국민 안심이 기준입니다
YOUR SAFETY IS OUR STANDARD

Domestic status of eCTD and electronic submissions for clinical trials

Woosun Lee

2024.11.13.

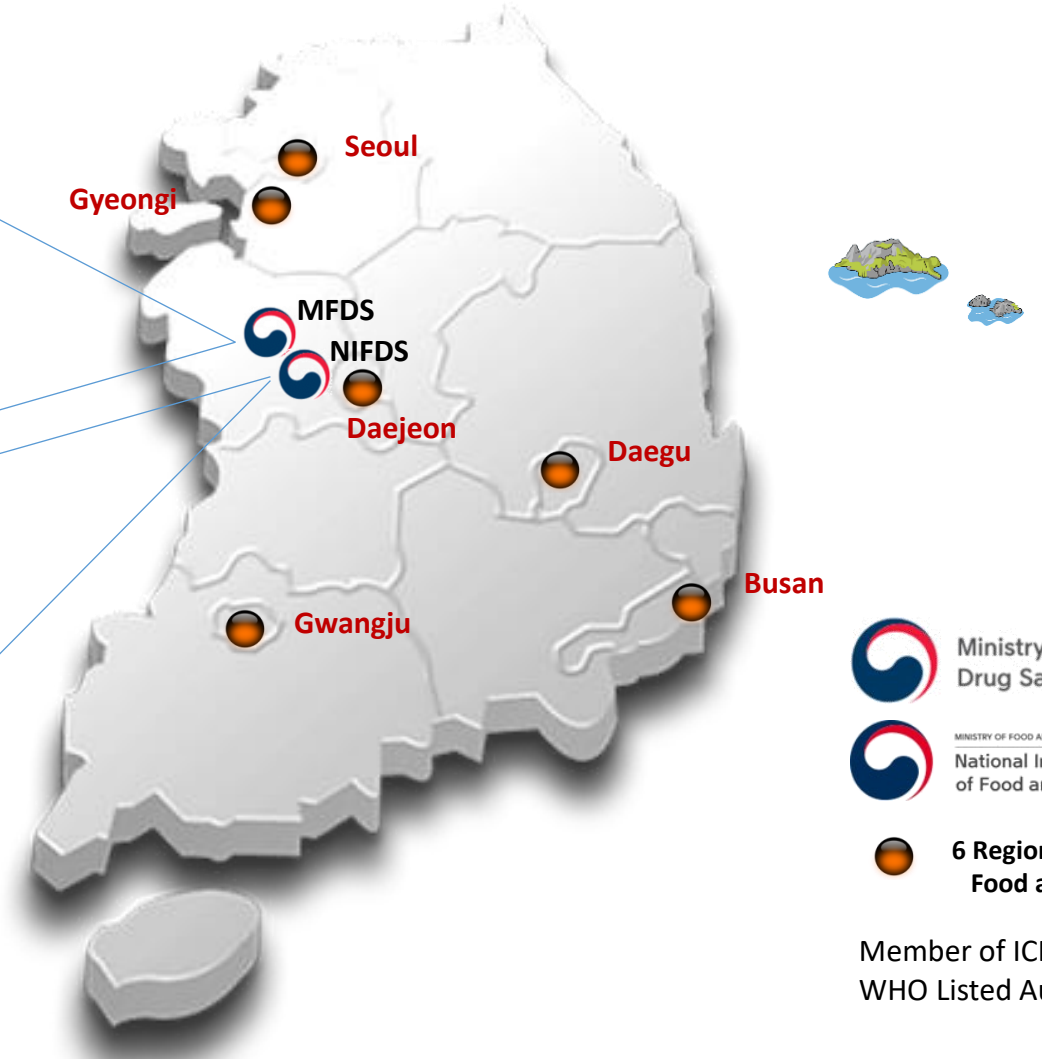
Pharmaceutical Policy Division, Pharmaceutical Safety Bureau
Ministry of Food and Drug Safety

CONTENS

Status of CDISC in Korea

1. Introduction of MFDS

Introduction of MFDS



Ministry of Food and Drug Safety

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~)

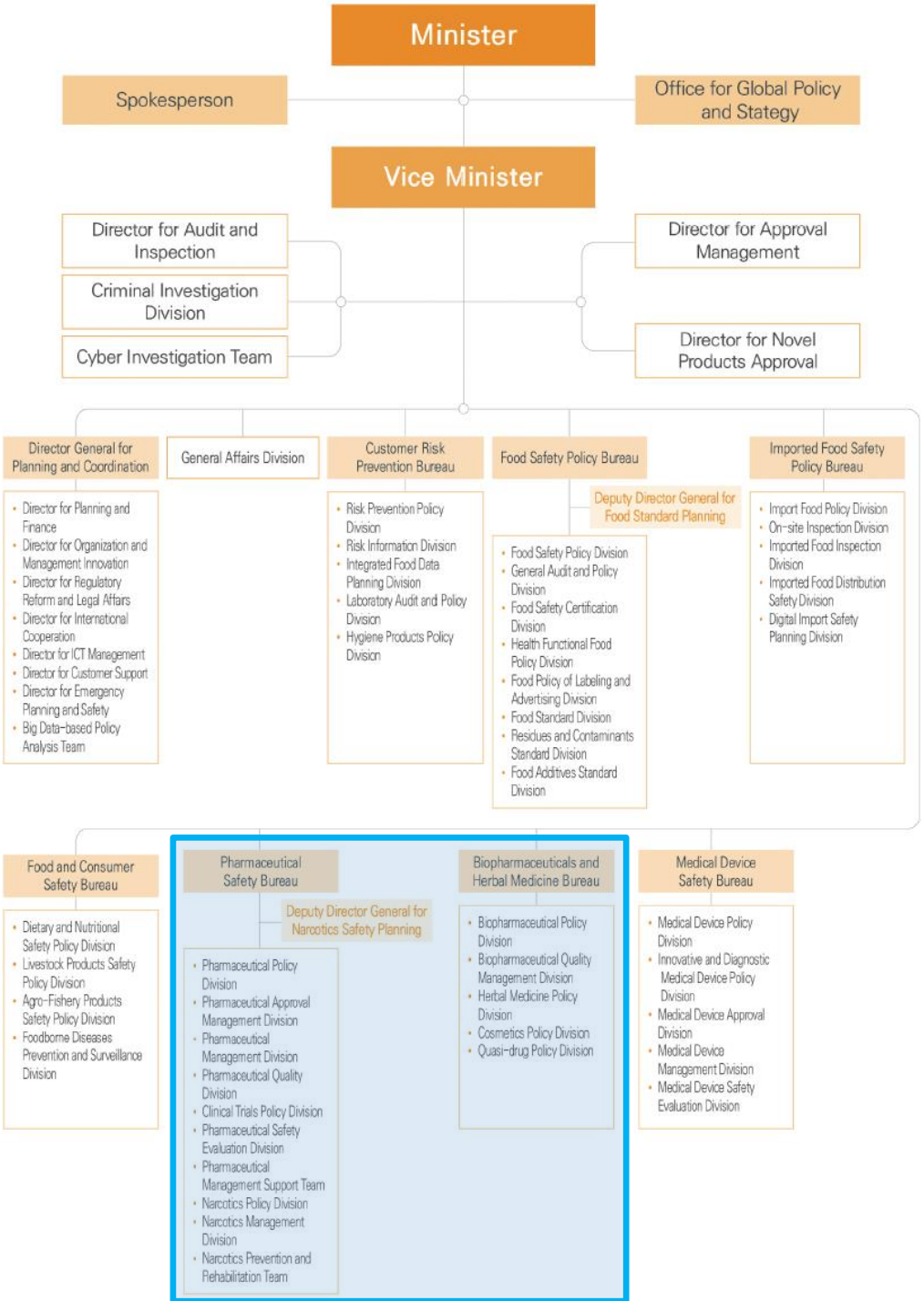
Our Vision, Core Strategies

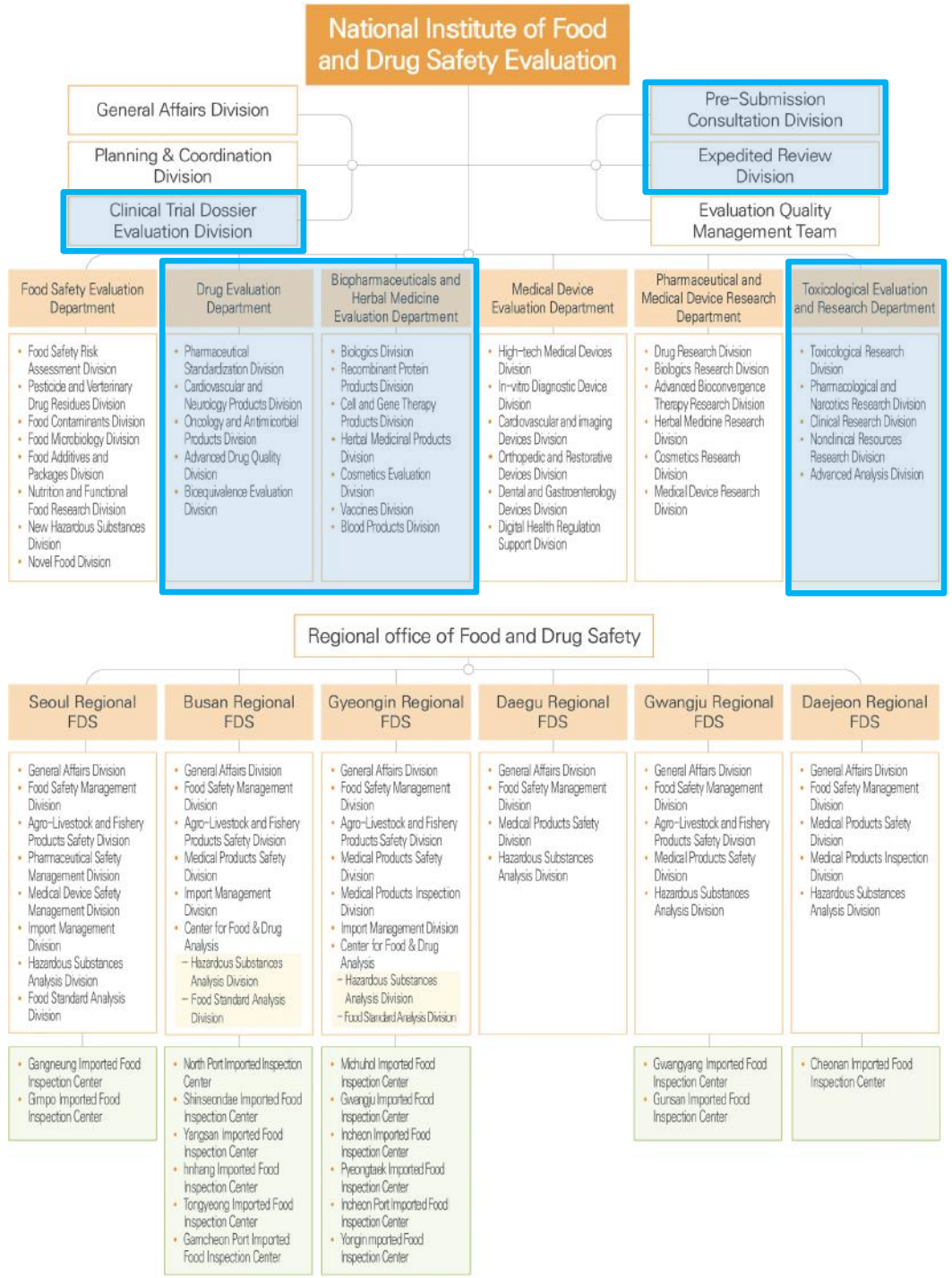
Vision

A world where food and drug **safety** are a **routine**

Core Value

Organization



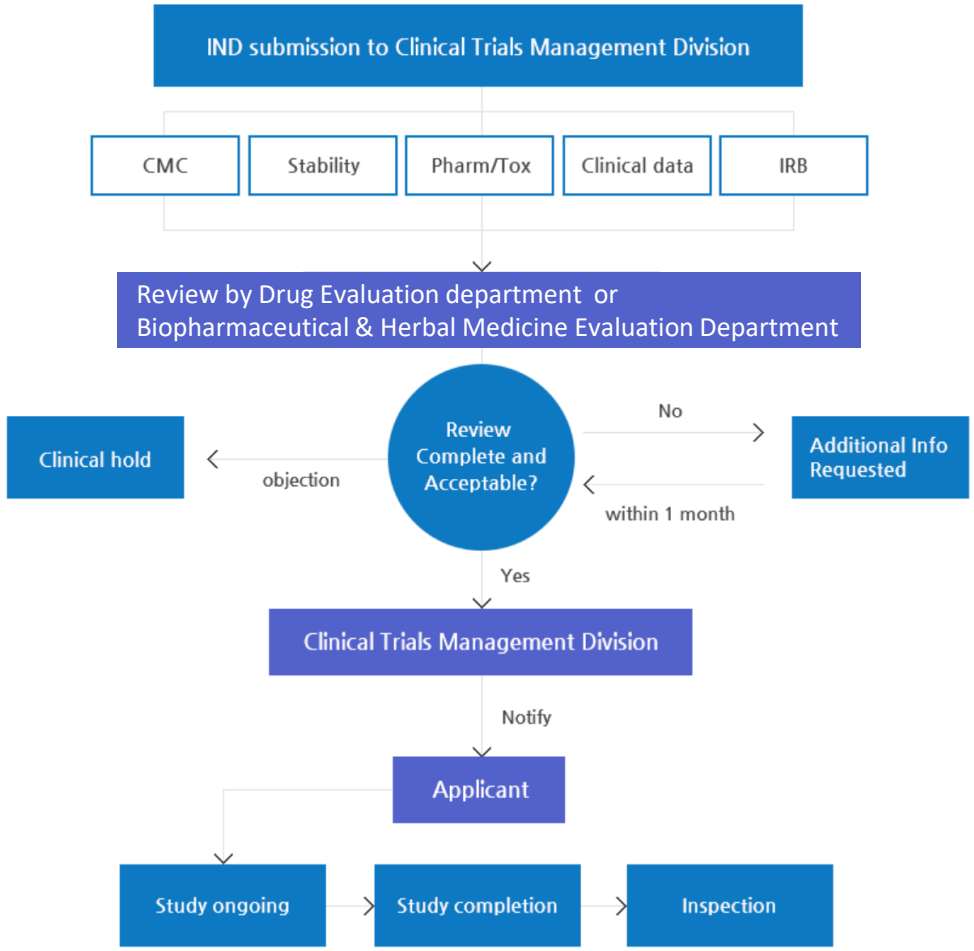


Status of CDISC in Korea

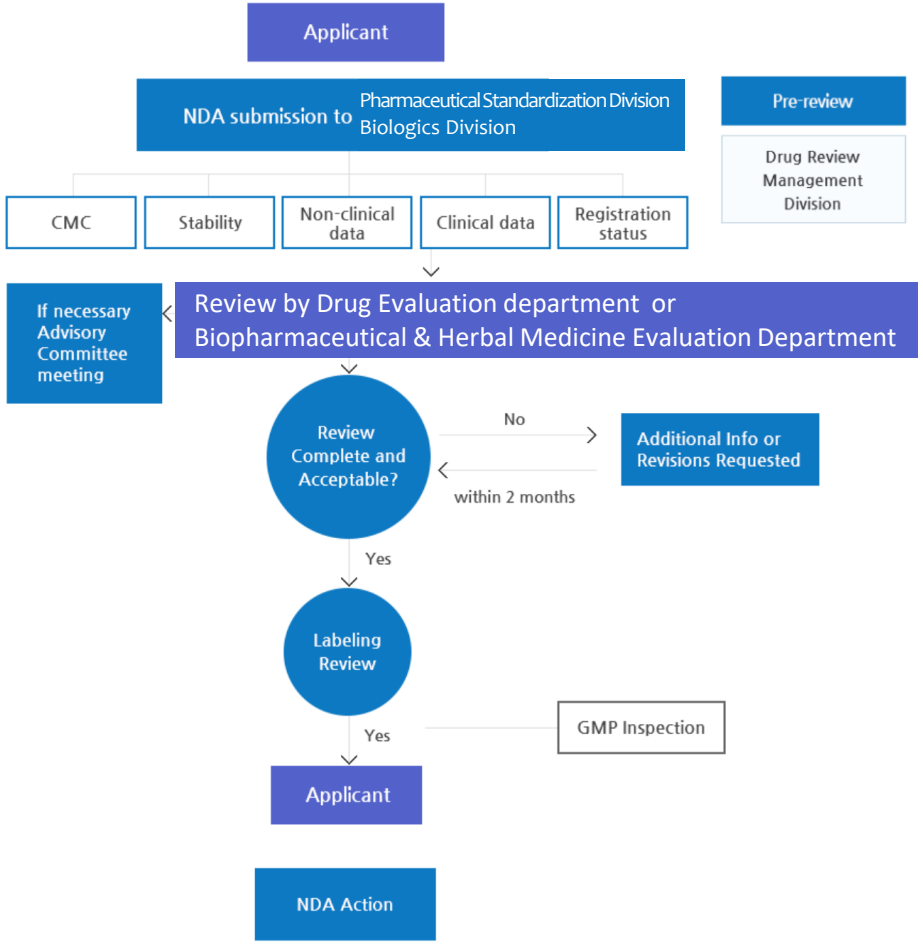
2. NDA/BLA Approval Process & Data Submission

NDA/BLA Approval Process

IND(Investigational New Drug Application) Review Process



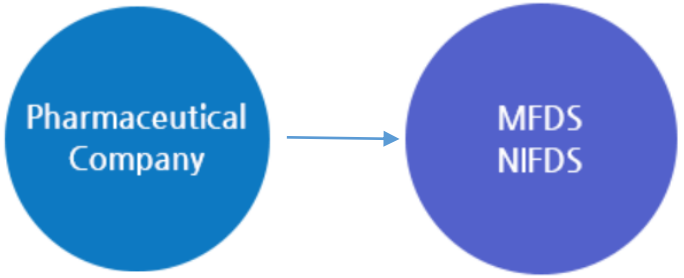
NDA (New Drug Application) Review Process



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)



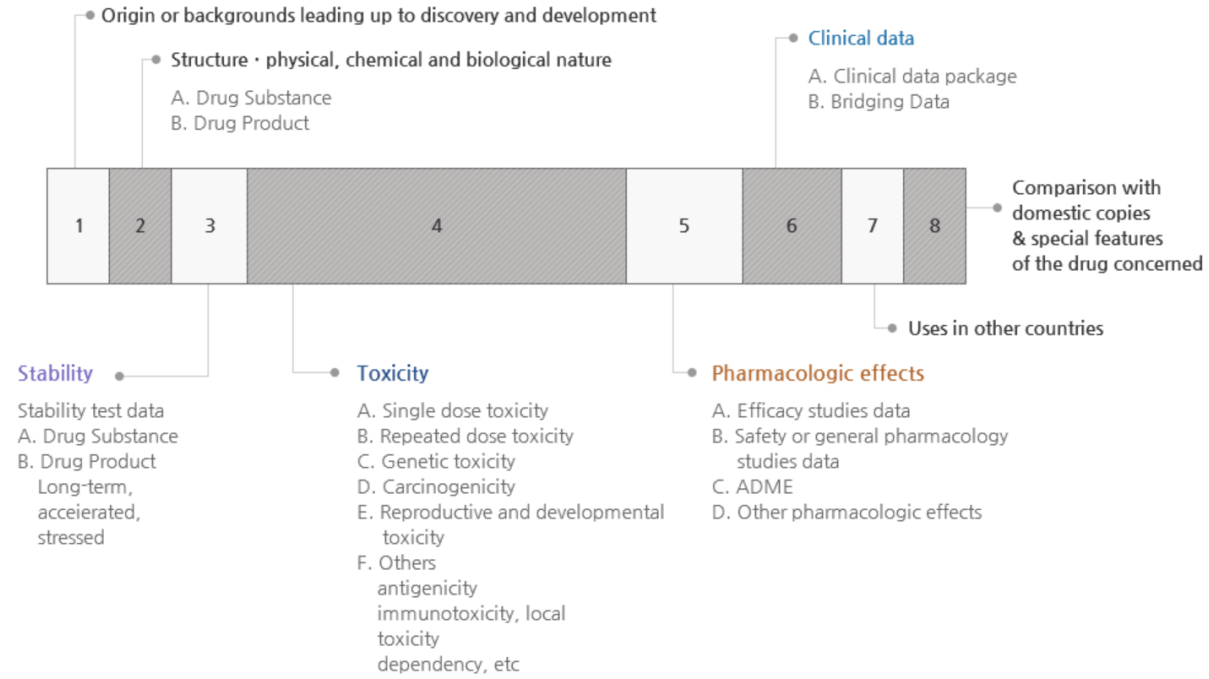
Electronic Data Submission

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

Data Requirements for Approval

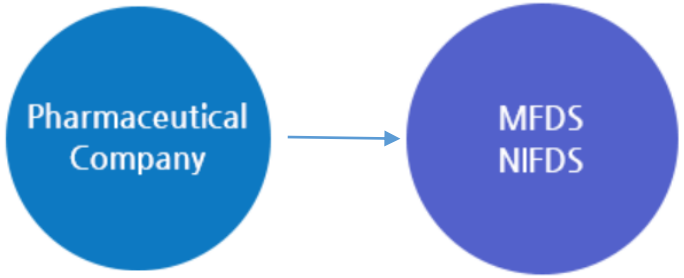
› New Drug (「Regulation on Safety of Pharmaceuticals」(Ordinance of the Prime Ministerial) Article 9)

- (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)



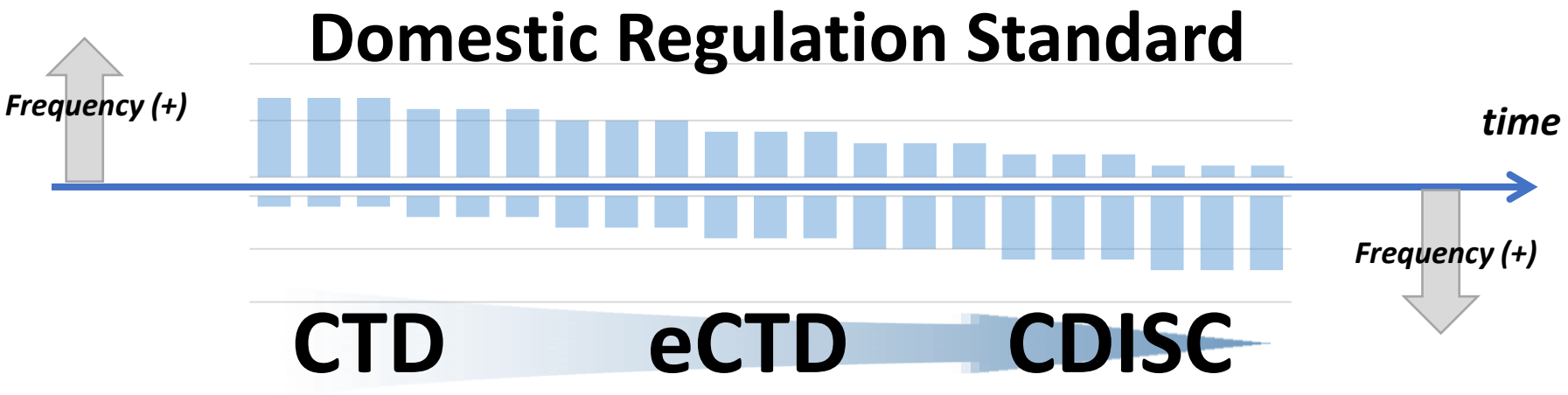
Dossier for Safety & Efficacy Evaluation

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~)
  - ❖ CDISC Sample Submission Technical Pilot

Status of CDISC in Korea

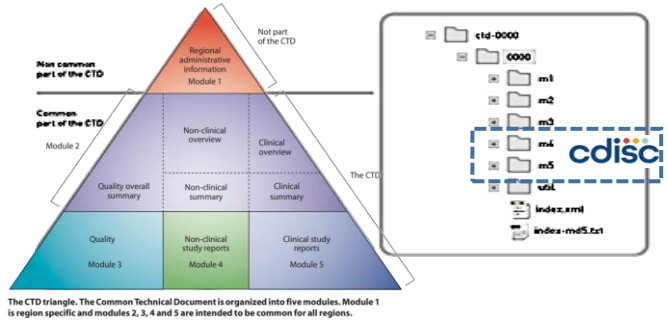
5. Submit an eCTD or Standardized Data to the MFDS

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

Common Technical Document [CTD] eCTD



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

cdisc

Phase 2. Create eCTD include CDISC & Prepare for Submission

< Create eCTD >

LORENZ docuBridge, Veeva, EXTEDO eCTD manager, etc.

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

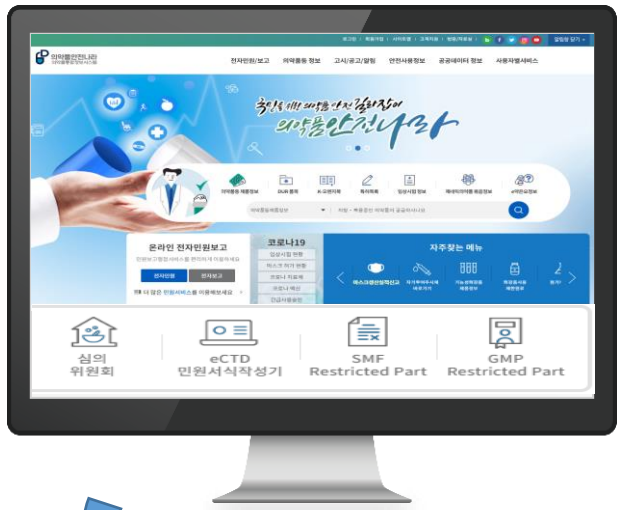
< Temporarily upload to my account >

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)

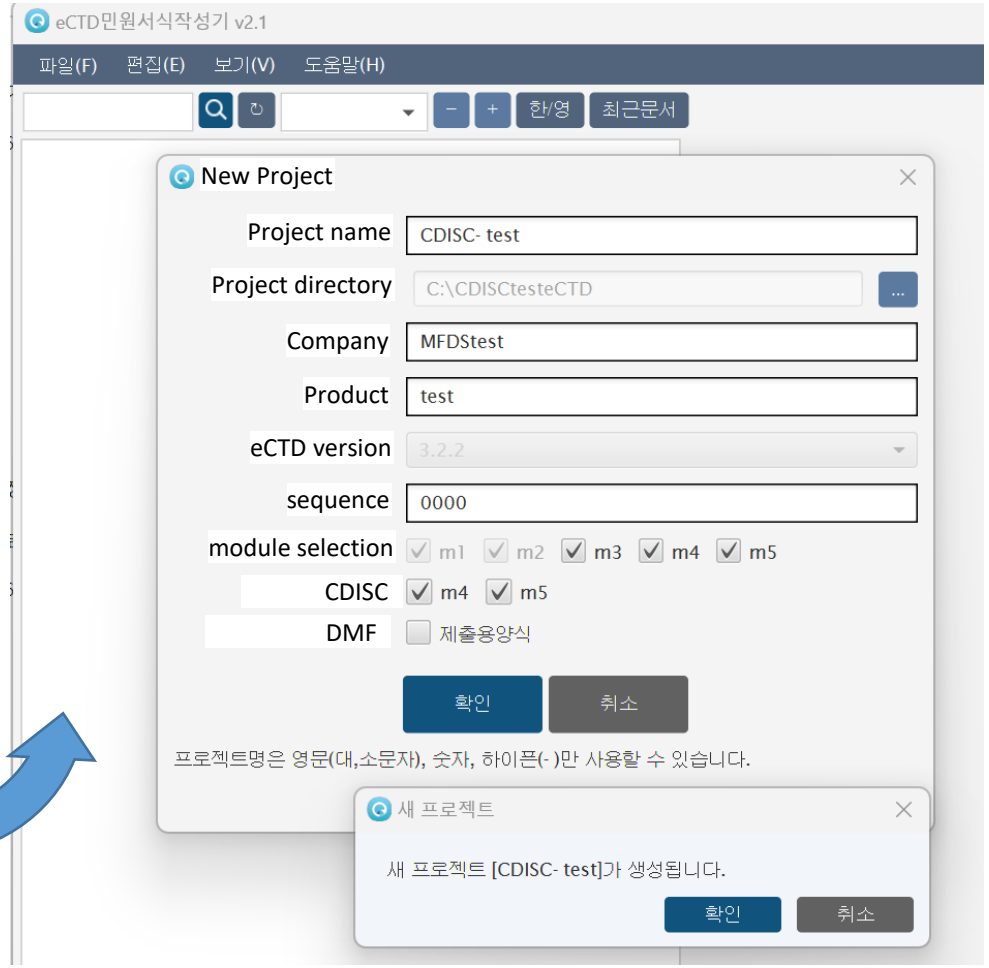
eCTD software by MFDS

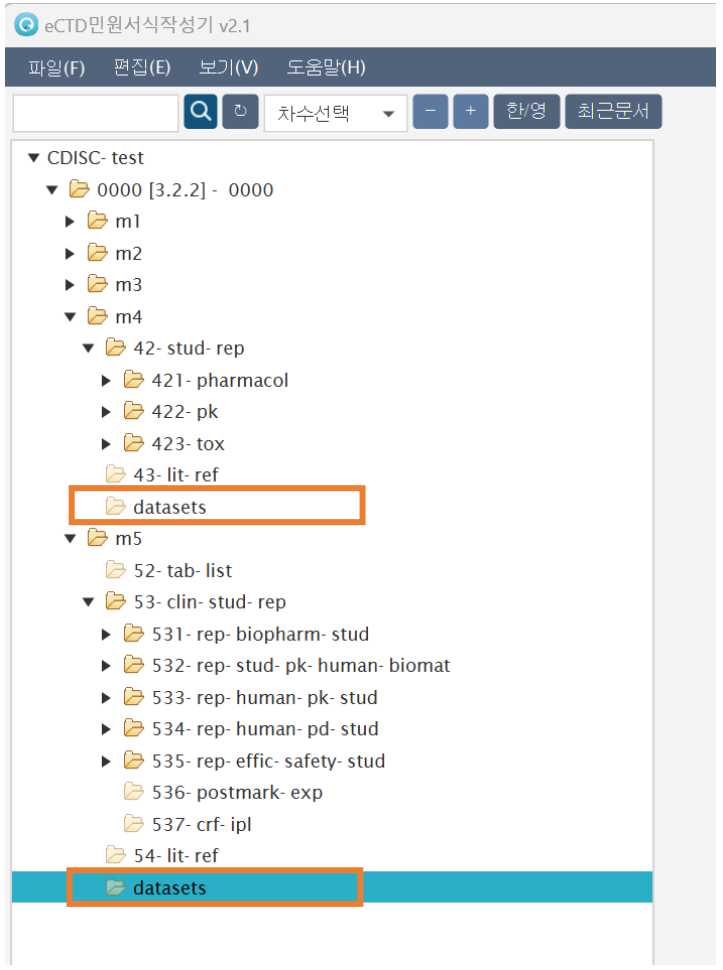


eCTD민원서
식작성기
v2.1

Download

64 bit OS
64 bit JAVA



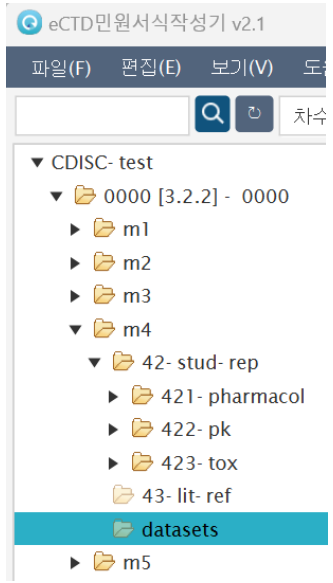


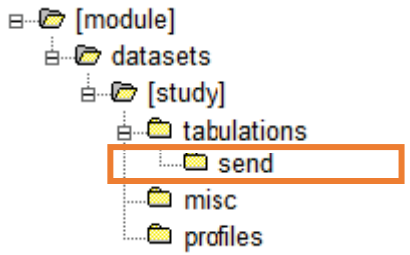
Location of CDISC in eCTD (in Phase 2)

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

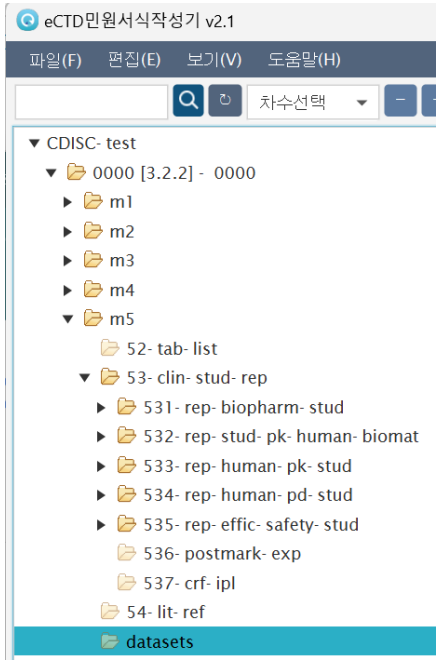
Folder	Files	Definition
	(e123456.zip)	eCTD submission filename(e-Identifier)(ex: e123456)
0000		A folder with a sequence name indicating the number of submissions as a four-digit number.(ex: 0000)
	index.xml	index file ICH standard
	index-md5.txt	MD5 checksum file
m1		Module 1 Application details and 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 (SDTM 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

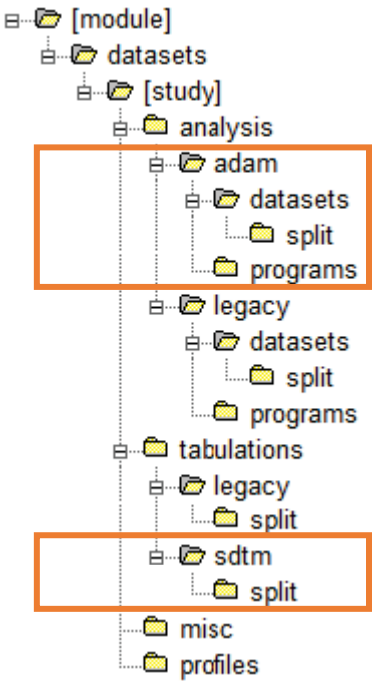
eCTD M4





eCTD M5

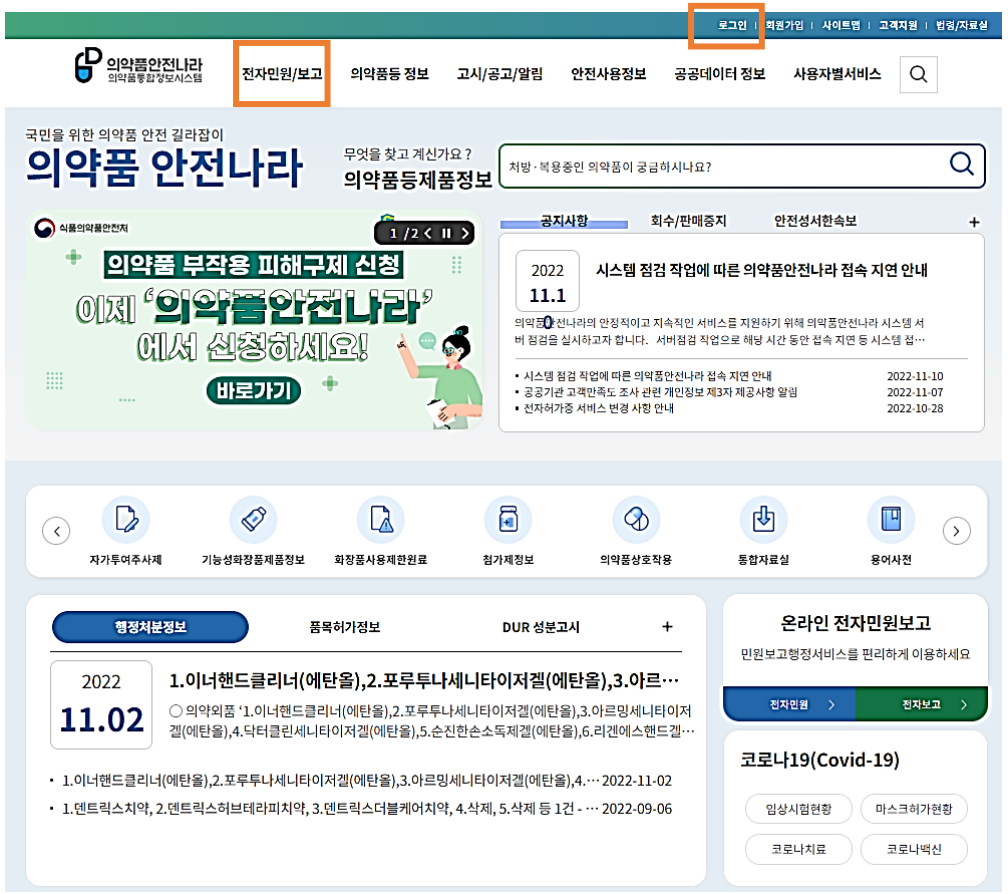


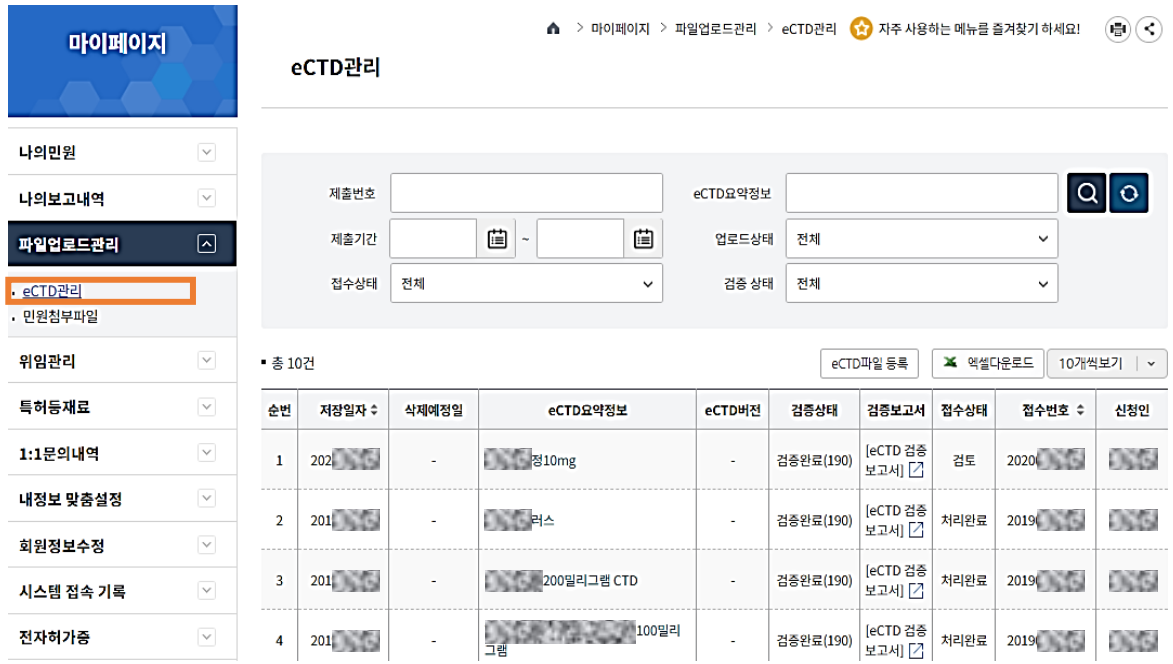


Temporarily upload eCTD to my account (in Phase 2)

Electronic Application

Log-in to my account

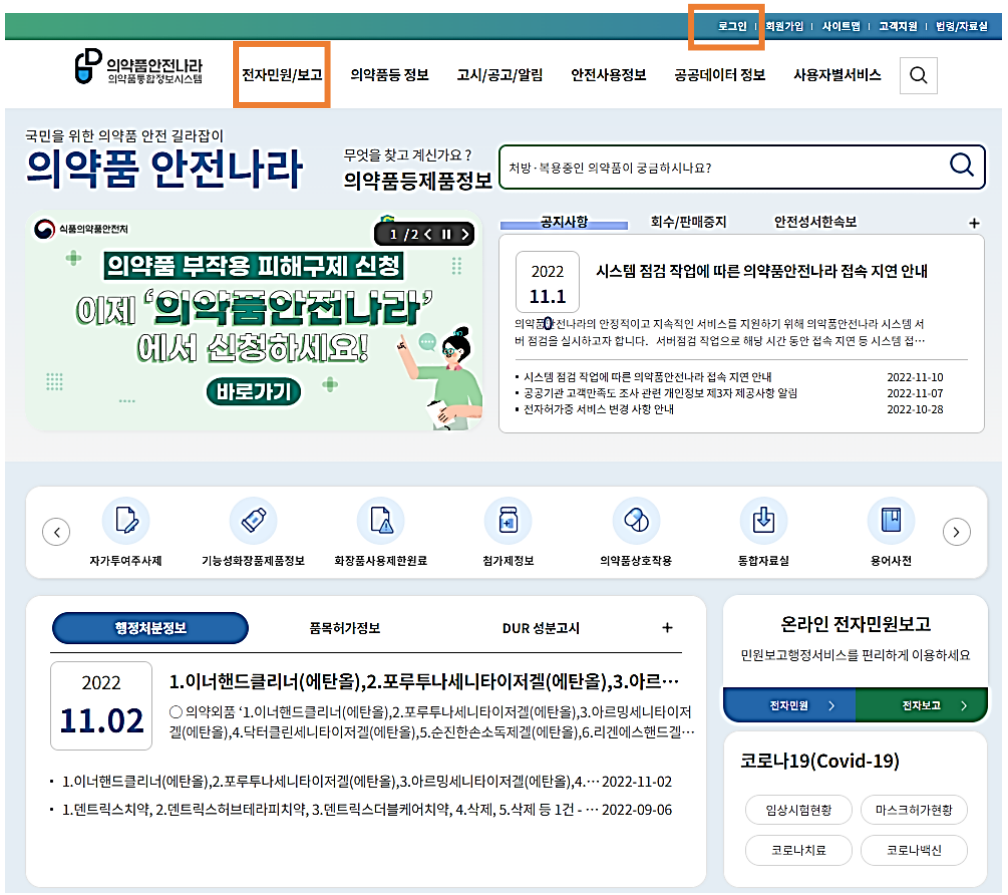




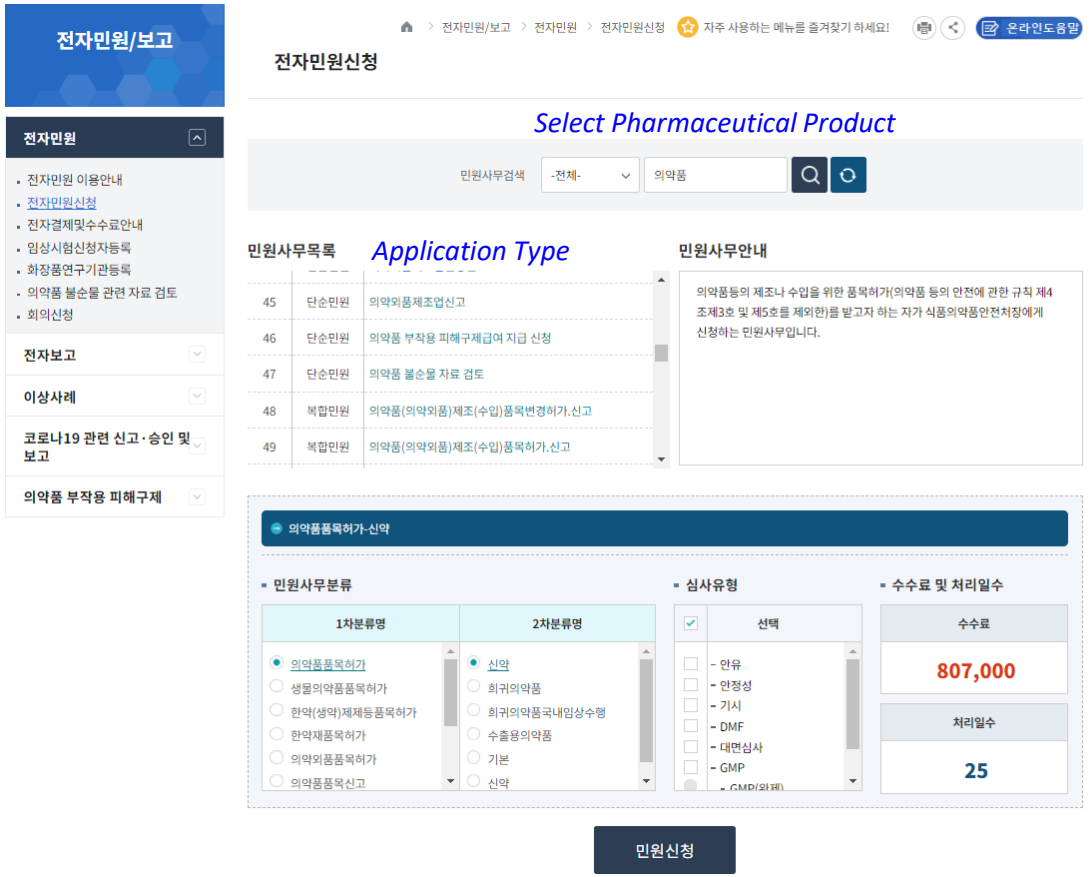
Electronic Application (in Phase 3)

Electronic Application

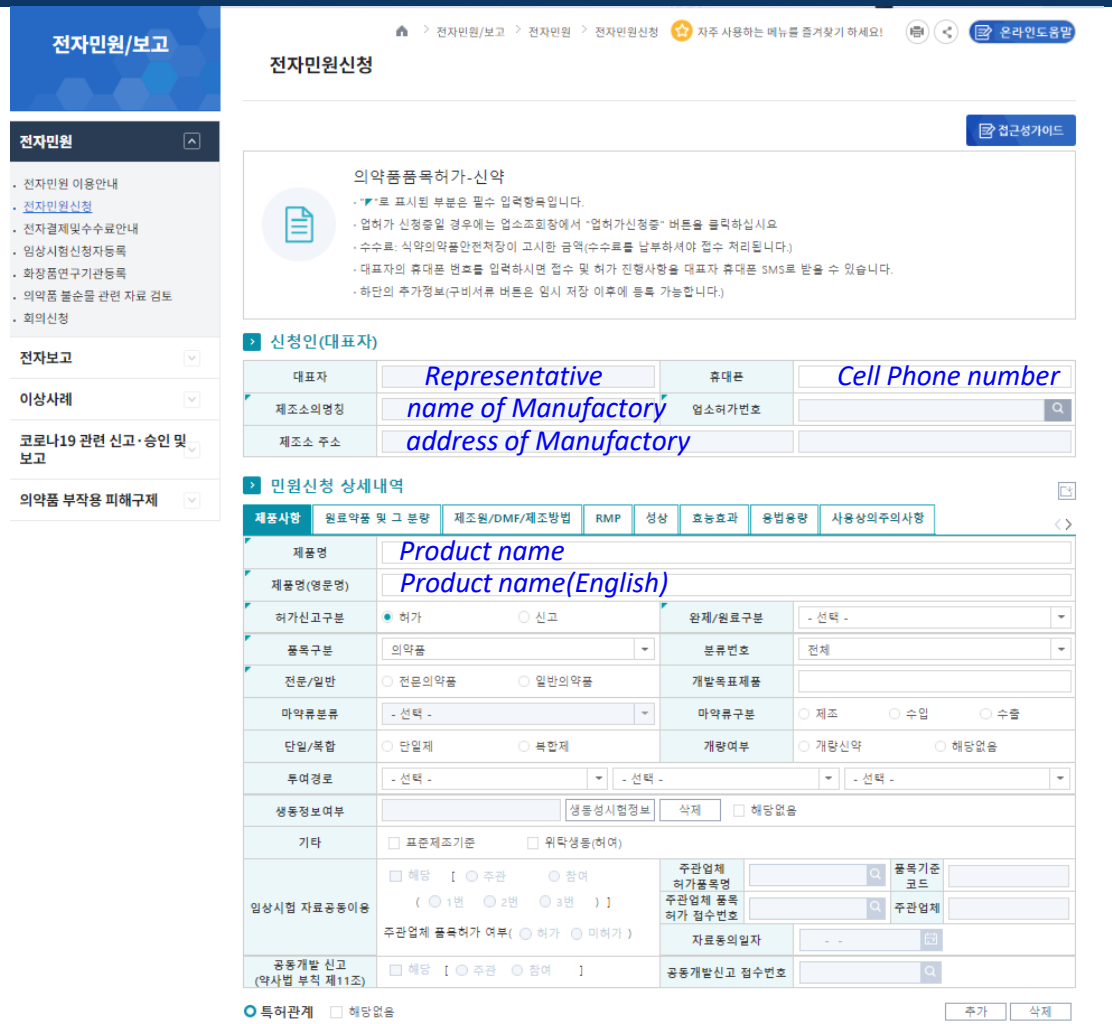
Log-in to my account



Electronic Application



Electronic Application (in Phase 3)



Whether to submit eCTD

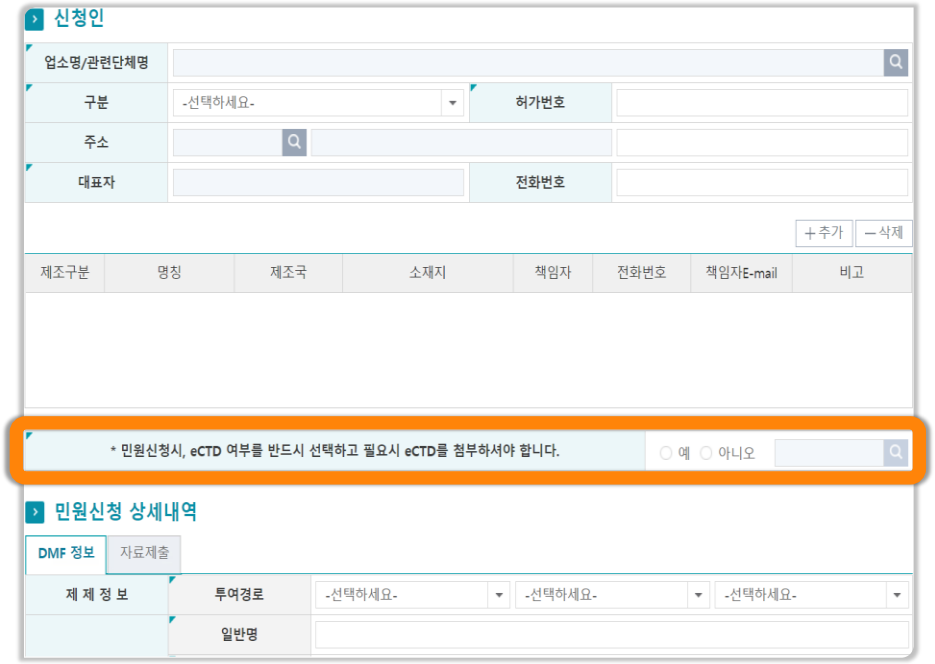
1. *Select Yes/No*
2. *Attach eCTD file already uploaded to my account*

submit data for domestic regulation standard

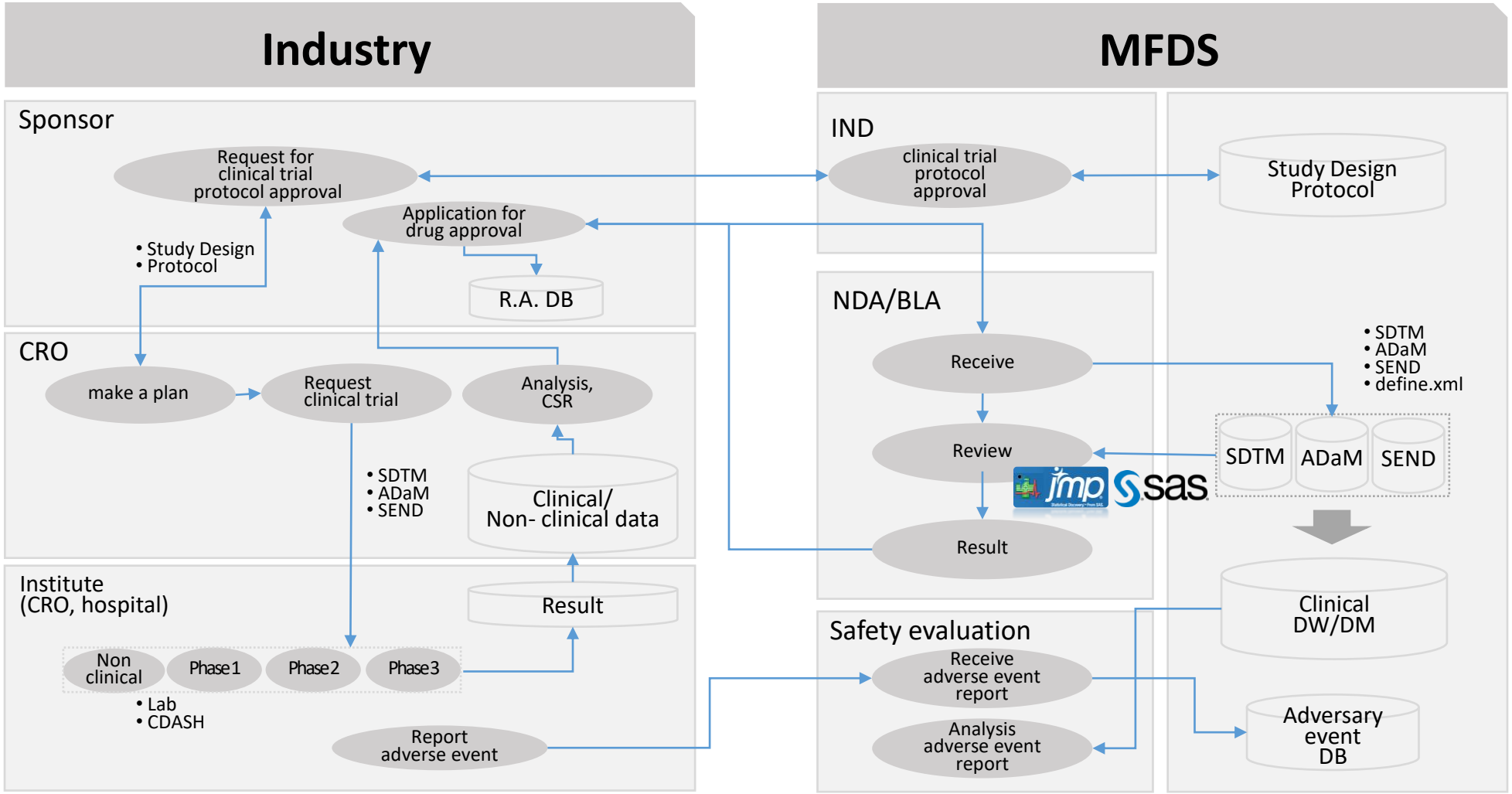
Electronic Application (in Phase 3)

✓First Submission

✓Supplementary Submission



Workflow between Industry and MFDS



Small feature of eCTD in KR

MFDS

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

FDA, etc.

- ✓ e-identifier of eCTD is the same as application registration number
- ✓ Application details : only list in eCTD leaf
- ✓ Store separate documents and materials not defined in advance within eCTD

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
NIFDS
National institute of Food and Drug Safety Evaluation
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

CDISC Sample Submission Technical Pilot

Summary of Pilot Status

- ✓ **(Preparation) '23. April~'24. April**
  - ❖ Internal consultation, recruitment of participating companies, system configuration, arrange items, preparing company's sample submission materials
- ✓ **(Implementation) '24.May ~ November**
- ✓ **(Participating companies) 6 companies supported, 3 companies conducted**
- ✓ **(Submission) SDTM, ADaM, SEND submitted for one item each of diabetes, hyperlipidemia, and cancer**
- ✓ **(Confirmation) synthetic drug/biologics & statistics review department personnel**
  - ❖ Provided technical support from the pharmaceutical policy department

CDISC Sample Submission Technical Pilot

✓ CDISC sample list

Company	Indication	CDISC Standards	categories	Evaluation Department
DONG-A ST	Diabetes	SDTM ADaM SEND	synthetic drug	Bioequivalence Evaluation Division Pre-Submission Consultation Division
Chong Kun Dang Pharm. Seoul, Korea	hyperlipidemia	SDTM ADaM	synthetic drug	Cardiovascular and Neurology Products Division Pre-Submission Consultation Division
LSK Global PS	cancer (non-small cell)	SDTM ADaM	Biologics	Recombinant Protein Products Division Pre-Submission Consultation Division

CDISC Sample Submission Technical Pilot

Results

- ✓ **Applicants can submit CDISC materials through the MFDS Industry system for electronic application submission, and reviewers can review CDISC submissions through dedicated software.**
  - ✓ (Electronic submission) The necessary information for the CDISC is prepared by the company through the guidelines issued by the CDISC.

    * The reviewer downloads the CDISC data submitted by the applicant to a PC through the internal administrative portal and checks the CDISC data through dedicated software (JMP Clinical, SAS).

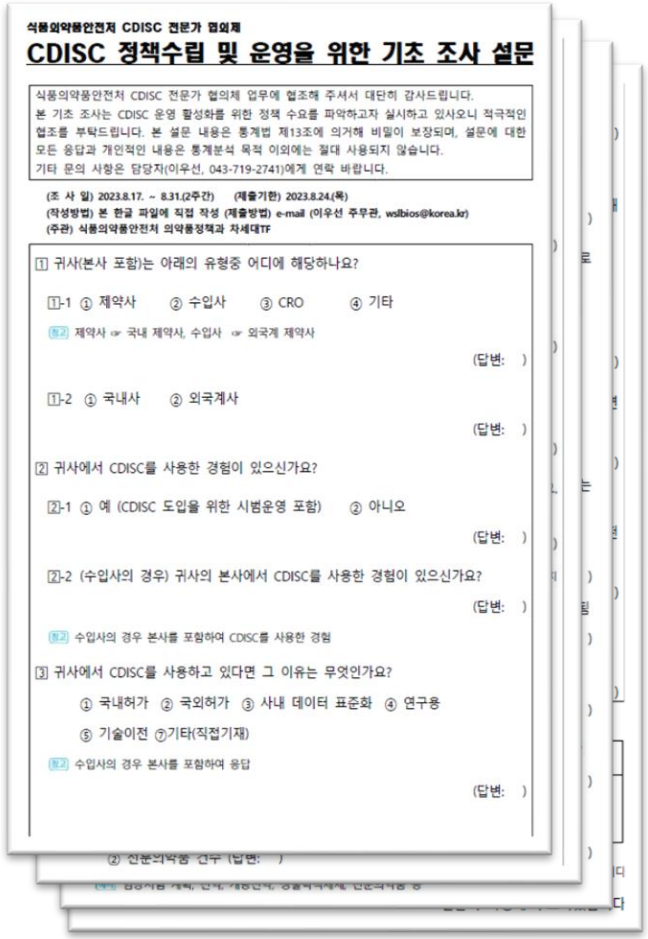
    ** SDTMIG, ADaMIG, SENDIG, published by the Consortium for the Development of International Standards for Clinical Trials
  - ✓ (Electronic submission) If CDISC is included in the eCTD, the current system does not have a problem submitting CDISC materials.

Status of CDISC in Korea

6. CDISC Status in Domestic Pharmaceutical Industry

5.

Cross-sectional survey of CDISC



식품의약품안전처 CDISC 전문가 협의체

CDISC 정책수립 및 운영을 위한 기초 조사 설문

식품의약품안전처 CDISC 전문가 협의체 업무에 협조해 주셔서 대단히 감사드립니다.
본 기초 조사는 CDISC 운영 활성화를 위한 정책 수요를 파악하고자 실시하고 있사오니 적극적인 협조를 부탁드립니다. 본 설문 내용은 통계법 제13조에 의거해 비밀이 보장되며, 설문에 대한 모든 응답과 개인적인 내용은 통계분석 목적 이외에는 절대 사용되지 않습니다.
기타 문의 사항은 담당자(이우선, 043-719-2741)에게 연락 바랍니다.

(조 사 일) 2023.8.17. ~ 8.31.(2주간) (제출기한) 2023.8.24.(목)
(작성방법) 본 한글 파일에 직접 작성 (제출방법) e-mail (이우선 주무관, wslbios@korea.kr)
(주관) 식품의약품안전처 의약품정책과 차세대TF

[1] 귀사(본사 포함)는 아래의 유형중 어디에 해당하나요?

[1]-1 ① 제약사 ② 수입사 ③ CRO ④ 기타

참고 제약사 ☞ 국내 제약사, 수입사 ☞ 외국계 제약사

(답변:)

[1]-2 ① 국내사 ② 외국계사

(답변:)

[2] 귀사에서 CDISC를 사용한 경험이 있으신가요?

[2]-1 ① 예 (CDISC 도입을 위한 시범운영 포함) ② 아니오

(답변:)

[2]-2 (수입사의 경우) 귀사의 본사에서 CDISC를 사용한 경험이 있으신가요?

(답변:)

참고 수입사의 경우 본사를 포함하여 CDISC를 사용한 경험

[3] 귀사에서 CDISC를 사용하고 있다면 그 이유는 무엇인가요?

① 국내허가 ② 국외허가 ③ 사내 데이터 표준화 ④ 연구용
⑤ 기술이전 ⑦기타(직접기재)

참고 수입사의 경우 본사를 포함하여 응답

(답변:)

② 전문의약품 건수 (답변:)

< 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 >

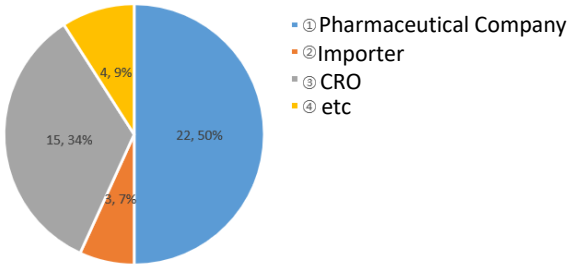
'23.8.22 ~ 9.22

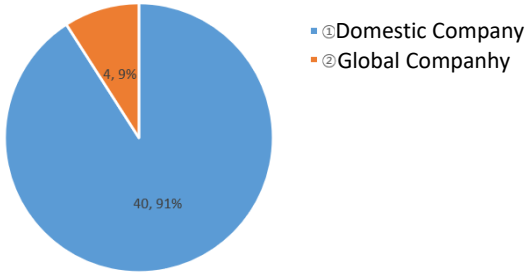
< Method >

Email survey through 4 associations

< Response >

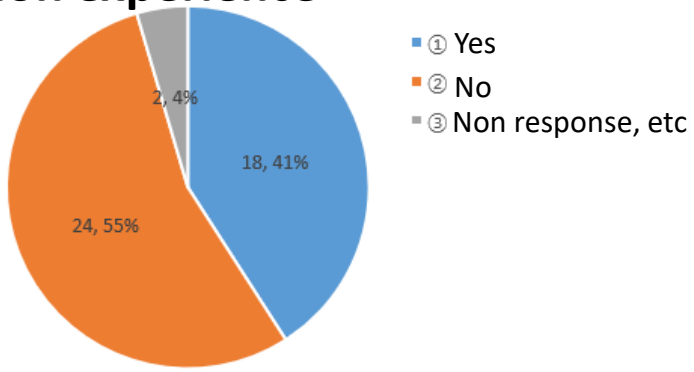
44 companies responded (9%)



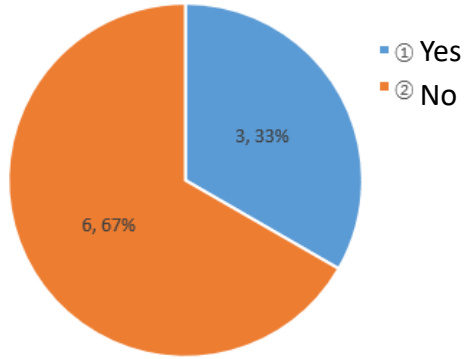


Experience & Purpose of use CDISC

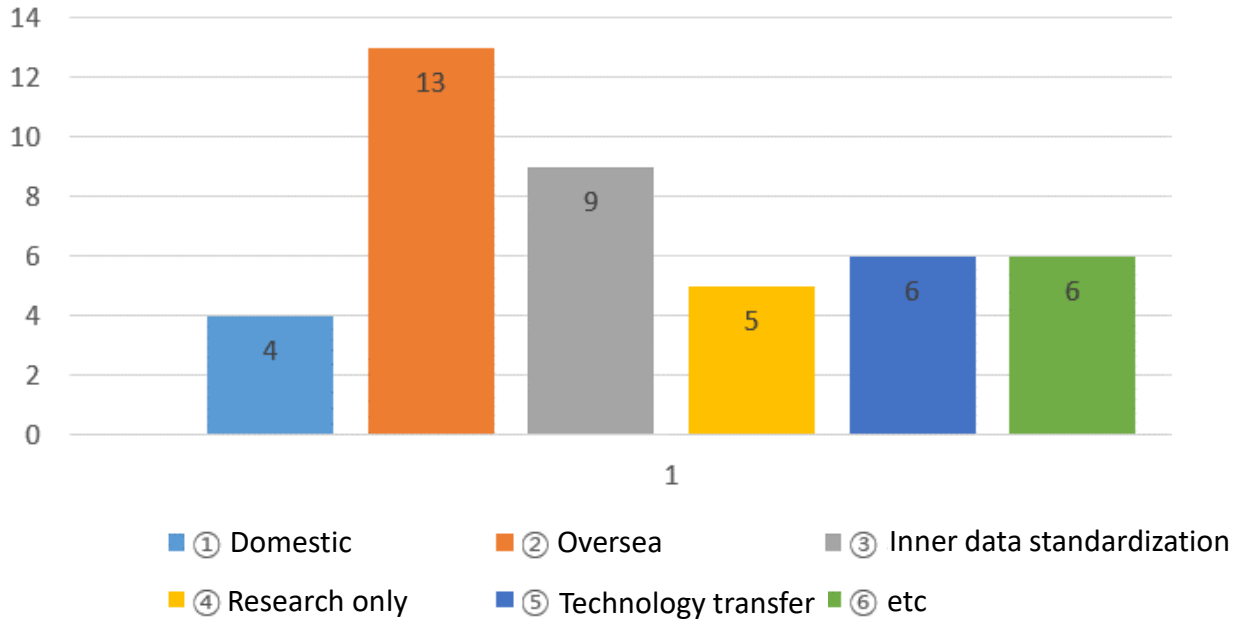
- **CDISC Utilization experience**



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



- **CDISC Utilization Objectives in the industry**



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, the agency 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.

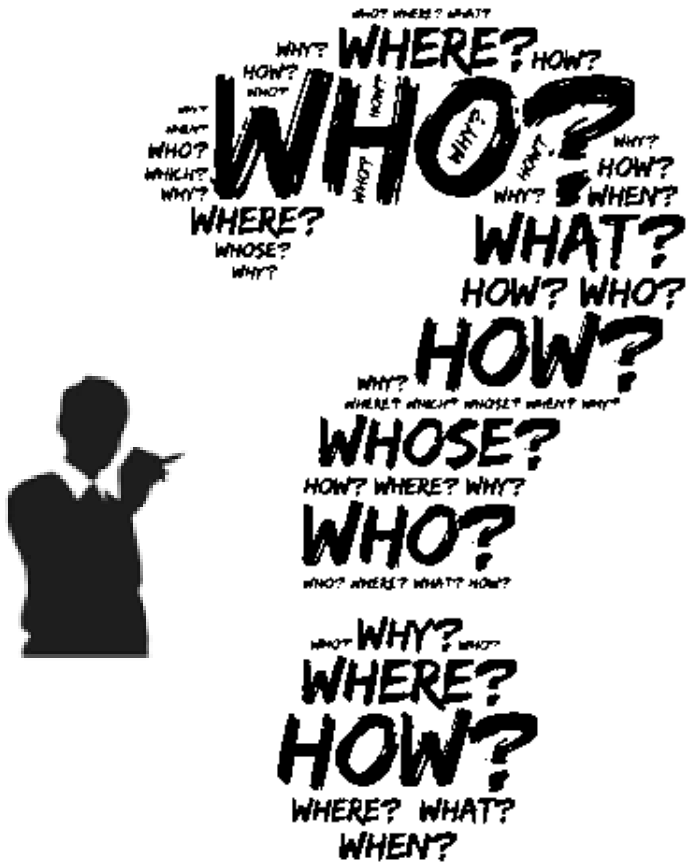
✓ **Consideration of Industry Environment**

- Recognizing the industry’s unique characteristics, MFDS aims to tailor the CDISC implementation environment to suit industry needs, emphasizing practical feasibility and efficiency.

✓ **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 is intended to smooth the application of CDISC standards in the Korean regulatory process.

Q & A



국민 안심이 기준입니다

YOUR SAFETY IS OUR STANDARD

식품의약품안전처