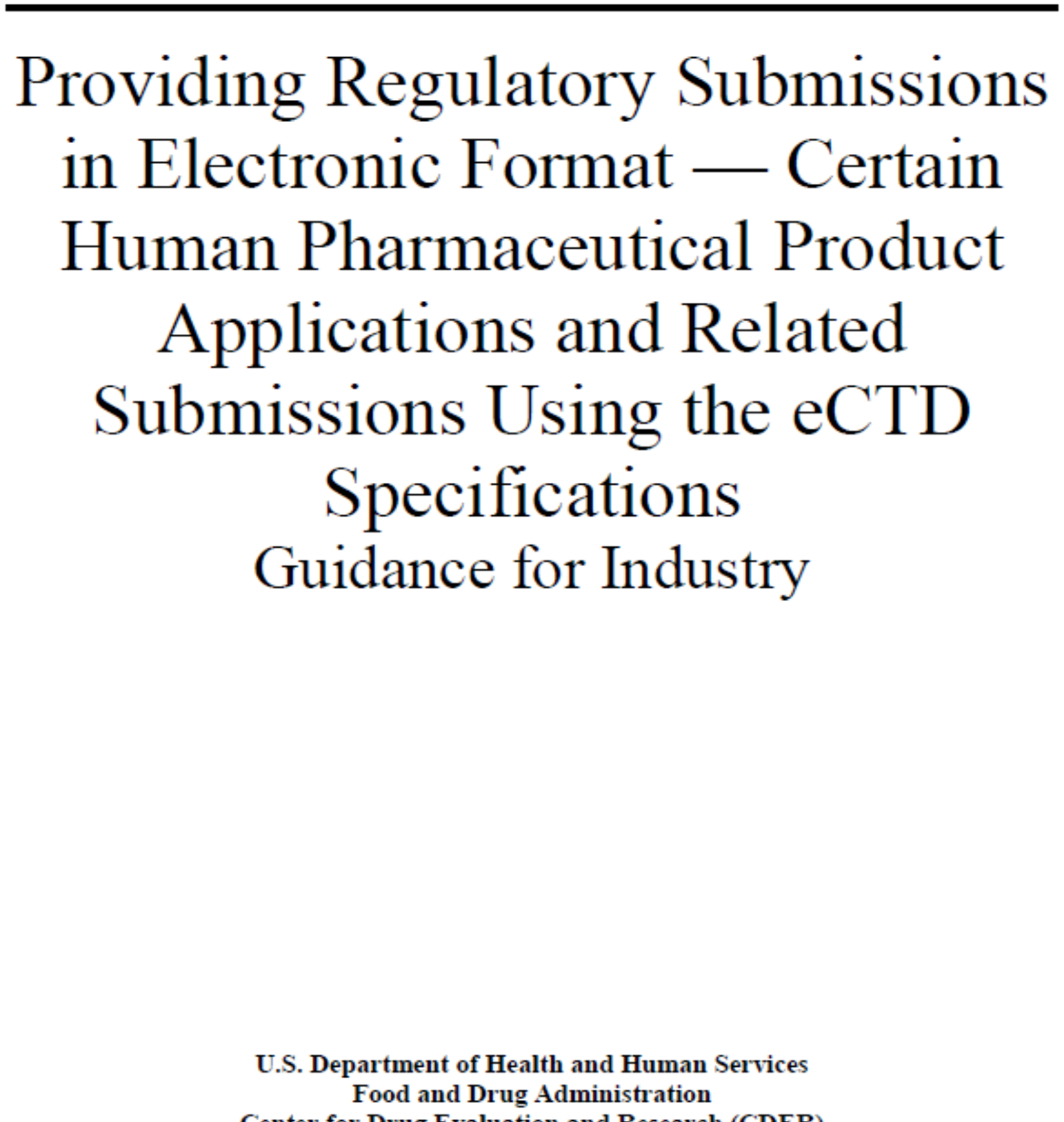
Biometric Department Submission

- Submission Documents
  - SAP
  - Protocol
  - CSR

- Submission Data Packages
  - SEND
  - SDTM
  - ADaM

Introduction of eCTD (Electronic Technical Document)

Electronic Formats of Submission Package According to eCTD (electronic Common Technical Document)



Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

January 2019
Electronic Submissions
Revision 6

Electronic Common Technical Document (eCTD)

- Introduction of eCTD - The Standard format for submitting applications, amendments, supplements, and reports to FDA CDER and CBER

- File formats (i.e., pdf, txt, xml and xpt)

- eCTD Submission folder - modules and their contents
  - Module 1 – Administrative information
  - Module 2 – Summary document
  - Module 3 – Quality
  - Module 4 – Non-clinical Study Reports
  - **Module 5 – Clinical Study Information**

Naming Conventions of Electronic Files According to eCTD Guidance

- Lower case of letter from “a” to “z” (i.e., ae.xpt)
- Number from “0” to “9”
- “-” hyphen (i.e., c-adae-sas.txt)
- No special character (#, %, $ and etc.)
- File name should be less than or equal to 64 characters including the appropriate file extension
- The length of entire path of the file should not exceed 230 characters. (m5/datasets/study001/tabulations/sdtm/ae.xpt)

pdf File Guidance According to eCTD Guidance

Version – 1.4 thru 1.7 are acceptable

Fonts

- Standard : Arial, Courier New, Times Roman
- Sizes : range from 9 to 12 point (Times New Roman 12-point font is recommended for narrative text)

Page

- Print area : 8.5 inches by 11 inches
- Margin : at least ¾ inch

xpt File Formats Guidelines

Length

- Variable length is less than or equal to 8
- Variable label is less than or equal to 40
- Dataset name length is less than or equal to 8
- Dataset label is less than or equal to 40

Dataset Size

- less than 5 GB

The length of character variables

- should be minimized – i.e., if the maximum length of USUBJID is 20 characters long, keep the length as 20, not 200.

xpt File Formats Guidelines (2)

Variable

- Variable name should consist of Upper case and numbers.
- Variable name must start with a letter.

Dataset

- Dataset name should consist of lower case and numbers.
- Dataset name must start with a letter.

Label

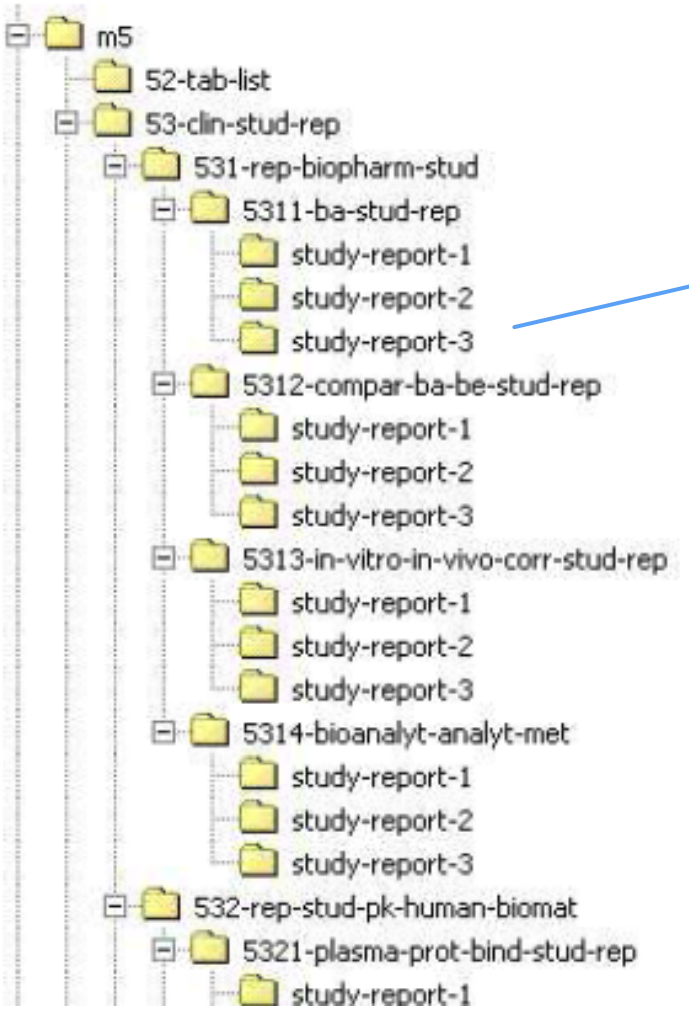
- Variable and dataset labels can include punctuation characters. No special characters such as >, < apostrophe, quotation marks.

Format of Electronic Files in a compliance with eCTD

Protocol	pdf (i.e., protocol.pdf)
SAP	pdf (i.e., sap.pdf)
eCRF	pdf (i.e., crf.pdf)
SDTM	xpt (i.e., dm.xpt, ae.xpt, and ds.xpt)
ADaM	xpt (i.e., adsl.xpt, adae.xpt, adtteos.xpt)
SEND	xpt (i.e., dm.xpt, se.xpt, and bw.xpt)
CSR	pdf (i.e., csr.pdf)
Define	xml (i.e., define.xml)
ADaM SAS programs	txt (i.e., c-adsl.sas.txt)
Efficacy SAS programs	txt (i.e., t-14-01-001-ds.sas.txt)
SDRG/ADRG/SDSP	pdf (i.e., csdrg.pdf, adrg.pdf, nsdrg.pdf)

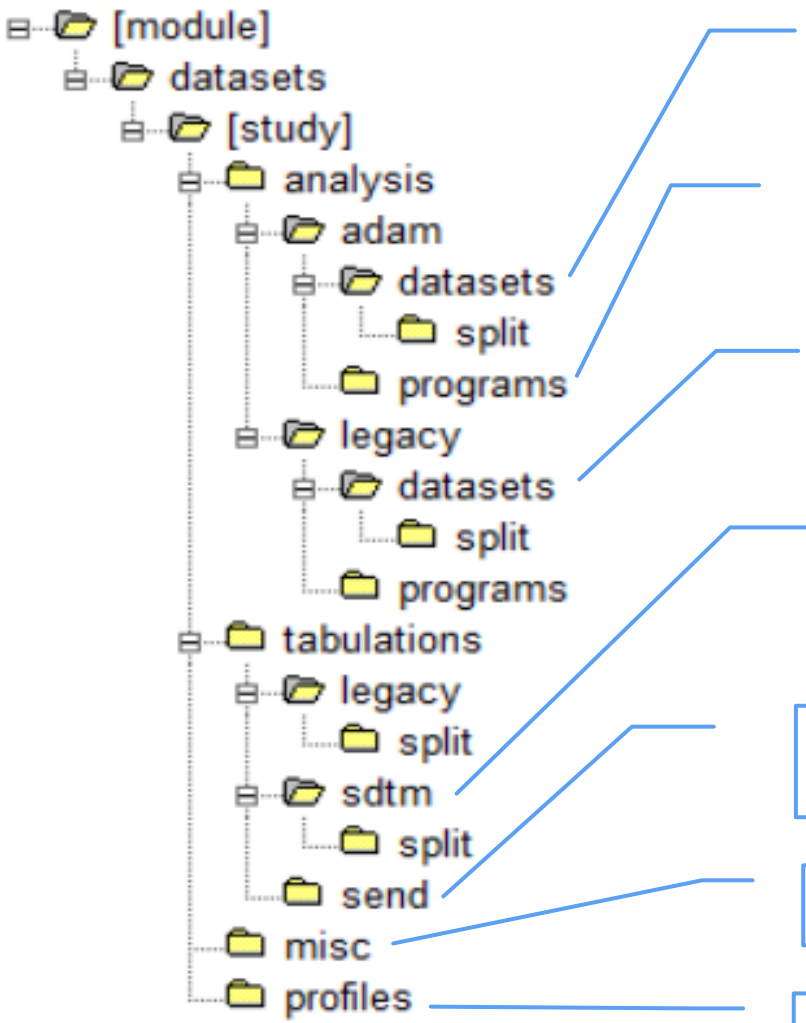
Biometric Submission Package based on eCTD

Documents in Module 5.3.1.1



CSR, SAP, Protocol, CRF

CDISC Datasets in Module 4.datasets or 5.datasets



ADaM xpt datasets, Define.xml, ADRG

ADaM SAS programs, TFL SAS programs

Legacy xpt datasets, Define.xml, RG

SDTM xpt datasets, define.xml, SDTM annotated blank CRF, cSDRG

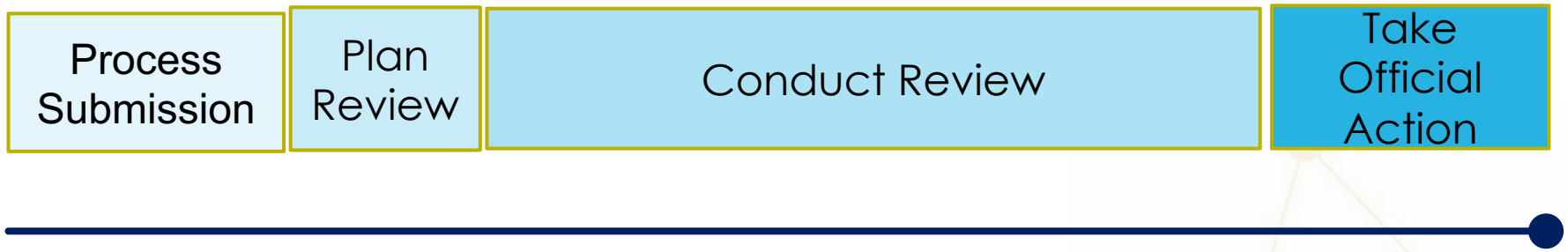
SEND xpt datasets, define.xml, nSDRG

Any xpt datasets

Patient profile

How can we validate eCTD – Specification for eCTD Validation Criteria

FDA Rejection Process



Month :

0 1 2 3 4 5 6 7 8 9 10

Technical Rejection (Day 1 - 3)

RTF (Day 60)

How to Validate eCTD - Specification for eCTD Validation Criteria

Specifications for eCTD Validation Criteria

These specifications detail the validation criteria applied when FDA processes eCTD submissions. They provide a description of the error, an explanation of the error, the corrective steps necessary to correct the error and the severity level that has been assigned to the error.

Severity Levels

The severity levels outline the impact on the official receipt of your submissions.

Severity	Description
High	The error is a serious technical error which prevents the processing of the submission and will require resubmission. The submission is considered not received by FDA.
Medium	The error may impact the reviewability of the submission but cannot be determined without further inspection by the review staff. The submission might be considered received by FDA.
Low	The error is a technical error which may or may not impact the reviewability or the integrity of the submission. The submission will likely be considered received by FDA.

Note: The FDA utilizes a commercial off-the-shelf product to validate eCTD submissions. The vendor provides the error numbers, groups, and sections. These may be subject to change from time to time. Should they change, this document will be updated accordingly. Error codes 2-7 are not validated by a commerical off-the-shelf product.

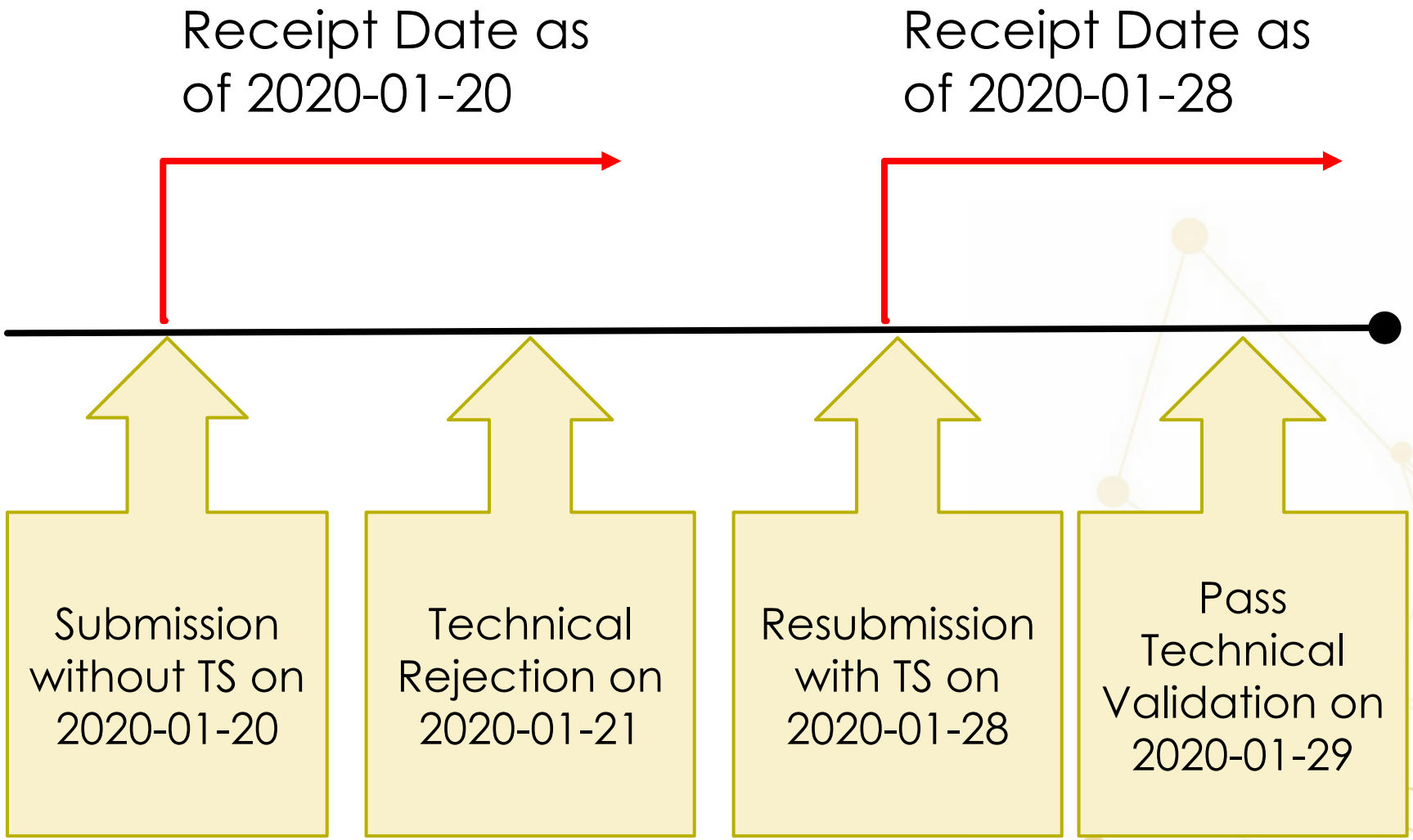
Examples of eCTD Validation Criteria

Number	1734
Group	General
Description	A Trial Summary (TS) dataset must be presented for each study in section 4.2 or in section 5.3
Severity Description	High
US DTD Version	2.01 and 3.3
Effective Date	TBD
Problem	You have not submitted a Trial Summary (TS) dataset for each study in Module 4, section 4.2 or in Module 5, section 5.3
Corrective Action	Resubmit, including a Trial Summary for each study in Module 4, section 4.2 or in Module 5, section 5.3
Guidance Source	Providing Regulatory Submissions in Electronic Format – Standardized Study; Study Data Technical Conformance Guide

Examples of eCTD Validation Criteria

Number	1255
Group	File checks
Description	Invalid file extension
Severity Description	Medium
US DTD Version	2.01 and 3.3
Effective Date	3/10/2008
Problem	You provided a file extension that is not allowed in this section.
Corrective Action	Only certain file extensions are valid in certain sections, therefore it is important to submit extensions only in the sections in which they are allowed. Corrective action may be necessary based on where the file with the invalid extension appears in the submission. You will be contacted if corrective action is necessary.
Guidance Source	ICH eCTD Specification V3.2.2 Appendix 2; Specifications for File Format Types Using eCTD Specifications V1.0

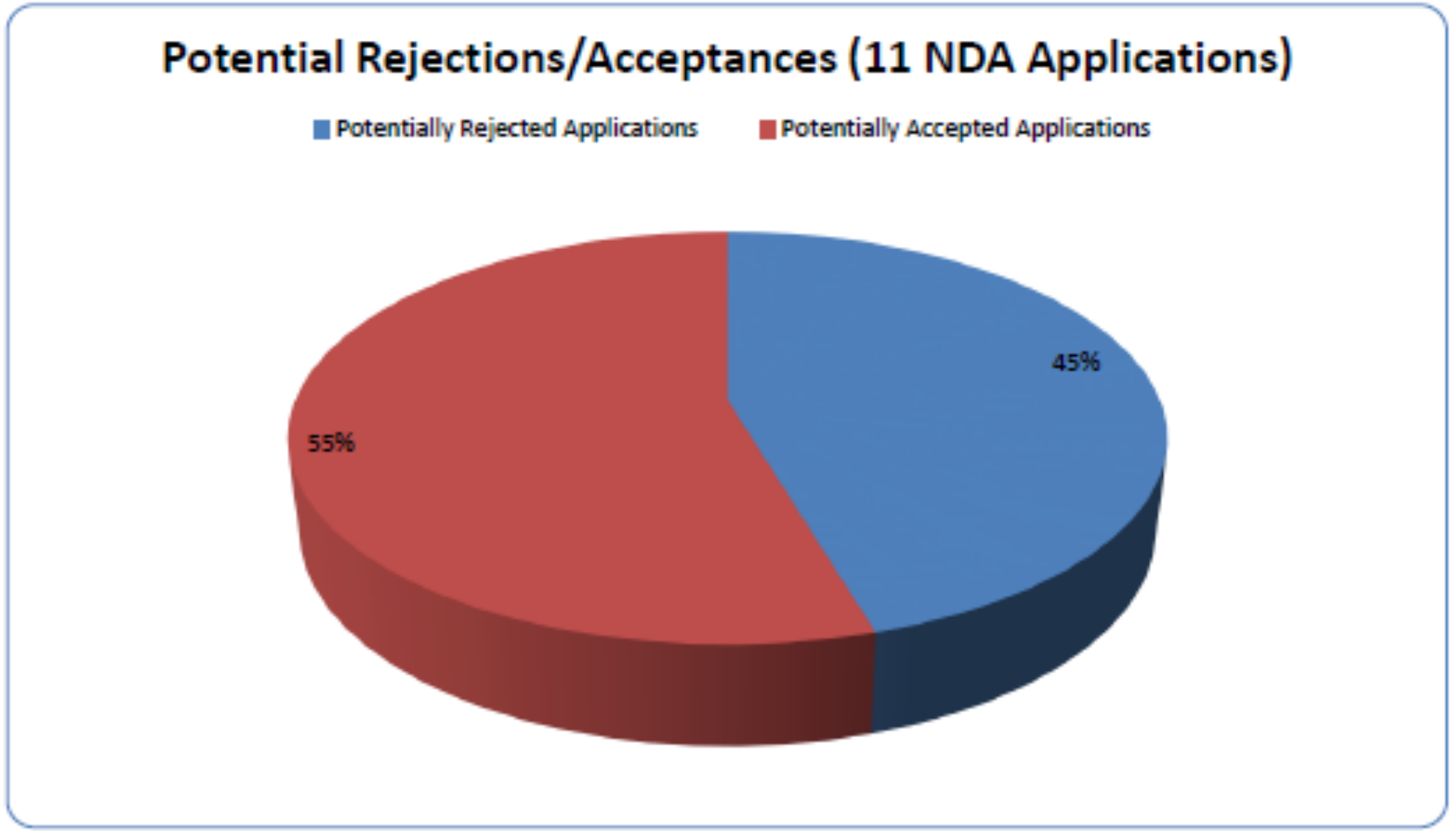
Use Case 1


Receipt Date as of 2020-01-20
Receipt Date as of 2020-01-28
Submission without TS on 2020-01-20
Technical Rejection on 2020-01-21
Resubmission with TS on 2020-01-28
Pass Technical Validation on 2020-01-29

Biometric Department Responsibilities for Submission

- Standards compliant FDA submission
  - CDISC
  - eCTD
  - Rejection Criteria
- BIMO packages
- Advancement in technology
- Regulatory changes / advancements

FDA Pilot Project



Data source: PHUSE/Computational Science Symposium 2017, FDA presentation


PASSPORT CONTROL
CUSTOMS
REISEPASS

What is Our Best Game Day?

- No Rejection due to FDA compliance issues
- No / Fewer Questions from FDA related to FDA compliance issues

Thank you!

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