국민 안심이 기준입니다
YOUR SAFETY IS OUR STANDARD

Status of CDISC in Korea

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2023.12.13.

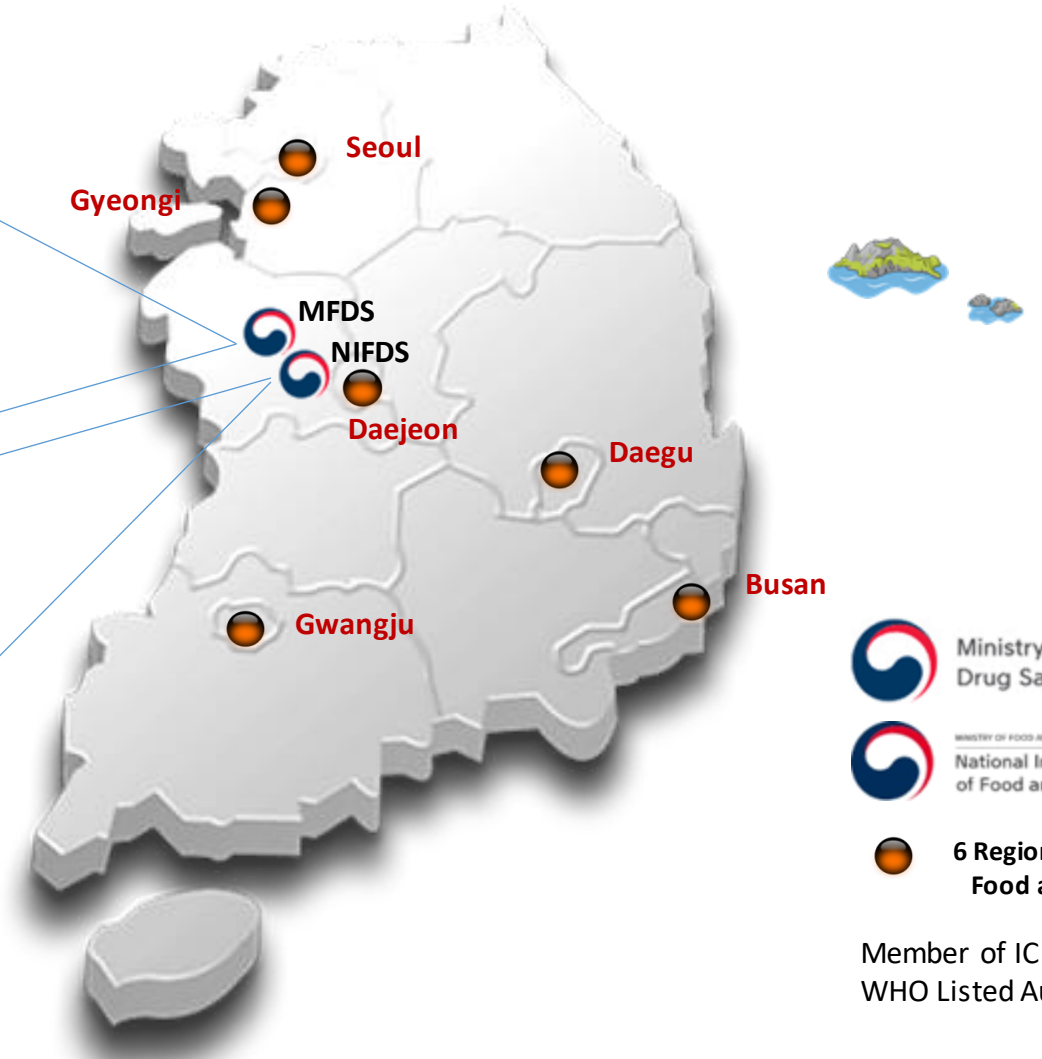
Pharmaceutical Policy Division, Pharmaceutical Safety Bureau
Ministry of Food and Drug Safety

CONTENS

Status of CDISC in Korea

1. Introduction of MFDS

Introduction of MFDS



Ministry of Food and Drug Safety

National Institute of Food and Drug Safety Evaluation

6 Regional Office of Food and Drug Safety

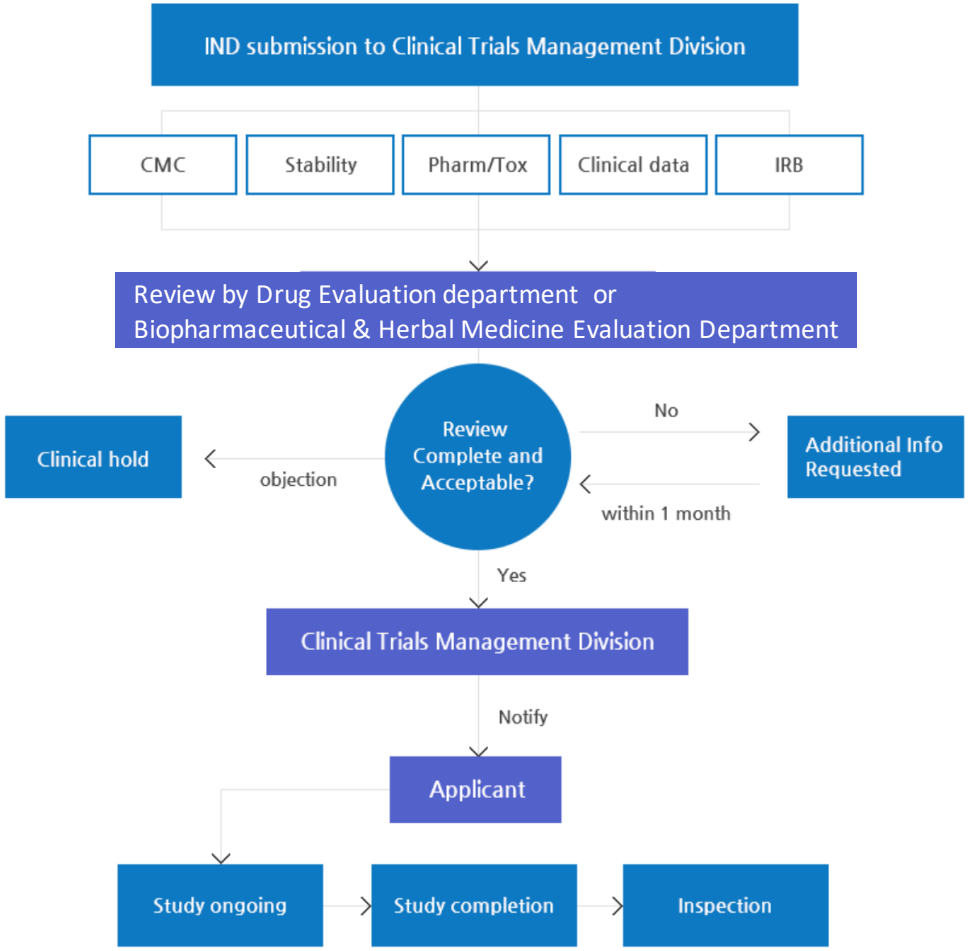
Member of ICH (2016~)
WHO Listed Authorities(2023~)

Status of CDISC in Korea

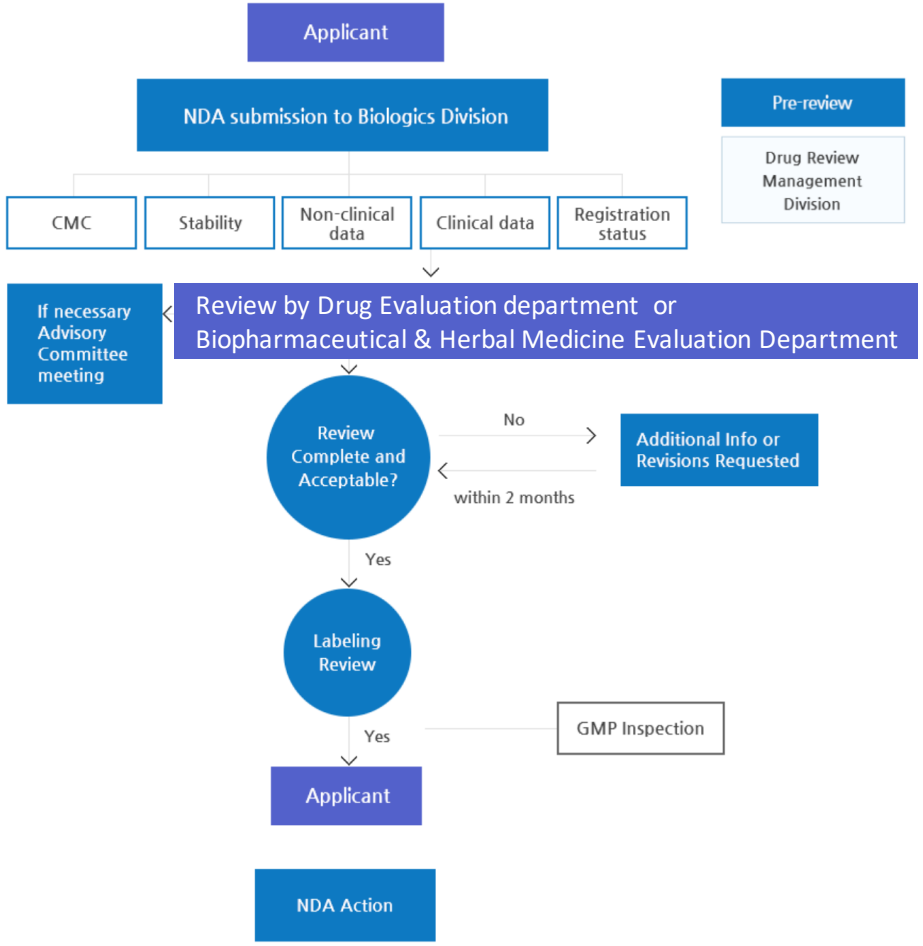
2. NDA/BLA Approval Process & Data Submission

NDA/BLA Approval Process

IND(Investigational New Drug Application) Review Process



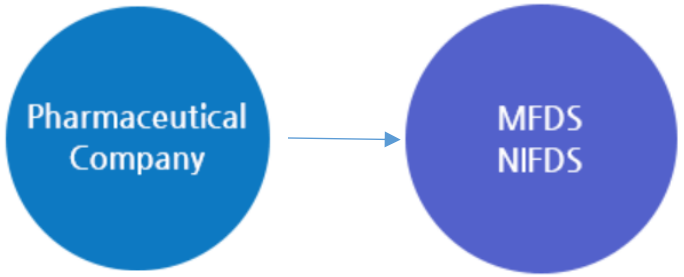
NDA (New Drug Application) Review Process



Data Requirements for Approval

Dossier for IND

- Development plan
- Introduction
- Data on structural identification and psychochemical and biological properties (including data for a placebo)
- Data on non-clinical studies
  Data on Pharmacology
  Data on Toxicity
- Data on clinical studies (if applicable)
- Study protocol
- References
- Investigator's Brochure (IB)



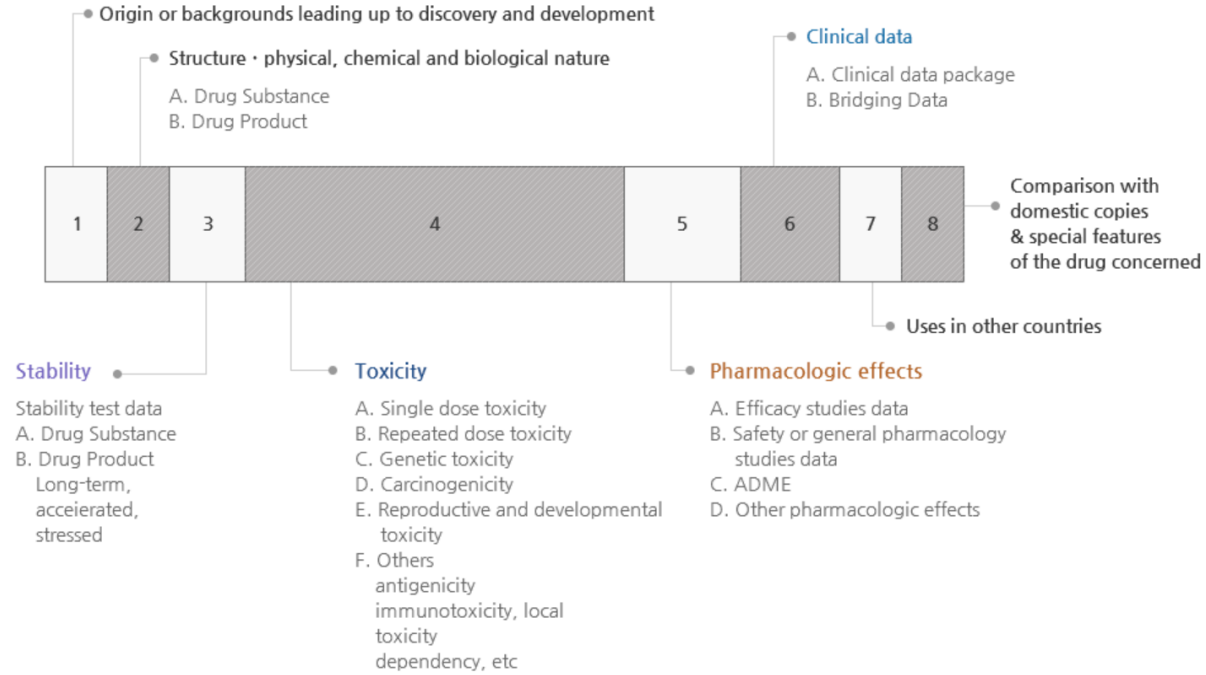
Electronic Data Submission

By 「 Pharmaceutical Affairs Act 」 & 「Regulation on Safety of Pharmaceuticals」(Ordinance of the Prime Ministerial)

Data Requirements for Approval

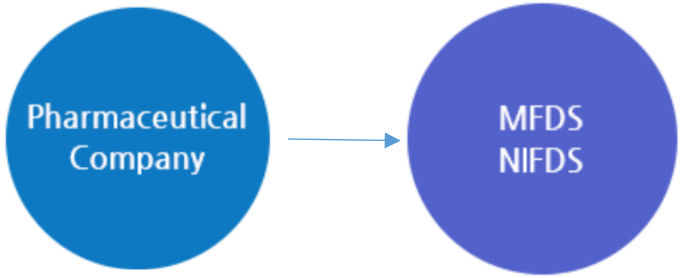
› New Drug (「Regulation on Safety of Pharmaceuticals」(Ordinance of the Prime Ministerial) Article 9)

- (Review by Drug Evaluation Department) Safety & efficacy data, specifications & test methods, Drug Master Files (DMF), certificate of manufacturing and marketing(Imported Pharmaceutical) Data such as name and address of manufacturers of active pharmaceutical ingredients
- (Review by Other Departments) Evaluation data of conducting of Good Manufacturing Practice (GMP)



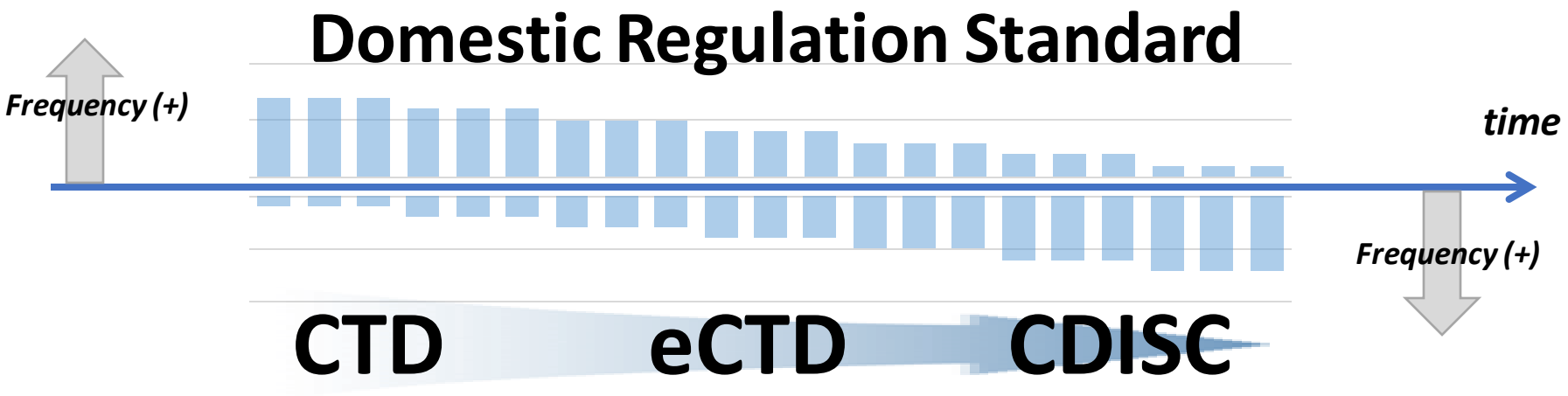
Dossier for Safety & Efficacy Evaluation

Electronic Data Standard for International Harmonization in Korea



Electronic Data Submission

By 「Pharmaceutical Affairs Act」& 「Regulation on Safety of Pharmaceuticals」(Ordinance of the Prime Ministerial)



3. Regulations related to eCTD/CDISC

Regulations, etc. related to CTD/eCTD submission

- 「PHARMACEUTICAL AFFAIRS ACT」Articles 31, 42
- 「Regulation on Safety of Pharmaceuticals, Etc.」(Ordinance of the Prime Ministerial) Articles 4, 8, 9, 10
- **「Regulation for Pharmaceutical Approvals, Notifications and Reviews」Articles 6**
- 「Regulation for Biopharmaceutical Approvals, Notifications and Reviews」Articles 8
- 「Regulation for Herbal Medicines Approvals, Notifications and Reviews」 Articles 7
- 「Regulation for Novel Product Approvals, Notifications and Reviews」 Articles 6
- 「Regulation on Approval of Clinical Trial Plans for Pharmaceuticals 」Articles 5
- 「Guidelines for processing and managing clinical trial electronic data」
- 「Guidance Document for Electronic Common Technical Document (eCTD) Compilation (Applicant's Instruction Manual)」

Article related to CDISC submission

Regulation for Pharmaceutical Approvals, Notifications and Reviews

Ministry of Food and Drug Safety Notification No. 2021-90
Partially Amended and Enforced on Nov 11, 2021

Chapter I General Rules

Article 1 (Purpose)

This regulation is intended to stipulate detailed information regarding target articles, types of data submitted, description tips, requirements, and exemption scopes of data, specifications and controls, etc. for the manufacturing and marketing approval or notification of pharmaceuticals, the importing approval or notification of pharmaceuticals, and the review of safety and efficacy, specifications, test methods of drugs in accordance with Articles 31, 35, 42, and 76 of the "Pharmaceutical Affairs Act (PAA)," Articles 4, 5, 8 through 13, 39, 40, and 57 through 59 of the "Regulation on Safety of Pharmaceuticals, Etc.", Articles 18, 21, and 24 of the "Narcotics Control Act" Articles 32 and 33 of "Enforcement Decree of the Narcotics Control Act" and Article 19 of the "Rare Diseases Management Act".

Article 6 (Preparation of Common Technical Documents)

(1) In spite of Article 5, for new drugs and drugs requiring data submission and drugs falling under Article 25 (2) 3 (except for orphan drugs, high pressure gas for medical use, radiopharmaceuticals, drugs for export, and other products that are not directly applied to humans) among prescription drugs, shall be prepared in the Common Technical Document (CTD) format. In these cases, detailed preparation tips are governed by Annex 3 Preparation Method for Drugs CTD. However, for items beyond items stated above, the CTD format should still be used.

(3) The pharmaceutical approval application or notification prepared in accordance with Articles 4 and 6 may be submitted as electronic documents according to the preparation tips, when the Minister of Ministry of Food and Drug Safety notifies eCTD preparation tips. In this case, nonclinical study data and clinical study data may be submitted by applying Clinical Data Interchange Standards Consurtium.

Module 1 ADMINISTRATIVE INFORMATION AND PRESCRIBING INFORMATION

1.1 Table of contents of Module 1

1.2 Copy of the manufacturing and marketing approval and notification application or the importing approval or notification application

Status of CDISC in Korea

4. Efforts to Domestic Implementation for CDISC standard

Efforts to Domestic Implementation for CDISC standard

- 1st ISP for stand alone eCTD/CDISC management system(2013)
- eCTD/CDISC Submission System construction(2014)
- 2nd ISP for integrate 25 systems include eCTD/CDISC system(2017)
- Pharmaceutical integrated information system construction(2018~)
  - Including eCTD/CDISC Submission System
- Amendments Regulation for Pharmaceutical Approvals to include CDISC standards(2021)
- Civilian Government Engagement Advisory Group(2023)

Civilian Government Engagement Advisory Group

(Purpose) Communication and collaboration with major policy users, including the establishment of CDISC guidelines tailored to the domestic pharmaceutical industry situation

(Period/Cycle) ’23.8. ~ / Twice a year, semiannually

(Member) Government side 10, Civilian side 17, total 27.

MFDS
Ministry of Food and Drugs Safety
KIDS
Korea Institute of Drug Safety and Risk Management

KPBMA
Korea Pharmaceutical and Bio-Pharma Manufacturers Association
KRPIA
Korean Research-based Pharma Industry Association
KoBIA
Korea Biomedicine Industry Association
KSQA
The Korean Society of Quality Assurance

K3C
CERTARA

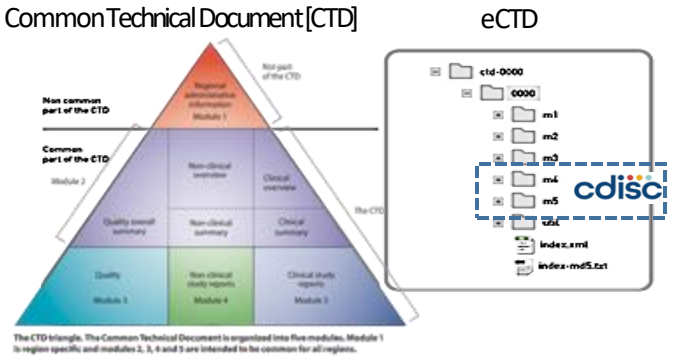
Status of CDISC in Korea

5. Submit an eCTD or Standardized Data to the MFDS

Submit eCTD and CDISC to the MFDS

Phase 1. Create CTD/CDISC

① Create CTD documents and PDF files for submission
② Complete CDISC for submission



Phase 2. Create eCTD include CDISC & Prepare for Submission

< Create eCTD >

① Install and run eCTD software by MFDS
② Create eCTD with CTD documents(PDF files)
③ Mount CDISC during the eCTD creation process
④ Verification in software and finish all process

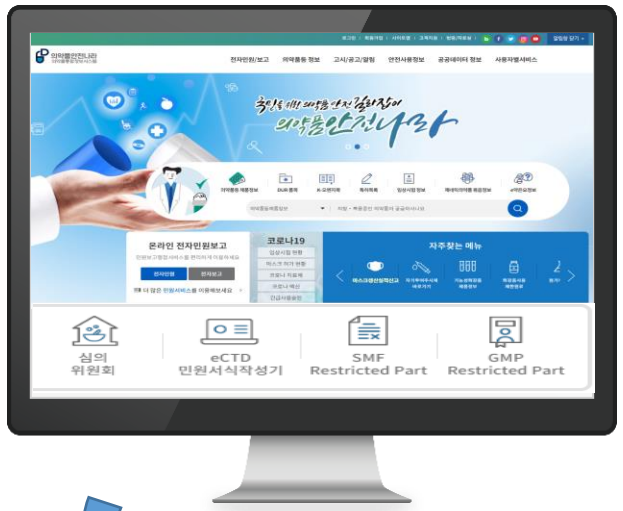
< Temporarily upload to my account >

① Log-in to the 'https://nedrug.mfds.go.kr'
② Temporarily upload eCTD file
* my page > file upload> eCTD file management
③ Verification on website

Phase 3. Electronic Application

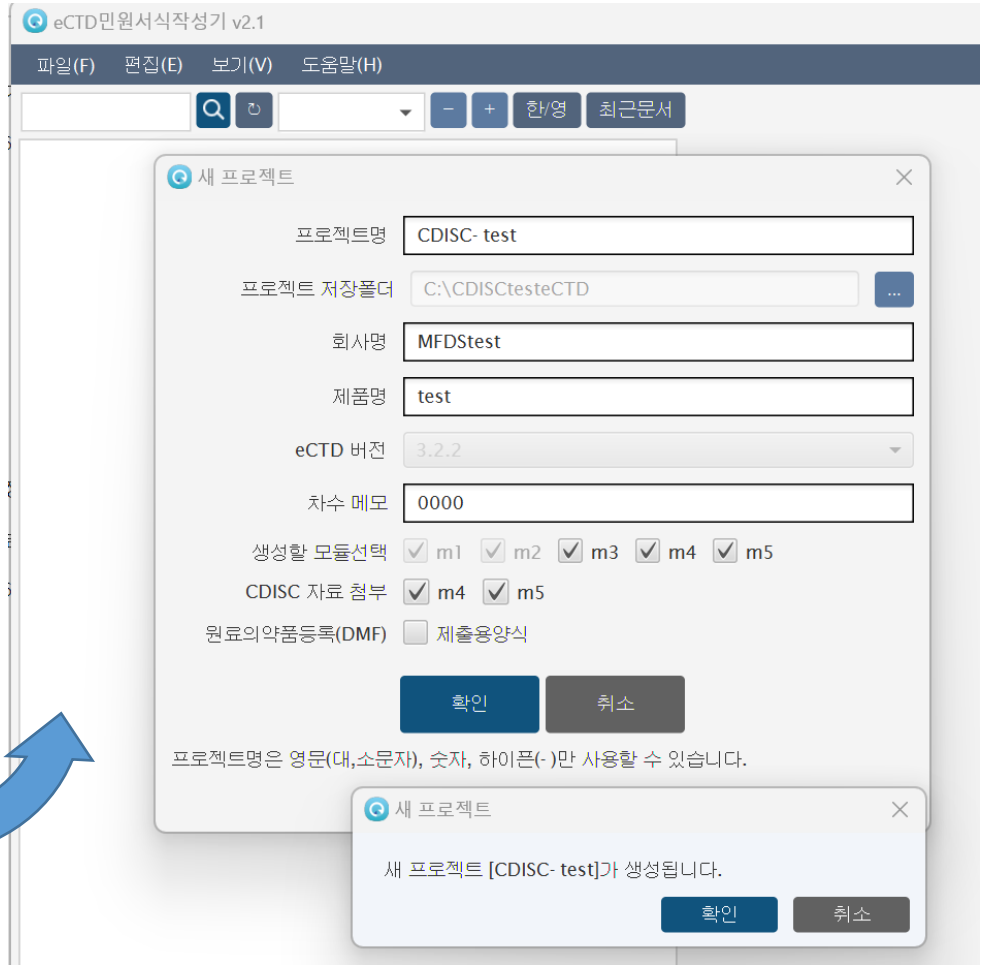
① Fill out the electronic application
② Attach eCTD file already uploaded to my account
③ Complete the application form and go to next process(fee payment, etc)

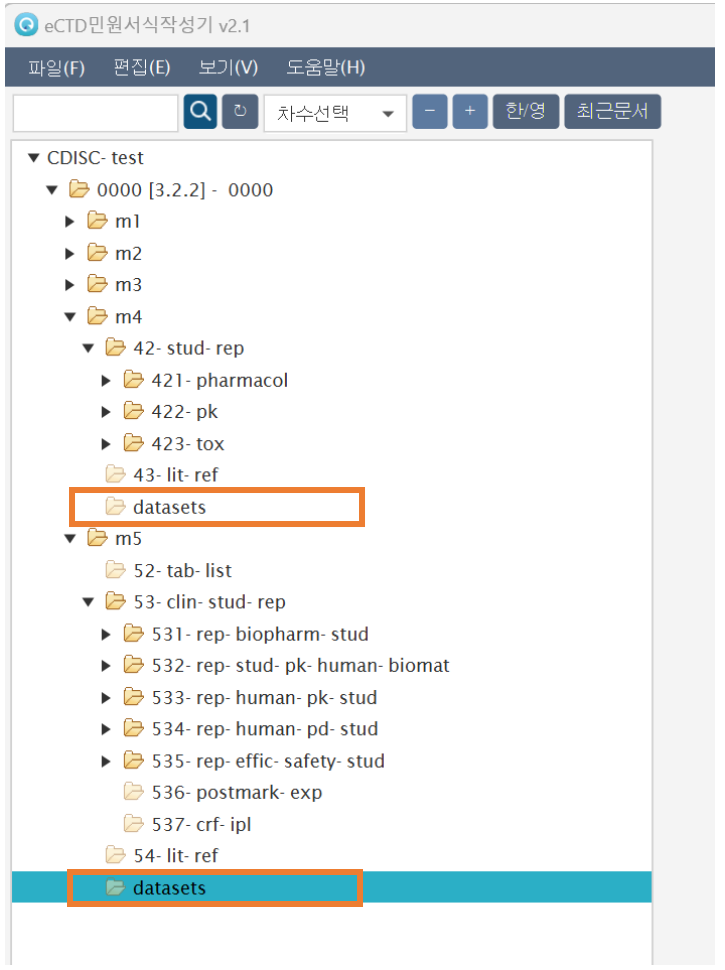
eCTD software by MFDS



Download

64 bit windows
64 bit JAVA



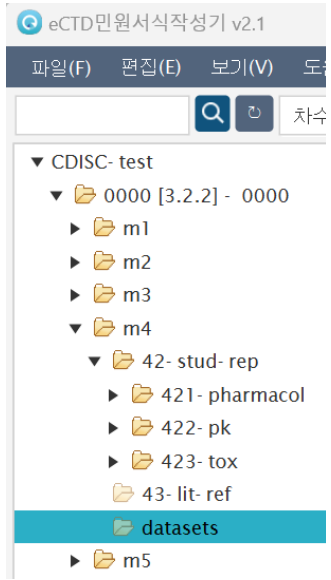


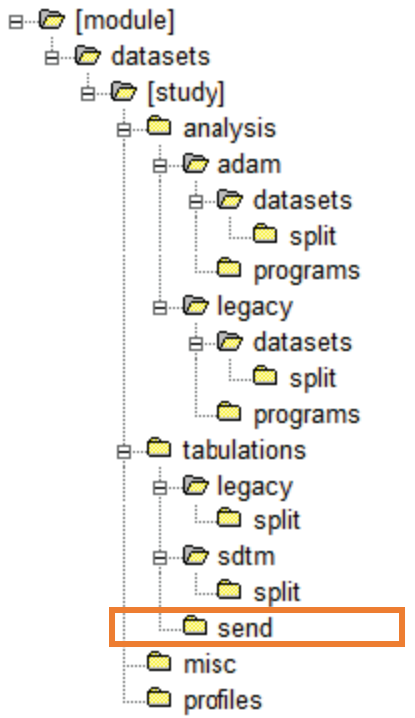
Location of CDISC in eCTD (in Phase 2)

< Internal structure of eCTD submission file Folders and required utility files >

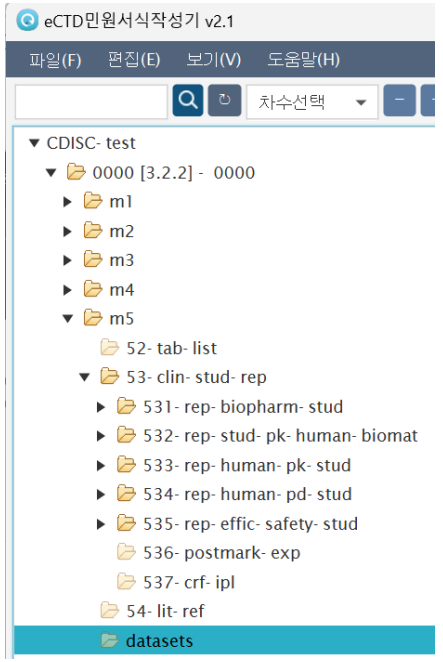
Folder	Files	Definition
	(e123456.zip)	eCTD submission filename(e-Identifier)(ex: e123456)
0000		A folder with a sequence name indicating the number of submissions as a four-digit number.(ex: 0000)
	index.xml	index file ICH standard
	index-md5.txt	MD5 checksum file
m1		Module 1 Application details and administrative information folder
kr		Korean domain codename(kr) folder
	kr-regional.xml	Index file of M1 with MFDS standard configuration applied
m2		Module 2 Submission data overview and summary folder(ICH CTD m2)
m3		Module 3 Quality evaluation data folder (ICH CTD m3)
m4		Module 4 Non-clinical trial data folder (ICH CTD m4) CDISC (SEND)
m5		Module 5 Clinical trial data folder (ICH CTD m5) CDISC (STDM, ADaM)
util		ICH eCTD specification utility folder
dtd		ICH eCTD specification DTD and schema folder
	ich-ectd-3-2.dtd	ICH standard DTD file applied from m2 to m5
	kr-regional-1-0.dtd	MFDS standard DTD file applied to m1
style		Stylesheet folder for the ICH eCTD specification
	ectd-20.xsl	ICH standard style sheet file applied from m2 to m5
	kr-regional.xsl	MFDS standard style sheet file applied to m1

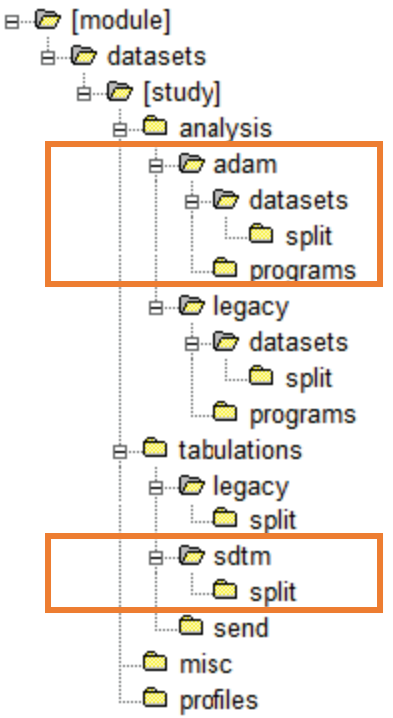
eCTD M4





eCTD M5

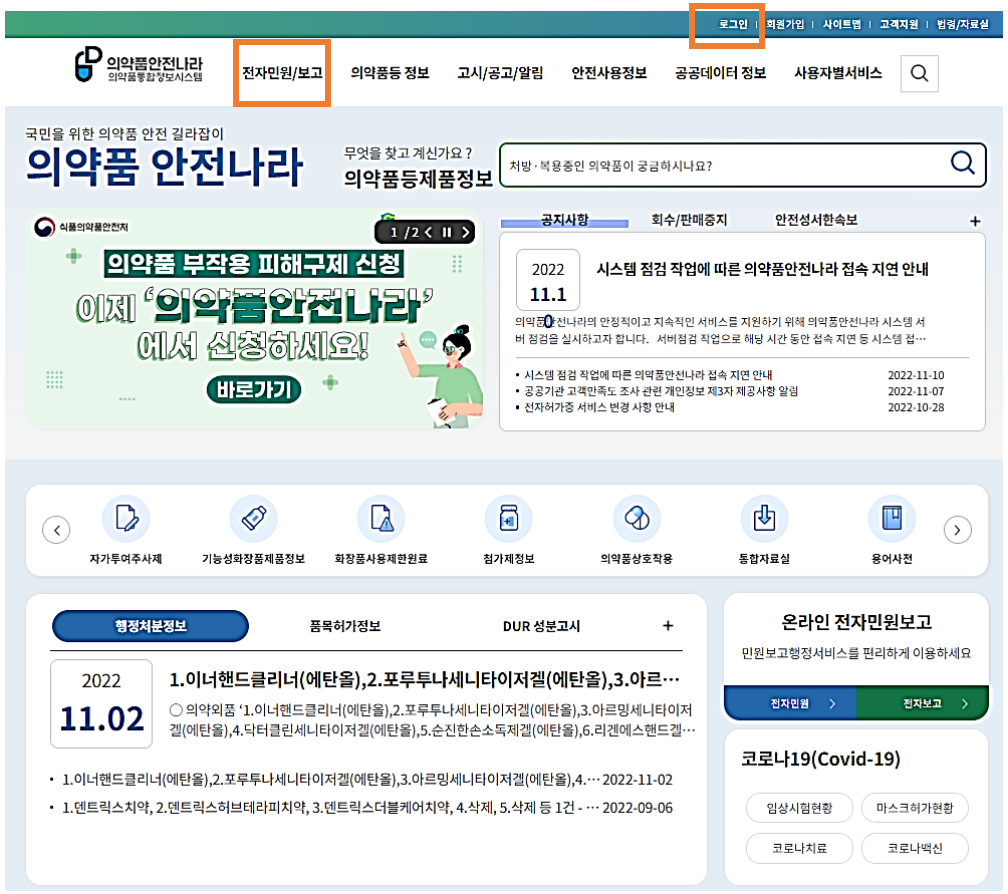


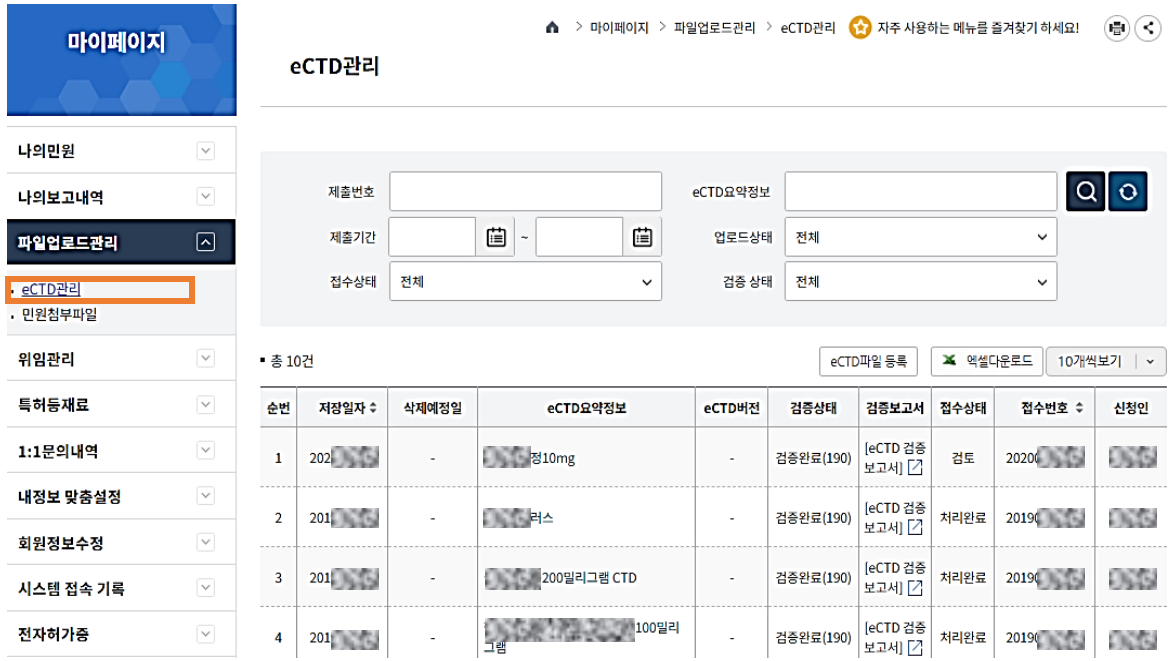


Temporarily upload eCTD to my account

Electronic Application

Log-in to my account

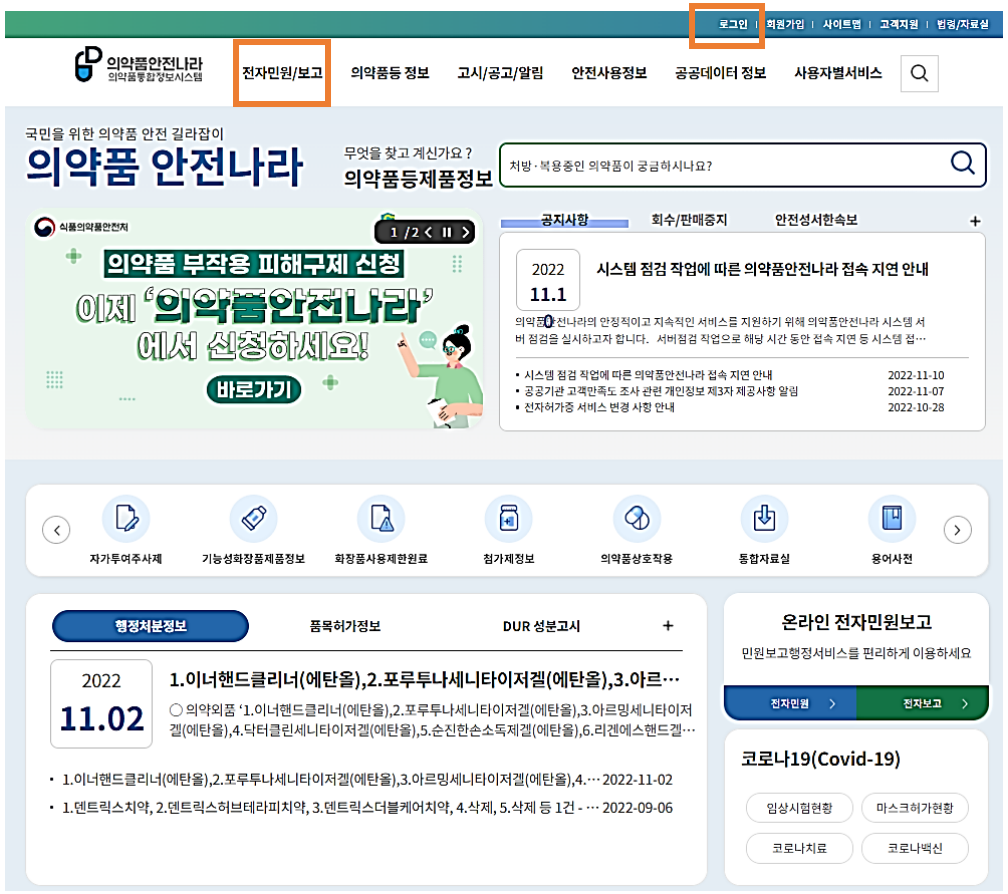




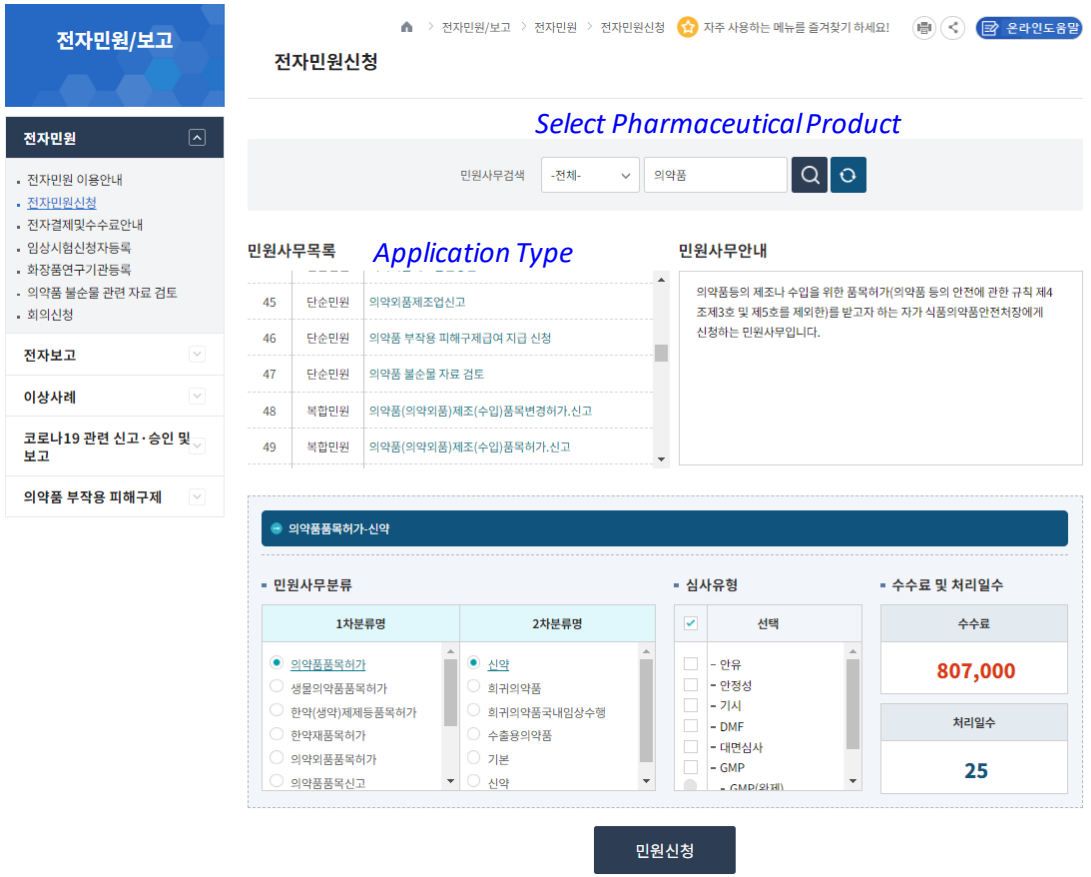
Electronic Application (in Phase 3)

Electronic Application

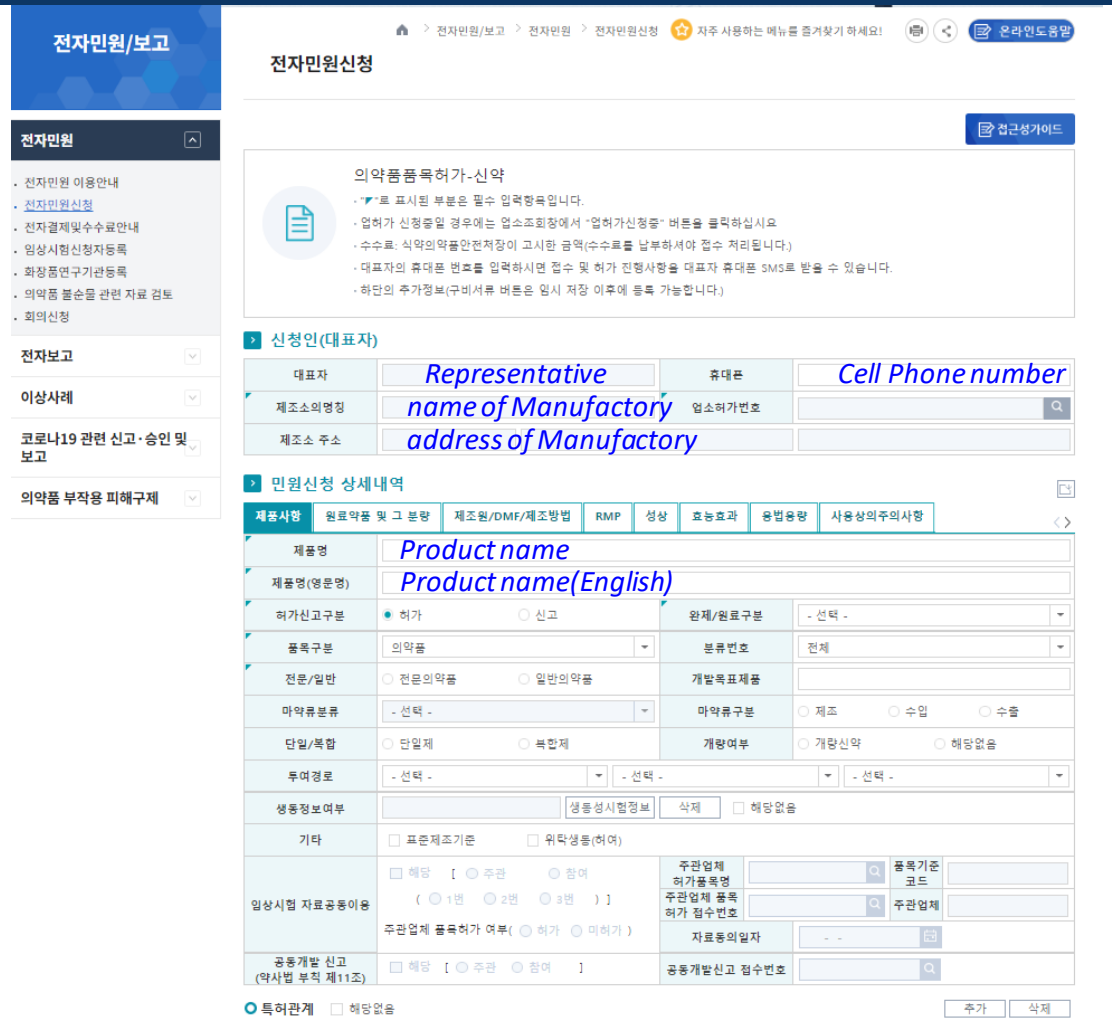
Log-in to my account



Electronic Application



Electronic Application (in Phase 3)



Whether to submit eCTD

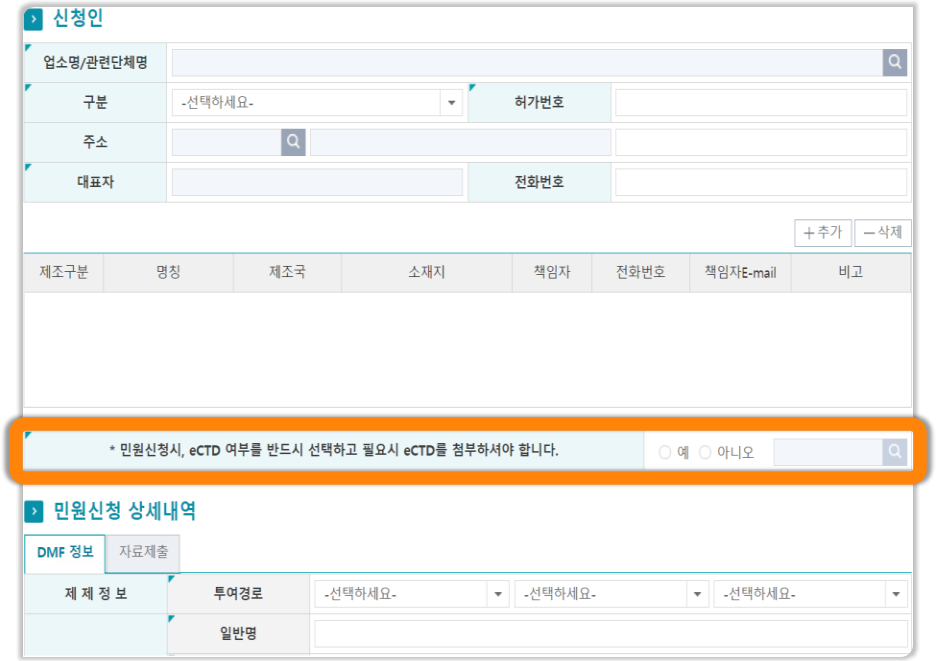
1. *Select Yes/No*
2. *Attach eCTD file already uploaded to my account*

submit data for domestic regulation standard

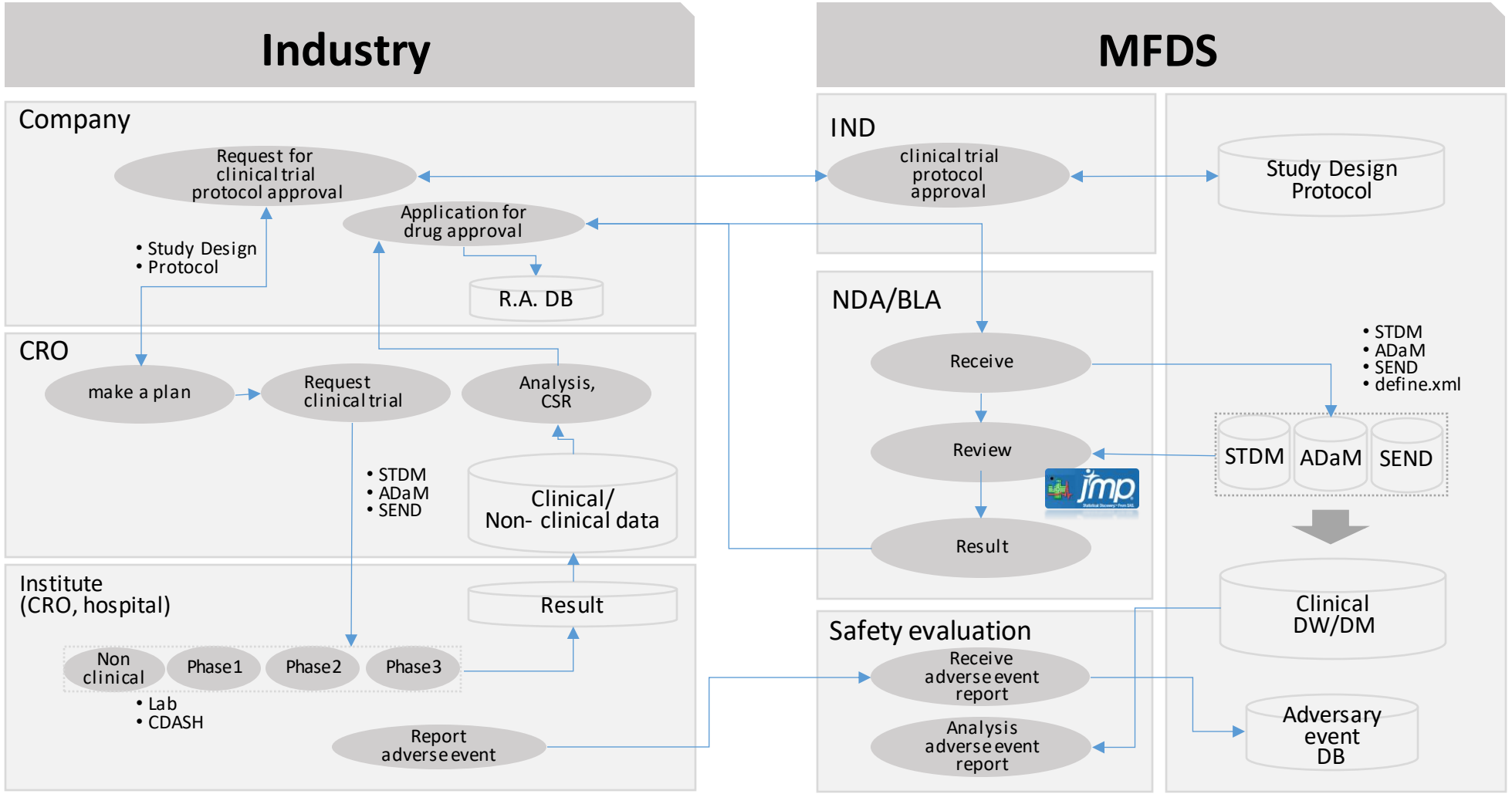
Electronic Application (in Phase 3)

- First Submission

- Supplementary Submission



Workflow between Industry and MFDS



Small feature of eCTD in KR

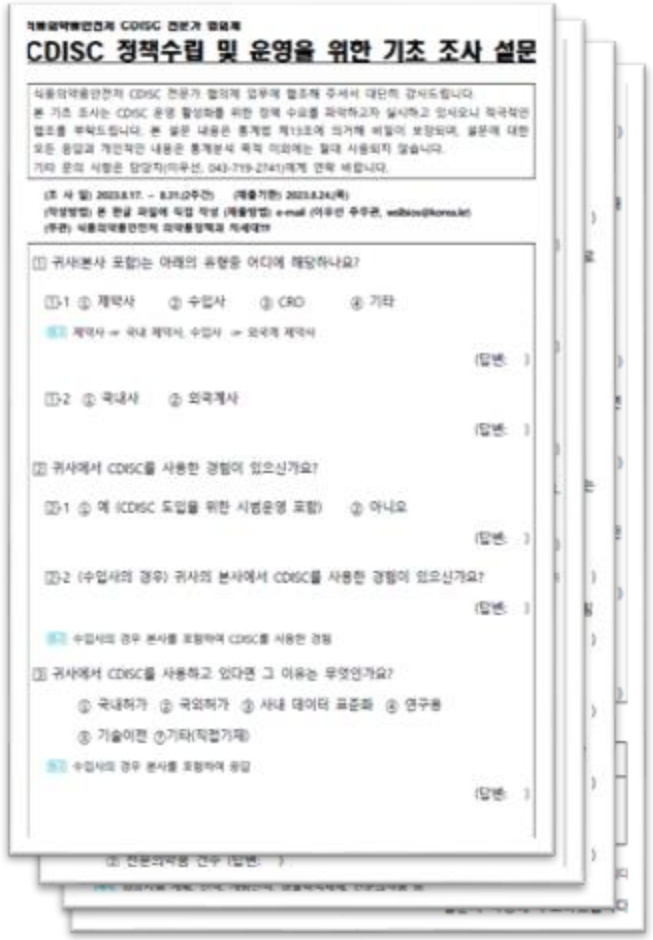
MFDS	FDA, etc.
• e-identifier of eCTD is **under** electronic application registration number	• e-identifier of eCTD is the same as application registration number
• Application details : **Not only** list in eCTD leaf, one should fill out the electronic application form	• Application details : only list in eCTD leaf
• Store separate documents and materials not defined in advance within eCTD, **but also can be submitted outer eCTD**	• Store separate documents and materials not defined in advance within eCTD

Status of CDISC in Korea

6. CDISC Status in Domestic Pharmaceutical Industry

5.

Cross-sectional survey of CDISC


CDISC 정책수립 및 운영을 위한 기초 조사 설문

< 490 Population >

KPBMA : 200 company

Korea Pharmaceutical and Bio-Pharma Manufacturers Association

KRPIA : 50 company

Korean Research-based Pharma Industry Association

KoBIA : 170 company

Korea Biomedicine Industry Association

KSQA : 70 company

The Korean Society of Quality Assurance

< Period >

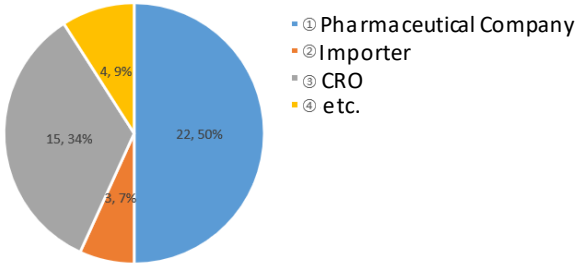
'23.8.22 ~ 9.22

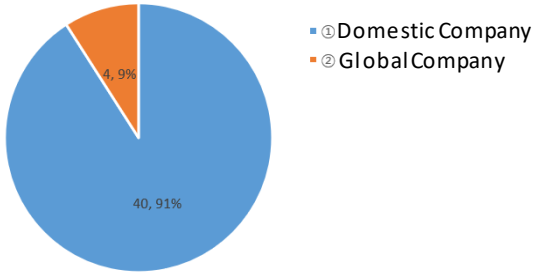
< Method >

Email survey through 4 associations

< Response >

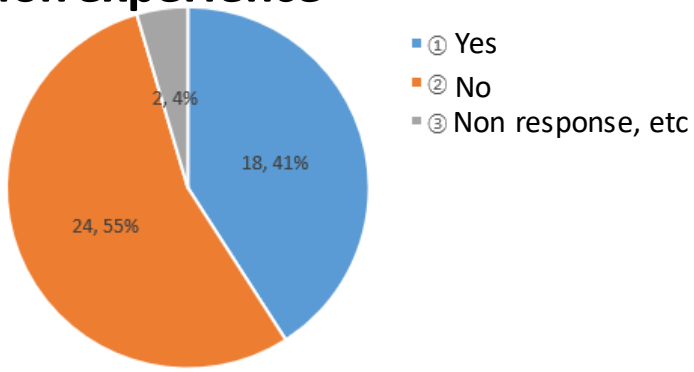
44 companies responded (9%)



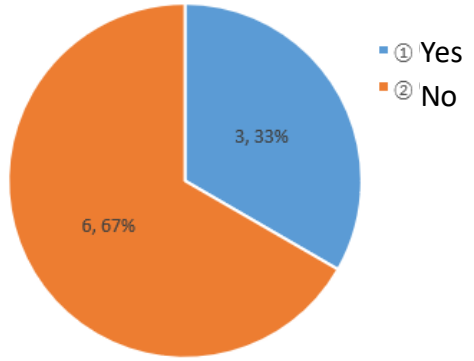


Experience & Purpose of use CDISC

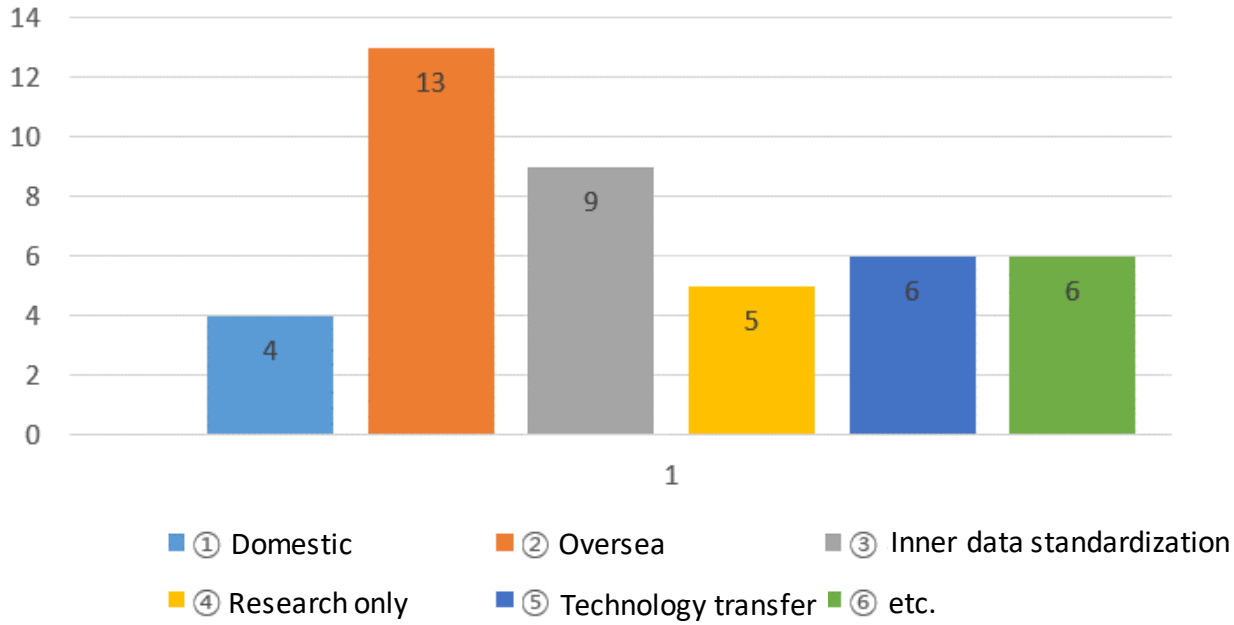
- **CDISC Utilization experience**



- (importer) **CDISC Utilization experience of headquaters**



- **CDISC Utilization Objectives in the industry**



Experience with CDISC

- Cumulative number of studies with CDISC

Type	Min	Mean	Max	sum	respondent
① Pharmaceutical Company	1	8.3	25	83	10
② Importer	900	900.0	900	900	1
③ CRO	37	70.8	153	283	6
④ other	4	4.0	4	4	2
Total	1	79.4	900	1,270	19

- Number of studies with CDISC in 22 years

Type	Min	Mean	Max	sum	respondent
① Pharmaceutical Company	1	2.2	4	13	6
② Importer	240	240	240	240	1
③ CRO	5	26	51	130	5
④ other	2	2	2	2	1
Total	1	29.6	240	385	13

Submissions by Regulatory Agency

- The number of submissions to regulatory authorities using CDISC.

Regulatory Agency	① Pharmaceutical Company	② Importer	③ CRO	Total
FDA	7	2	3	12
PMDA	1	2	1	5
EMA	1	1	1	3
NMPA	-	2	-	2
MFDS	1	-	-	1
Other			1	1
Total	10	7	6	23

- Number of CDISC by application type

	Pharmaceutical Products	Biological Products	Advanced Biopharmaceuticals	General Pharmaceuticals	Specialized Pharmaceuticals	Initial Submission	Amendment Submission
① Pharmaceutical Company	44	14	0	0	58	38	1
② Importer	0	0	0	0	89	278	2
③ CRO	101	13	17	0	0	0	0
Total	145	27	17	0	147	316	3

Preference

- Positive/Negative perspectives regarding the utilization of CDISC in regulation.

Business Type	Very Positive	positive	Neutral	Negative	Very Negative	Non response	Total
① Pharmaceutical Company	0	9	6	3	3	1	22
② Importer	2	0	0	1	0	0	3
③ CRO	6	2	7	0	0	0	15
④ other	1	2	0	0	0	1	4
Total	9	13	13	4	3	2	44

- The burden associated with the utilization of CDISC in regulation

Business Type	Not at all	Not	Neutral	Burdensome	Very Burdensome	Non response	Total
① Pharmaceutical Company	0	1	9	5	6	0	22
② Importer	1	0	1	1	0	0	3
③ CRO	6	0	5	3	1	0	15
④ other	1	1	1	0	0	1	4
Total	8	2	16	9	7	1	44

Cause of Burden

- Burden Cause

Burden Cause	Response Count
Cost burden	14
Time burden	7
Insufficient manpower	6
Lack of experience	5
Lack of expertise, High complexity, Educational burden	2
Difficulty in updating SDTM versions,	
Burden of managing raw and analysis data through SDTM,	
Different standards across regulatory agencies,	1
Anticipated challenges in CDISC adoption from clinical planning,	
Lack of perceived necessity	

- CDSIC-related organization and budget

Business Type	① Yes	② No	respondent
① Pharmaceutical Company	6	16	22
② Importer	2	1	3
③ CRO	5	10	15
④ other	2	2	4
Total	15	29	44

Readiness

- If submission of CDISC becomes mandatory in Korea, can a company submit CDISC immediately?

Business Type	① CDISC Prepared and Immediately Submittable	② CDISC Prepared but Time Required for RA Review, Decision on Submission Scope, etc.	③ CDISC Not Prepared and Significant Time Required	No Response	Total Companies
① Pharmaceutical Company	2	4	16	1	23
② Importer	0	2	1	0	3
③ CRO	6	0	9	0	15
④ Other	1	0	1	2	4
Total	9	6	27	3	44

- If it is difficult to submit the CDISC right away, how much time will take?

	① Pharmaceutical Company	② Importer	③ CRO
Average Duration (Years)	2.0	5.0	2.0

- Other opinions

Content	Respondent
Time-consuming for CRO preparation, data review, etc.	5
Ready for immediate submission if using the same criteria and form at as the FDA	1
Time required for RA review, decision on submission scope, etc., if separate criteria established by MFDS	1
Internal infrastructure construction required	1
Can be known depending on the trial submission	1
Depends on the requirements of the MFDS	1
Clinical Trials	1

CDISC application areas in industry

Type	① Pharmaceutical Company	② Importer	③ CRO	④ Other	Total
Clinical (STDM, ADAM)	7	1	2	2	12
Non-clinical (SEND)	2	1	4	1	8

Therapeutic Indication	**Number of mentioned study**
Antineoplastic Agents	11
Vaccines and Viruses, Gastrointestinal disorders	5
Cardiac disorders	3
Endocrine disorders, Metabolism and nutrition disorders, Nervous system disorders, Respiratory disorders	2
IPF, Idiopathic Pulmonary Fibrosis, Microbiome, Osteoarthritis, Endocrine, Cerebrovascular disorders, Botulinum toxin, Genitourinary disorders, Obesity, Live Biotherapeutic Products, Cell Therapy Products, Inflammation, Nutrition and Metabolism Disorders, Autoimmune disease and antibody therapy, Pain, Skin, Synthetic drugs, Anti-inflammatory agents, Orphan drugs	1

CDISC implementation & Software

- CDISC implementation stage

Business Type	① Study Design	② Study Execution	③ Post study closure
① Pharmaceutical Company	1	4	9
② Importer	2	2	2
③ CRO	1	3	6
④ Other	0	1	0
Total	4	10	17

- Software

SW	User
SAS	17
Submit, Savante	2
Bluepine, DataDefine, imtrial, Python, R, Safesoft,	1

Positive expectations for CDISC adoption and Requests to MFDS

Expected Benefits	Respondent
Increased operational efficiency through data standardization	19
Global-level data construction	13
Reduction in review period	14
Online archive of data	4
Securement of high-quality data	2
Ease of global expansion and increased efficiency in related operations	2
Predictive data provision based on artificial intelligence	1
Global regulatory harmonization	1
Shortening of analysis/review period	1
Increase in revenue due to diversified business	1
Unlimited data processing and analysis capabilities	1

Category	Proposed Suggestions	Responses
Education and Training	Training and education for specialized personnel related to CDISC submission	5
CDISC Adoption Difficulties	Request for mandatory adoption three years or more after sufficient recommendation period	2
	Gradual adoption needed due to the need for clinical design (approval schedule/CRO cost) for CDISC	1
	Request for gradual adoption as it is difficult for all pharmaceutical companies	1
	Small companies face outsourcing burden when CDISC is introduced domestically	1
	Immediate application of CDISC requires time and procedures for company system changes and construction	1
	Long-Term Approach Needed	1
Manual and Standards Application	Detailed guidelines and manuals for CDISC submission requested	3
	Request for guidelines specifying compatibility with FDA standards, allowing full English usage, and not mandating Korean as NMPA	2
	Applying all CDISC specifications domestically is difficult, and there is a hope to avoid strict verification of all standards	2
	Request for guidance on regulatory evaluation contents (safety based on SDTM review)	1
	Awareness needed that standardizing all data per study is not feasible	1
	Application of the same guidelines and standards as FDA	1
	Mandatory compliance rules and selection of target data required for adoption	1
	Notification and promotion of the necessity before domestic application	1
	Consideration for companies difficult to comply with policies, focusing on export-oriented operations	1
System Building	Building a system that allows easy and accurate submission	1
Soliciting Opinions	Soliciting opinions on industry conditions and voices (cost, education, timing of CDISC obligation)	3
Other Opinions	Hope for CDISC activation and mandatory adoption domestically	3
	Desire for quick implementation	1
	Activation of existing eCTD	1

Summary of survey results

- **CDISC Utilization Objectives:**
  - Primary objectives in the industry are, in order of priority, 'Overseas Regulatory Approval,' 'Internal Data Standardization,' 'Research,' 'Technology Transfer,' and 'Domestic Regulatory Approval.'
- **CDISC Utilization in 2022:**
  - In 2022, CDISC utilization counts are reported as 13 cases for domestic pharmaceutical companies (6 companies), 240 cases for importers (1 company), and 130 cases for CROs (5 companies).
- **CDISC Application in Therapeutic Areas:**
  - The CDISC application is diverse, covering 26 therapeutic areas, with the top 5 being 'Anticancer Drugs and Tumors,' 'Vaccines and Viruses,' 'Digestive System,' 'Cardiovascular System,' and a group of four including 'Endocrine System,' 'Metabolic Disorders,' 'Neurology,' and 'Respiratory System.'
- **Experience of Domestic Pharmaceutical Companies with Regulatory Agencies:**
  - Domestic pharmaceutical companies report having submission experience with regulatory agencies such as FDA, PMDA, EMA, and NMPA.
- **Preference and Concerns Regarding CDISC Regulatory Application:**
  - The preference for CDISC regulatory application is positive, with 79.5% expressing a 'Very Positive' or 'Positive' stance. However, concerns about the burden are notable, with 36.3% finding it 'Very Burdensome' or 'Burdensome.' Main concerns include cost, workload, manpower, and lack of experience.
- **CDISC Regulatory Application Scope:**
  - Respondents consider the application scope appropriate for 'New Drugs,' 'Clinical Trial Plans,' and 'Biological Products.' There is a desire for gradual expansion of the application scope.
- **Readiness and Time Estimates for CDISC Mandatory Submission:**
  - Only 20.4% of the industry feels immediately ready for CDISC mandatory submission, while 61% expect a significant amount of time to be spent on preparation. The average estimated time for industry readiness is around 2 years.

Status of CDISC in Korea

7. Implications and Conclusions

Implications

- **Industry Snapshot**
  - Only 20% (6 companies) are currently ready for "immediate submission" under CDISC mandatory adoption, revealing a modest preparedness level.
  - Anticipated average preparation time is around 2 years, underscoring the significant commitment required.
  - Despite challenges, certain industry leaders are taking proactive steps in CDISC adoption.
  - Industry acknowledges the need for substantial preparation, including specialized personnel, organizational adjustments, and budget considerations.
  - Key players are already at the forefront of CDISC implementation.
- **Strategic Industry Approach**
  - Industry prioritizes leveraging specialized knowledge and experience, with a focus on new drug development.
  - Emphasis on knowledge dissemination and gradual expansion of CDISC application scope.
- **Stance of MFDS**
  - MFDS concerns about the potential impact of immediate implementations of standardized systems.
  - Call for regulatory policies balancing industry needs and compliance, including sufficient recommendation periods, gradual application, and criteria alignment with industry expectations.
  - Collaborative approach suggested, involving industry stakeholders in CDISC standards formulation for mutual understanding and industry compliance.

MFDS's Position on CDISC Standards

- **Support for CDISC Activation**
  - MFDS expresses support for the activation of CDISC within the industry, aiming to foster the adoption of standards.
- **Mitigating Hurdles in Standard Adoption**
  - Striving to introduce minimal standards to prevent obstacles in the industry's adoption of CDISC, MFDS emphasizes a facilitative approach.
- **Collaboration with Foreign Regulatory Bodies**
  - While introducing minimal standards, MFDS seeks to provide sufficient information for effective communication with foreign regulatory bodies, facilitating entry into international regulatory frameworks.
- **Consideration of Industry Environment**
  - Recognizing the industry's unique characteristics, MFDS aims to tailor the CDISC implementation environment to suit industry needs, emphasizing practical feasibility and efficiency.
- **Focus on Key Research Areas**
  - Prioritizing key research areas such as therapeutic indications, MFDS underscores the importance of aligning standards with the industry's primary areas of interest.
- **Phased Application of CDISC Standards**
  - MFDS acknowledges the need for considering various stages of CDISC standard application, spanning from the early stages of research to post-study data transformation. This comprehensive approach aims to clarify the scope and timing of standard application.

Q & A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