Biotoxtech

인류의 생명과 건강을 지키는 생명공학벤처기업

SEND Needs in the Industry (KOREA) and Expected Changes in the Future

2024.11.13

Biotoxtech
이혜영

CONTENTS

Biotoxtech

1) FDA의 전자테이터 (eStudy Data) 제출 의무화 배경

FDA

제약회사로부터
방대한
신청데이터 입수

비임상시험 data
- Computer system
수기입력
- PDF 첨부

승인심사 시간의
대부분을 차지함

승인심사에 걸리는
노력/시간 경감
필요성

2012년
임상시험/비임상시험
신청용 데이터의
전자화 필요성 요구

<목적>
신약신청 심사의
신속화와
데이터 확인의 효율화

CDISC 주관

임상시험용 표준 포맷인
SDTM 바탕

SEND 개발
(Standard for Exchange of Nonclinical Data)

비임상시험 데이터의
전자데이터 표준 포맷

2) SEND (Standard for Exchange of Nonclinical Data)

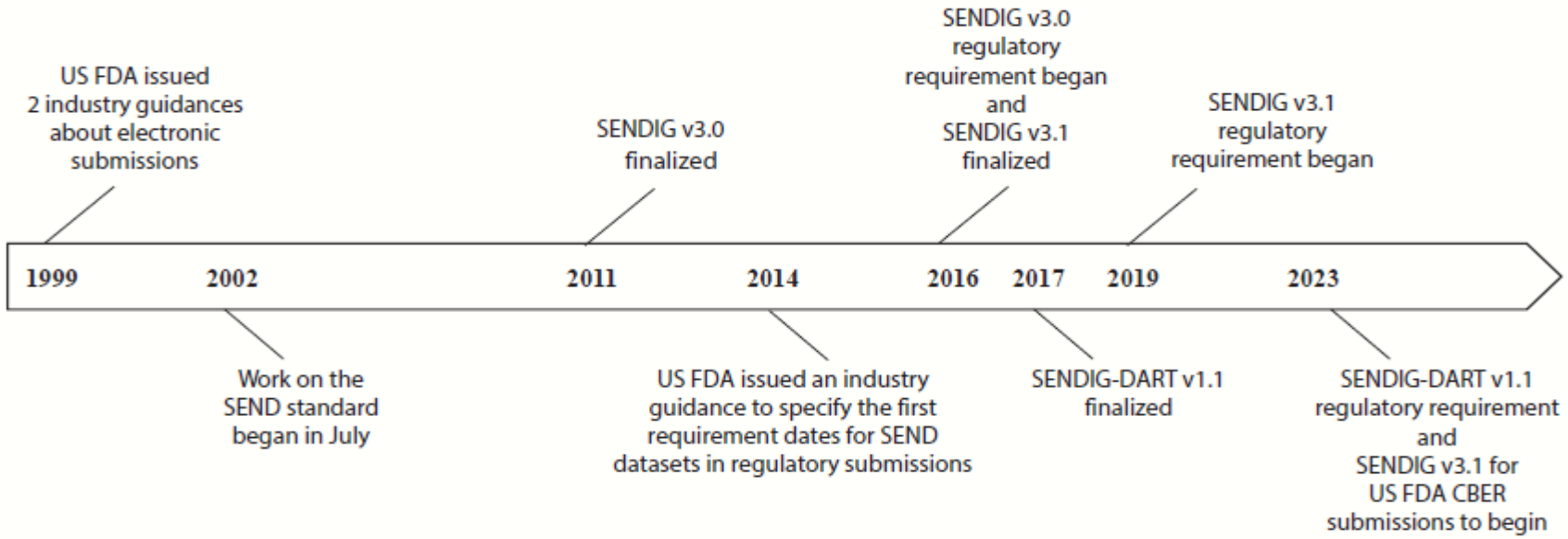


Figure 1 SEND Regulatory Requirement Timeline

- FDA: Organize the data, help us review the data in an efficient way, and provide a tool to create tables and graphs to present the most important findings.
- Submitters: simplifiers the process (same format used by drug regulatory agencies in other countries)
- Faster submission review, SEND datasets used to analyze submission, SEND-based data warehouses

출처: SEND Datasets for Regulatory Requirements and Beyond, 谷本学校 毒性質問箱 第23号 2021

3) FDA Data Standards Catalog (v10.4)

- The data standards and terminologies that FDA supports for use in regulatory submissions to better enable the evaluation of safety, effectiveness, and quality of FDA-regulated products.

Use	Standard	Exchange Format	SDO	Property	Related Properties	FDA Center(s)	Date Support Begins	Date Support Ends	Date Requirement Begins [10] [11]
Nonclinical study datasets	SEND	XPT	CDISC	SENDIGv3.0		CDER	06-13-2011	03/15/2019 [1] [12] 03/15/2020 [2] [12]	12/17/2016 [1] 12/17/2017 [2]
Nonclinical study datasets	**SEND**	**XPT**	**CDISC**	**SDTMv1.5**		**CDER**	**08-21-2017**		**03/15/2019 [1] 03/15/2020 [2]**
Nonclinical study datasets	**SEND**	**XPT**	**CDISC**	**SDTMv1.5**		**CBER**	**03-15-2021**		**03-15-2023**
Nonclinical study datasets	SEND	XPT	CDISC	SENDIGv3.1		CDER	08-21-2017		03/15/2019 [1] 03/15/2020 [2]
Nonclinical study datasets	SEND	XPT	CDISC	SENDIGv3.1		CBER	07-14-2020		03-15-2023
Nonclinical study datasets	SEND	XPT	CDISC	SENDIGv3.1.1		CDER, CBER	02-15-2022		03-15-2023
Nonclinical study datasets	SEND	XPT	CDISC	SENDIG-Genetoxv1.0		CDER, CBER	12/13/2023 [12]		03-15-2025
Nonclinical study datasets	**SEND**	**XPT**	**CDISC**	**SDTMv1.6**		**CDER**	**03-05-2021**		**03/15/2023 [1] 03/15/2024 [2]**
Nonclinical study datasets	SEND	XPT	CDISC	SENDIG-DARTv1.1		CDER	03-05-2021		03/15/2023 [1] 03/15/2024 [2]
Nonclinical study datasets	**SDTM**	**XPT**	**CDISC**	**SDTMv1.8**		**CDER**	**03-15-2020**		**03/15/2022 [1] 03/15/2023 [2]**
Nonclinical study datasets	SDTM	XPT	CDISC	SENDIG-ARv1.0		CDER	03-11-2020		03/15/2022 [1] 03/15/2023 [2]
Nonclinical study datasets	SDTM	XPT	CDISC	SENDIG-ARv1.0		CBER	03-26-2024		03/15/2027 [1], [2]
Study data definition	Define	XML	CDISC	Define.xmlv1.0		CDER, CBER	Ongoing	03/15/2018 [12]	12/17/2016 [1] 12/17/2017 [2]
Study data definition	Define	XML	CDISC	Define.xmlv2.0		CDER, CBER	08-07-2013		12/17/2016 [1] 12/17/2017 [2]
Study data definition	Define	XML	CDISC	Define.xmlv2.1		CDER, CBER	07-07-2020		03/15/2022 [1] 03/15/2023 [2]

4) SEND 제출 대상 시험

SENDIG 3.0

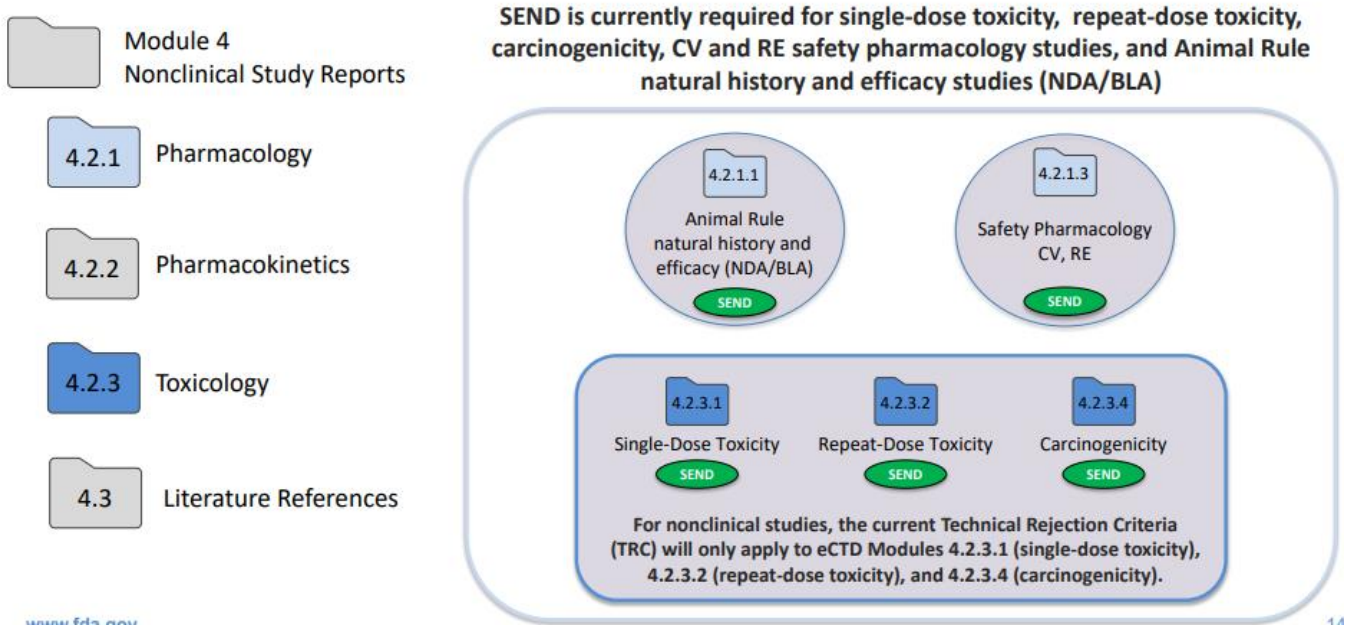
- Single dose general toxicity study
- Repeat dose general toxicity study
- Carcinogenicity study

SENDIG 3.1

- Respiratory safety pharmacology
- Cardiovascular safety pharmacology

SENDIG DART 1.1 (2023/3/15)

- Embryo-Fetal Development (EFD) study



- SEND 제출대상 시험유형에 대해서 SEND 요구 시점은 시험개시일을 기준으로 결정됨.

For CDER, the following nonclinical study types are required to have SEND datasets as defined by study initiation date:

SEND Requirement Dates for Nonclinical Studies Modeled in SEND (Studies started after these dates require SEND datasets)		
Study Types Modeled in SEND	**NDAs/BLAs**	**Commercial INDs**
Single Dose Toxicity, Repeat Dose Toxicity, and Carcinogenicity Studies	December 17, 2016 (SENDIG v3.0) March 15, 2019 (SENDIG v3.1)	December 17, 2017 (SENDIG v3.0) March 15, 2020 (SENDIG v3.1)
Cardiovascular and Respiratory Safety Pharmacology Studies	March 15, 2019 (SENDIG v3.1)	March 15, 2020 (SENDIG v3.1)

1) FDA Technical Rejection Criteria

- CDER and CBER began rejecting submissions that fail eCTD study data validations on September 15, 2021

- Technical Conformance Guide; Appendix F

eCTD validation for study data (Technical Rejection Criteria) **WILL APPLY** to the following eCTD sections:

- 4.2 Study Reports
- 5.3 Clinical Study Reports and Related Information

eCTD validation for study data (Technical Rejection Criteria) **WILL NOT APPLY** to the following eCTD sections:

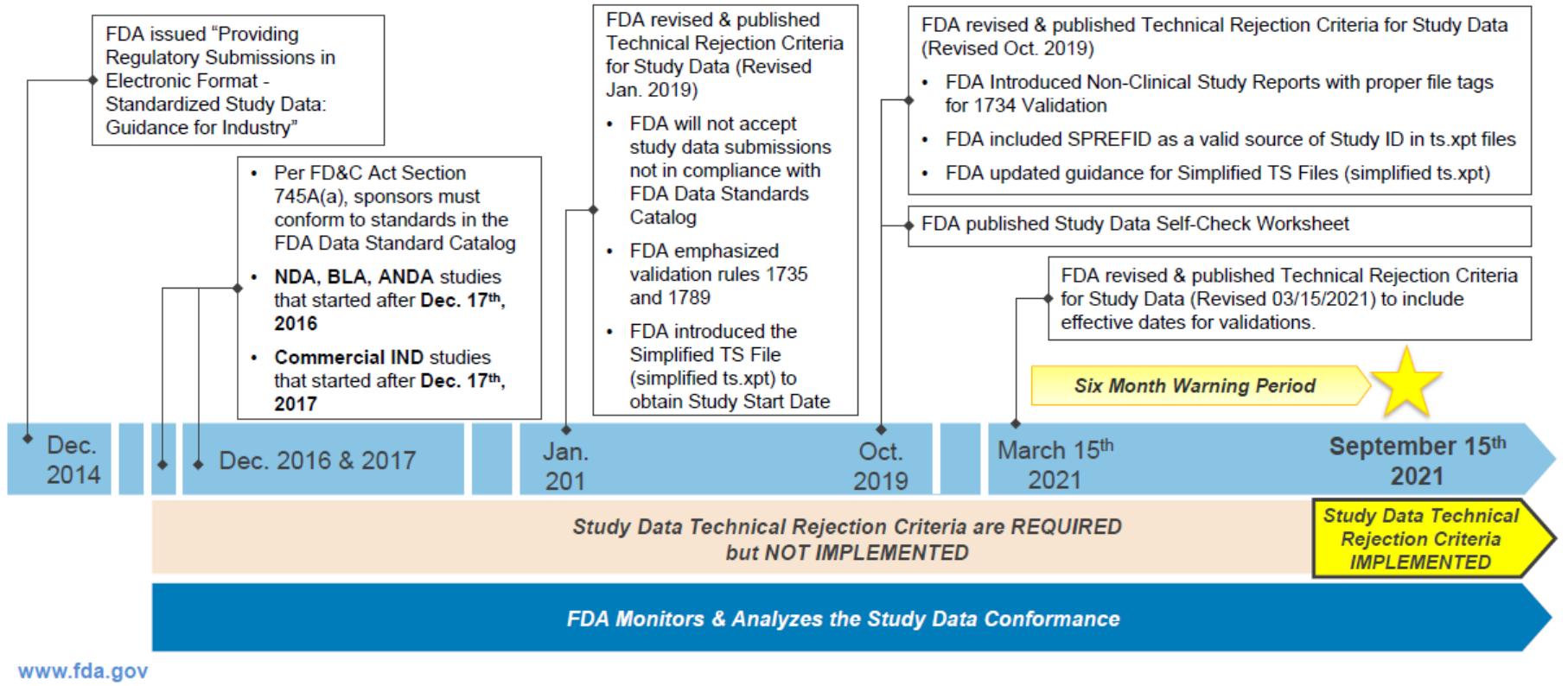
- 4.2.1 Pharmacology
- 4.2.2 Pharmacokinetics
- 4.2.3.3 Genotoxicity
- 4.2.3.5 Reproductive and Developmental Toxicity
- 4.2.3.6 Local Tolerance
- 4.2.3.7 Other Toxicity Studies
- 5.3.1.3 In Vitro – In Vivo Correlation Study Reports and Related Information
- 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies
- 5.3.2 Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials
- 5.3.3.5 Population PK Study Reports and Related Information[88]
- 5.3.5.3 Reports of Analyses of Data from More than One Study
- 5.3.5.4 Other Study Reports and Related Information
- 5.3.6 Reports of Postmarketing Experience

Table 6: eCTD Technical Rejection Criteria for Study Data Expectations[89]

Data Type	Modules & Submodules	Center	Application Type	Study Start Date	Requirement
Non-clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	CDER	NDA, BLA, ANDA	On/Prior to December 17, 2016	Submit simplified ts.xpt*
				After December 17, 2016	Comply with CDISC standards
			Commercial IND	On/Prior to December 17, 2017	Submit simplified ts.xpt*
				After December 17, 2017	Comply with CDISC standards
		CBER	NDA, BLA, ANDA, Commercial IND	On/Prior to March 15, 2023	Submit simplified ts.xpt*
				After March 15, 2023	Comply with CDISC standards
Clinical	5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2	CDER & CBER	NDA, BLA, ANDA	On/Prior to December 17, 2016	Submit simplified ts.xpt if study contains an xpt dataset (other than ts.xpt)
				After December 17, 2016	Comply with CDISC standards
			Commercial IND	Rejection criteria not applied	

**Rejection criteria will be applied if a study report with one of the three file tags, 'pre-clinical-study-report', 'legacy-clinical-study-report', or 'study-report-body' is included, and/or an xpt file (other than the ts.xpt) is submitted.*

Technical Rejection Criteria (TRC) Revisons Timeline



TRC IMPORTANT DATES

FDA

Data Standard Requirements

12/17/2016 – CDER & CBER Clinical Studies that start after require standardized data for NDAs, ANDAs, and certain BLAs

12/17/2017 – CDER Non-clinical Studies that start after require standardized data for commercial INDs.

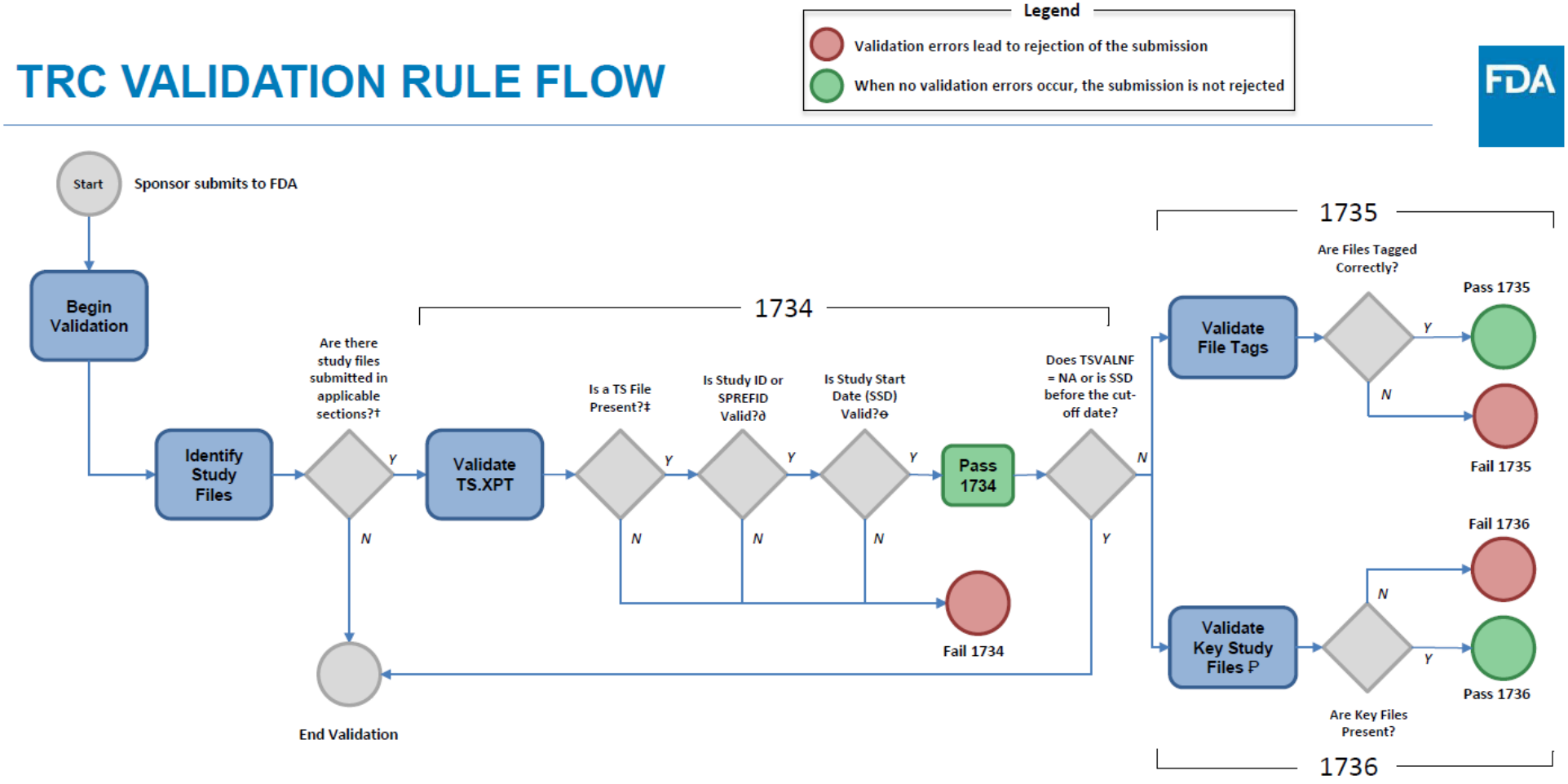
03/15/2023 – CBER Non-clinical Studies that start after require standardized data for NDAs, ANDAs, BLAs, and Commercial INDs

TRC Implementation

09/15/2021 – TRC rejections began

03/16/2023 – CBER Non-Clinical requirements begin

TRC VALIDATION RULE FLOW



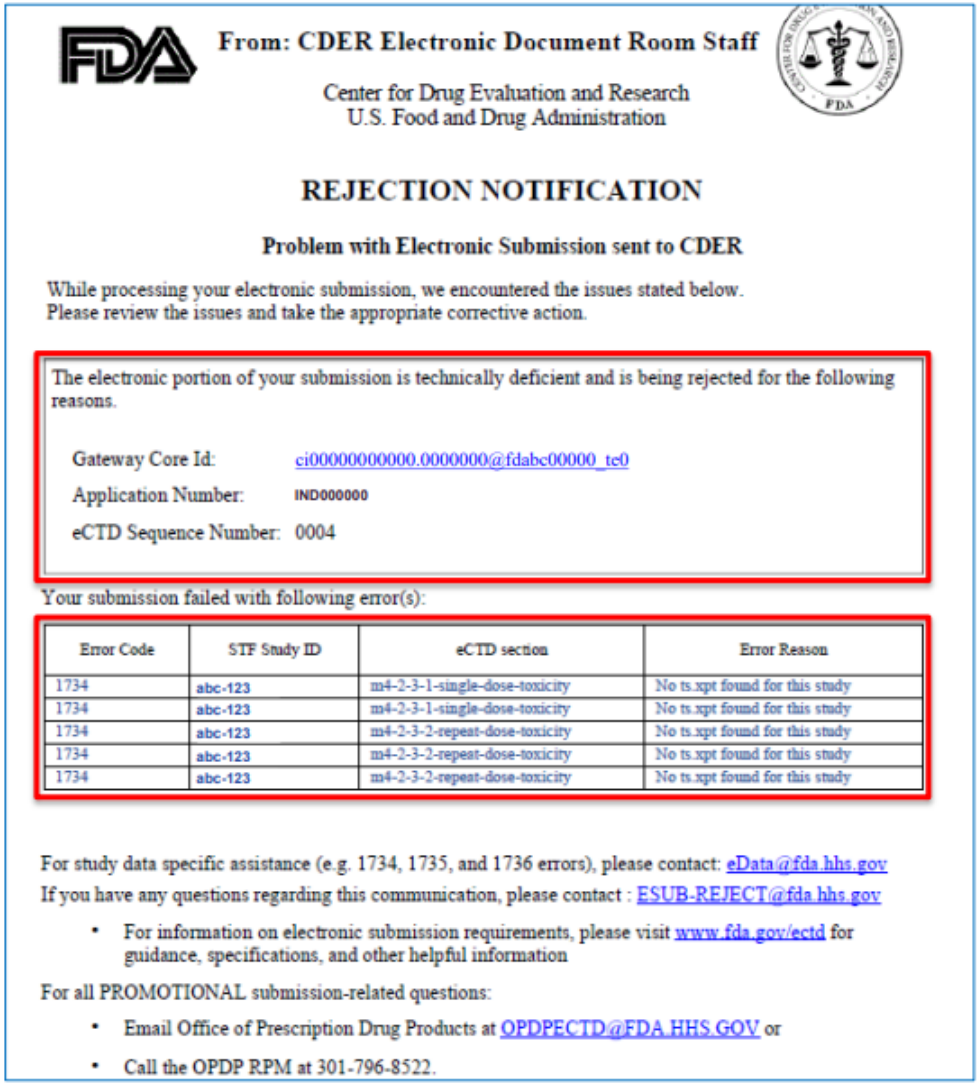
† XPT file type submitted in M5 or any file type submitted in M4 that has a file tag of "pre-clinical-study-report," "legacy-clinical-study-report," or "study-report-body"
‡ TS file does not need to be in the current sequence if it has been previously submitted and referenced by the STF
∂ Study ID or SPREFID should match the STF Study ID
ɵ Valid Study Start Date in ISO 8601 format (i.e. YYYY-MM-DD)
Ᵽ Key Files are dm.xpt or adsl.xpt and corresponding define.xml

출처: FDA Study Data Technical Rejection Criteria (TRC): What you need to know!, May 25, 2022

- eCTD validation error가 확인되면, FDA로부터 rejection notice를 받게 됨.

- Rejection notifications: 각각의 error에 대해서 제공
  - Error Code
  - Error Reason
  - STF Study ID (if applicable)
  - eCTD Section

출처: FDA Study Data Technical Rejection Criteria (TRC): What you need to know!, May 25, 2022



From: CDER Electronic Document Room Staff

Center for Drug Evaluation and Research
U.S. Food and Drug Administration

REJECTION NOTIFICATION

Problem with Electronic Submission sent to CDER

While processing your electronic submission, we encountered the issues stated below. Please review the issues and take the appropriate corrective action.

The electronic portion of your submission is technically deficient and is being rejected for the following reasons.

Gateway Core Id: ci00000000000.0000000@fdabc00000_tc0
Application Number: IND000000
eCTD Sequence Number: 0004

Your submission failed with following error(s):

Error Code	STF Study ID	eCTD section	Error Reason
1734	abc-123	m4-2-3-1-single-dose-toxicity	No ts.xpt found for this study
1734	abc-123	m4-2-3-1-single-dose-toxicity	No ts.xpt found for this study
1734	abc-123	m4-2-3-2-repeat-dose-toxicity	No ts.xpt found for this study
1734	abc-123	m4-2-3-2-repeat-dose-toxicity	No ts.xpt found for this study
1734	abc-123	m4-2-3-2-repeat-dose-toxicity	No ts.xpt found for this study

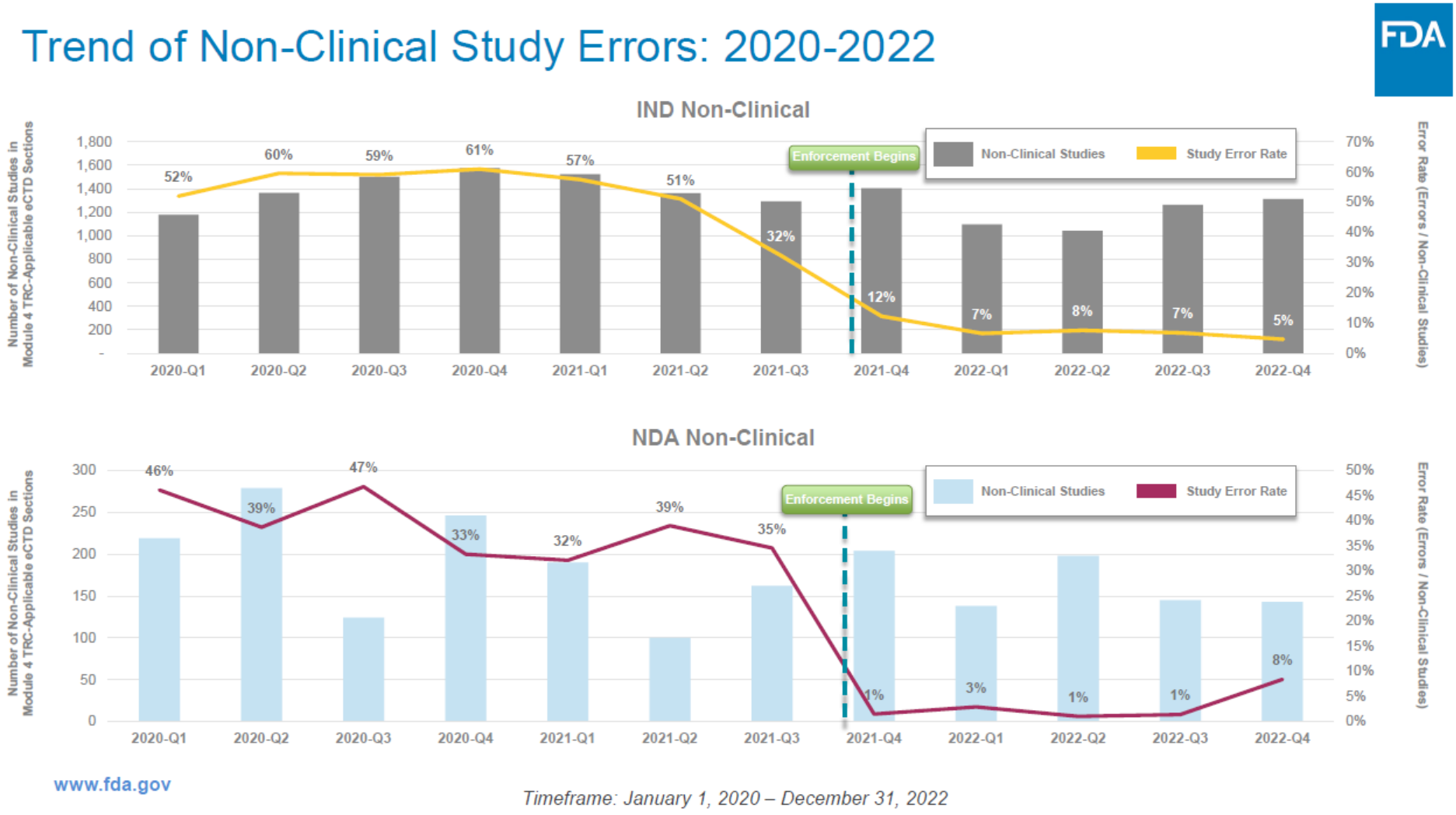
For study data specific assistance (e.g. 1734, 1735, and 1736 errors), please contact: eData@fda.hhs.gov
If you have any questions regarding this communication, please contact : ESUB-REJECT@fda.hhs.gov

- For information on electronic submission requirements, please visit www.fda.gov/ectd for guidance, specifications, and other helpful information

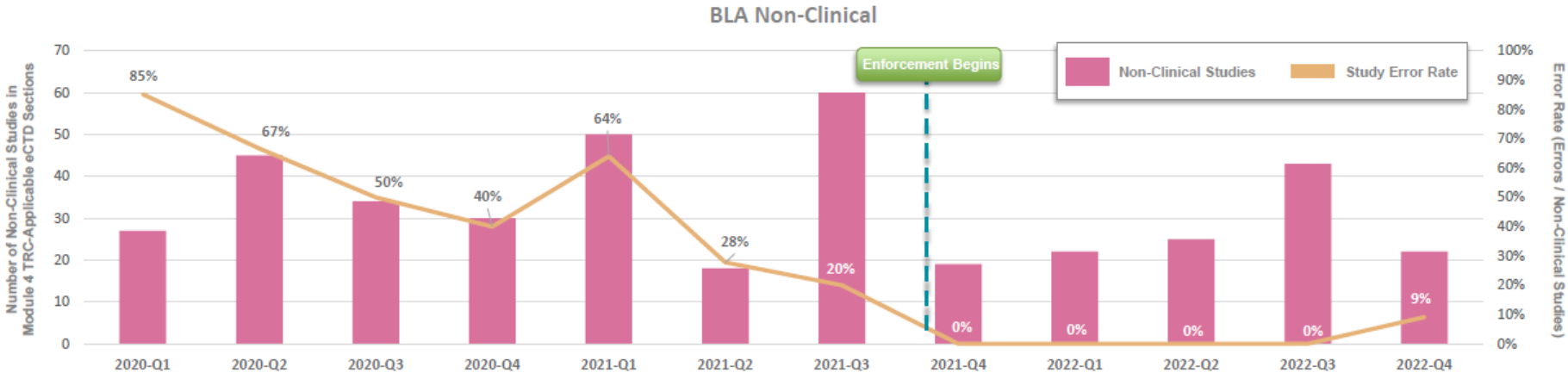
For all PROMOTIONAL submission-related questions:

- Email Office of Prescription Drug Products at OPDPECTD@FDA.HHS.GOV or
- Call the OPDP RPM at 301-796-8522.

FDA의 SEND Face-to-Face 자료 (2023/4/23)



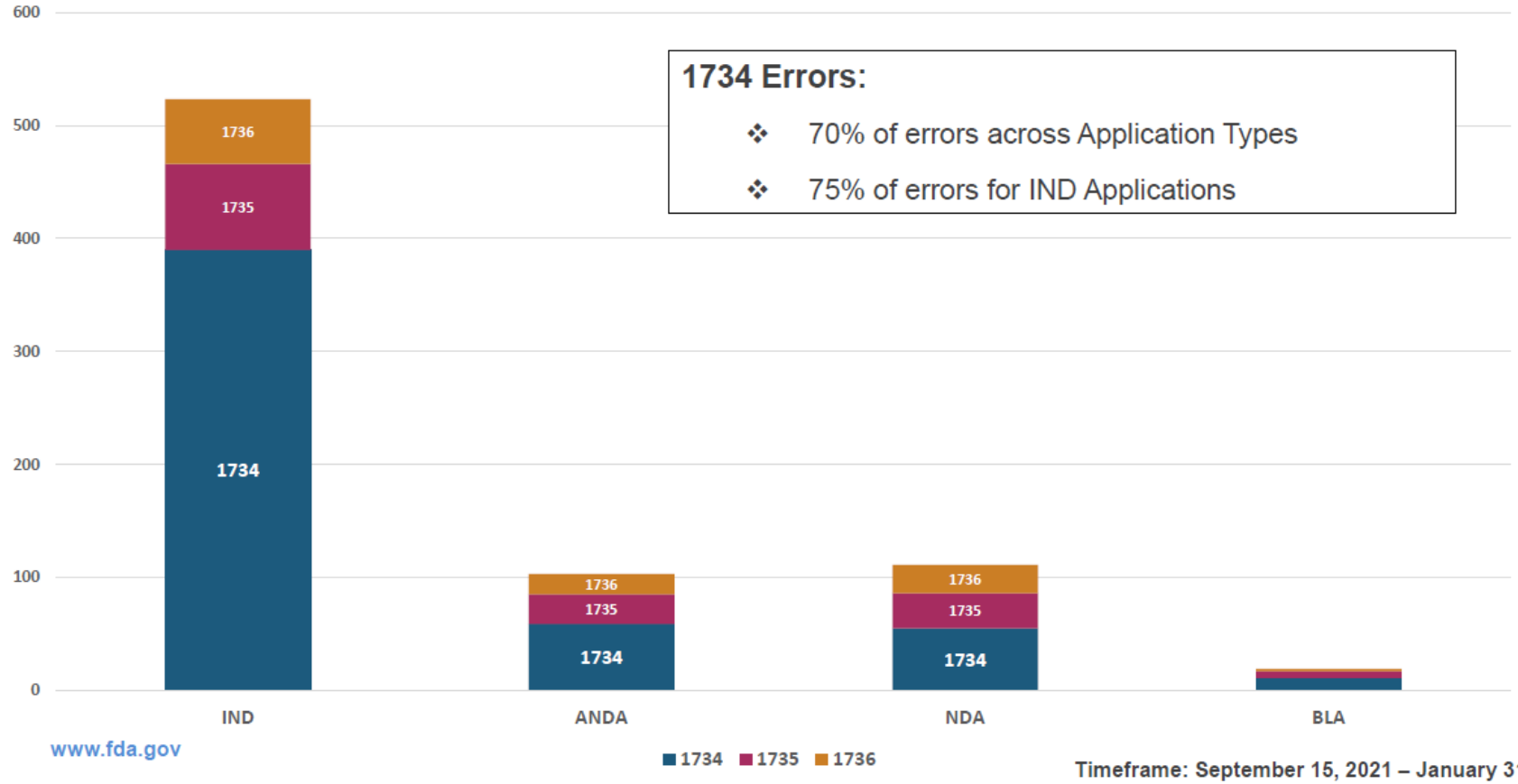
Trend of Non-Clinical Study Errors: 2020-2022



www.fda.gov

Timeframe: January 1, 2020 – December 31, 2022

CDER TRC REJECTIONS



1734 Error Reasons: September 15, 2021 – February 15, 2023

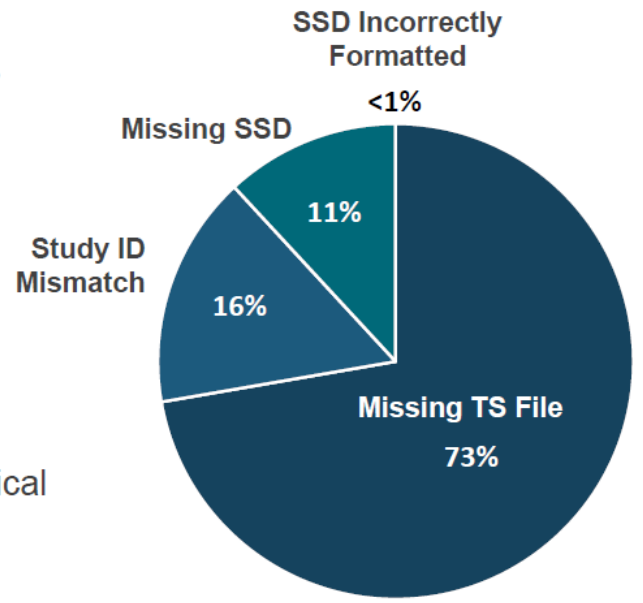
- 453 IND, NDA & BLA non-clinical studies failed Rule 1734
- 73% (329 of 453) failed due to a missing ts.xpt
- 71% (322 of 453) were Repeat Dose Toxicology studies

Toxicology Sections	Count
Repeat dose toxicology (m4.2.3.2)	322
Single dose toxicology (m4.2.3.1)	100
Carcinogenicity (m4.2.3.4)	31
	453

- Submitting a simplified ts.xpt for many of these non-clinical studies will greatly reduce the 1734 error rate
- SEND datasets require a full ts.xpt

www.fda.gov **SSD = Study Start Date*

453 Non-clinical Studies with Error 1734:



Timeframe: September 15, 2021 – February 15, 2023

Addressing 1734 Errors: Missing TS File

CDER and CBER expectations for standardized data:

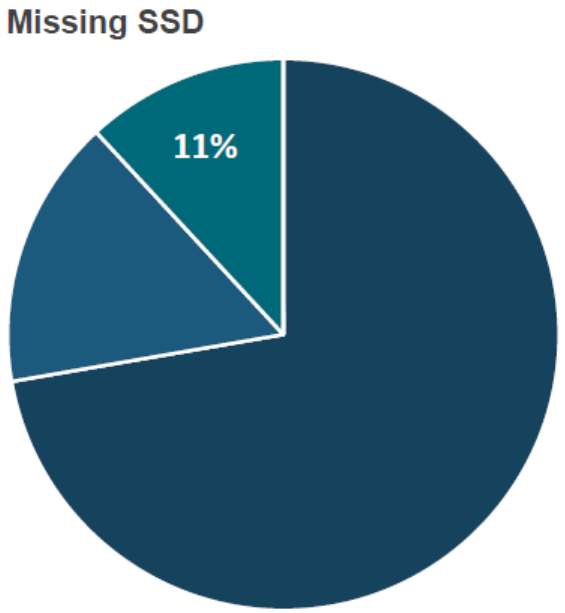
Data Type	Modules & Submodules	Center	Application Type	Study Start Date	Requirement
Non-clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	CDER	NDA, BLA, ANDA	On/Prior to December 17, 2016	Submit simplified ts.xpt*
				After December 17, 2016	Comply with CDISC standards
			Commercial IND	On/Prior to December 17, 2017	Submit simplified ts.xpt*
				After December 17, 2017	Comply with CDISC standards
		CBER	NDA, BLA, ANDA, Commercial IND	On/Prior to March 15, 2023	Submit simplified ts.xpt*
				After March 15, 2023	Comply with CDISC standards
Clinical	5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2	CDER & CBER	NDA, BLA, ANDA	On/Prior to December 17, 2016	Submit simplified ts.xpt if study contains an xpt dataset (other than ts.xpt)
				After December 17, 2016	Comply with CDISC standards
		CDER & CBER	Commercial IND	Rejection criteria not applied	

**Rejection criteria will be applied if a study report with one of the three file tags, 'pre-clinical-study-report', 'legacy-clinical-study-report', or 'study-report-body' is included , and/or an xpt file (other than the ts.xpt) is submitted.*

www.fda.gov

출처: FDA-Electronic Submissions Presentations, SEND Face-to-Face, Virtual

Addressing 1734 Errors: Missing Study Start Date



Simplified ts.xpt when Study Start Date is available:

	STUDYID	TSPARMCD	TSVAL	TSVALNF
1	90-day-oral-tox-s...	STSTDTC	2018-06-14	

Causes of 1734 Missing Study Start Date:

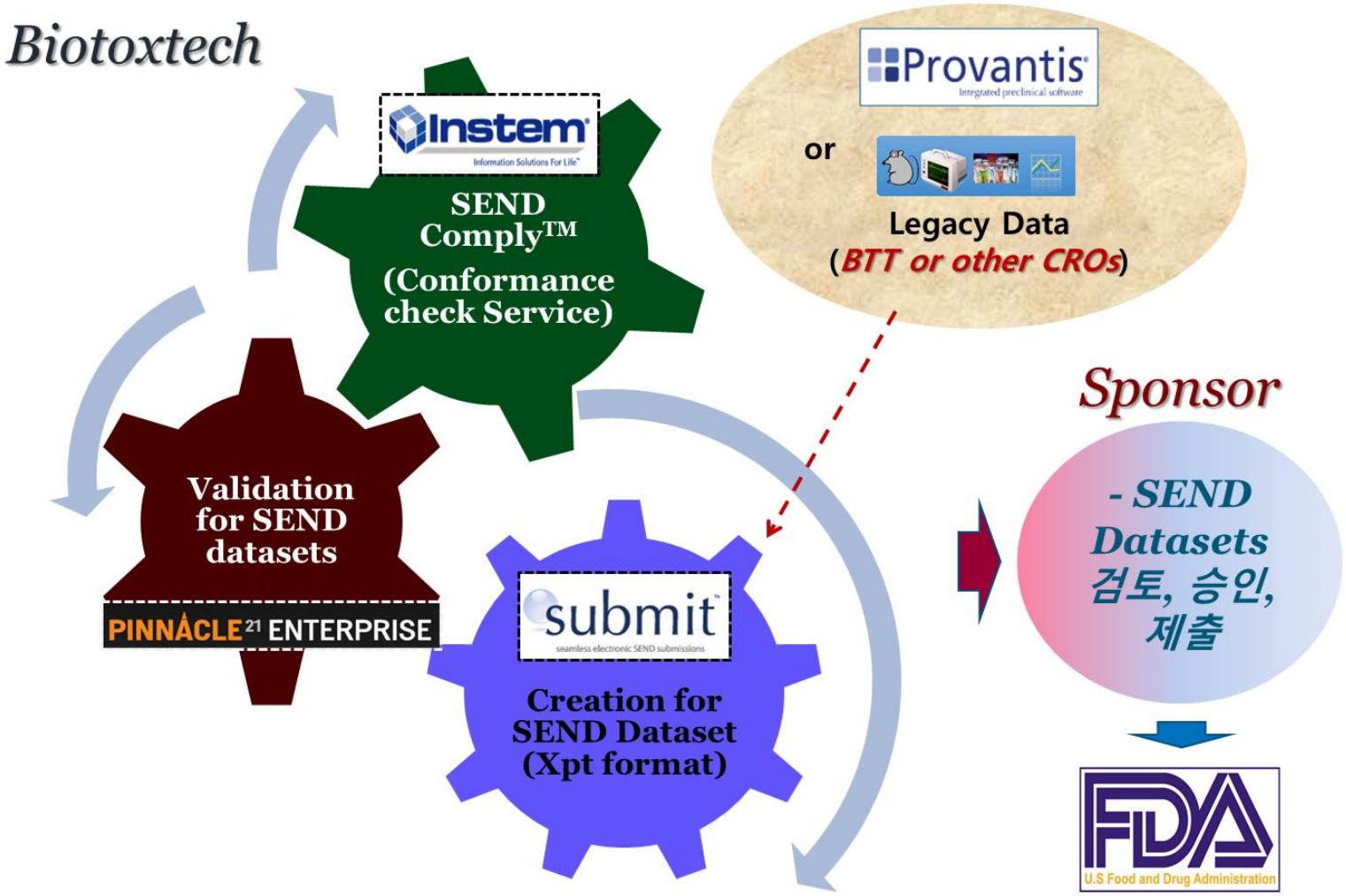
- Missing value for SSD

	STUDYID	TSPARMCD	TSVAL	TSVALNF
1	90-day-oral-tox-s...	STSTDTC		

www.fda.gov

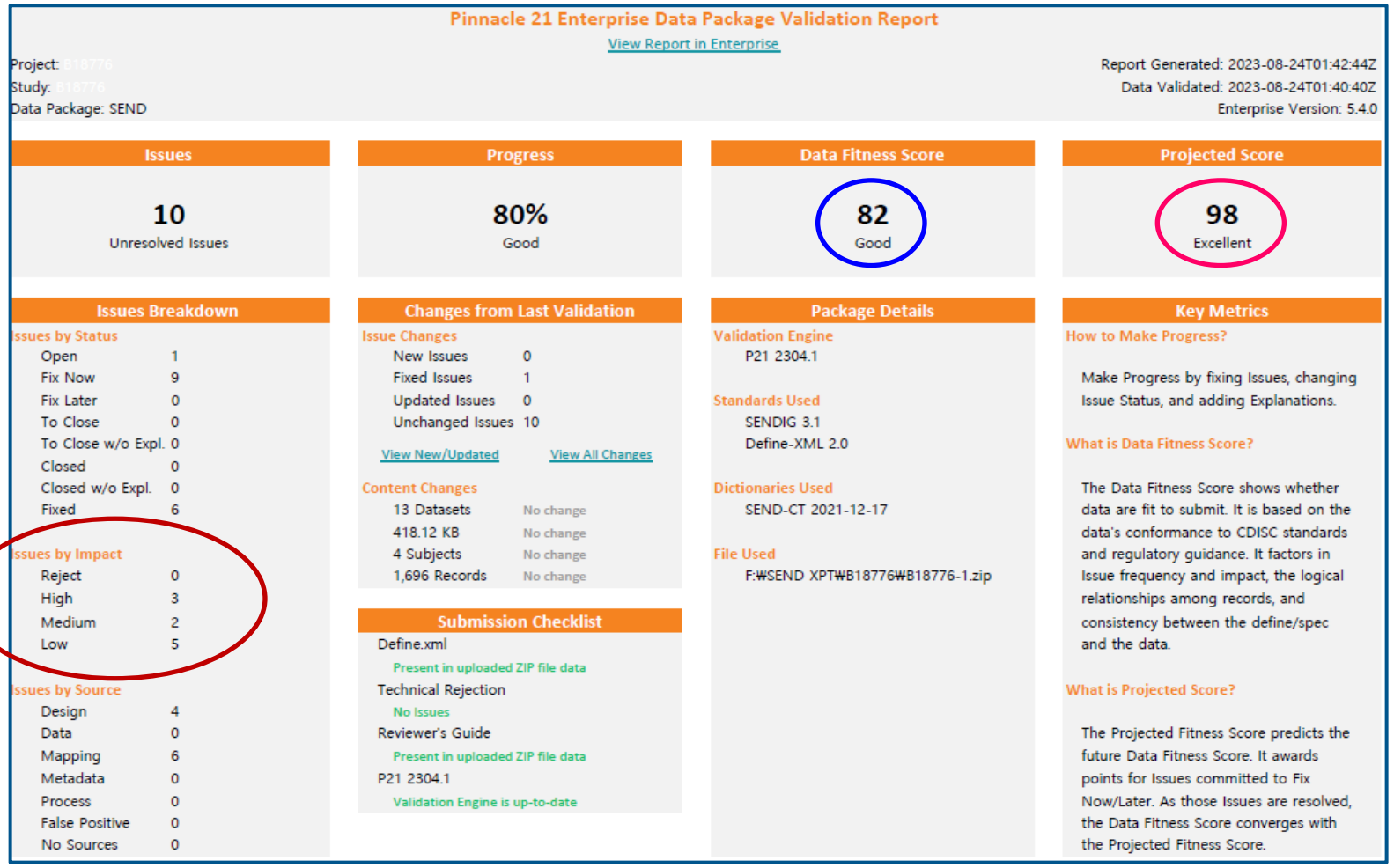
출처: FDA-Electronic Submissions Presentations, SEND Face-to-Face, Virtual

SEND 변환 Flow


Biotoxtech
Instem
Information Solutions For Life
SEND Comply™ (Conformance check Service)
Provantis
Integrated preclinical software
or
Legacy Data (BTT or other CROs)
Validation for SEND datasets
PINNACLE 21 ENTERPRISE
submit
seamless electronic SEND submissions
Creation for SEND Dataset (Xpt format)
Sponsor
- SEND Datasets 검토, 승인, 제출
FDA
U.S Food and Drug Administration

SEND Dataset Validation: **Pinnacle 21 Enterprise 사용**

- 규제기관 제출 전 datasets을 사전에 확인하여 위험요소에 대한 문제를 해결



Pinnacle 21 Enterprise Data Package Validation Report

View Report in Enterprise

Project: B18776
Study: B18776
Data Package: SEND

Report Generated: 2023-08-24T01:42:44Z
Data Validated: 2023-08-24T01:40:40Z
Enterprise Version: 5.4.0

Issues

10
Unresolved Issues

Progress

80%
Good

Data Fitness Score

82
Good

Projected Score

98
Excellent

Issues Breakdown

Issues by Status

Open	1
Fix Now	9
Fix Later	0
To Close	0
To Close w/o Expl.	0
Closed	0
Closed w/o Expl.	0
Fixed	6

Issues by Impact

Reject	0
High	3
Medium	2
Low	5

Issues by Source

Design	4
Data	0
Mapping	6
Metadata	0
Process	0
False Positive	0
No Sources	0

Changes from Last Validation

Issue Changes

New Issues	0
Fixed Issues	1
Updated Issues	0
Unchanged Issues	10

View New/Updated View All Changes

Content Changes

13 Datasets	No change
418.12 KB	No change
4 Subjects	No change
1,696 Records	No change

Submission Checklist

Define.xml
Present in uploaded ZIP file data
Technical Rejection
No Issues
Reviewer's Guide
Present in uploaded ZIP file data
P21 2304.1
Validation Engine is up-to-date

Package Details

Validation Engine
P21 2304.1

Standards Used
SENDIG 3.1
Define-XML 2.0

Dictionaries Used
SEND-CT 2021-12-17

File Used
F:₩SEND XPT₩B18776₩B18776-1.zip

Key Metrics

How to Make Progress?

Make Progress by fixing Issues, changing Issue Status, and adding Explanations.

What is Data Fitness Score?

The Data Fitness Score shows whether data are fit to submit. It is based on the data's conformance to CDISC standards and regulatory guidance. It factors in Issue frequency and impact, the logical relationships among records, and consistency between the define/spec and the data.

What is Projected Score?

The Projected Fitness Score predicts the future Data Fitness Score. It awards points for Issues committed to Fix Now/Later. As those Issues are resolved, the Data Fitness Score converges with the Projected Fitness Score.

SEND Dataset Check: Instem사의 SEND Comply Conformance Check Service 이용

Objective

The purpose of this report is to provide Biotoxtech (hereinafter "the Client") with the results of Instem's Conformance Check of the SEND deliverables for Study No.B , as well as recommendations on any conformance issues that should be addressed prior to submission. For the original review these items are highlighted in red font in Column B of Appendix A.

Scope

Instem's analysis was performed on the following SEND deliverables provided by the Client.

Description	Files
SEND Datasets	bw 7/12/2024 4:34 AM SAS Xport Transpo... 27 KB cl 7/12/2024 4:34 AM SAS Xport Transpo... 135 KB dm 7/12/2024 4:34 AM SAS Xport Transpo... 6 KB ds 7/12/2024 4:34 AM SAS Xport Transpo... 6 KB ex 7/12/2024 4:34 AM SAS Xport Transpo... 9 KB fw 7/12/2024 4:34 AM SAS Xport Transpo... 16 KB lb 7/12/2024 4:34 AM SAS Xport Transpo... 458 KB ma 7/12/2024 4:34 AM SAS Xport Transpo... 8 KB mi 7/12/2024 4:34 AM SAS Xport Transpo... 31 KB om 7/12/2024 4:34 AM SAS Xport Transpo... 122 KB relrec 7/12/2024 4:34 AM SAS Xport Transpo... 2 KB se 8/5/2024 11:12 PM SAS Xport Transpo... 8 KB suppma 7/12/2024 4:34 AM SAS Xport Transpo... 3 KB suppmi 7/12/2024 4:34 AM SAS Xport Transpo... 3 KB ta 7/12/2024 4:34 AM SAS Xport Transpo... 3 KB te 7/12/2024 4:34 AM SAS Xport Transpo... 3 KB ts 7/12/2024 4:34 AM SAS Xport Transpo... 10 KB tx 7/12/2024 4:34 AM SAS Xport Transpo... 5 KB
Data Definition File (define file)	define 8/5/2024 11:27 PM XML Document 262 KB define2-0-0 8/2/2024 11:37 AM XSL Stylesheet 184 KB
Nonclinical Study Data Reviewer's Guide (nsdrg)	nsdrg 8/7/2024 6:53 AM Adobe Acrobat D... 407 KB nsdrg 8/7/2024 6:53 AM Microsoft Word D... 81 KB

- BTT SEND 제출 사례 (2019년부터 2024년까지)

SPONSOR	28 개 (21)

STUDY TYPE	수행 건수
Single Dose Toxicity	21
Repeat Dose Toxicity	51
Respiratory Function Test	9
Cadiovascular Function Test	9
Simplified TS	36
DART-FED	2
TOTAL	*128*

< 2019년 > INA/PDS 의뢰

STUDY TYPE	A사	B사	C사
Single Dose Toxicity	1		
Dose Range Finding	1		
Repeat Dose Toxicity	1		
Repeat Dose Toxicity with TK		1	
Respiratory Function Test			
Cadiovascular Function Test			
Simplified TS (2017/12/17 이전 개시 시험)			3

< 2020년 > INA / PDS / Instem 의뢰

STUDY TYPE	D사	E사	F사	G사
Single Dose Toxicity		1		1
Dose Range Finding		1		
Repeat Dose Toxicity	1	1		2
Repeat Dose Toxicity with TK				2
Respiratory Function Test		1		1
Cadiovascular Function Test				1
Simplified TS (2017/12/17 이전 개시 시험)			11	

< 2021년 > BTT 수행

STUDY TYPE	H사	I사	J사
Single Dose Toxicity		2	
Dose Range Finding		2	
Repeat Dose Toxicity		2	1
Repeat Dose Toxicity with TK	1		
Respiratory Function Test		1	
Cadiovascular Function Test		1	
Simplified TS (2017/12/17 이전 개시 시험)			

< 2022년 > BTT 수행

STUDY TYPE	K사	L사	M사	N사	O사	P사
Single Dose Toxicity	2	1	2	4		
Dose Range Finding		2	2	1		
Repeat Dose Toxicity		2	2			
Repeat Dose Toxicity with TK	2				1	
Respiratory Function Test			1	1		
Cadiovascular Function Test			1			
Simplified TS (2017/12/17 이전 개시 시험)	1					4

< 2023년 > BTT 수행

STUDY TYPE	Q사	R사	S사	T사	U사
Single Dose Toxicity		2			1
Dose Range Finding					
Repeat Dose Toxicity				1	1
Repeat Dose Toxicity with TK	1				
Respiratory Function Test		1			
Cadiovascular Function Test	1	1	1		
Simplified TS (2017/12/17 이전 개시 시험, 제출대상 제외 시험)	16				

< 2024년 > BTT 수행

STUDY TYPE	V사	W사	X사	Y사	Z사	a사	b사	c사
Single Dose Toxicity	2		2					
Dose Range Finding	2	2	2	2				2
Repeat Dose Toxicity				1				
Repeat Dose Toxicity with TK	2	2	2				1	2
Respiratory Function Test	1		1		1			
Cadiovascular Function Test	1	1	1					
Simplified TS (제출대상 제외 시험)						1		
Embryo-Fetal Development study (EFD / SENDIG DART 1.2)								2

FDA (12/13/2023)
SENDIG-Genetox v1.0
(03/15/2025 의무화)

SUMMARY:

The Food and Drug Administration's (FDA or Agency) Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER) are announcing that support begins for version 2.0 of the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTMv2.0), version 3.4 of the CDISC Study Data Tabulation Model Implementation Guide (SDTMIGv3.4), and version 1.0 of the Standard for Exchange of Nonclinical Data Implementation Guide—Genetox (SENDIG-Genetoxv1.0) and announcing the date that these version updates are required in certain submissions. CBER and CDER are also announcing the date that requirement ends for version 3.2 of the CDISC SDTMIG (SDTMIGv3.2). The Agency will update the FDA Data Standards Catalog (Catalog) to reflect these changes. The Agency will publish in the technical specifications document entitled "Study Data Technical Conformance Guide" additional details on how to implement new variables.

DATES:

Support for version CDISC SDTMv2.0, SDTMIGv3.4, and SENDIG-Genetoxv1.0 begins December 13, 2023.

The requirement for electronic submissions to be submitted using CDISC SDTMv2.0, SDTMIGv3.4, and SENDIG-Genetoxv1.0 begins March 15, 2025, for new drug applications (NDAs), abbreviated new drug applications (ANDAs), certain biologics license applications (BLAs), and certain investigational new drug applications (INDs). The requirement for electronic submissions to be submitted using version CDISC SDTMIGv3.2 ends December 13, 2023.

식품의약품안전처
2023년
CDISC 전문가 협의체
회의를 진행

<예정>

전자국제공통기술문서 (eCTD)를 이용하여 전자적으로 자료를 제출하는 경우, 임상시험 관련 국제표준 개발 컨소시엄 (CDISC)의 표준을 적용하여 자료 제출

경청해 주셔서 감사합니다.