U.S. FOOD & DRUG ADMINISTRATION

PDUFA VI Public Meeting on Electronic Submissions and Data Standards

April 12, 2022

Agenda

9:00 – 9:10 am Welcome and Opening Remarks *(Ron Fitzmartin)*

Topic 1

9:10 – 9:50 am IT Modernization in Action – 2022 *(Vid Desai)*
Industry Comment
Public Comment

Topic 2

9:50 – 10:20 am Electronic Submissions Gateway *(Lowell Marshall)*
Industry Comment
Public Comment

Topic 3

10:20 – 11:00 am PQ/CMC Data Standards *(Norman Schmuff)*
Industry Comment
Public Comment

11:00 – 11:10 am Break

Agenda (cont.)

Topic 4

11:10 – 11:40 am Identification of Medicinal Products *(TJ Chen)*
Industry Comment
Public Comment

Topic 5

11:40 – 12:20 pm IND Safety Reporting *(Suranjan De)*
Industry Comment
Public Comment

12:20 – 12:40 pm Break

Topic 6

12:40 – 1:20 pm eCTD *(Mark Gray)*
Industry Comment
Public Comment

Agenda (cont.)

Topic 7

1:20 – 2:00 pm	Technical Rejection of Study Data *(Heather Crandall)* Industry Comment Public Comment
2:00 pm	Meeting Adjourned

Modernization In Action 2022

Vid Desai, FDA CIO

April 12, 2022

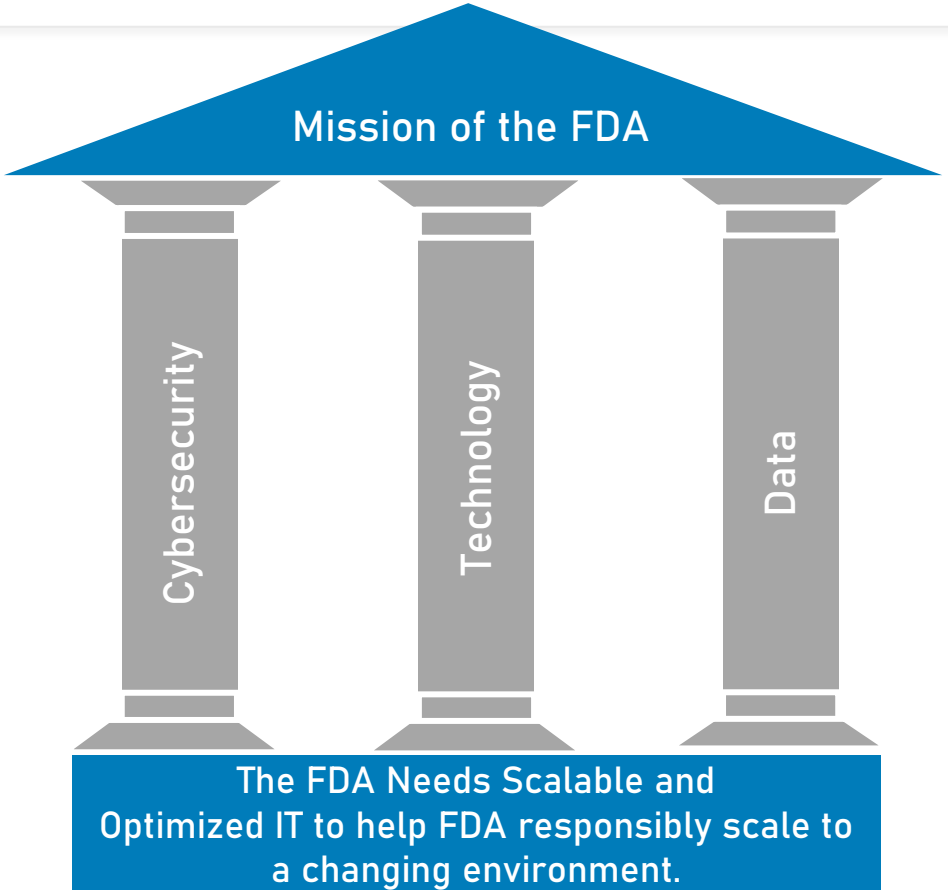
Technology Supports FDA's Mission

U.S. FOOD & DRUG ADMINISTRATION

FDA-regulated products account for about 20 cents of every dollar spent by U.S. consumers ($2.8 Trillion). The FDA must have a strong Information Technology foundation to support its mission and optimize efficiency with an exponentially increasing workload.

The FDA Expects an Exponential Increase in Workload

- Regulates 78% of U.S. Food Supply
- Approved 20,000+ Prescription Drugs
- Regulates $2.5T Imports and $1.6T Exports
- Oversees 270,000 Registered Facilities



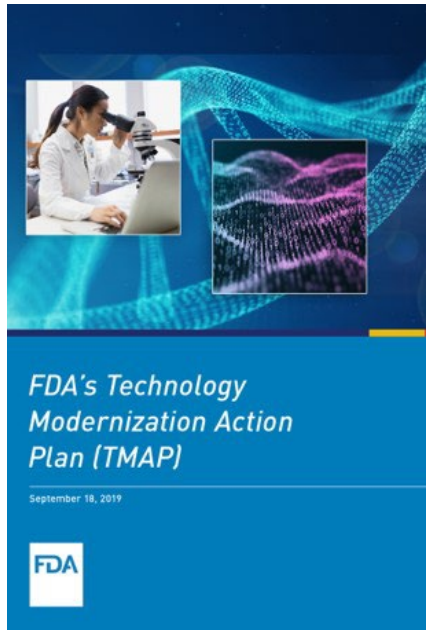
The Science is Changing
From Chemistry to Genetics
From PDFs to Large Genetic and DNA Sequencing Data Sets
Personalized Care & Treatments

Regulations are Changing
21st Century Cures Legislation
Real World Data / Evidence

Technology is Changing
Cybersecurity, Cloud, Big Data, Internet of Things (IoT), Artificial Intelligence

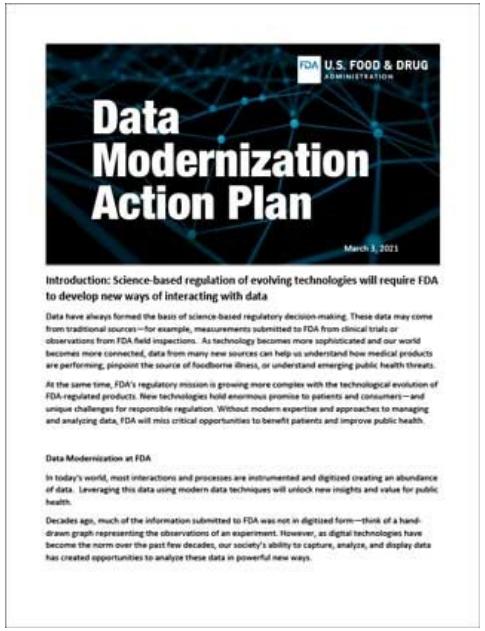
FDA's Modernization Framework

Technology Modernization Action Plan (TMAP)

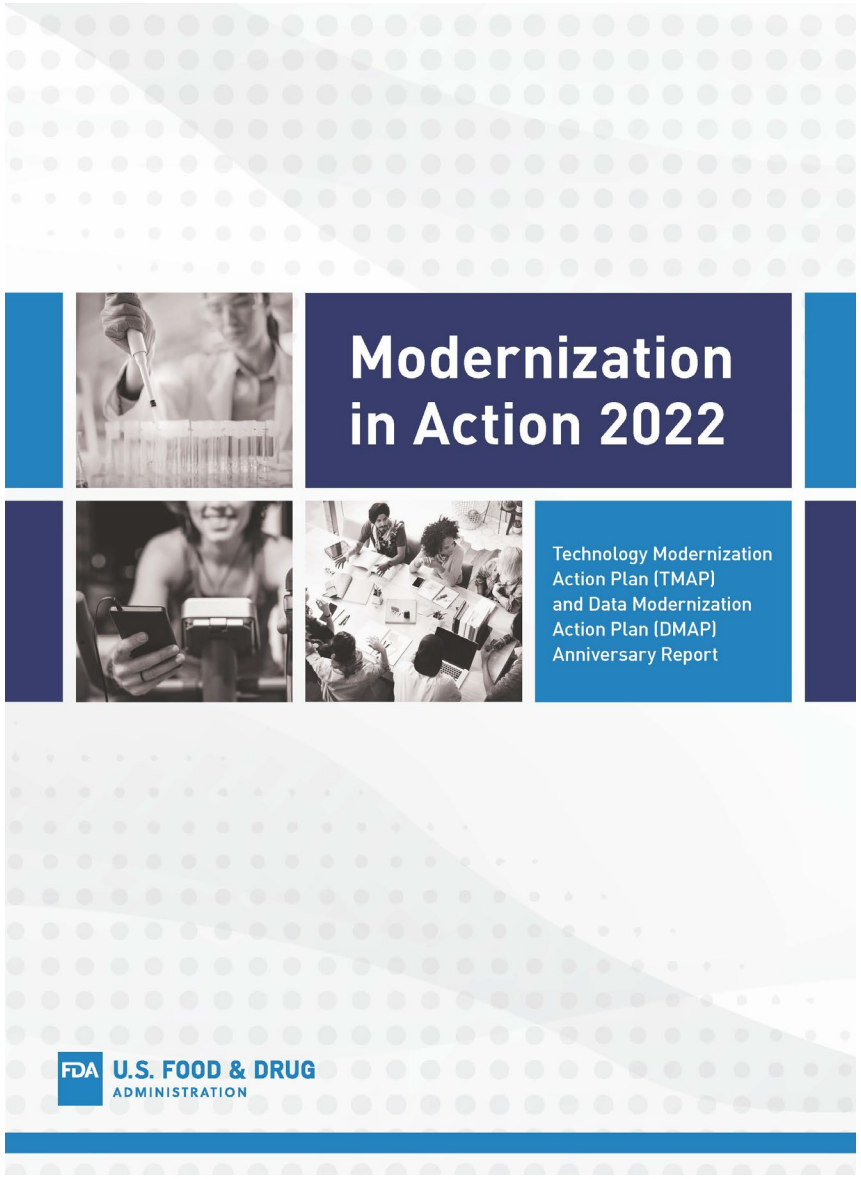


- Released in September 2019, TMAP's three focus areas include:
  - Modernizing the FDA's technical infrastructure and operations
  - Enhancing the FDA's capabilities to develop technology products
  - Communication and collaboration with external stakeholders

Data Modernization Action Plan (DMAP)



- Released in March 2021, DMAP's three focus areas include:
  - Identifying and executing high-value driver projects
  - Developing consistent and repeatable data practices
  - Creating and sustaining a strong talent network



FDA U.S. FOOD & DRUG ADMINISTRATION

A Remarkable Transformation Journey

- As we mark the one-year anniversary of DMAP, and nearly three years since launching TMAP, we are pleased to provide an update on our progress with the Modernization in Action 2022 report.
- TMAP and DMAP have provided important frameworks for the FDA's modernization over the past three years.
- Our continued journey will increasingly focus on integration into all aspects of FDA operations in support of cross-agency initiatives to optimize shared business processes.
- These efforts will enhance operational efficiency and use of our data, while strengthening the alignment between Agency-wide strategic objectives and investments.

Changing Landscape Impacted by COVID-19

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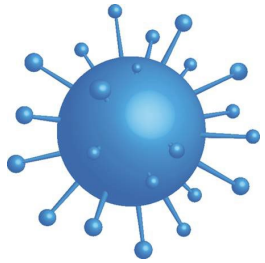
The COVID-19 pandemic created new challenges for the Agency to address. ODT worked hard to leverage our strategic approach to create an IT infrastructure backbone to sustain operations.

COVID-19 Pandemic Response



- The COVID-19 pandemic had an unprecedented impact to our core operations.
- ODT worked to enhance user experience, facilitate Real-World Data, and protect the Agency from the increased threat of cyberattack.

The organization went from about 9.5k remote workers to over 21k in mid-2021.

FDA experienced a 457% increase in cyber threats, compared to pre-pandemic levels.

Established the Covid-19 Evidence Accelerator (EA) which advanced the use of real-world data to inform our nation's pandemic response.

Rising to the Challenge

Despite the new challenges COVID-19 pandemic created for the Agency, ODT achieved success across all aspects of IT Operations including Cybersecurity, Technology, and Data.

Cybersecurity

- Identification of 152,144 mobile device and network threats
- Reduction of spam/phishing incidents by 86%
- Addressed 15,025 cyber incidents (malware/spam/phishing)
- Over 10 billion firewall blocks monthly
- Over 11 million blocked e-mails per month

Technology

- Modernization of production environments to increase performance, reduce physical devices, and eliminate discontinued devices
- Facilitated 429k virtual meetings
- 234k Help Desk customer interactions
- Continued rollout of Office 365:
  - A combined 268.6M OneDrive and SharePoint files
  - 26k active users
  - 27k active sites

Data

- Enhanced capabilities for reviewers with over 6k users and 110 terabytes of data
- Implementation of an interactive data capability for work on complex analyses of biomedical data
- Public-facing version of the Global Substance Registration Systems (GSRS) system with over 125k curated substances

New Office, Continued Focus

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The Office of Digital Transformation (ODT) was established in September 2021 and reports directly to the FDA Commissioner. ODT builds on past successes, applies modern approaches to today's challenges and positions the FDA for the future in information and data management to drive solutions.

Office of Digital Transformation (ODT)

The Office of Information Management and Technology (OIMT)
Develops, communicates, and operates FDA's overall technology vision, mission, values, and roadmap.

The Office of Information Security (OIS)
Directs and implements the FDA Cybersecurity, Counterintelligence, and Insider Threat Program to ensure security controls and cyber defenses are appropriately applied to FDA systems to protect the confidentiality, integrity, and availability of data and sensitive information.

The Office of Data, Analytics, and Research (ODAR)
Manages and improves FDA's ability to leverage data as a strategic asset by establishing enterprise data strategy and priorities.

VISION
To collaborate as partners to enable data and technology leadership to improve health for all Americans

MISSION
To provide high-quality, secure, and efficient IT and data solutions that enable the FDA to promote and protect public health

HISTORY
The creation of ODT was a milestone in an ongoing transformation journey, starting with the publication of TMAP in September 2019 and the release of DMAP in March 2021

FY 2022 ODT Strategic Priorities

The FDA's TMAP and DMAP drive the direction of the organization's enterprise IT and data strategy for FY 2022 and beyond. Based on the strategic direction of the organization, there are seven key priorities. These strategic priorities and supporting initiatives are designed to enhance the mission capabilities of ODT and FDA.

- Cybersecurity
- Cloud Forward
- User Experience
- Data Modernization
- Operational Excellence
- Governance
- People and Culture

Reimaging Strategic Planning

- The FDA invests disproportionally into “Running the Business” versus modernizing operations.
  - ODT has focused on aligning IT resources to modernize and optimize efforts, and make strategic decisions for the future state of IT.
- Efforts are underway to apply more resources towards modernization associated with “Growing” and “Transforming” the business.
  - This includes taking an enterprise approach where data can be utilized to advance FDA’s mission.
- Technology and Data investments can be force multipliers when effectively prioritized and leveraged.

Remaining Challenges and Opportunities

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The FDA's ability to execute its core mission areas is utterly dependent on our Technology, Cybersecurity, and Data infrastructure, which has been acting as a bottleneck to FDA's progress and needs significant modernization.

Cybersecurity

The FDA is a prime and persistent target for cyber-crime and economic espionage due to trillions of dollars of industry commercial and intellectual property. Investment in Cybersecurity is needed to enhance FDA's cybersecurity capabilities.

Technology

The Technology Modernization Action Plan (TMAP) focuses on modernizing the FDA's IT infrastructure, including cloud computing, data interfaces, and legacy systems. We need to invest in our IT infrastructure to build the necessary capacity to meet the FDA's core mission areas.

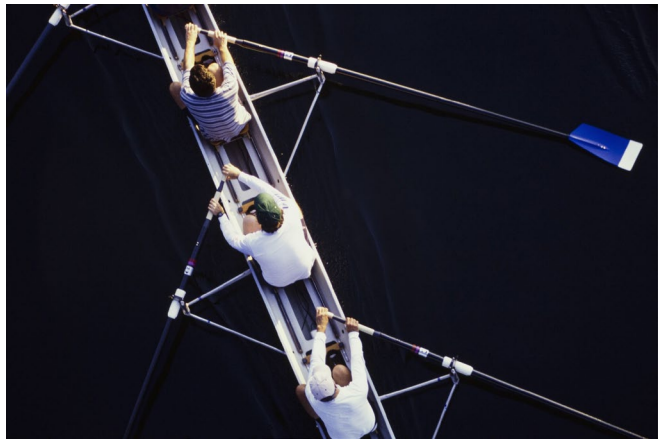
Data

The Data Modernization Action Plan (DMAP) is anchored on driver projects that help generate value while building critical capabilities, enhancing critical data practices and projects (e.g., data lake, Real World Data Research Lab, data catalog, data glossary).

Blueprint for Good IT

Matured, Modernized IT Operations
Planning and Alignment
Governance
Financial Management

Laying the Blueprint for Good IT



- Center IT and ODT must plan and execute like “one team” to maximize value for FDA.
  - IT Solutions are inter-dependent; neither Center/Office IT nor ODT can provide efficient, independent end-to-end IT services.
  - The lack of effective planning and alignment creates resource redundancies and inefficiencies.
- ODT has established a new internal consulting and engagement model service to advance technology modernization and adopt industry standards.
- Services include partnering with FDA Centers in governance bodies within the areas of program and IT finance management, enterprise architecture, service management, and data management.

Enabling Broader Transformation

- TMAP and DMAP created the vision and ODT enhanced planning and governance.
- The Enterprise Transformation Operation (ETO) is a newly created function in the Office of the Commissioner that provides the executive engagement and alignment to drive enterprise business modernization.
- We'll take this initial work and learning opportunity to build the Enterprise Modernization Plan (EMAP) to drive process optimization, better use of our data, and more efficient IT development.

INDUSTRY COMMENT

PUBLIC COMMENT

U.S. FOOD & DRUG ADMINISTRATION

FDA Electronic Submissions Gateway (ESG)

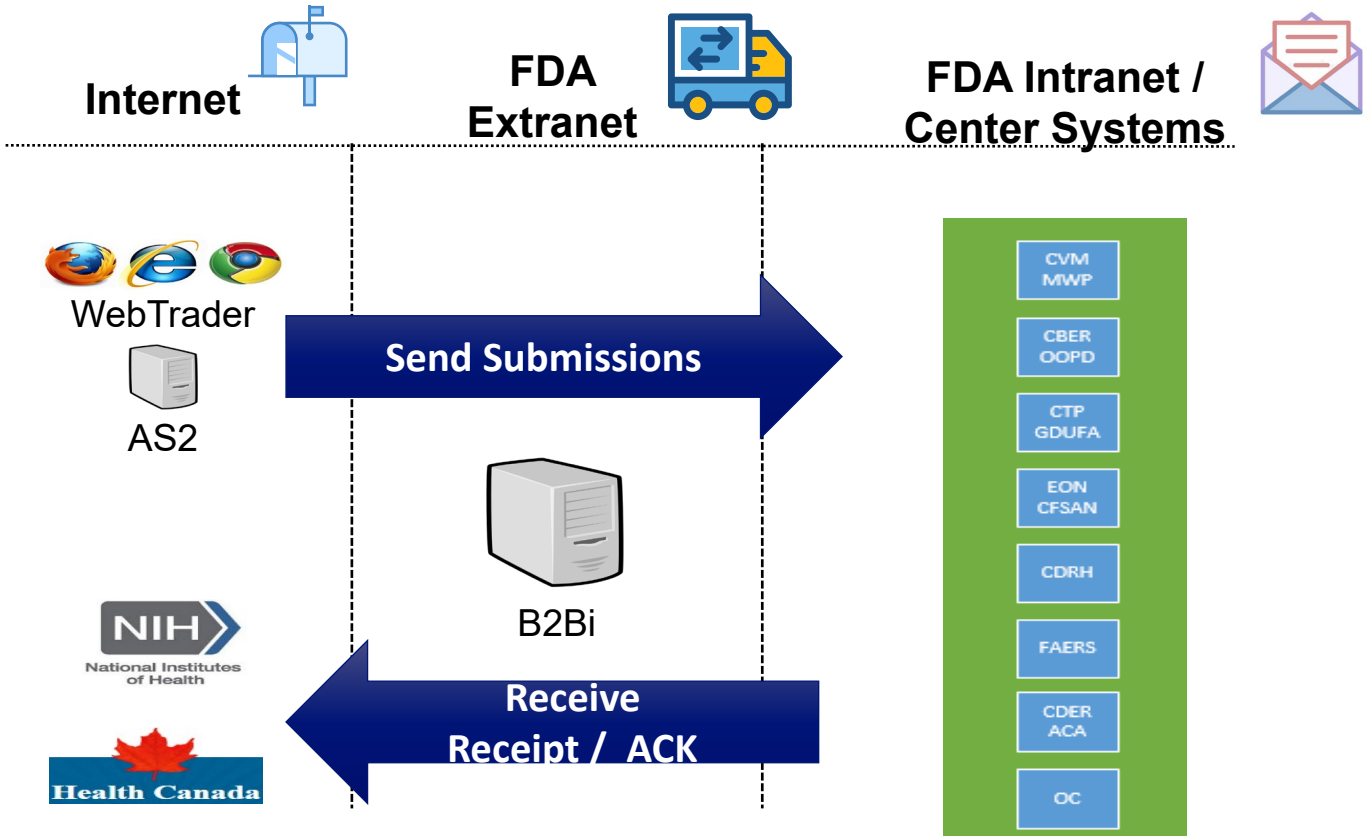
PDUFA VI
Annual Public Meeting

OIMT Division of Application Services (DAS)
Enterprise Application Branch (EAB)

April 12, 2022

ESG Big Picture

The FDA ESG is the central transmission point for sending information electronically to the FDA. Within that context, the FDA ESG is a conduit along which submissions travel to reach the proper FDA Center or Office, who in turn send a receipt(s) back to the submitter. The process is like a certified letter traveling through the postal system.



*HC submissions are forwarded to HC AS2 system

ESG Metrics

FDA ESG 2015-2022 Total Submission Statistics

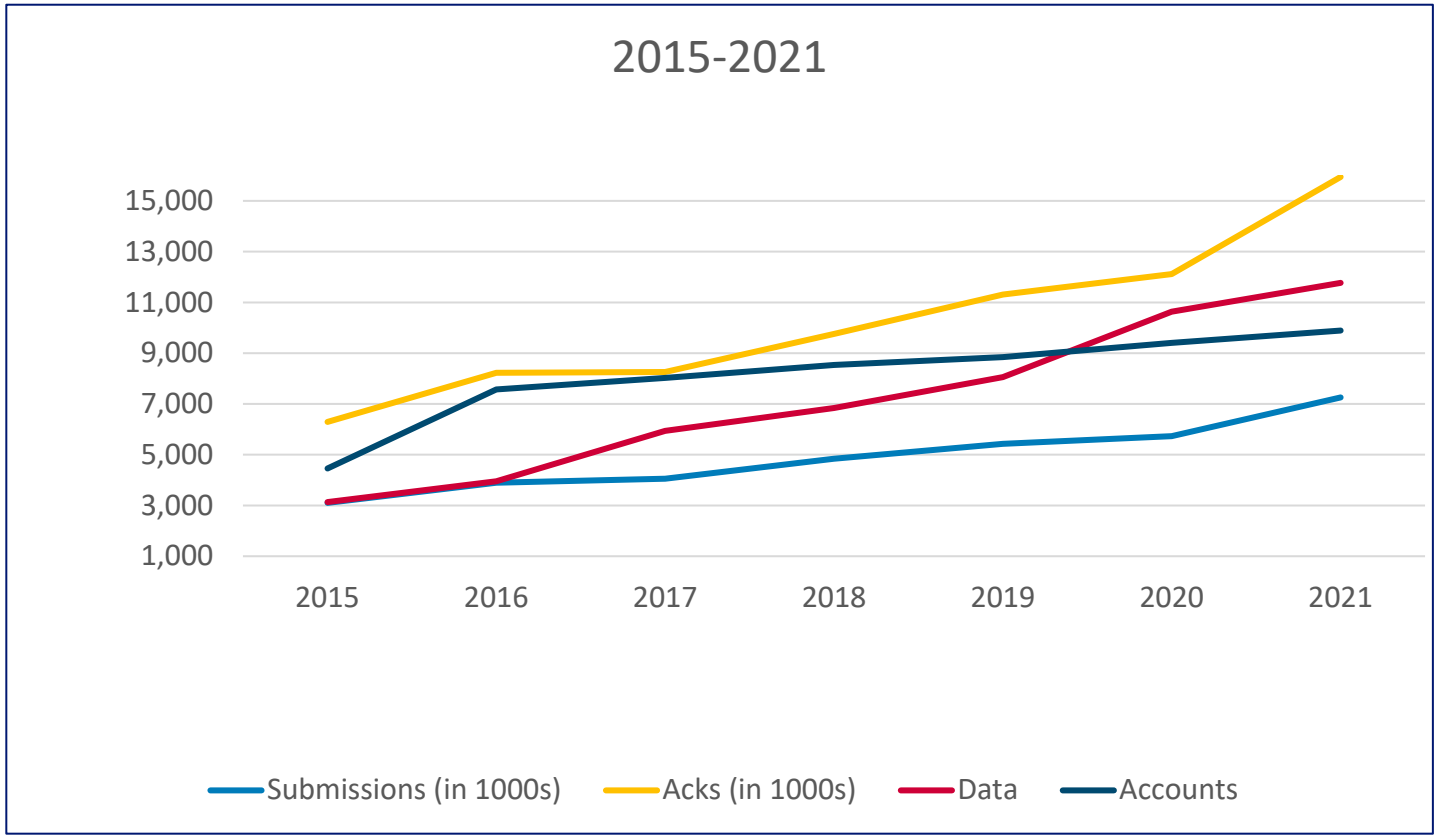
2015	2016	2017	2018	2019	2020	2021
3,100,970	3,895,669	4,055,342	4,841,844	5,428,492	5,728,006	7,258,031

FDA ESG 2021 Total Transaction Statistics

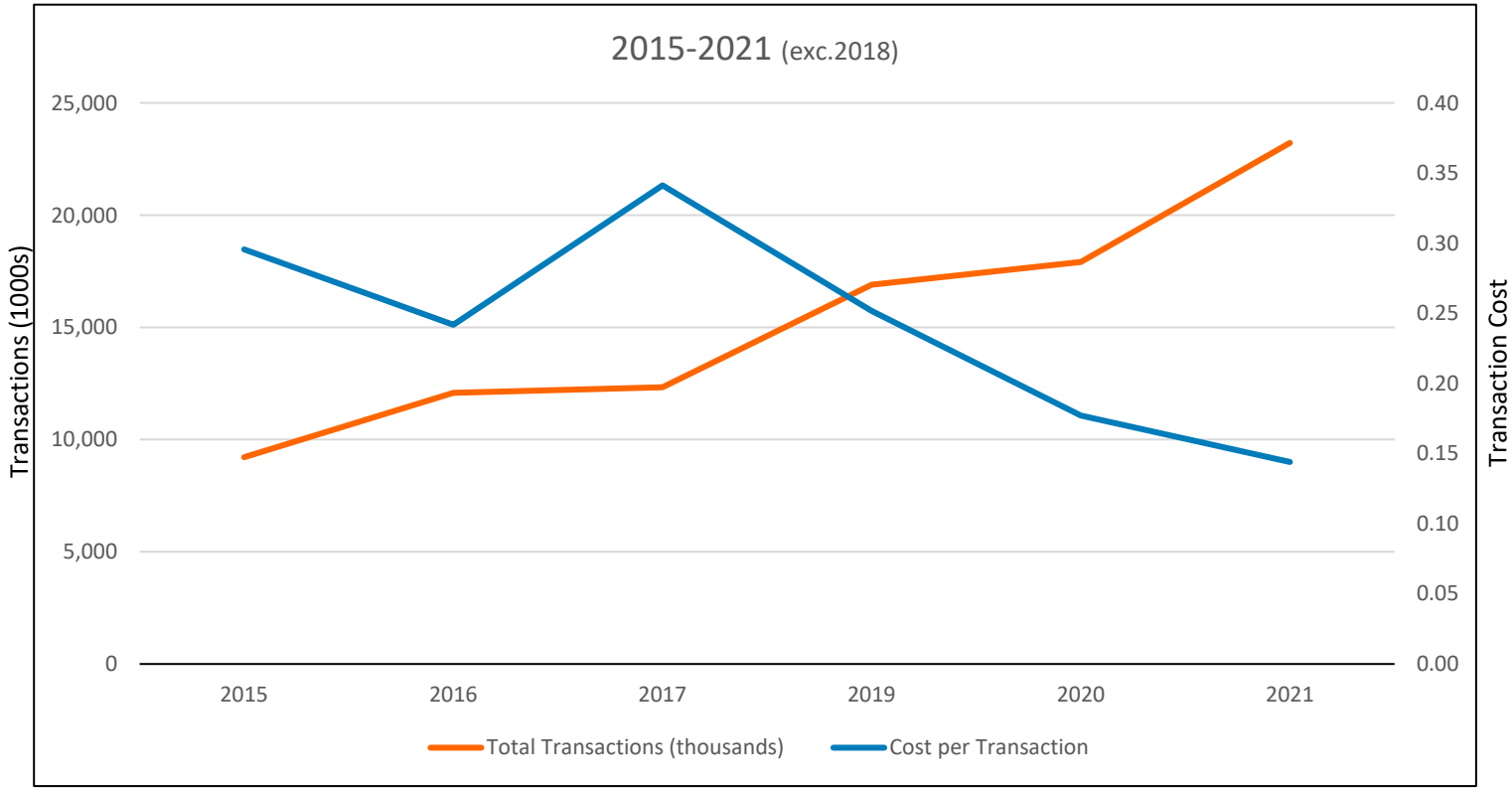
2015	2016	2017	2018	2019	2020	2021
9,209,782	12,082,860	12,333,127	14,596,282	16,898,047	17,917,796	23,218,281

The Growth of ESG

Average Annual Growth 2015-2021	
Submissions	16%
Acknowledgments	17%
Data	25%
Accounts	16%



Transaction Volume & Transaction Cost



ESG Modernization – Phased Approach

Phase 1: Account Portal and Virus Scanning

- Enhanced User Experience
- Enhanced Security

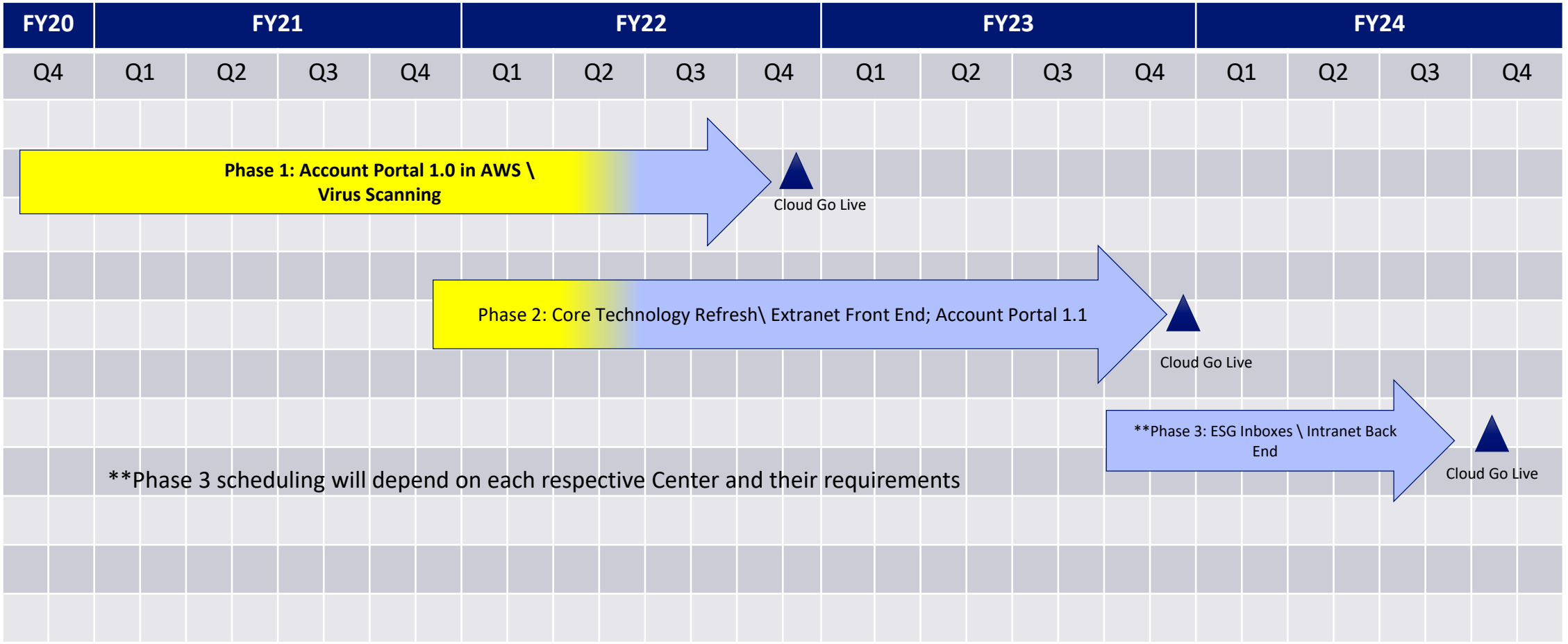
Phase 2: ESG Core Technology Refresh

- Certified FedRAMP High Environment
- Higher Availability Infrastructure
- Significant Performance Improvements

Phase 3: Enhanced ESG Architecture

- Streamlined Submission Processing

ESG Modernization High Level Timeline



Key:
Completed
Planned

Phase 1 – ESG Account Portal & Virus Scanning *Features*

Account Portal

ESG Account Portal is a single point of entry for all ESG applications/services for Industry users and FDA admins. ESG Account Portal automates account on-boarding and maintenance. It also introduces Industry power user functionality to allow company account management and self-service functionality for WebTrader (WT) users.

- **Features:**
  - User Onboarding Automation: automate account registration and approval process
  - Industry power user: Powers user account to manage company accounts and ability to track company WT submissions
  - Self-Service: Self-service for all user types. Ability for user to update certificates and unlock accounts
  - Automate Internal program reporting
  - Cloud Native: highly available and auto-scalable

Virus/Malware Scanning:

Implement additional malware scanning of all inbound submissions to enhance ESG security.

- **Features:**
  - Scan inbound files to enhance ESG security
  - Daily update of virus definitions

Phase 1 - Account Portal & Virus Scanning Industry *Benefits*

Account Portal

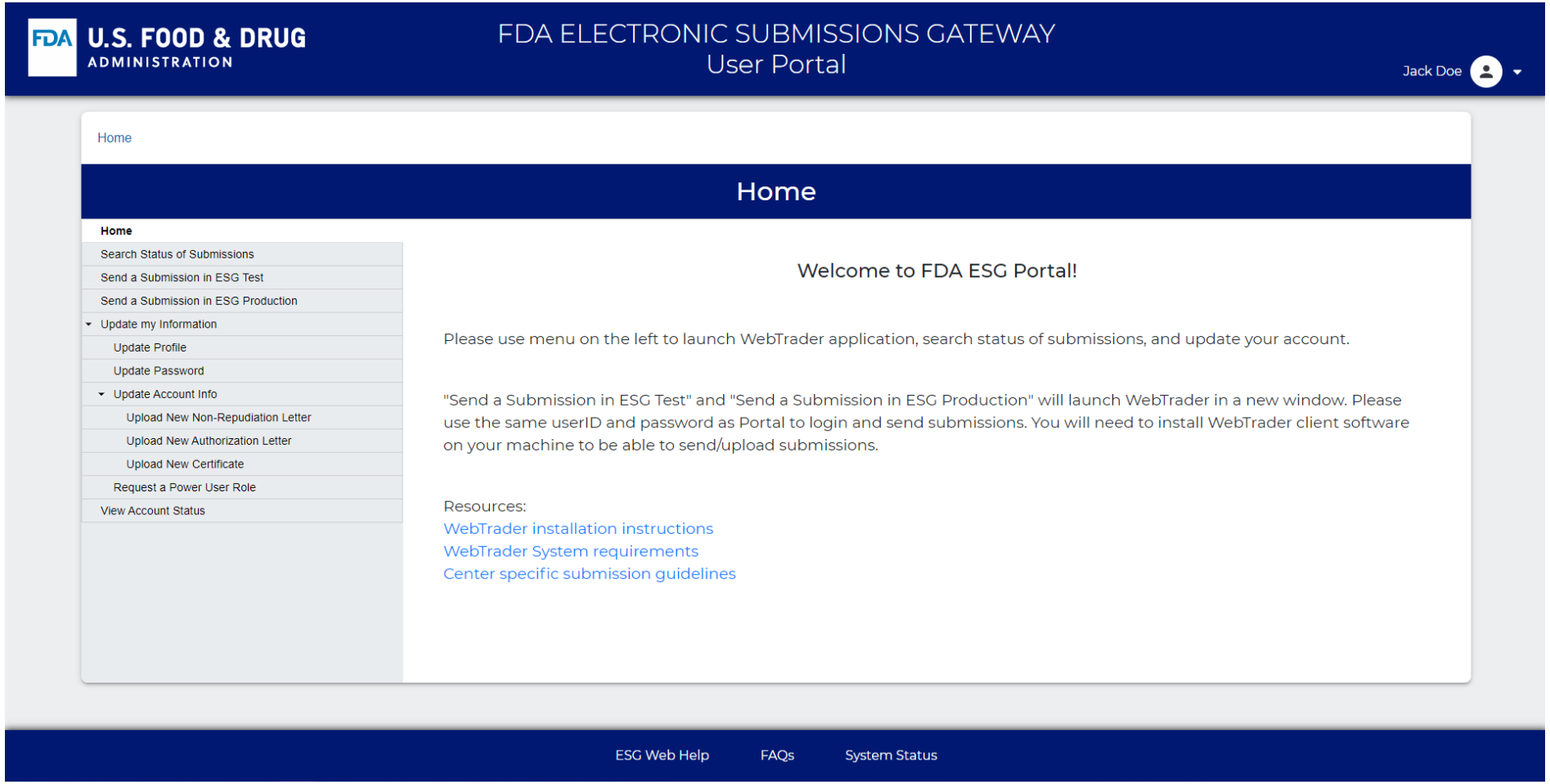
- Automate Industry account registration and approval process aims to reduce onboarding time and improve data quality control
- Create ability for users to perform self-service functions such as password reset, unlock accounts, upload and create certificates, and submission tracking
- Industry Power Users allows companies to manage their user accounts, track company WT submission status, and update certificates
- Single portal to access Pre-production and Production WebTrader and track submissions

Virus/Malware Scanning

- Enhance security for inbound electronic submissions by adding automated scanning prior to storing in FDA environment

Phase 1 - Account Portal & Virus Scanning

Account Portal - **WebTrader**



Phases 2 and 3 - ESG Modernization

Phase 2 – ESG Technology Refresh and Improved Performance

- Modernize ESG on-prem infrastructure with AWS GovCloud environment
- Develop Account Portal 1.1 (Center-user functionality)
- Migrate legacy NFS storage (Solaris hardware) to AWS EFS storage

Phase 3 – Enhance ESG Architecture

- Implement API-based submission processing and replace CFT COTS product
- Migrate SAN storage to AWS S3 storage

Aligns with Agency IT Strategy – Technology Modernization Action Plan (TMAP)*

- Building the foundation modernization of FDA's technology infrastructure
- Demonstrating innovation: development targeted to technology "Use Cases"

ESG Modernization Status Today

Account Portal 1.0

- Development Complete and System Test in Progress
- UAT Target May 2022
- FDA Infrastructure to AWS Infrastructure integration implementation underway

OPSWAT Virus Scanning

- Industry User Test Plan updates completed
- Target UAT April 25 & 26

Account Portal 1.1

- Design Completed
- Development in Progress

AWS Migration

- Data migration strategy for each component underway
- Application and Database data
- FDA Infrastructure to AWS Infrastructure integration implementation underway

INDUSTRY COMMENT

Electronic Submissions Gateway

PhRMA
RESEARCH + PROGRESS + HOPE

Electronic Submissions Gateway

Industry Panelists

Arvind Ala
Regulatory Project Management, Global Regulatory Operations
EMD Serono

James Li
Senior Regulatory Submission Manager
Roche

Vishu Manegari
Sr. Director, Regulatory Operations
Gilead Sciences

Electronic Submissions Gateway

Benefits

- Streamlined and efficient ESG account creation
- Implementation of self-service functionality for WebTrader (WT) users to update certificates, reset password, and track submissions
- Higher availability of ESG for industry with less downtime

PDUFA VI Accomplishments

- User Acceptance Testing (FDA) of new ESG cloud features
  - Account portal
  - File scanning
- Technical Rejection Criteria implementation
- Improved communication of planned downtime and process changes

Electronic Submissions Gateway

Challenges/Questions

- Large submission experience (>50GB)
  - Concerns with long upload times, submissions timing out, and issues in validation and receiving Acknowledgment(s)
  - Occurs during off-hours and during test submissions
- Trusted site setting needs to be setup again after maintenance updates
- Impact of transition to cloud-based architecture
- Long-term vision for the ESG

Electronic Submissions Gateway

Recommendations/PDUFA VII Opportunities

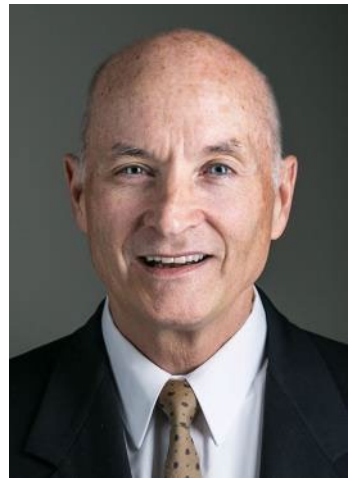
- PDUFA VII commitment - Modernize the ESG
  - PhRMA looks forward to continued industry pilot testing of the ESG cloud environment and the potential benefits of the cloud environment
    - Performance improvement and faster uploads, particularly for large submissions
    - Power user functionality to allow company account management

- PDUFA VII commitment – develop a Data and Technology Modernization Strategy
  - Engage with stakeholders to develop recommendations that address long-term planning for the ESG and its relationship with ongoing modernization initiatives (e.g., regulator-sponsor exchange, 3rd party cloud-based platforms)

PUBLIC COMMENT

Structured Product Quality Submissions – PQ CMC

Norman R. Schmuff
Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Pharmaceutical Manufacturing Assessment

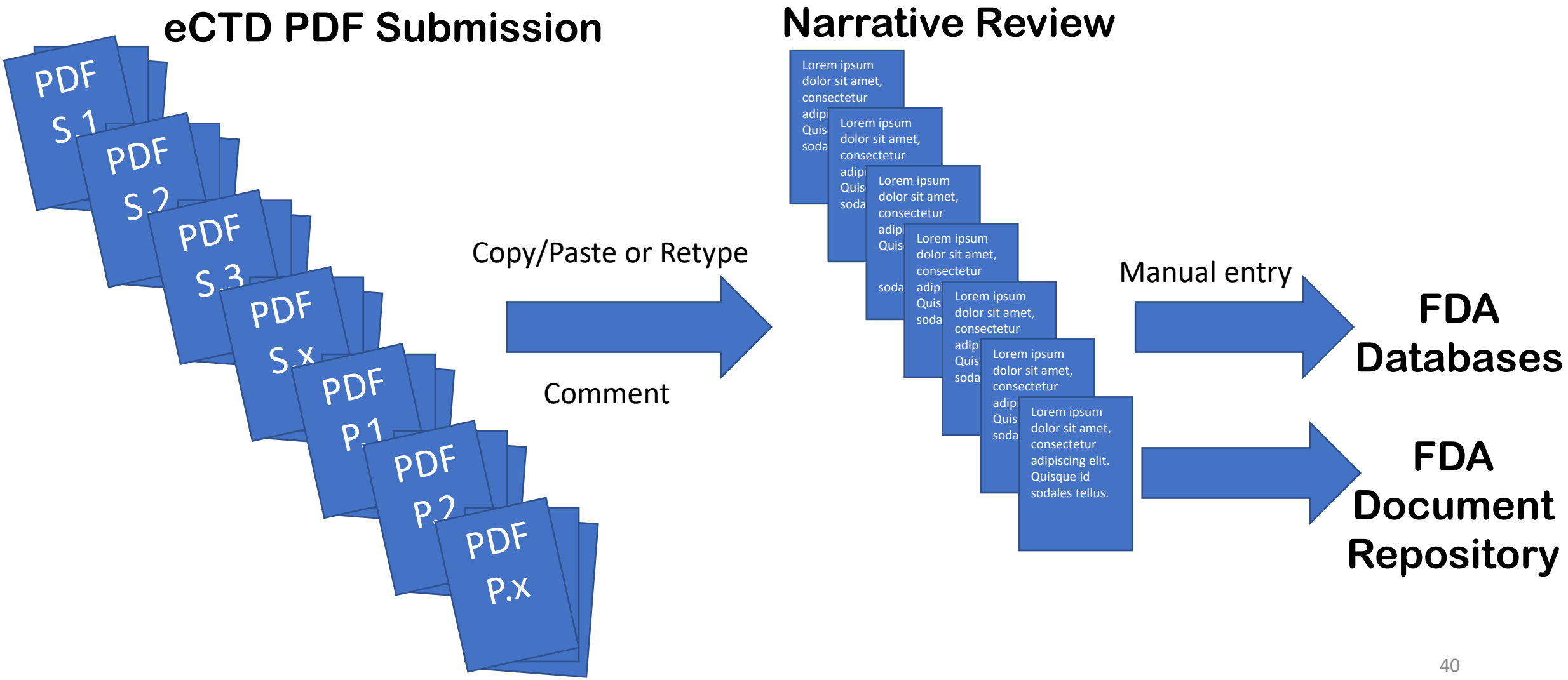


April 12, 2022, PDUFA VI Public Meeting on Electronic Submissions and Data Standards

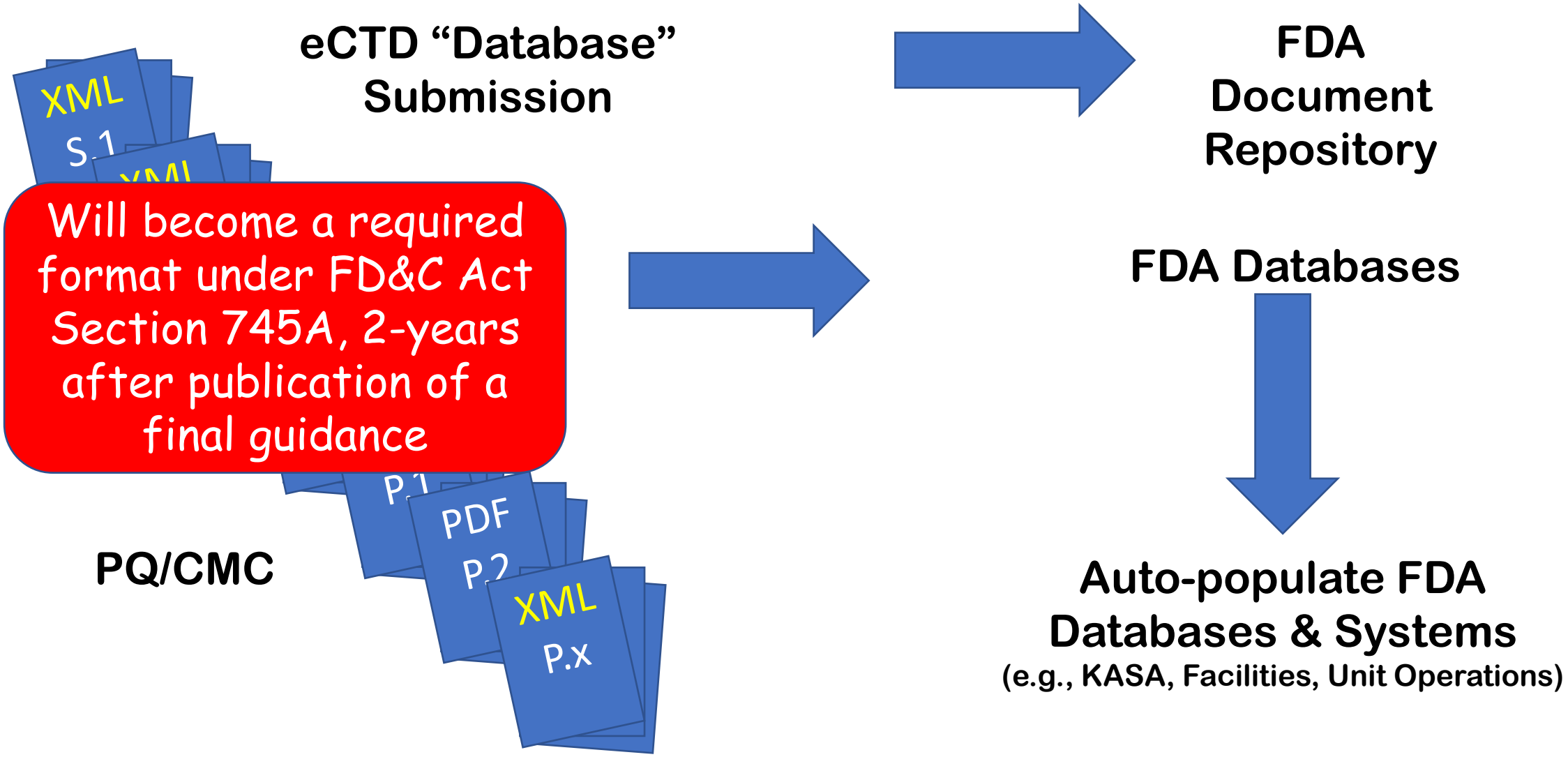
Outline

- Our vision
- What we've done
- IDMP
- ICH
- Current work
- Terminology challenges
- Future plans
- Challenges

Current Module 3 Submission Model

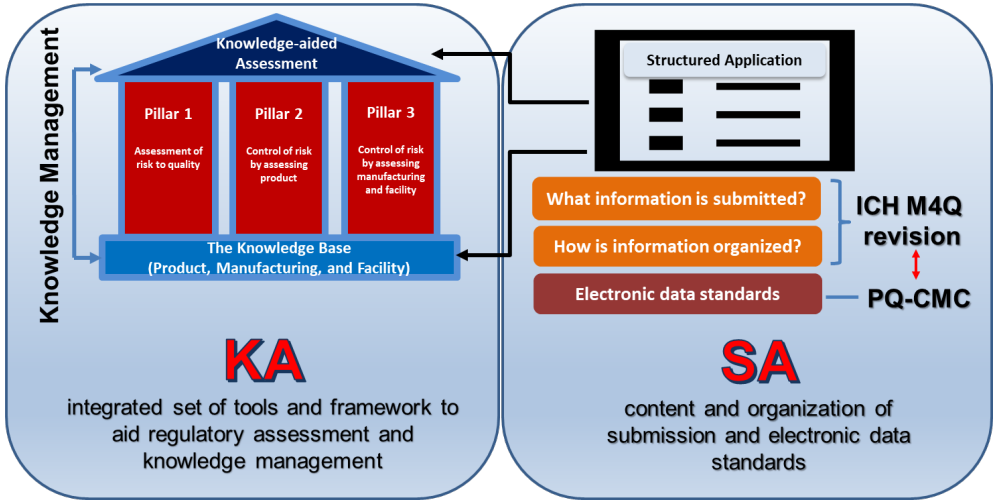


Possible Future Module 3 Submission Model



PQ/CMC and KASA

- PQ/CMC:
  - Standardize & structured eCTD **submissions**
  - XML, JSON? and HL7 FHIR
  - Controlled vocabularies for drop-down lists
- KASA System:
  - Pre-populated structured **assessments**
  - Risk-ranking algorithms
  - Pre-analyzed data, e.g., linear regression of stability data
  - Data analytics
  - Comparison to historical data
  - Lifecycle knowledge management
- Implementation of PQ/CMC will significantly enhance the KASA system, by removing manual (semi-automated) data transposition



What we've done

- Contracted technical support
- Assembled SMEs across CDER, CBER & CVM
- Standardized terminology and definitions
- Modeled specification & components and composition
- Proof of Concept with 7 PhRMA firms
- Data element harmonization with the KASA system
- 2017 Federal Register Notice*: Responded to comments
  - Effort should be international
  - Terminology should conform to ISO IDMP** terminology
    - Completed a 157-page mapping document
    - Held a collaborative mapping webinar
- 2022 Federal Register Notice***: PQ/CMC to HL7 FHIR Mapping

* http://go.usa.gov/xNe8S

** Identification of Medicinal Products (5 ISO standards) http://go.usa.gov/xzuxc

*** http://go.usa.gov/xzVdc

PQ/CMC and ICH

- Structured Product Quality Submissions (SPQS) accepted as a topic by the ICH Assembly
- Prioritized as follows:
  - After Q13 completes Step1/Step 2 (Step 2b completed:27 July 2021)
  - New M4-Q (CTD-Q) Expert Working Group only recently formed with Lawrence Yu, FDA as Rapporteur
  - SPQS group formation to be determined by new M4-Q EWG
- FDA's PQ/CMC will continue

“Terminology should conform to ISO IDMP”

- Mapping is problematic, e.g., different granularity
- Many code lists are deferred to regional implementation
- Some terms are regionally mandated
- Some regions have multiple code lists used in different contexts, e.g., FDA dosage forms
  - USP terminology is required by FD&C Act in labeling
  - SPL uses a list from the NCI Enterprise Vocabulary Service
  - Orange book uses a list for acceptable ANDA submissions
  - ICH suggests, but does not require, the EDQM list for E2B submissions
- Terminology will be aligned where feasible,
  but conformance frequently not feasible

Table D.1 — Ingredient roles (classCodes) From ISO 20443 (2017)

Code	Description
INGR	Ingredient not otherwise specified, used in cases of devices or foods where further classification is not common.
ACTI	Active ingredient – ingredient that has the pharmacological action. Use only if basis of strength *cannot* be specified, otherwise use ACTIB, ACTIM, or ACTIR
ACTIB	
ACTIM	
ACTIR	
ADJV	
IACT	
COLR	
FLVR	
PRSV	
STBL	
MECH	
BASE	The base of a preparation, i.e. water, vaseline, ethanol.
ADTV	Any additive added, use only when there is no described pharmacological action and classification as merely "inactive" ingredient is not appropriate.
CNTM	Contaminant - ingredient whose presence is not intended but may not be reasonably

Only 4 terms shown below are "current," others are "nullified" or "non-current"

4 "Active ingredient" terms

15 terms for "Ingredient roles"

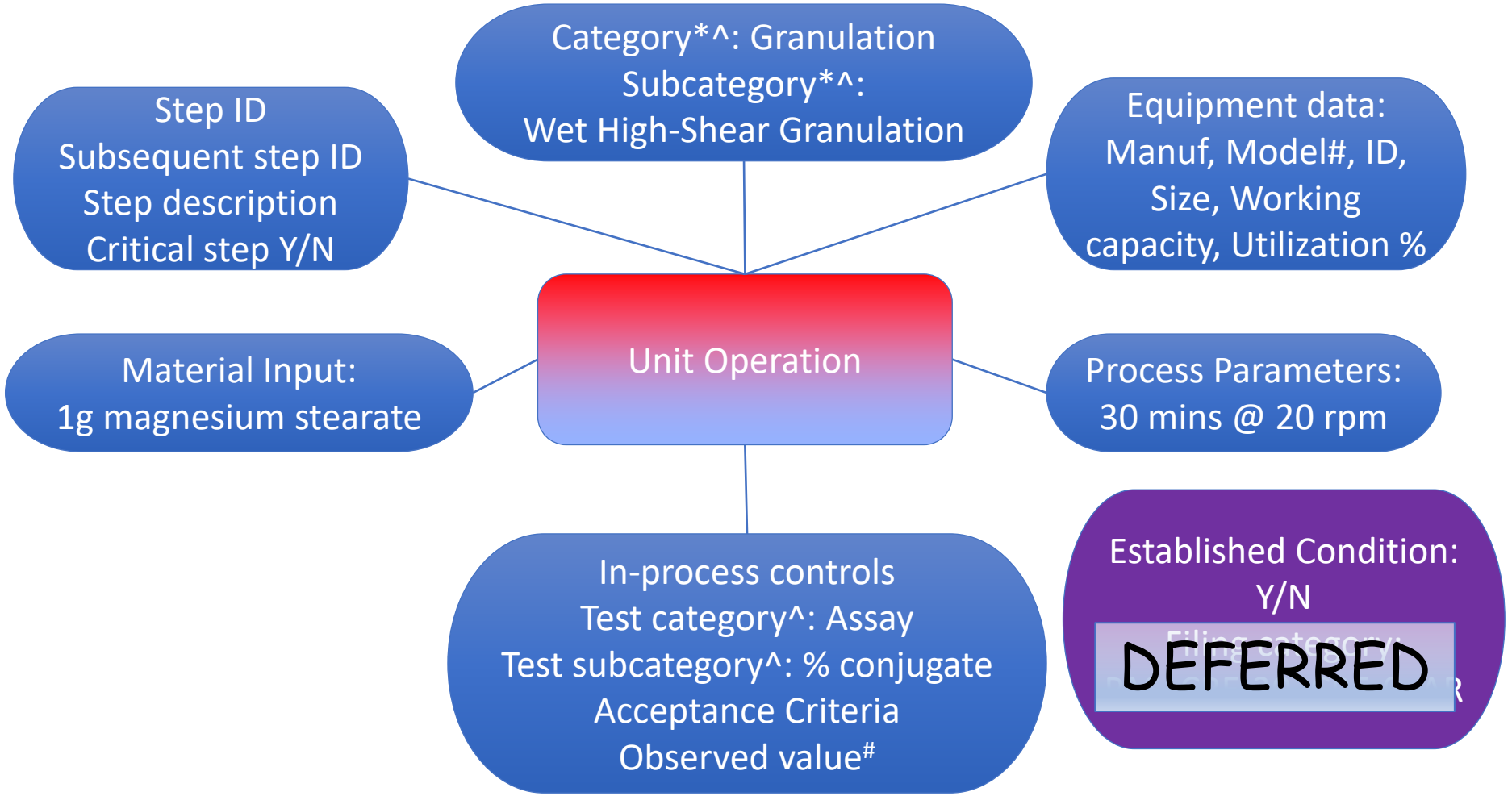
FDA PQ/CMC Ingredient Roles

- Active
- Adjuvant
- Excipient

Standardized Terminology & Definitions

- Why
  - Eliminates confusion about synonymous, potentially synonymous terms
  - Enables an ontology (i.e., properties and the relations between them)
  - Permits data analytics (e.g., how many assay procedures use CZE, for what classes of drugs)
  - Facilitates risk-ranking
- Controlled vocabularies (ISO: coded concepts)
  - Enables drop-down lists
  - E.g., “Ingredient role” for PQ/CMC
    - Active
    - Inactive
    - Adjuvant

Drug Product Unit Operations



- * From 2014 “SUPAC: Manufacturing Equipment Addendum Guidance for Industry”
- # For manufactured exhibit lots
- ^ Controlled vocabulary code list

Typical WG Meeting Activity

PQ/CMC - KASA - Trk 2 meeting - 8/6/2021 --Harmonization Notes for Excipient Function Names

#	KASA Excipient Function List	PQ/CMC Excipient Function Names Mapping to KASA list	NEW values to be added to PQ/CMC Excipient Function Names List	Recommendations/ Notes for KASA & PQ/CMC
1	API	NA		
2	Acidfier	pH Modifier		
3	Adhesive	Adhesive		
4	Alkalizing Agent	pH Modifier		
5	Anti-Adherent	Lubricant		
6	Anti-foaming Agent	GAP	NEW - Anti-foaming Agent	
7	Antioxidant	Antioxidant		
8	Anti-static Agent	GAP	NEW- Anti-static Agent	
9	Anti-tacking Agent	Lubricant		
10	Binder	Binder		
11	Buffer	Buffering agent		
12	Chelating Agent	Chelating agent		
13	Colorant	Organoleptic agent		
14	Crystallization inhibitor	GAP	NEW- Crystallization inhibitor	
15	Cushioning agent	Filler		
16	Diluent/Filler	??		
17	Disintegrant	Disintegrant		
18	Emulsifier	Emulsifying Excipient		

Notes here on harmonization of:

- Consensus terminology
- Who will make the change

What we plan to do

- Continue external collaboration
  - International Pharmaceutical Regulators Programme (IPRP)
  - ICH M4Q
  - UNICOM
  - EMA
  - HL7
  - Industry Partners
  - IRISS IDMP
  - ISO TC215 WG 6 IDMP
  - Global IDMP Working Group (WHO Uppsala)
- Continue internal collaboration
  - FDA IDMP Steering Committee
  - FDA Global Substance Registration System (GSRS)
  - FDA Data Standards Board
  - CDER Data Standards and Data Governance Board
  - CDER Product Data Control Board
- Model other Module 3 & 2.3 CTD sections
- Publish a Draft PQ/CMC Guidance (estimated in 2023)

PQ/CMC IDMP Challenges

- In IDMP standards
  - 11238 SSG 4 specification use case differs from PQ/CMC
  - Not all terms are defined
  - Most controlled vocabulary code (“coded concept”) lists undefined
- PQ/CMC items not included in IDMP
  - Stability
  - Quality data for drug product,
    e.g., specification (may include test stages)
  - Quality data for excipients
  - Lifecycle model for specification
  - Batch Analysis Tables
  - Control of Excipients

Challenges

- Standards
  - Diversity e.g., IDMP, UNICOM, SPOR, ICH, CFR, EMA, MEDDRA, EDQM
  - Gaps e.g., controlled vocabulary (CV) for analytical procedures, chemical & physical attributes for characterization, specification, in-process controls; IDMP code lists
- Developing data models & ontologies
- Vendor support for HL7 FHIR transport format
- Internal FDA infrastructure

Conclusion

- PQ/CMC will
  - Substantially change the submission process
  - Necessitate new business processes and infrastructure for FDA and applicants
- Years in the future
  - To become a required submission under 745A(a)
  - ICH “Structured Product Quality Submissions”

INDUSTRY COMMENT

PQ/CMC

PhRMA
RESEARCH + PROGRESS + HOPE

PQ/CMC

Industry Panelists

Craig Anderson
Director, Information Management
Pfizer

Rodrigo Palacios
Director, Global Regulatory Policy
Genentech

David S Ross
Director, Strategy and Continuous Improvement, Global Regulatory Excellence
AstraZeneca

PQ/CMC

Benefits/PDUFA VI Accomplishments

- Draft Standardization of Pharmaceutical Quality/Chemistry Manufacturing and Control Data Elements and Terminologies Document
- PQ/CMC – Phase 1 Pilot Testing
- PQ/CMC – FHIR Mapping Document

PQ/CMC

Challenges/Questions

- Timeline for standards development
  - Consider different models for standard development
  - Engagement with industry/other stakeholders

- Earlier vendor engagement

- Ensuring consistency across the various regional and international structured data initiatives (e.g., terminologies)

PQ/CMC

Recommendations/PDUFA VII Opportunities

- PDUFA VII commitment – engaging with stakeholders and international consortia (e.g., ICH, ICMRA) on technology and innovation initiatives to promote convergence
  - Structured Product Quality Submissions (SPQS)
  - Pharmaceutical Quality Knowledge Management System (PQKMS)

- An overall strategy/roadmap for the application of structured CMC data to future use cases would help ensure a coherent and efficient implementation for all stakeholders
  - Modernization of regulatory submissions and review
  - Standards development
  - Data sharing/collaboration among health authorities, as appropriate

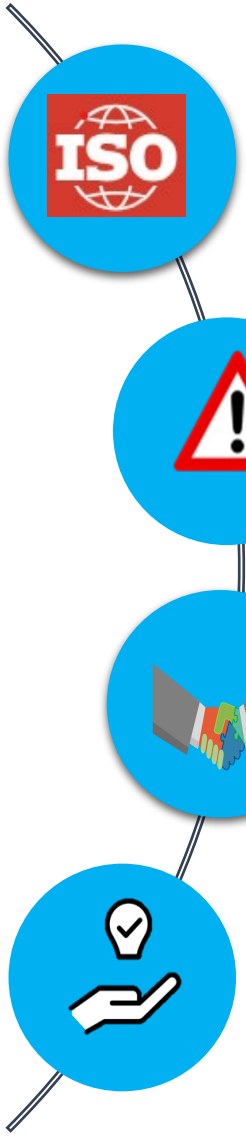
PUBLIC COMMENT

Identification of Medicinal Products (IDMP)

Ta-Jen (TJ) Chen
Sr. Project Management Officer
Office of Strategic Programs (OSP)
Center for Drug Evaluation and Research (CDER) | FDA

April 12th, 2022

Topics



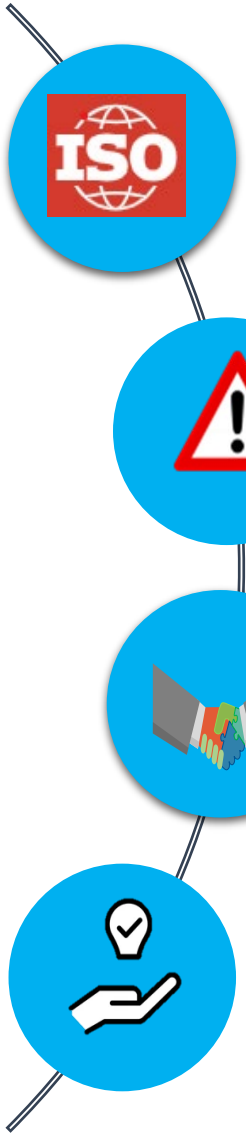
ISO IDMP Standards

Challenges to Global IDMP Implementation

Cross-Region Collaboration on Global IDMP Implementation

Projects for Global IDMP Implementation

ISO IDMP Standards



Challenges to Global IDMP Implementation

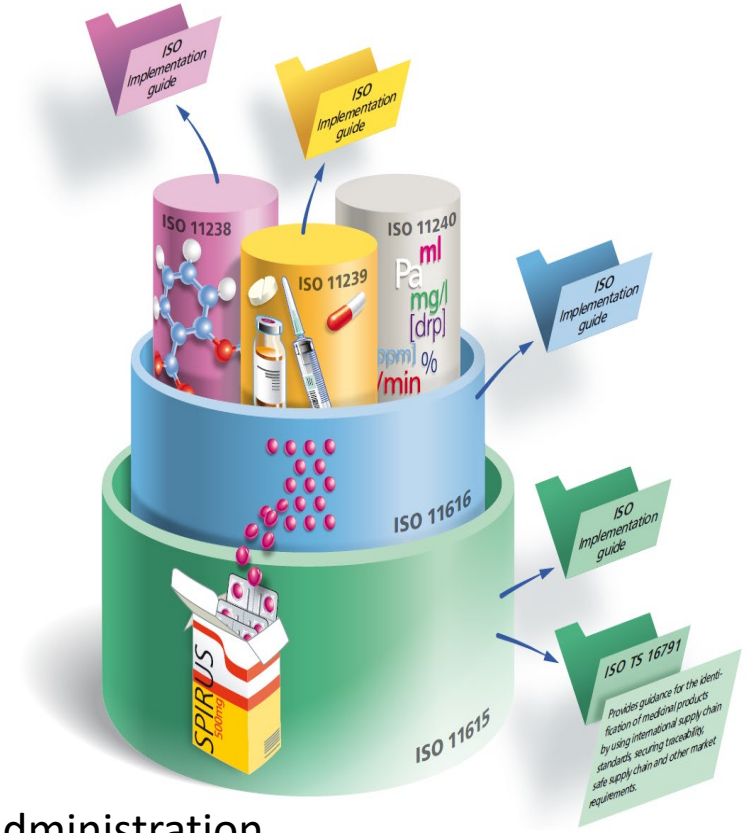
Cross-Region Collaboration on Global IDMP Implementation

Projects for Global IDMP Implementation

What is IDMP

The Identification of Medicinal Product (IDMP) is a suite of five ISO standards that:

- Data elements and structure to **uniquely** and **unambiguously** identify medicinal product, Pharmaceutical Product, and substance
- **common vocabularies** for improved people communication
- **common message standards** for improved IT system communication



- ISO 11615 – Medicinal Product Identification
- ISO 11616 – Pharmaceutical Product Identification
- ISO 11238 – Substance Identification
- ISO 11239 – Pharmaceutical dose forms, units of presentation and routes of administration
- ISO 11240 – Units of measurement

Closer Look at Pharmaceutical Product Identification (PhPID)

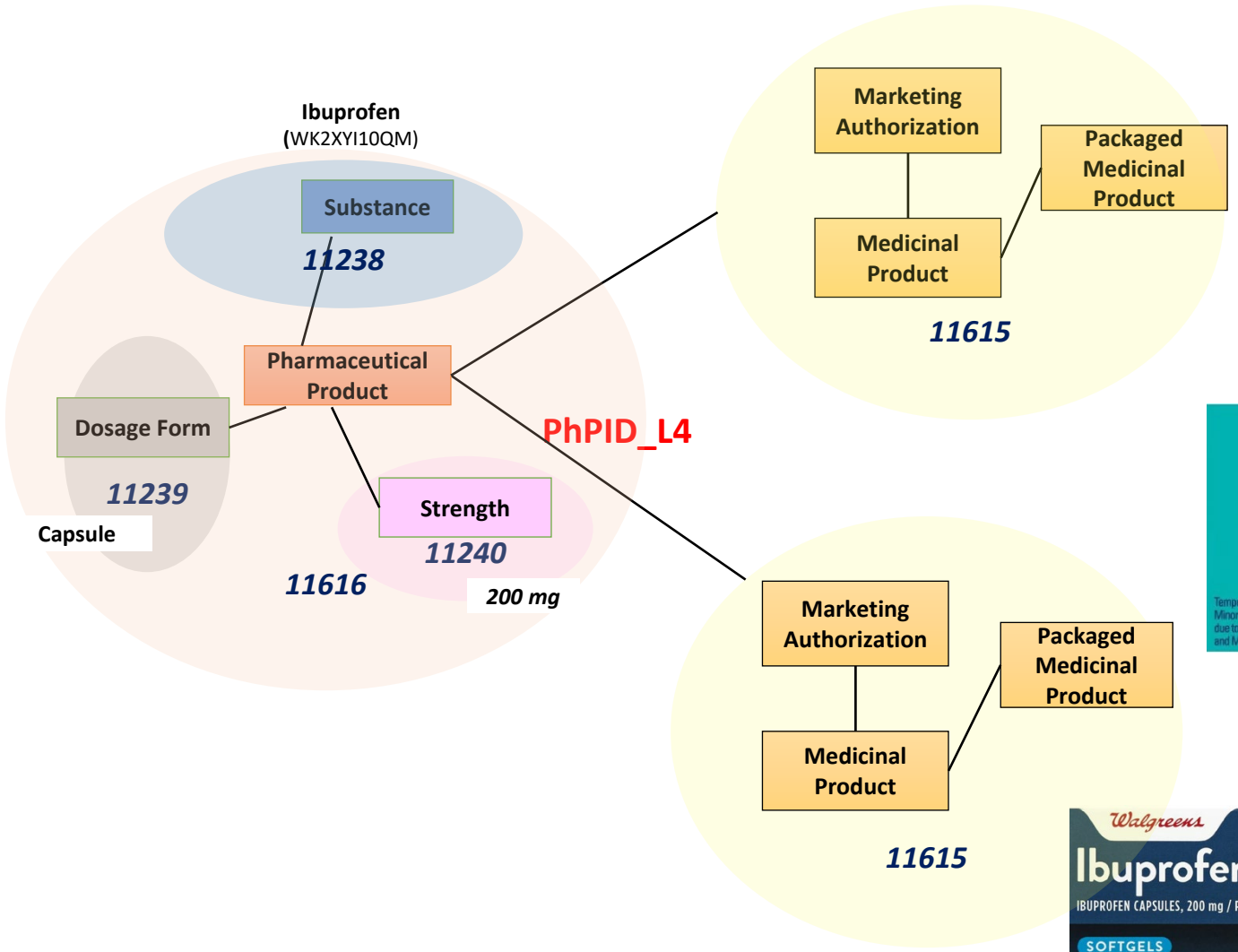
ISO 11616 defines PhPID as a set of 4 levels

- PhPID_Substance Level_L1 → Substance(s) Term
- PhPID_Substance Level_L2 → Substance Term(s) +Strength+ reference strength
- PhPID_Substance Level_L3 → Substance Term(s) + *Administrable Dose Form*
- PhPID_Substance Level_L4 → Substance(s) Term+ Strength + reference strength + *Administrable Dose Form*

Key Benefits of IDMP

- Cross-regions or global agreement on common substance ID and dose form is needed to maximize the benefits

Connecting Medicinal Products



ISO IDMP Standards

Challenges to Global IDMP Implementation

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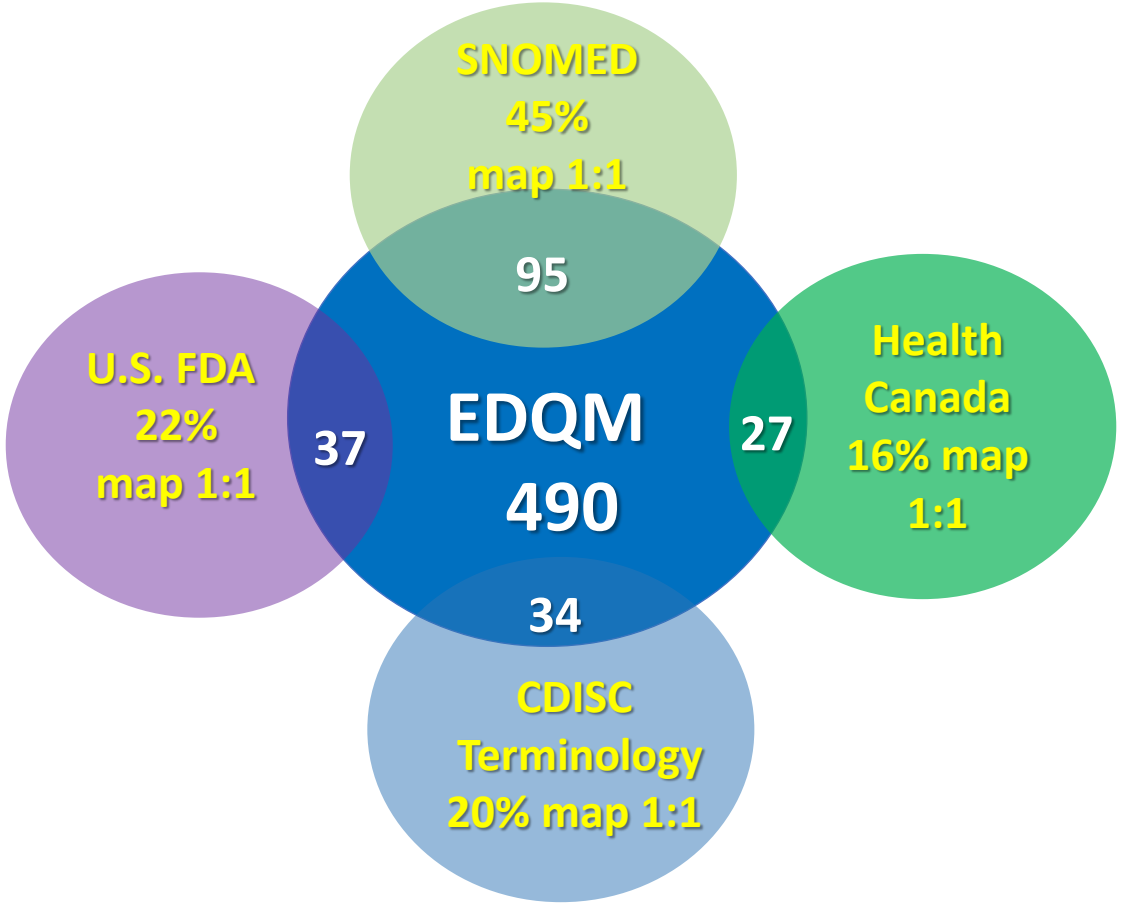
Issues with dose form (ISO 11239 / TS 20440)

- Various regions use their own set of dose form terminologies
- Different regional terminologies have different levels of granularity
- Different regional terminologies can have different definition for the same term

❖ **Mapping among regional terms is not viable**

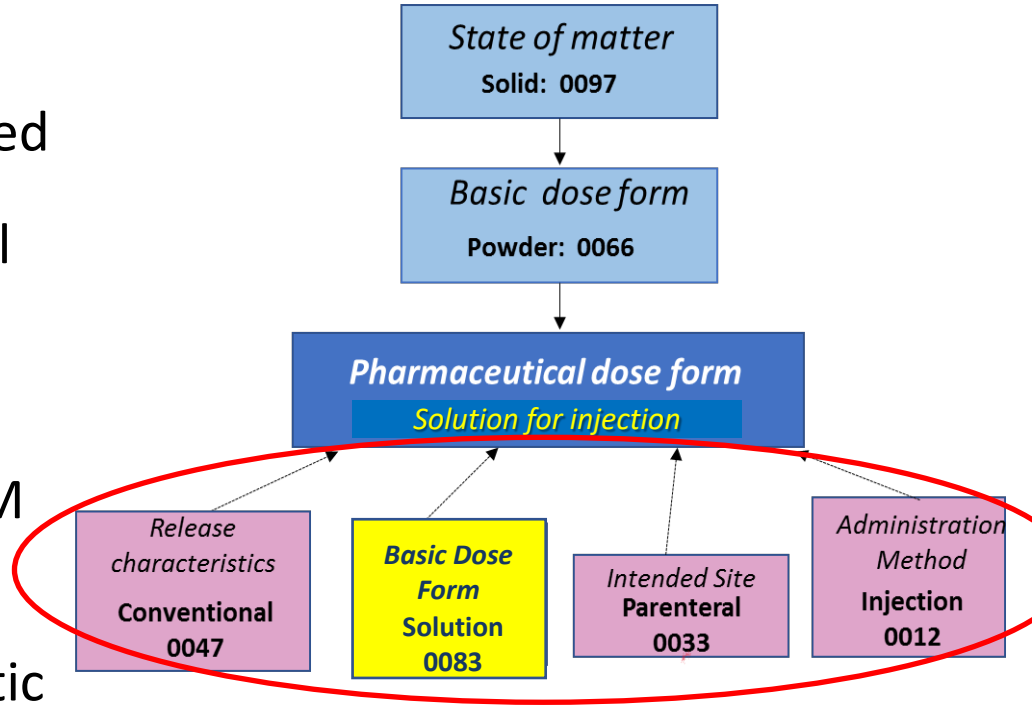


Alternative for dose form (ISO 11239 / TS 20440)

- **Proposed Solution:**
  1. To use centrally maintained dose form characteristics to generate global PhPID

  2. A pilot project with FDA and WHO-UMC was conducted in 2020 / 2021 that demonstrated that dose form characteristics (and codes) is viable solution for global PhPID

- **Outcomes**
  1. Based on the Pilot project findings, as well as UNICOM findings, ISO TC 215 WG6 has revised the standard documents (in draft)
  2. Conduct an additional pilot for dose form characteristic mappings



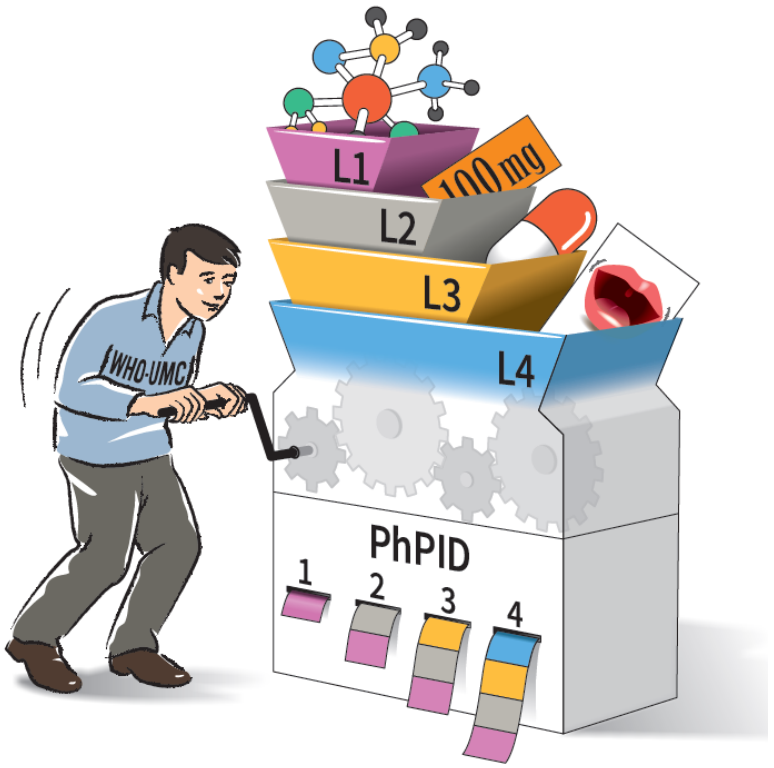
Additional Findings about Dose Form and Strength

- Consistent business rules for PhPID generation are needed
  - use of different dose forms in different regions

Covid-19 vaccine Pfizer/BNT	
Authority of approval	**Dose Form**
EMA	dispersion for injection
US	suspension for injection

  - Express in different strength/unit in different regions

Covid-19 vaccine AstraZeneca	
Authority of approval	**Strength per dose (0.5 ml)**
EMA	2.5×10^8 infectious units
UK	5×10^{10} viral particles
Australia	5×10^{10} viral particles



ISO IDMP Standards

Challenges to Global IDMP Implementation

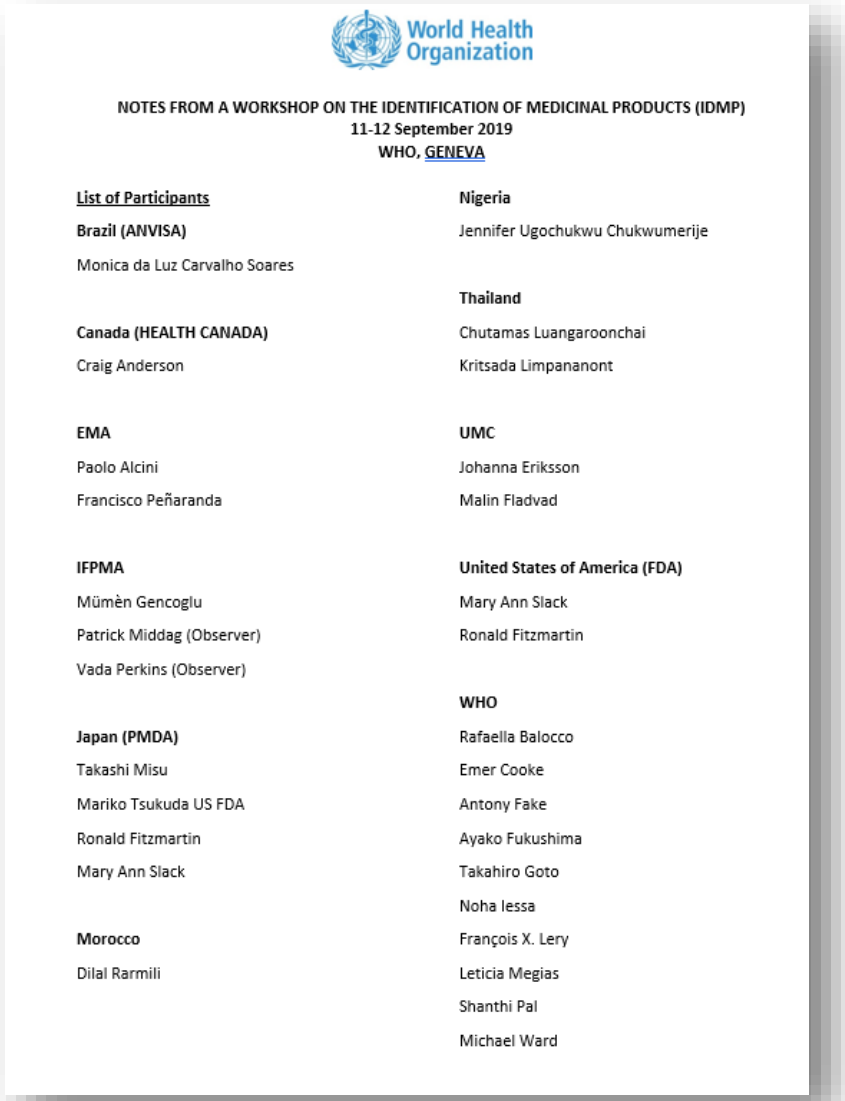
Cross-Region Collaboration on Global IDMP Implementation

Projects for Global IDMP Implementation

Global Implementation Requires a Global Working Group

- Regulatory collaboration via the EMA-FDA IDMP Collaboration Framework facilitates consistency and alignment
- ISO TC 215 WG 6 collaboration facilitates improving the standards themselves to be ‘fit for purpose” in global implementation
- EU-SRS and Global Vaccine Initiative
- However, there was *no* organization to focus entirely on global implementation and use of the IDMP standards

Global IDMP Working Group (GIDWG)



World Health Organization

NOTES FROM A WORKSHOP ON THE IDENTIFICATION OF MEDICINAL PRODUCTS (IDMP)
11-12 September 2019
WHO, GENEVA

List of Participants

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Shanthi Pal
Michael Ward

- Global Identification of Medicinal Products Working Group (GIDWG) is chartered based on the recommendations from the IDMP Workshop in Geneva hosted by the World Health Organization on 11-12 September 2019

- Founding members are European Medicines Agency (EMA), United States Food and Drug Administration (US FDA) and the World Health Organization Collaboration Center for International Drug Monitoring / Uppsala Monitoring Center (WHO-UMC)

Goal of the Global IDMP Working Group (GIDWG)

Conduct and report on projects leading to the establishment of a framework for the global implementation of the ISO IDMP standards and maintenance of global identifiers.

GLOBAL IDMP WORKING GROUP

Charter

1. INTRODUCTION

This charter establishes the Global Identification of Medicinal Products Working Group (GIDWG). The initial Phase 1 members are European Medicines Agency (EMA), United States Food and Drug Administration (US FDA) and the World Health Organization Collaboration Center for International Drug Monitoring / Uppsala Monitoring Center (WHO-UMC). The Charter sets the GIDWG's mission, scope, membership, roles and responsibilities, and governance.

This working group was established as a result of the IDMP Workshop hosted by the World Health Organization on 11-12 September 2019 in Geneva, The summary notes of the workshop proposed a set of actions and recommendations that included the formation of a working group to explore and conduct pilot projects focused on the creation and maintenance of global substance and pharmaceutical product IDs (PhPIDs) that would lead to the global implementation of the IDMP standards and further outreach and collaboration with stakeholders.

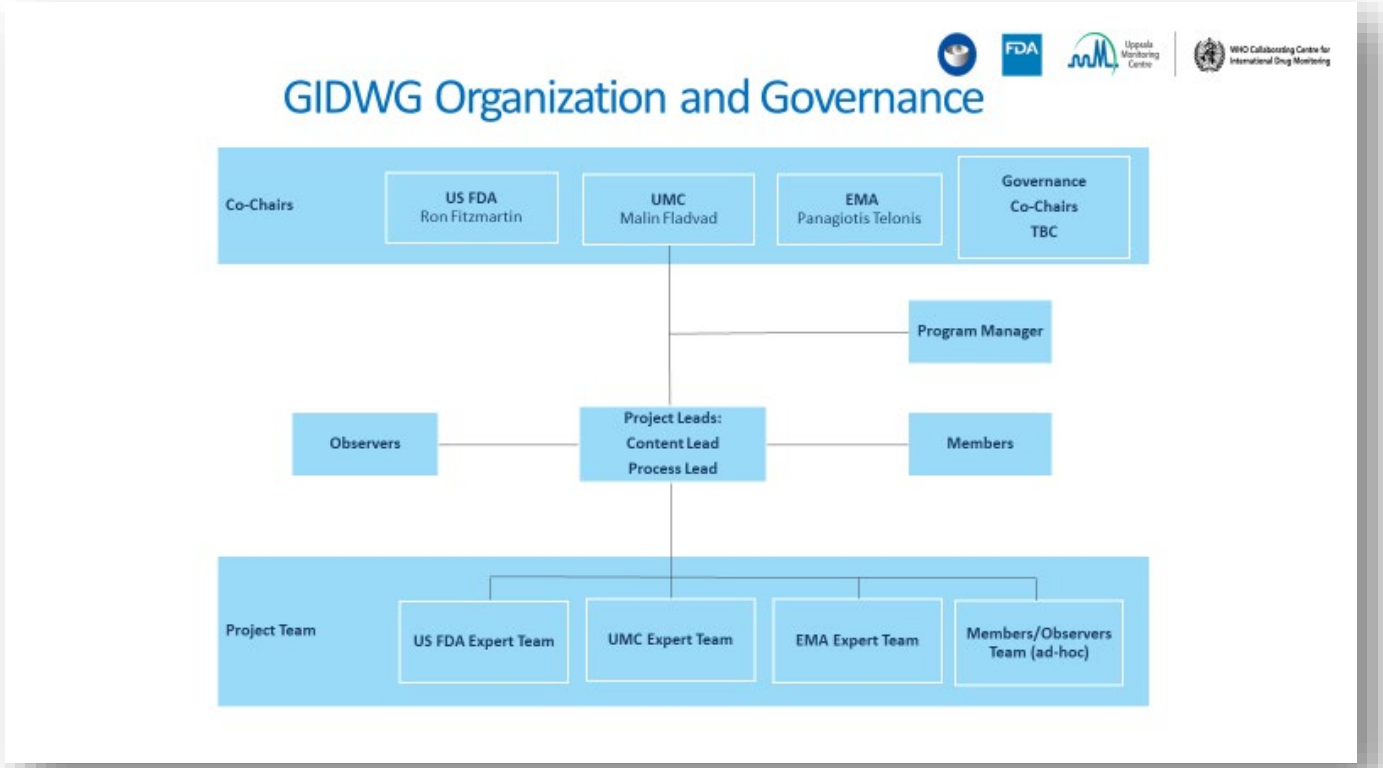
2. MISSION

The GIDWG will conduct and report on projects leading to the establishment of a framework for the global implementation of the ISO IDMP standards and maintenance of global identifiers.

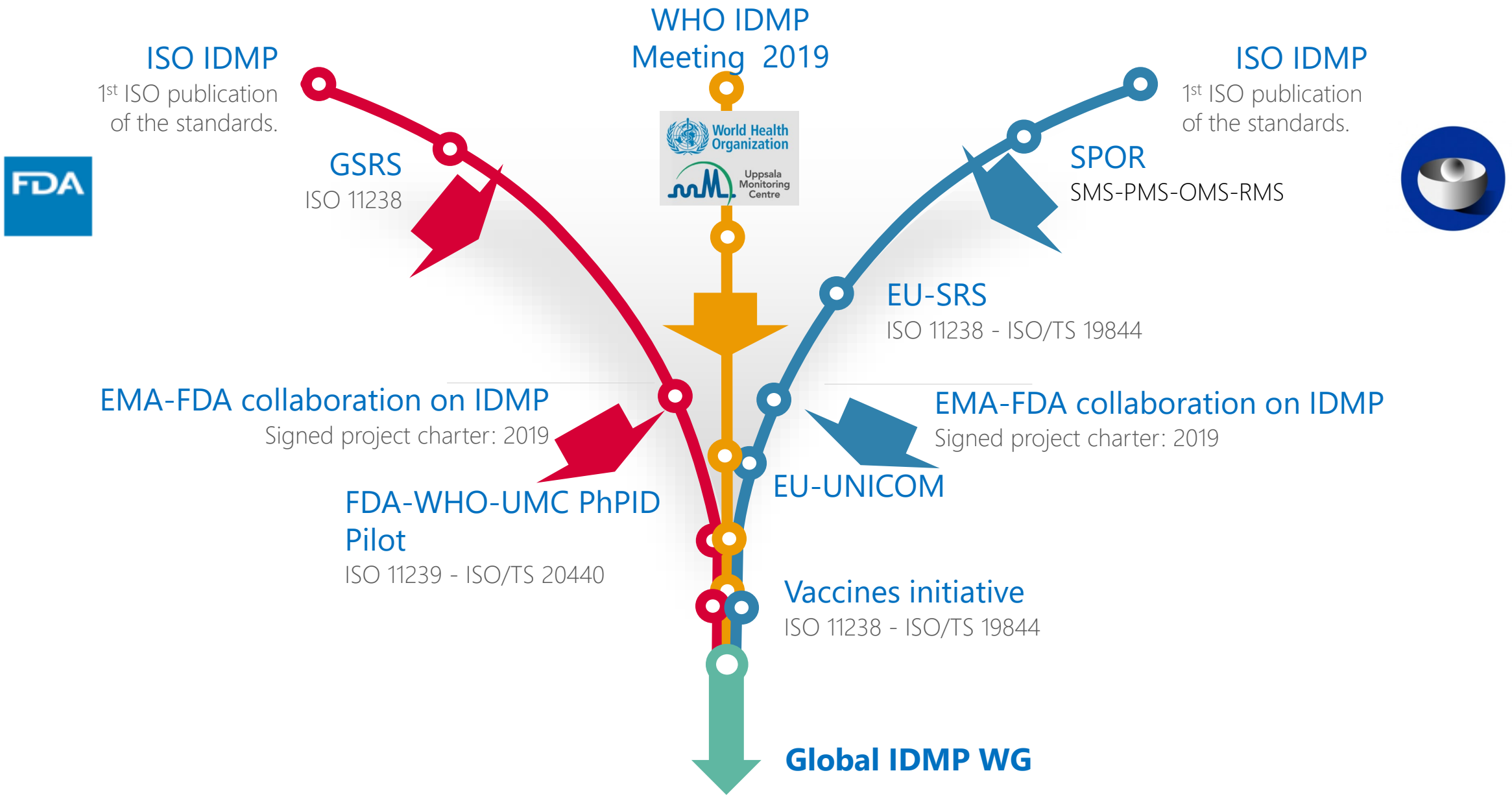
3. SCOPE

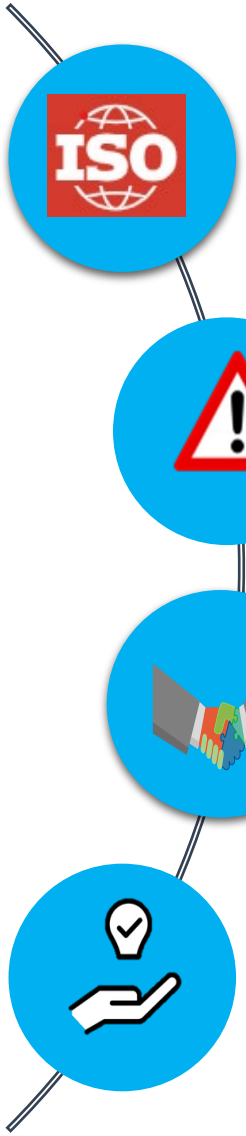
The scope includes:

1. Understand and develop consensus on the issues and mitigation strategies with the ISO IDMP standards, their Technical Specifications and message infrastructure.
2. Develop and prioritize a list of global IDMP implementation use cases.
3. Understand the IDMP implementation status and challenges in each region.
4. Understand and develop a consensus on what is the best pathway to a global substance ID.
5. Articulate and develop consensus on use of UMC as the organization for maintenance of global identifiers, i.e., Substance ID and PhPID.
6. Develop a consensus on best practices, processes, operating model for maintenance of global identifiers for marketed medicinal products.
7. Identify, recommend, and participate in pilot projects.
8. Identify and recommend best approaches for communicating outcomes / summary of findings to other stakeholders.



Convergence in Cross Region Collaboration





ISO IDMP Standards

Challenges to Global IDMP Implementation

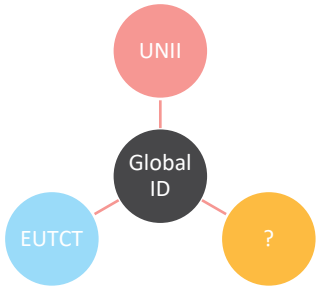
Cross-Region Collaboration on Global IDMP Implementation

Projects for Global IDMP Implementation

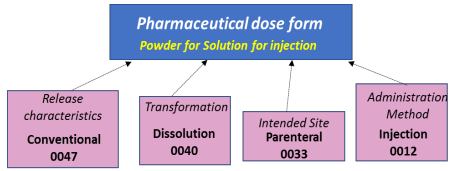
GIDWG Programme Scope

Identify and develop consensus on processes, best practices and operating model for maintenance of global identifiers for marketed medicinal products

1. Global Substance ID



2. Global Dose Form Identifier

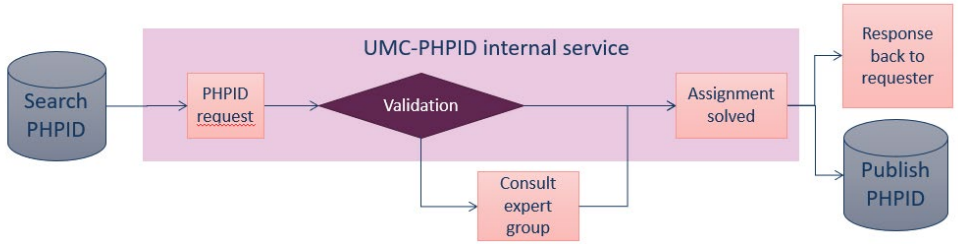


3. Strength Definitions Identifier

Pattern	Type of product
A	
B	
C	
D	

4. HL7 FHIR for IDMP

5. Operating model



GIDWG project time plan 2022

Month 1-3

- Evaluate pilot data to explore processes and business rules

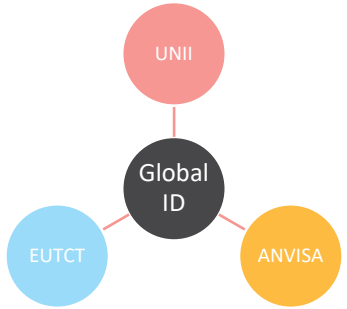
Month 4-6

- Define business rules & processes
- Suggest updates to ISO

Month 7-9

- Document business rules & processes
- Global IDMP Implementation report on pilots

Global Substance ID



Problem statement

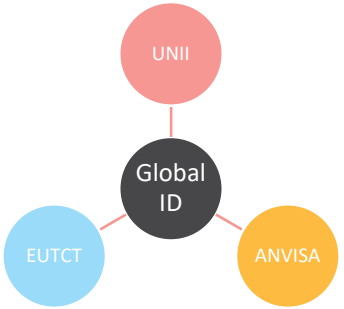
To have consistent generation of global PhPID, a single controlled Global Substance ID is needed.

Project description

To globally harmonize and define capture of standardized information for global Substance identification and hereby ensure consistent PhPID construction through/by:

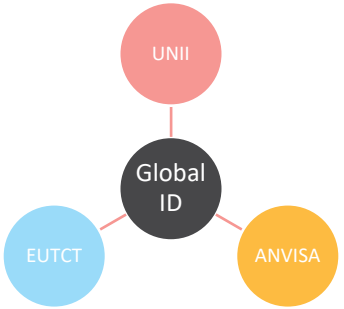
- Identifying the core information set via the ISO/TC 215 WG6 signature field sub-group.
- Adopting a global substance ID
- Establishing a global maintenance organization, i.e., UMC.
- Establishing a framework within ISO 11238 or technical specification that will allow the capture of standardized information on hydrates and expression of substance versus reference substance

Global Substance ID
Proposed key activities



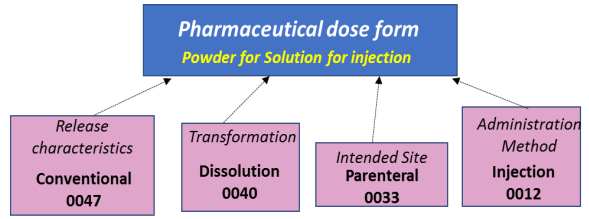
- Mapping EU-SRS EUTCT, FDA UNII and ANVISA substances to Global substance identifier for a set of selected substances
- Review all substance classes including more complex scenarios like certain biologics
- Investigate and draw conclusions from current regional substance identifier processes
- Global substance ID service ability in PhPID construction
- Assert the scalability and automation of the process
- Formalize transparent and sustainable business rules for each substance type

Global Substance ID
Proposed deliverables



- Business rules and process including documentation:
  1. Chemicals and Covid vaccines
  2. Polymers and proteins including biosimilars
  3. Additional substance types
- Suggest updates to ISO/TC 215 WG6
- Global IDMP Implementation report, including substance identification

Global dose form identifier



Problem statement

For consistent PhPID generation, there is a need for standardized identification of dose form. There is currently no agreement on the use of a global controlled dose form vocabulary for PhPID generation.

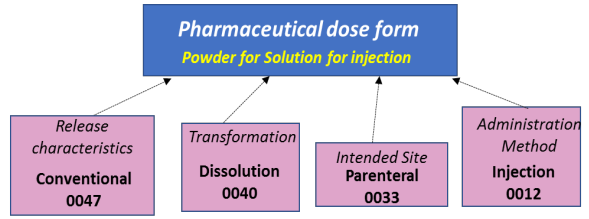
Project Description

The goal of this project is to globally harmonize and define capture of standardized information for global dose form identification by:

- Evaluate the EDQM dose form characteristics approach demonstrated in PhPID generation in the FDA/WHO-UMC pilot on a larger dataset
- Propose solutions to issues identified, for example different use of similarly expressed dose forms in different regions
- Establish strict business rules for PhPID generation

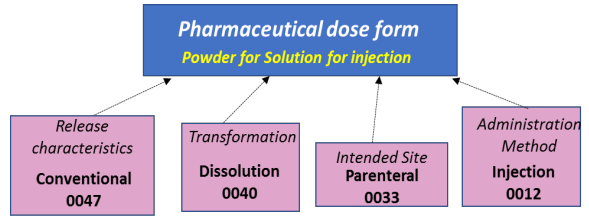
Global dose form identifier

Proposed key activities



- Evaluation of the 4 EDQM dose form characteristics approach for:
  - Products corresponding to UNICOM PPL 35 substances in ANVISA data set
  - Products corresponding to UNICOM PPL 35 substances + additional selected products in US FDA data set
- Investigate and propose solution for dose form characteristic combinations and EDQM dose form characteristics with multiple values
- Assert the scalability and automation of the process
  - Verify automation of AdmDF in PhPID construction
- Formalize and recommend Business Rules & Process

Global dose form identifier Proposed deliverables



- Business Rules & process
- Global IDMP Implementation Report, including dose form

Global Strength Definitions Identifier

Pattern	Type of product
A	
B	
C	
D	

Problem statement

For consistent PhPID generation, clarification of requirements, and structures and rules for strength expression within the ISO IDMP standard is needed, especially for the use of strength presentation versus strength concentration for different products.

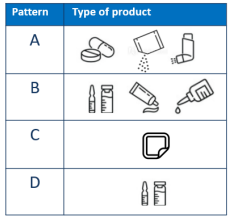
The ISO IDMP standard only defines the standard units, not necessarily how to present/use the units and how to define additional units not in the scope of UCUM.

Project Description

The goal of this Project is to globally harmonize and define capture of standardized information for global Strength Definitions identification

- Clarifying presentation strength versus concentration strength in the context of IDMP.
- Further developing and evaluate the FDA/ WHO-UMC pilot developed concepts on how to use strength presentation versus strength concentration for different products
- Defining the use of units (e.g., 0,1 g or 100 mg), value figures and unit of presentation

Global Strength Definitions Identifier
Proposed key activities



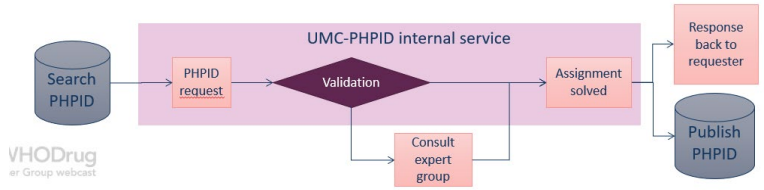
- Identify and address different representation of strength for products in at least one another region
- Clarify the use of presentation strength and concentration strength
- Explore the Pattern Framework further to ensure clear business rules for prioritized dose forms in EDQM and additional regional product data sets
- Review existing Business Rules
- Assert the scalability and automation of the process
- Formalize Business Rules and processes for each pattern and investigated dose forms
- Investigate need for an additional pattern

Global Strength Definitions Identifier
Proposed deliverables

Pattern	Type of product
A	
B	
C	
D	

- Business Rules and processes
- Proposal to ISO/TC 215 WG6 regarding framework for use of presentation strength and concentration strength
- Global IDMP Implementation Report, including strength definitions

Operating Model for PhPID Construction



Problem statement

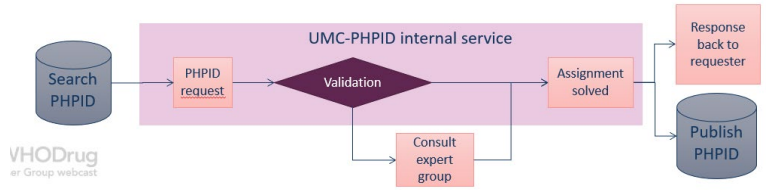
For stakeholders to have access to global PhPIDs, a PhPID operating model needs to be put in place.

Project Description

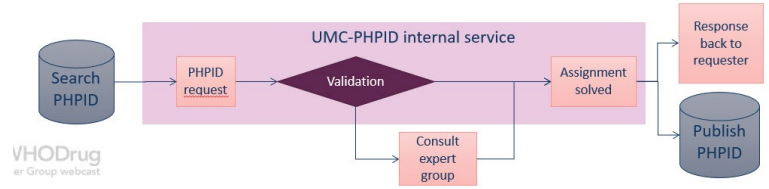
The goal of this project is to define the operating model for global PhPIDs through/by:

- Identifying the main requirements for the operating model from regulators, industry, health care professionals and other stakeholders
- Develop a proposal for a solution to provide the information needed regarding quality, timelines, and access
- Establish business rules for the PhPID generation and assess feasibility for publishing in ISO technical report
- Establishing the global maintenance organization, i.e., UMC and propose framework and processes for international working group

Operating Model for PhPID Construction
Proposed key activities



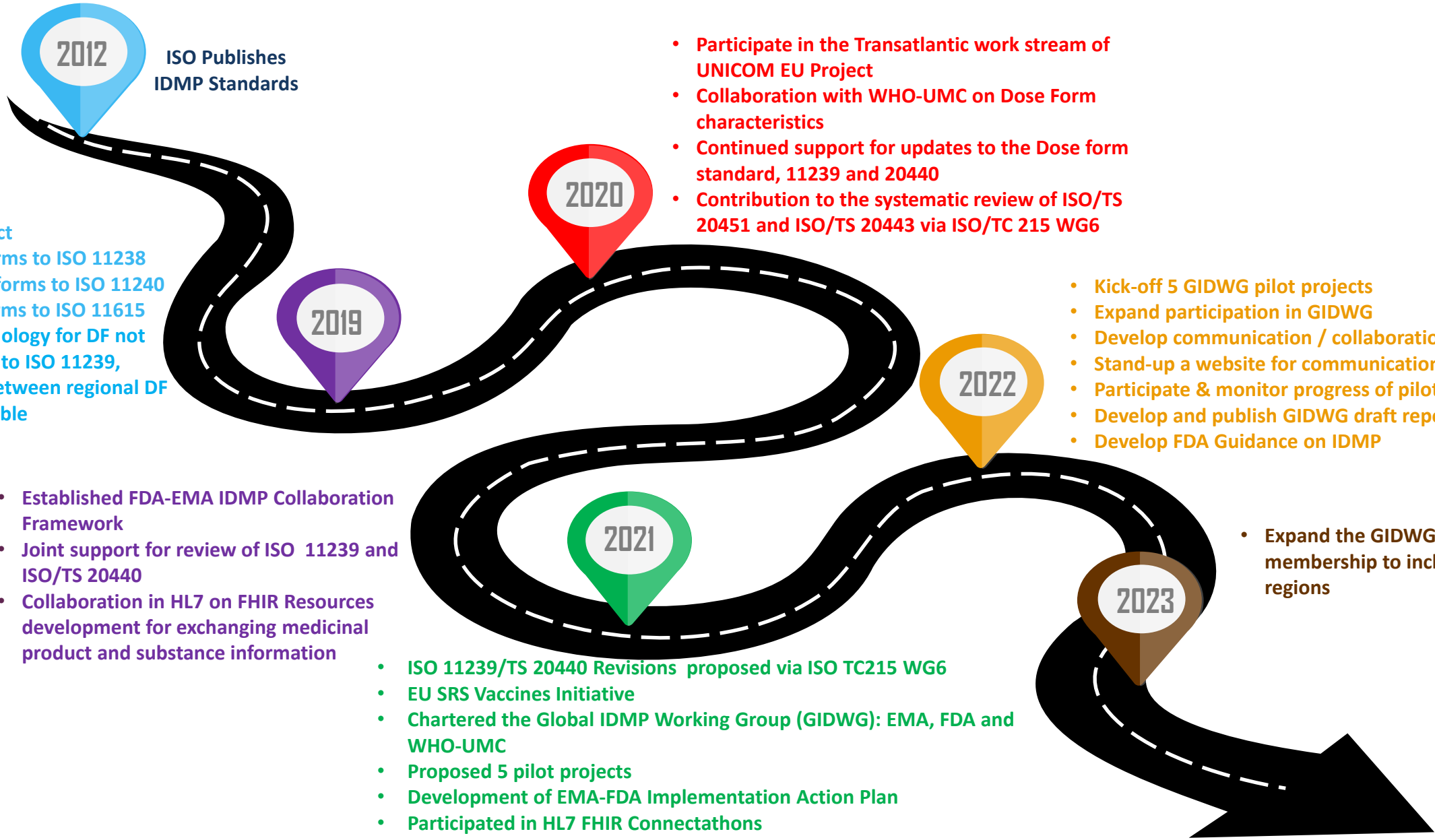
- Demonstration of the consensus-based operating model for WHO-UMC as the international maintenance organization as an end-to-end pilot for the following use cases, including product level associations when applicable
    - Pharmacovigilance
    - Drug shortages
    - Drug utilization
    - Cross border prescription
- Process definition by three jurisdictions (EMA, US-FDA AND ANVISA) including an international expert group supporting the process



Operating Model for PhPID Construction Proposed Deliverables

- End-to-end process model (high-level requirements)
- Detailed requirements for all use cases/´personas´
- Proof of concept developed
- ´Real data´ test run
- Global IDMP Implementation report, including business rules, processes and operating model

FDA IDMP Roadmap to Implementation - 2012-2023



- GSRS Project
- UNII conforms to ISO 11238
- UCUM conforms to ISO 11240
- NDC conforms to ISO 11615
- FDA Terminology for DF not conformed to ISO 11239, mapping between regional DF terms is viable

- Participate in the Transatlantic work stream of UNICOM EU Project
- Collaboration with WHO-UMC on Dose Form characteristics
- Continued support for updates to the Dose form standard, 11239 and 20440
- Contribution to the systematic review of ISO/TS 20451 and ISO/TS 20443 via ISO/TC 215 WG6

- Established FDA-EMA IDMP Collaboration Framework
- Joint support for review of ISO 11239 and ISO/TS 20440
- Collaboration in HL7 on FHIR Resources development for exchanging medicinal product and substance information

- ISO 11239/TS 20440 Revisions proposed via ISO TC215 WG6
- EU SRS Vaccines Initiative
- Chartered the Global IDMP Working Group (GIDWG): EMA, FDA and WHO-UMC
- Proposed 5 pilot projects
- Development of EMA-FDA Implementation Action Plan
- Participated in HL7 FHIR Connectathons
- ISO/TS 19844 Revision via ISO/TC 215 WG6

- Kick-off 5 GIDWG pilot projects
- Expand participation in GIDWG
- Develop communication / collaboration plan
- Stand-up a website for communication
- Participate & monitor progress of pilots
- Develop and publish GIDWG draft report
- Develop FDA Guidance on IDMP

- Expand the GIDWG membership to include other regions

INDUSTRY COMMENT

Identification of Medicinal Products (IDMP)

PhRMA
RESEARCH + PROGRESS + HOPE

IDMP

Industry Panelists

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Vada A. Perkins
Executive Director
Regulatory Policy & Innovation; Head, Research & Policy-Regions
Bayer Pharmaceuticals

IDMP

Benefits/PDUFA VI Accomplishments

- ISO IDMP identified to impact many initiatives
  - PQ/CMC and ICH M4Q to structure CTD Module 3
  - ISO IDMP reflected in HL7 messaging standard (FHIR)

- Global collaboration is progressing the implementation of IDMP
  - Shared views on the key benefits of IDMP
  - GSRS (US/FDA) and EU-SRS moving towards Global Substance ID
  - Common characteristics for Pharmaceutical Dose Form alignment
  - WHO-UMC recommended to maintain global PhPIDs (based on Pilot)
  - FDA-EMA Collaboration Charter and Global IDMP Working Group (GIDWG)

IDMP

Challenges/Questions

- Regional differences on IDMP implementation
  - Scope / use cases
  - Diverse implementation timelines

- Health Authority implementation roadmaps needed
  - Can help plan out industry workloads (e.g., resource allocation)
  - Opportunity to highlight regulatory use cases for how IDMP data submissions will be used

- Impact on Regulatory Information Management (RIM) System implementation

IDMP

Recommendations/PDUFA VII Opportunities

- Prioritize Global Harmonization in Implementation
  - PhRMA supports FDA in taking a global approach
  - EMA-FDA Collaboration Framework & GIDWG
    - 5 planned pilot projects (international in scope)

- Industry as a key stakeholder in Global IDMP Implementation
  - GIDWG Industry Stakeholder Participation (future opportunity)

- ISO IDMP is a foundational data management driver
  - PDUFA VII commitments- Digital health, cloud-based submissions, IT modernization
  - Industry Master Data Management (MDM) initiatives *beyond compliance*
    - One harmonized global RIM System

PUBLIC COMMENT

U.S. FOOD & DRUG ADMINISTRATION

Digital IND Safety Reporting Program

PDUFA VI Public Meeting

APRIL 12, 2022

Agenda

- Background
- Implementation plans
  - Description of new process, including requirements and implementation
  - Data flow
  - Types of IND safety reports to be sent to FAERS
- Routing Mechanisms & Data Elements for IND safety reports using ICH E2B(R3)

IND Safety Reports

Sponsors of clinical trials are required to submit IND safety reports as per 21 CFR 312.32

Current Process: **PDFs in eCTD format**	**New Process:** **ICH E2B XML files to FAERS**
• Inefficient and labor-intensive review • ~50,000/yr • Lack of universal tracking system	• Allows for use of data visualization and analytic tools for review and tracking • Leverages existing processes in use for postmarket safety reporting (ICH E2B data standards & FDA gateway) • Complies with existing federal regulations 21 CFR 312.32(c)(1)(v)

Requirements and Timelines

- **Required change in format under 745A(a) of FD&C Act**
  - Sponsors of commercial INDs will be required to submit certain IND safety reports* to FAERS by one of two methods:
    - Electronic Submissions Gateway (ESG)

      or
    - Safety Reporting Portal (SRP)
  - Requirement effective 24 months after publication of final guidance
  - Voluntary submissions from all sponsors will be accepted and encouraged prior to requirement

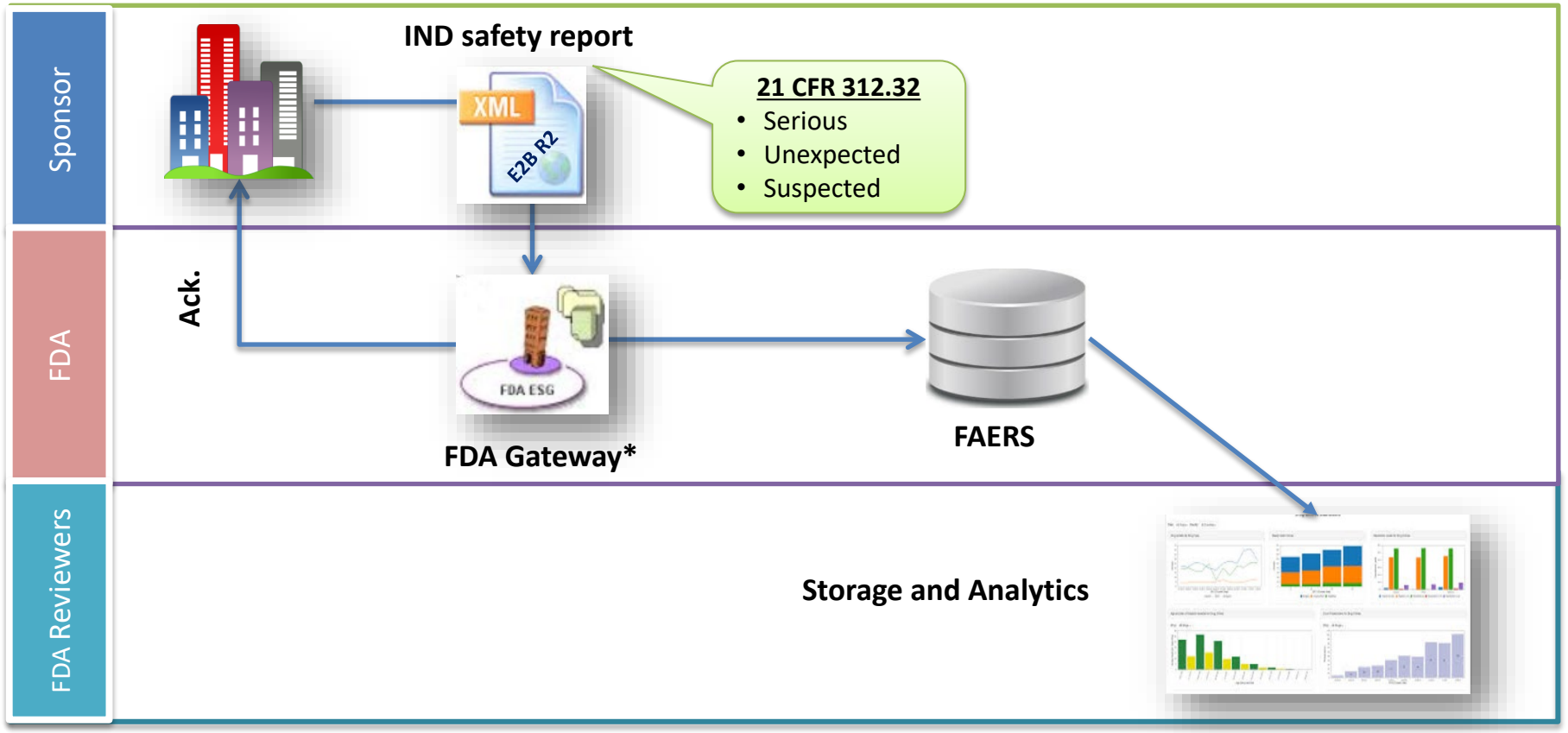
FDA will announce when the voluntary submission process will begin

*Serious and unexpected suspected adverse reactions that contain individual patient data

Communication Plan

- *Providing Regulatory Submissions in Electronic Format: IND Safety Reports - Draft Guidance for Industry (October 2019) Final (TBP)*
- *Electronic Submission of IND Safety Reports - Technical Conformance Guide (TBP)*
- *FDA Regional Implementation Specification for E2B(R3) (TBP)*
- FAERS website will be updated with links to the Guidance and technical specification documents specific to IND safety reports
- Other FDA communications when voluntary submissions begin

IND Safety Report Data Flow



Ack= Acknowledgement
FAERS= FDA Adverse Event Reporting System
*= separate submission path for IND safety reports

Where to Submit IND Safety Reports

(when FDA announces readiness to accept)

Type of IND safety report	Submit to FAERS	Submit in eCTD format
A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (21 CFR 312.32(c)(1)(i)(A)	X	
One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug 21 CFR 312.32(c)(1)(i)(B)	X	
An aggregate analysis of specific events observed in a clinical trial (known consequences of the underlying disease or condition) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group. (21 CFR 312.32(c)(1)(i)(C)	X	
Findings from other studies (21 CFR 312.32(c)(1)(ii))		X
Findings from animal or in vitro testing (21 CFR 312.32(c)(1)(iii))		X
Increased rate of occurrence of serious suspected adverse reactions (21 CFR 312.32(c)(1)(iv))		X

Technical Specifications

- *FDA Regional Implementation Specification for E2B(R3)* is being updated with information for IND reporting

- Regional E2B(R3) elements specific to IND safety reporting
  - IND Number
  - Cross reported IND
  - Reports from aggregate analysis

Technical specifications

- **IND numbers**
  - Data elements for IND number(s)
  - IND Number where AE Occurred (FDA.C.5.5a)
  - *Required for processing and routing to appropriate FDA review division*
- **Cross-reporting**
  - As per 2012 guidance
  - Only ONE IND safety report should be submitted per event
  - IND number of cross reported IND (FDA.C.5.6.r)
    - Repeat this element, as many times as needed for cross-reported INDs
- **Reports from aggregate analysis**
  - Required as per (21 CFR 312.32(c)(1)(i)(C) or (21 CFR 312.32(c)(1)(i)(B) where several events are included

Benefits to Industry

- Efficiency gains in processing and submission
  - Direct electronic submission to FDA from PV
    - no 1571 or cover letter
  - Eliminates need to send duplicate reports

- More comprehensive and structured format than Medwatch form

- Consistent with format for NDA/BLA and ex-US submissions

Routing Mechanism - Process

- Capture the IND# by using the IND Number where AE Occurred - support triage of ICSRs
- Two separate “Routes” for submission
  - Senders will send pre and post market ICSRs to separate routes
  - Sponsors will be responsible for sending the ISCR to the correct destination based on whether it is a pre- or post- market ICSR
- For premarket ICSRs set
  - Batch Receiver Identifier(N.1.4) as ‘ZZFDA_PREMKT’
  - Message Receiver Identifier(N.2.r.3)
    - For CDER IND use the value "CDER_IND"
    - For CBER IND use the value "CBER_IND"
- The pre-market (IND) ICSR submission would include the study name and the study number

Routing Mechanism - Triage of ICSRs

Sponsor Submission

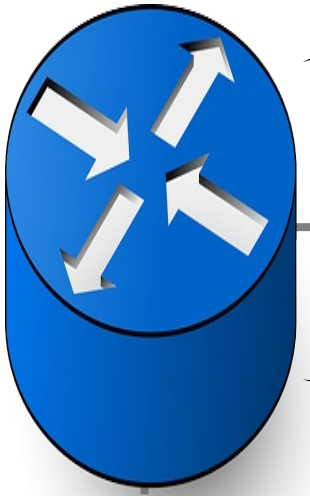
FDA Adverse Event Reporting System

Pre-Market ICSR Submission

AS2* Header: AERS_PREMKT_CDER or
AS2 Routing ID: FDA_AERS_PREMKT_CDER

C.1.1: Sender's (case) Safety Report Unique Identifier
N.1.4: ZZFDA_PREMKT
N.2.r.3: CDER_IND
C.1.3: 2
C.5.2: NCT+name
C.5.4: 1
FDA.C.5.5a : IND Number
…

C.1.1: Sender's Report ID + "-IND"
…
…
…



Post-Market ICSR Submission

AS2 Header: AERS or
AS2 Routing ID: FDA_AERS

C.1.1: Sender's (case) Safety Report Unique Identifier
N.1.4: ZZFDA
N.2.r.3: CDER
C.1.3: 1
G.k.3.2: NDA 07852
…

C.1.1: Sender's Report ID (stay as is)
…
…
…

*AS2: System-to-System. FDA ESG support two methods of communication: WebTrader and AS2 (System-to-System). WebTrader for small, simple, light submissions; AS2 for large, frequent submissions.

Routing Mechanism - Methods

- Two separate “Routes” for submission of safety reports (used for both pre or post market ICSRs)
  - Method 1: AS2 Header Attributes, or
  - Method 2: AS2 Routing IDs

- E2B Regional Data Elements designated specifically for pre-market

Validate E2B Submission

- Provide a mechanism for industry to: i) Validate the regional E2B R3 data files;
- Mechanism can be used before production submission
- Mechanism available for use via a public URL
- Uploaded file for validation are not stored
- Update FAERS Electronic Submission web page to provide this information

Summary

- **SRP Intended for**
  - Sponsors and CROs without infrastructure for direct ESG (gateway-to-gateway) submission
  - Individual reports only; no batch reporting via SRP
- **If CRO**
  - Separate account needed for each sponsor/license holder
- **Post-market and premarket reporting**
  - Maintained separately—select up front, can navigate between them
  - Cannot copy/paste or transfer data; manually enter
- **“Free” (no added cost to use)**
- Contact FAERSESUB@fda.hhs.gov to request an SRP account

INDUSTRY COMMENT

IND Safety Reporting

PhRMA
RESEARCH + PROGRESS + HOPE

IND Safety Reporting

Industry Panelists

Stephanie Gundermann
Senior Director, Business System Management and Innovation
Merck

Raymond Kassekert
Senior Director, PV Systems Management
GSK

Mark Ziobro
Senior Manager - Safety Data Analysis
Novo Nordisk

PhRMA
RESEARCH + PROGRESS + HOPE

IND Safety Reporting

Benefits/PDUFA VI Accomplishments

- Enhanced efficiency in direct submissions to FDA Adverse Event Reporting System (FAERS)
- Electronic submissions will reduce processing time
- Opportunity to participate in IND Safety Reporting E2B R2 Pilot and provide feedback on E2B implementation strategy

IND Safety Reporting

Challenges/Questions

- E2B R2 Pilot revealed technical challenges to electronic IND safety reporting submissions
  - Drug substance name
  - Cross reporting
  - Aggregate analysis/Similar terms attachments

- Understanding FDA's approach to implementation of electronic IND safety reporting requirements

- Advanced notice to industry prior to go-live of required changes needed

IND Safety Reporting

Recommendations/PDUFA VII Opportunities

- Share lessons learned from IND Safety Reporting E2B(R2) Pilot, as appropriate
  - Second phase of pilot testing
- Technical Conformance Guide to complement implementation of any new regulatory requirements for IND safety reports
- ICH E2B(R3) may address many of the challenges identified during the pilot
- Align requirements as closely as possible to the ICH E2B(R3) implementation guideline

PUBLIC COMMENT

U.S. FOOD & DRUG ADMINISTRATION

FDA Electronic Common Technical Document (eCTD) Update

PDUFA VI
Public Meeting on
Electronic Submissions and Data Standards

April 12, 2022

Mark Gray, Senior Project Manager CBER/Data Standards Branch

eCTD Guidance Updates

- eCTD 745A(a) Guidance
  - Requirement to submit using the eCTD format
  - Implementation
    - May 2017: NDA, BLA, ANDA
    - May 2018: Commercial IND & Master Files (exemption for Type III)
    - June 2021: Promotional Submissions
  - Waivers
    - Long-term
      - Certain Positron Emission Tomography (PET) submissions
      - Type II DMFs that solely support an application for a PET drug, or a noncommercial IND application may also qualify for a waiver
    - Short-term
      - unique and rare circumstances and for a limited duration
  - *Please review eCTD guidance all details are not included in this presentation*

eCTD Validation Updates

- Study Data Validation
  - Implemented September 15, 2021
    - CDER & CBER Clinical Studies
      - » NDA, BLA, ANDA studies that started after December 17, 2016
    - CDER Non-clinical Studies
      - » NDA, BLA, ANDA studies that started after December 17, 2016
      - » Commercial IND studies started after December 17, 2017
    - For studies that start on or prior to these dates, a simplified TS may be required
  - Implementation March 16, 2023
    - CBER: Non-clinical studies
      - » BLA, Commercial IND, NDA, ANDA studies that start after March 15, 2023
    - For studies that start on or prior to March 15,2023 , a simplified TS may be required
  - *Please review* Study Data Technical Conformance Guide *all details are not included in this presentation*

eCTD Validation Updates

- Study Data Validation Effective Date updated:

  9/15/2021 (CBER module 4 sections, 03/16/2023)

Error	Description
1734	A dataset named ts.xpt with information on study start date must be present for each study in required sections*
1735	Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*
1736	For SEND data, DM dataset and define.xml must be submitted in Module 4 required sections* For SDTM data, DM dataset and define.xml must be submitted in Module 5 required sections* For ADaM, ADSL dataset and define.xml must be submitted in Module 5 required sections*

** Module 4 sections: 4.2.3.1, 4.2.3.2, 4.2.3.4*
Module 5 sections: 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

Please review eCTD Validation Specification *all details are not included in this presentation*

eCTD Validation Updates

- 1789: A file has been submitted in a study section without providing an STF file
- Ended support of us-regional DTD 2.01 on March 1, 2022. The current version of M1, utilizing DTD 3.3, is required.
- Promotional Submissions (CDER-only)
  - 1551: 2253 submission does not include Product Labeling
  - 1553: The only valid FDA Form to include in a 2253 submission is FDA Form 2253
- Raised File/Document Reference validations to High
  - 1306: No leaf element for file (orphan file)
  - 1323: No file for leaf element

eCTD v4.0 Update – ICH M8 Activities

- ICH eCTD v4.0 Implementation Package
  - V1.4 June 2021
  - See Q&A Change Requests “Incorporated into Implementation package v1.4”
- Q&A/Change Requests
  - Approved
    - Keyword business rules and validation
    - Document Type keyword updates
  - Currently reviewing
    - UUID
    - Priority Number
    - Document Reference
- Regional Implementation Information posted on ICH eCTD v4.0 webpage
  - Regional planned Technical Pilots & Implementation Dates
  - Links to regional Implementation Documents

eCTD v4.0 Update – FDA Activities

- *eCTD v4.0 Technical Conformance Guide* and *FDA eCTD v4.0 Module 1 Implementation Package*
  - Posted February 2020 for public comment
  - Posted updates on January 26, 2021
- *Specifications for eCTD v4.0 Validation Criteria (June 2021)*
- *eCTD v4.0 Comprehensive Table of Contents Headings and Hierarchy (June 2021)*
- Software updates and testing
  - Currently testing eCTD v4.0 vendor software
  - Preparing for eCTD v4.0 Technical Pilot

eCTD v4.0 Update – FDA Implementation Strategy

- Initial release/acceptance for new applications in eCTD v4.0
  - Allows for development of eCTD v4.0 applications across regions
  - Perform testing with industry in 2022
  - Begin accepting new applications in eCTD v4.0 in 2023
- Future phases
  - Transition of current applications
  - Two-way communication

eCTD v4.0 Update – Technical Pilot

- The objective of this testing is to determine if the implementation satisfies the requirements in the technical specification and make any changes prior to accepting eCTD v4.0 submissions in the production environment.
- Identified companies to perform testing
- Technical Pilot Scope
  - Submission Scope
    - Original eCTD v4.0 applications and subsequent submissions (e.g., amendments, supplements)
    - Grouped eCTD v4.0 submissions
  - Enhancement Scope
    - Life-cycle (one-to-one, one-to-many, many-to-one)
    - Document reuse
    - Document ordering
    - Keyword modifications
    - “Group Title” Keyword

eCTD v4.0 Update – How to Prepare

- Discuss eCTD v4.0 development plans with your vendor and/or IT organization
  - Understanding the specifications
  - Is there a plan for transitioning to eCTD v4.0?
  - Send questions to ICH M8 or FDA
- Become familiar with eCTD v4.0 concepts and enhancements
  - ICH Supplemental Documents for eCTD v4.0
    - Support Documentation for eCTD v4.0 Implementation Package - Explains contents enclosed in the Implementation Package. The target audience is business and technical personnel who build and/or review the eCTD v4.0 XML Messages and Transition Mapping Messages.
    - Orientation Material for eCTD v4.0 Implementation Package - Provides an outline of eCTD v4.0 concepts from business perspective. The target audience is business personnel and management involved in any aspect of eCTD submission design and preparation.
  - FDA eCTD v4.0 Technical Conformance Guide
- Know where to find the eCTD v4.0 information

eCTD V4.0 Websites

- ICH eCTD v4.0 Webpage (https://www.ich.org/page/ich-electronic-common-technical-document-ectd-v40)
  - ICH eCTD v4.0 Implementation Package
  - Supplemental Documents for eCTD v4.0 Implementation Package
  - Regional Implementation Information & Regional Links
  - Change Control
    - Process
    - Change Requests & Questions
    - Q&A document
- FDA eCTD v4.0 Webpage

  (https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd-v40)
  - FDA eCTD v4.0 M1 Implementation Package
  - eCTD v4.0 Technical Conformance Guide
  - Link to ICH eCTD v4.0 webpage

Thank you

INDUSTRY COMMENT

eCTD

eCTD

Industry Panelists

John Ferguson
Director, Regulatory Operations
Novo Nordisk Inc.

Teresa Martins
Senior Director, US Head Regulatory Submission Management
Bayer Pharmaceuticals

Faizan Rahim
Senior Regulatory Submissions Manager
Roche

eCTD

Benefits

- eCTD 3.2.2 has been a standard for industry submissions around the world, and continues to be adopted by countries
- eCTD 4.0 is expected to advance regulatory submission and review
  - More representative hierarchy of the business process of submissions
  - Enhanced life-cycle control
  - Reuse of content / previously submitted documents
  - Two-way communication

PDUFA VI Accomplishments

- Updating and maintaining software names and versions for eCTD validation and data validation tools
- Opportunity to participate in pilot testing
  - Promotional submissions
  - eCTD 4.0 vendor tools/submissions

PhRMA
RESEARCH + PROGRESS + HOPE

eCTD

Challenges/Questions

- Variability in global implementation
  - Supporting eCTD 3.2.2 and 4.0 in parallel across different regions
  - Ensuring a globally harmonized approach to implement the transition

- Earlier vendor engagement
  - Potential uncertainty for vendors developing tools for eCTD 4.0 and industry being able to take full advantage of the new standard

- Future of eCTD
  - Two-way communication timeline
  - 3rd party cloud-based platforms, real time data review processes, moving to data-oriented sections of the eCTD, and work sharing with other authorities

eCTD

Recommendations/Opportunities

- Roll-out of two-way communication
  - Develop a roadmap for implementation outside of eCTD v4.0
- Continued collaboration within ICH M8 to ensure global implementation and harmonization of eCTD 4.0
- Opportunity to collaborate on future eCTD4.0 pilot(s)
- PDUFA VII commitment – develop a Data and Technology Modernization Strategy
  - Recommend to address how eCTD 4.0 complements other data-driven regulatory initiatives (3rd party cloud-based platforms, PQ/CMC, IDMP, real-time data review, etc.)

PUBLIC COMMENT

U.S. FOOD & DRUG ADMINISTRATION

FDA Study Data Technical Rejection Update

PDUFA VI

Quarterly Meeting

April 12, 2022

Electronic Submission Guidance

"**Study Data Guidance**" - *Providing Regulatory Submissions in Electronic Format -- Standardized Study Data (last updated June 2021)*

- **Sponsors must conform to standards in the FDA Data Standards Catalog:**
  - CDER & CBER Clinical Studies
    - NDA, BLA, ANDA studies that started after December 17th, 2016
  - CDER Non-clinical Studies
    - NDA, BLA, ANDA studies that started after December 17th, 2016
    - Commercial IND studies that started after December 17th, 2017
  - CBER Non-clinical studies
    - NDA, BLA, ANDA, and Commercial IND studies that started after March 15, 2023
- **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 Specification for eCTD Validation Criteria.

For more information on how to submit and what will be validated, see the documents below:

- Study Data Technical Conformance Guide – Latest update March 2022
- Study Data for Submission to CDER and CBER website

eCTD Validation Updates

- Study Data Validation Effective Date updated:

  9/15/2021 (CBER module 4 sections, 03/16/2023)

Error	Description
1734	A dataset named ts.xpt with information on study start date must be present for each study in required sections*
1735	Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*
1736	For SEND data, DM dataset and define.xml must be submitted in Module 4 required sections* For SDTM data, DM dataset and define.xml must be submitted in Module 5 required sections* For ADaM data, ADSL dataset and define.xml must be submitted in Module 5 required sections*
1737	For each study in required sections, no more than one dataset of the same name should be submitted as new*

** Module 4 sections: 4.2.3.1, 4.2.3.2, 4.2.3.4*
Module 5 sections: 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

Please review eCTD Validation Specification all details are not included in this presentation

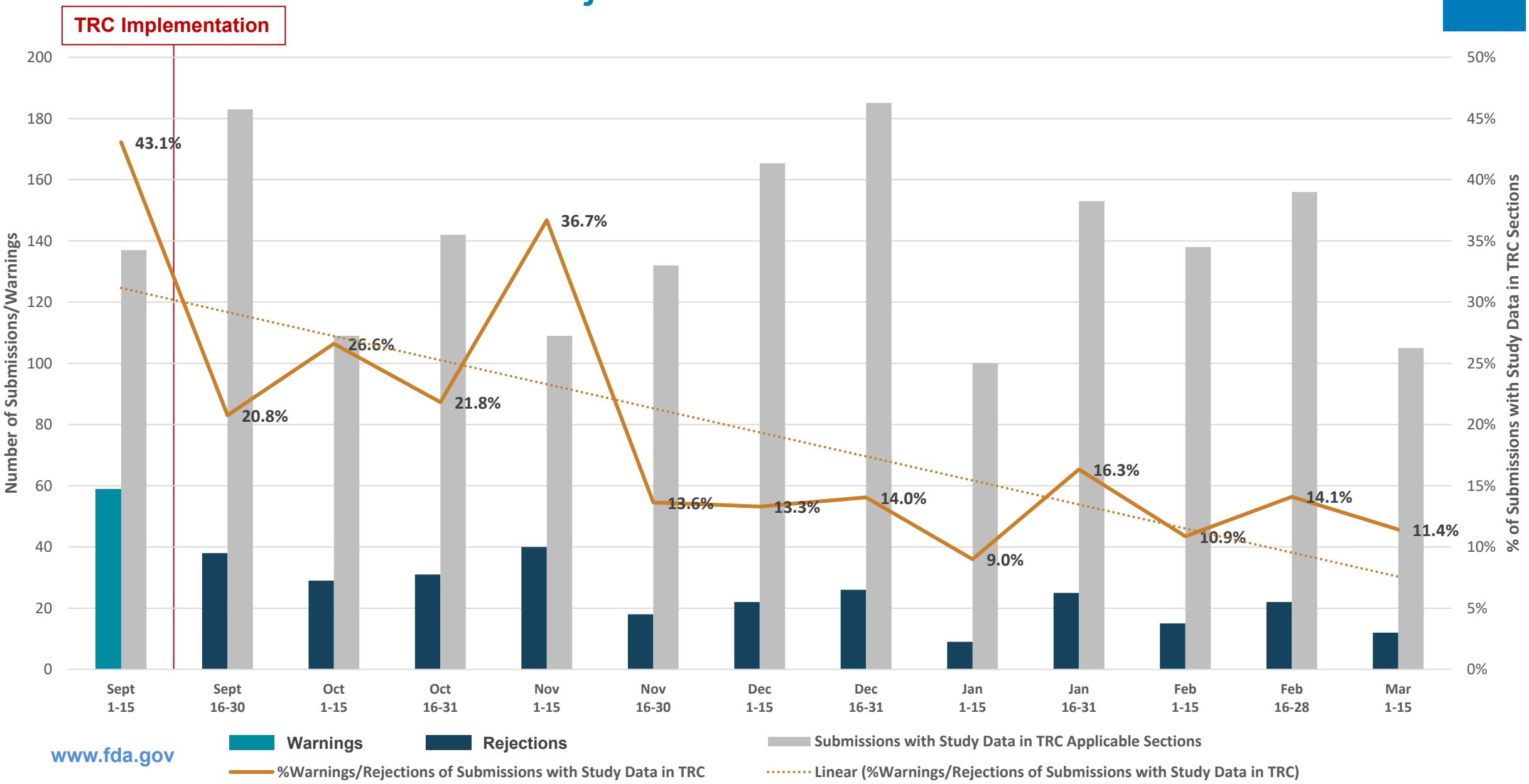
eCTD Validation Updates

eCTD validation rule 1789 has a different expectations than 1734, 1735, and 1736.

Error	Description
1789	A file has been submitted in a study section without providing an STF file. STFs are not required for 4.3 Literature references, 5.2 Tabular listings, 5.4 Literature references and 5.3.6 Postmarketing reports

- 1789 applies to all subsections of modules 4 and 5 except:
  - sections 4.3, 5.2, 5.4, and 5.3.6
- An STF must be provided for all applications and data types for both CDER and CBER regardless of study start date

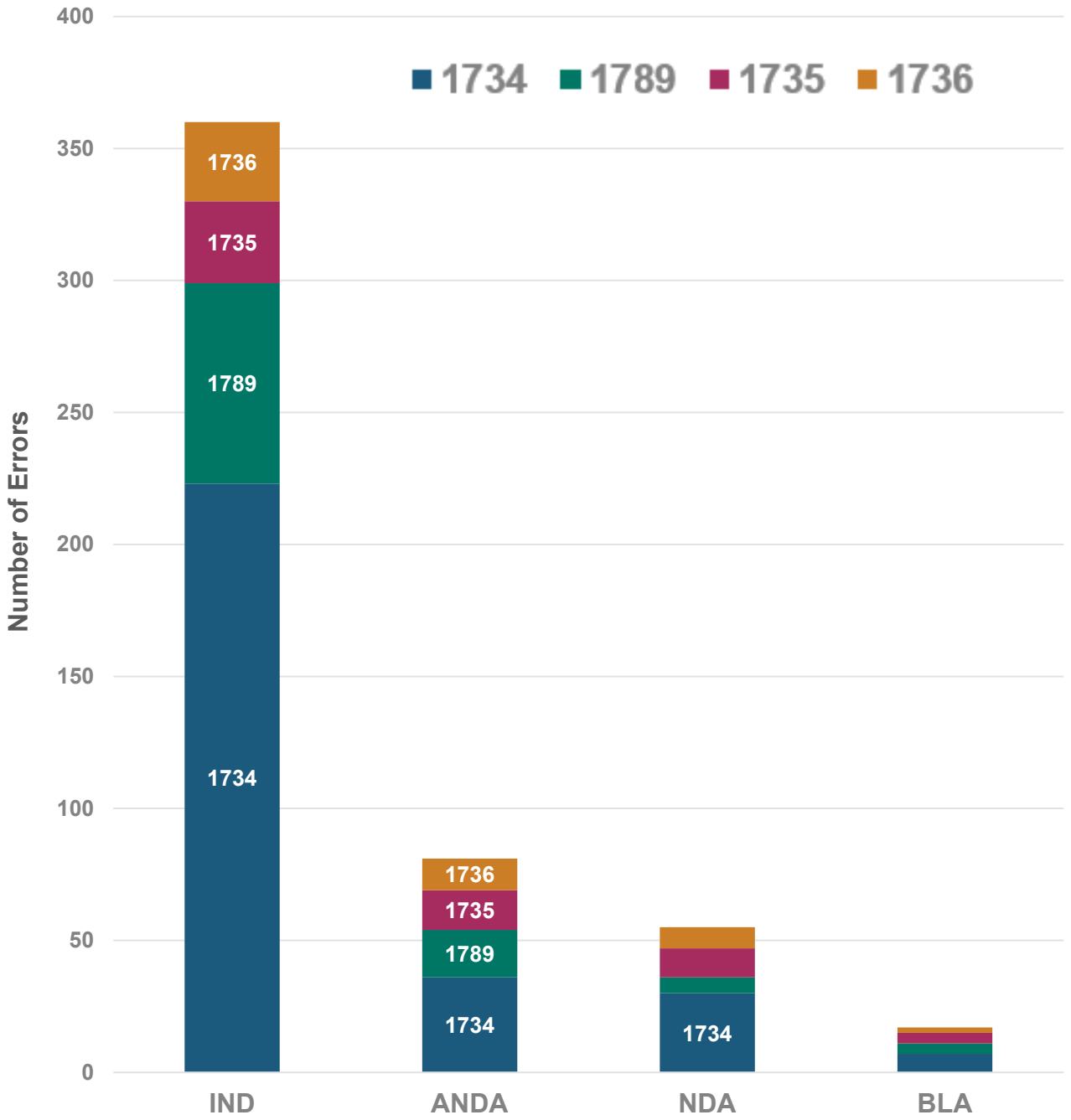
CDER Trend of TRC Rejections



www.fda.gov

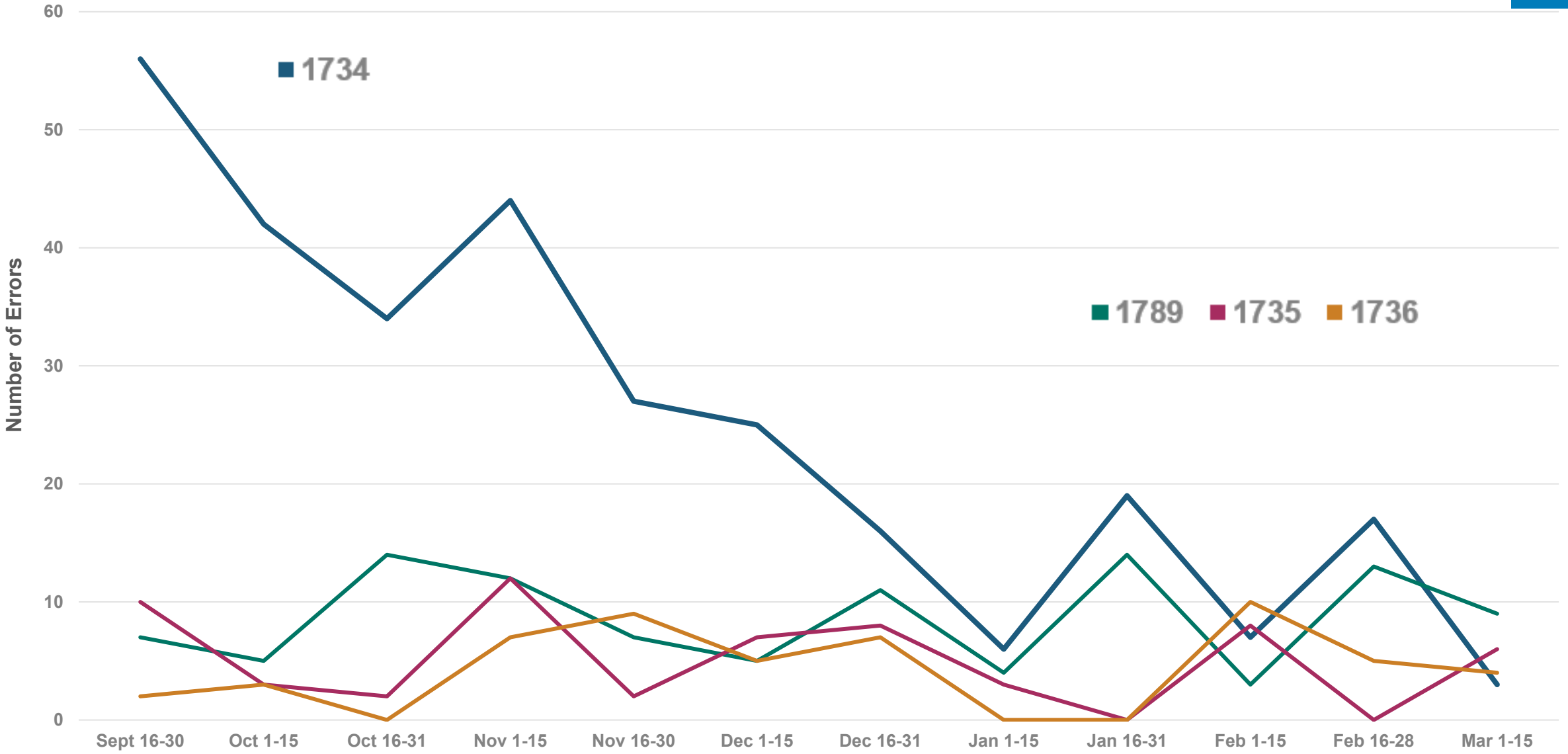
CDER TRC Rejections

- 1734 is the most common error and failure reason for all application types for a missing ts.xpt
- 1789 is the second most common error and failure reason
- Commercial IND submissions have highest number of failures overall and have particularly high numbers of both 1734 and 1789 errors



Notes: *Metrics generated from data between September 15, 2021 and March 15, 2022*

CDER Trend by Error Reason

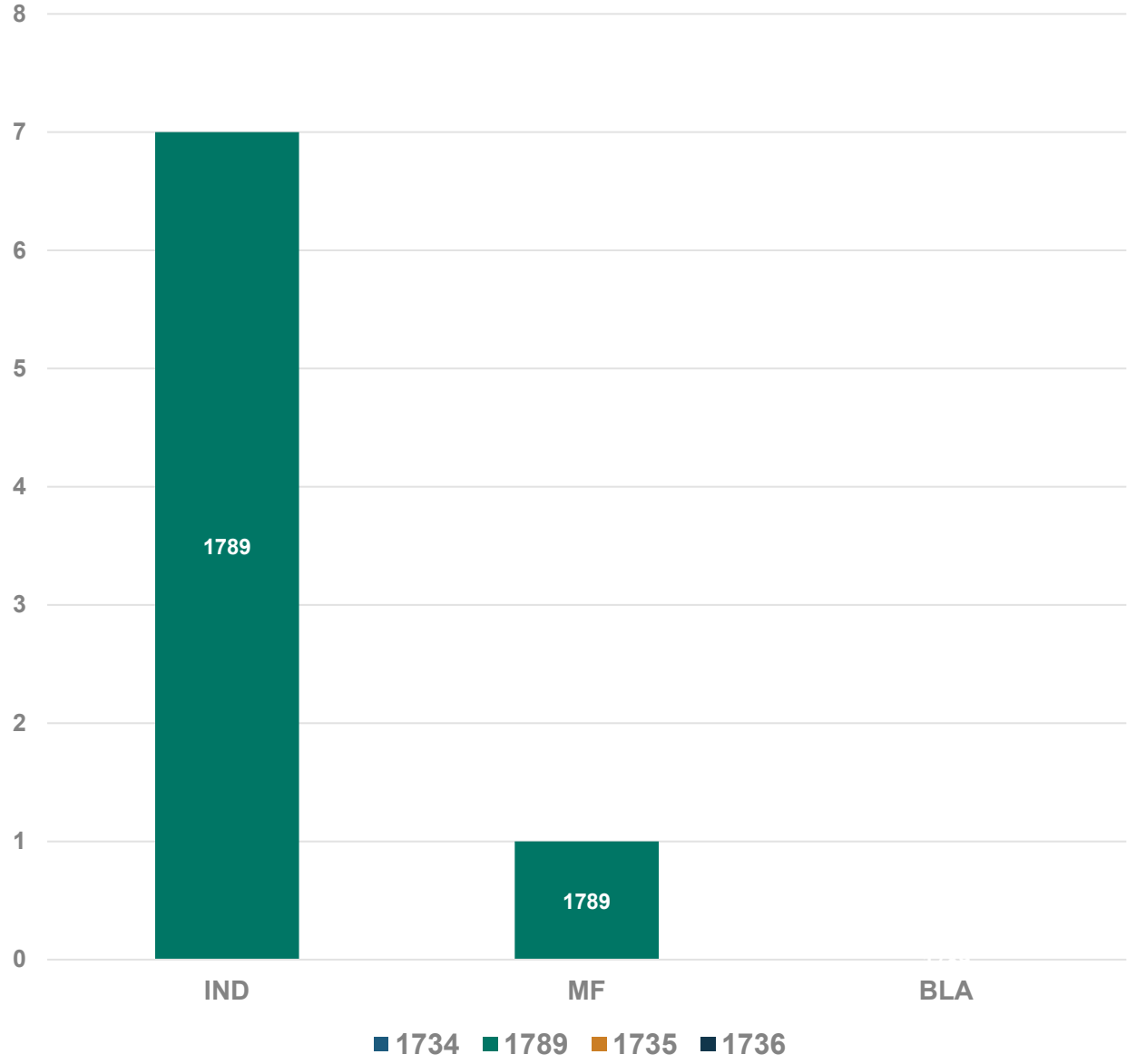


www.fda.gov

Notes: *Metrics generated from data between September 15, 2021 and March 15, 2022*

CBER Study Rejections (Total)

- 1789 has been the only study data validation rejected upon for CBER



Notes: *Metrics generated from data between September 15, 2021 and March 15, 2022*

Addressing Top Errors: 1734

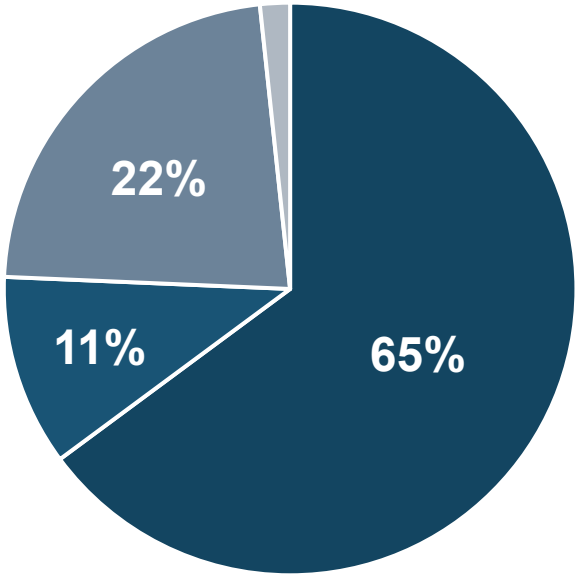
- **58% of errors across Application Types**
- **62% of errors for IND Applications**

1734 Validation

A dataset named ts.xpt with information on study start date must be present for each study in required sections*

- ✓ Trial Summary Dataset (ts.xpt) is present
- ✓ Study ID (or SPREFID) matches STF Study ID
- ✓ Study start date is provided (or TSVALNF = NA)
- ✓ Study start date is in a valid format

22% due to Study ID Mismatch



65% due to Missing ts.xpt

86% of Missing ts.xpt 1734 Errors are for Non-Clinical Studies in M4

- No ts.xpt found for this study
- Study ID in ts.xpt does not match study ID from STF
- No ts.xpt with value for SSD found (and no null flavor value)
- Study start date is incorrectly formatted and TSVALNF has no null flavor value

Note: 296 1734 Study Errors between Sept. 15 – Mar. 15, 2022

VERIFYING STUDY DATA EXPECTATIONS FOR RULES 1734, 1735, & 1736

Application Type	Data Type	Modules & Sub-Modules	Expectation by CDER	Expectation by CBER
NDA, BLA, ANDA	Non-Clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	*Study Start Date: On or prior to 2016-12-17* Rejection criteria will be applied if a study report with the proper file tags and/or an xpt file is submitted. Submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)	***Study Start Date: On or prior to 2023-03-15*** **Rejection criteria will be applied if a study report with the proper file tags and/or an xpt file is submitted. Submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)**
NDA, BLA, ANDA	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	*Study Start Date: On or prior to 2016-12-17* Rejection criteria will be applied; submit a simplified TS if the study contains an xpt dataset (other than the ts.xpt)	
Comm. INDs	Non-Clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	*Study Start Date: On or prior to 2017-12-17* Rejection criteria will be applied if a study report with the proper file tags and/or an xpt file is submitted. Submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)	***Study Start Date: On or prior to 2023-03-15*** **Rejection criteria will be applied if a study report with the proper file tags and/or an xpt file is submitted. Submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)**
Comm. INDs	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	*Study Start Date: On or prior to 2017-12-17* Rejection criteria will not be applied	
NDA, BLA, ANDA	Non-Clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	*Study Start Date: After 2016-12-17* Rejection criteria will be applied; submit a full TS	***Study Start Date: After 2023-03-15*** **Rejection criteria will be applied; submit a full TS**
NDA, BLA, ANDA	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	*Study Start Date: After 2016-12-17* Rejection criteria will be applied; submit a full TS with standardized data	
Comm. INDs	Non-Clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	*Study Start Date: After 2017-12-17* Rejection criteria will be applied; submit a full TS	***Study Start Date: After 2023-03-15*** **Rejection criteria will be applied; submit a full TS**
Comm. INDs	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	*Study Start Date: After 2017-12-17* Rejection criteria will not be applied	

Addressing Top Errors: 1789

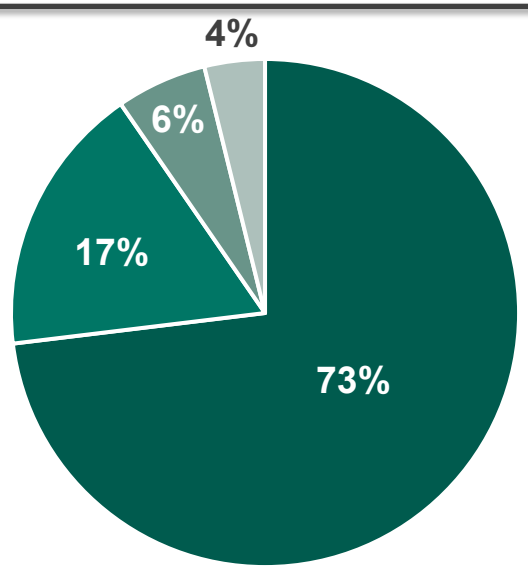
- **20% of errors across Application Types**
- **21% of errors for IND Applications**

1789 Validation:

A file has been submitted in a study section without providing an STF file (STFs are not required for 4.3 Literature references, 5.2 Tabular listings, 5.4 Literature references and 5.3.6 Postmarketing reports).

✓ All study files are included in a Study Tagging File (STF)

17% of all 1789 Errors for ANDA Applications



73% of all 1789 Errors for IND Applications

When placing files in applicable sections within Modules 4 and 5, they should also be referenced within an STF for the study to which they belong.

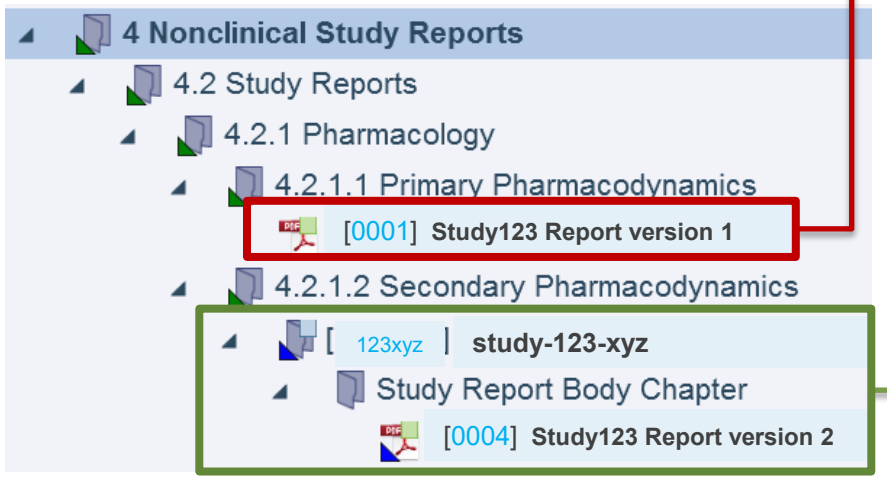
Note: 104 1789 Submission Errors between Sept. 15 – Mar. 15, 2022

Impacts & Improvements from Standardized Study Data

Why is 1789 important?

Each study has its own stf.xml file with a unique study id and study title. When files are not referenced in a study tagging file they will not be connected to a specific study and may lead to reviewers not being able to find or review the data.

eCTD Viewer:

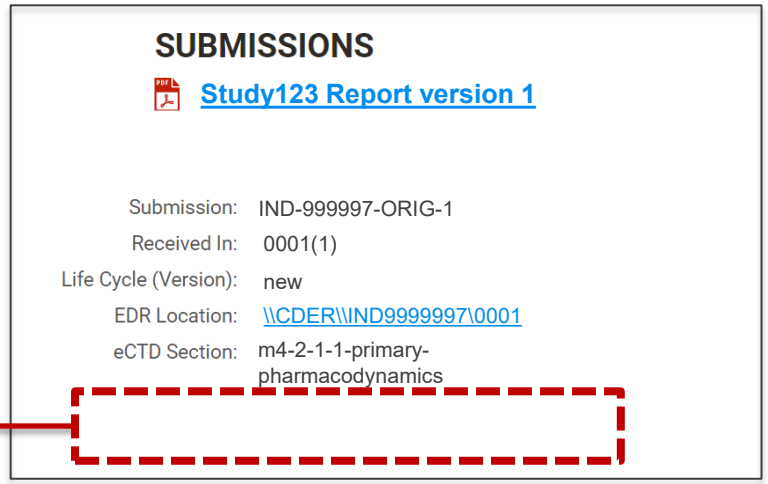


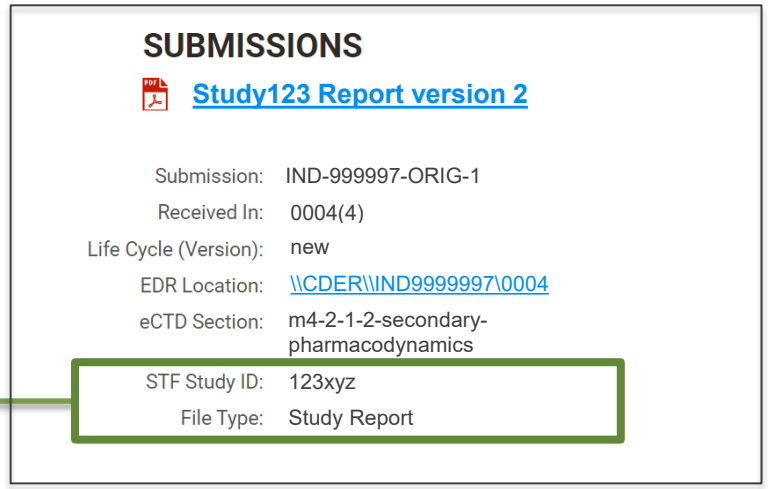
Unorganized and not connected to a study

Organized by Study Title and ID

File Tags indicate file types

Search:



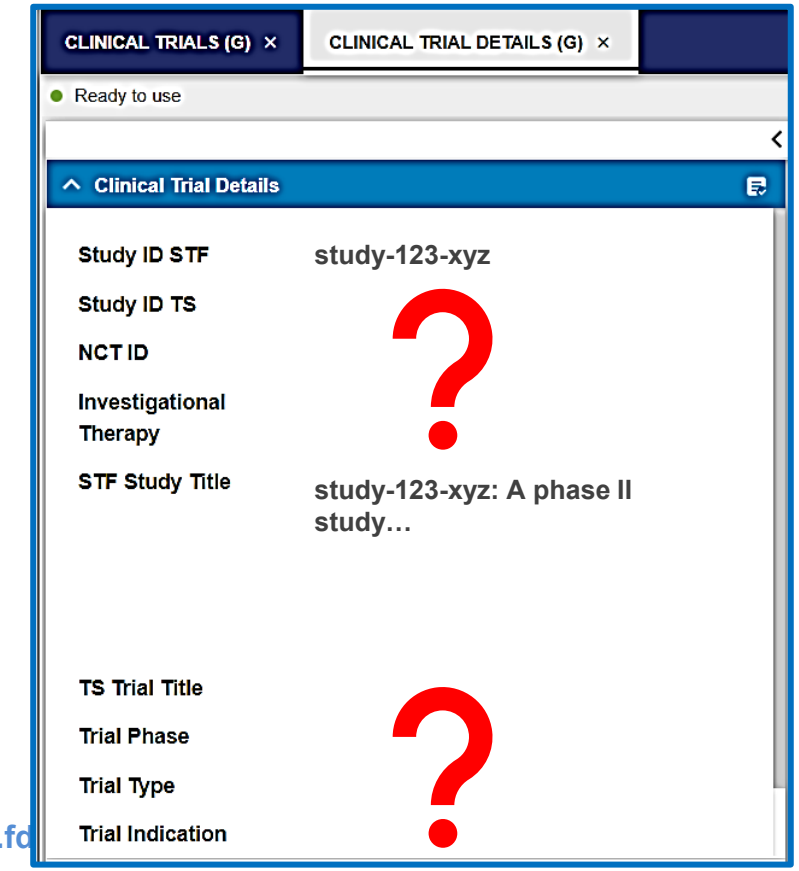


Why is 1734 important?

Missing ts.xpt:

X Can't determine the study start date, if TRC applies and whether standardized datasets are required

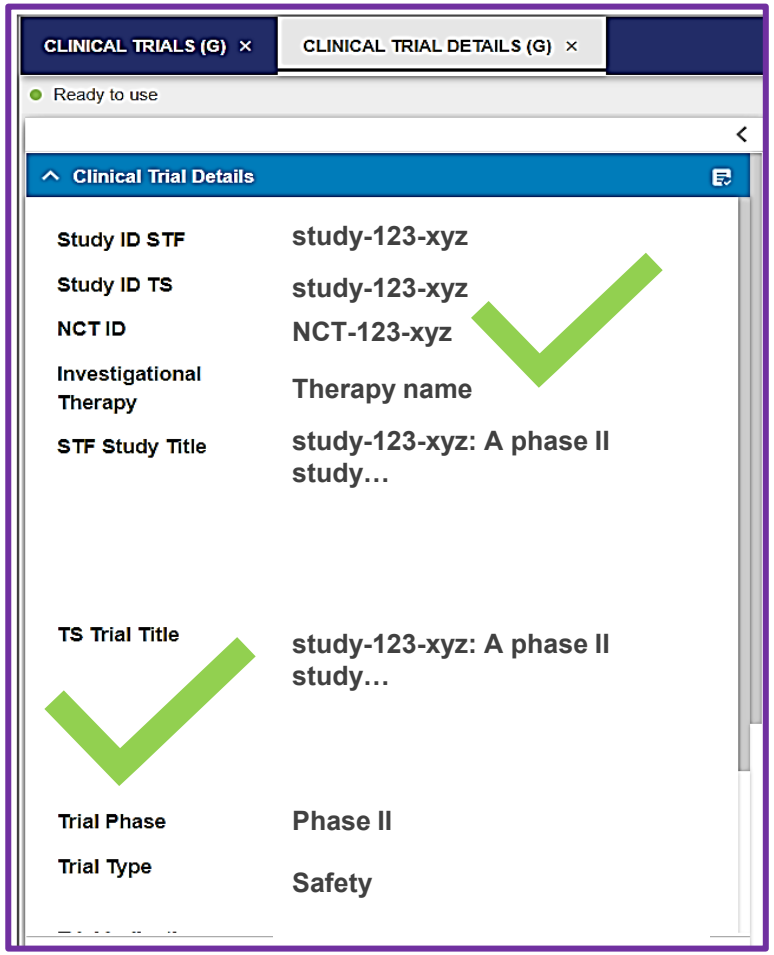
X Cannot connect to other clinical trial data and limits details available to reviewers



When a ts.xpt is included:

✓ Enables detailed searches

✓ Enables connections between data sources, such as ClinicalTrials.gov using NCT number



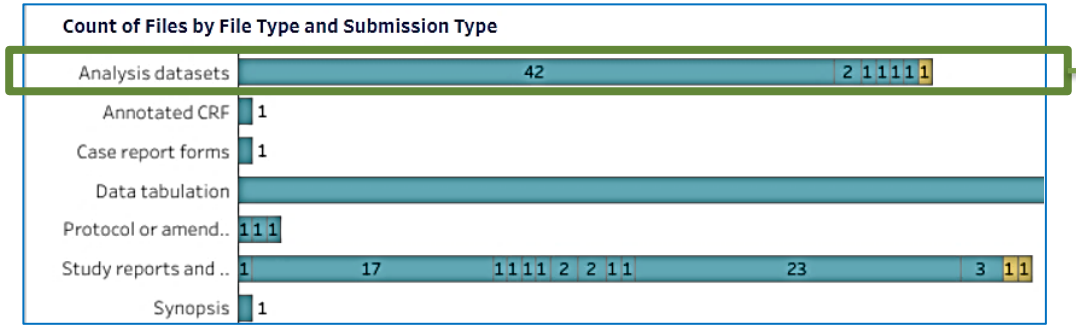
Why are 1735 & 1736 important?

File tags act as standardized sub-headings within a study to help distinguish and group files based on content.

When datasets are provided and tagged correctly:

- ✓ Enables detailed searches by file type
- ✓ Enables filtering by file type
- ✓ Enables locating essential study files, including dm.xpt, adsl.xpt, and define.xml
- ✓ Enables automated loading into analysis applications

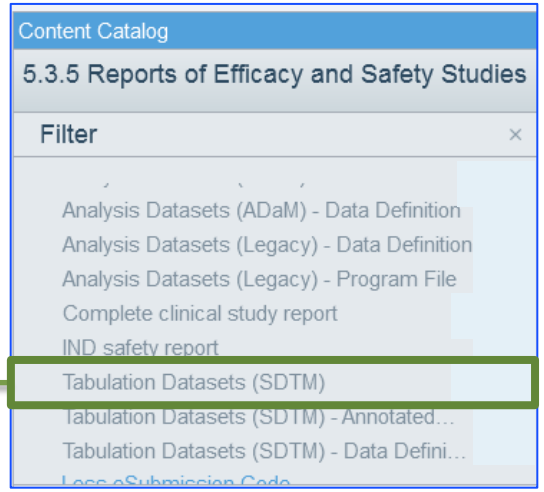
Reports & Filtering:

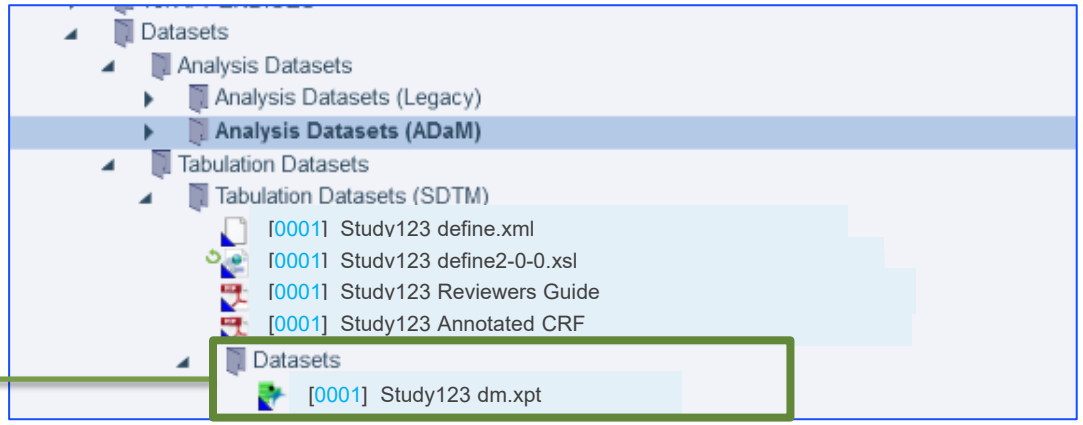


ADaM Datasets Grouped

eCTD Viewer:

SDTM Datasets Grouped





References

- **Study Data Standards Resources**
  - Providing Regulatory Submissions In Electronic Format - Standardized Study Data: Guidance For Industry [June 2021]
  - Study Data Technical Conformance Guide [March 2022]
  - FDA Data Standards Catalog [September 2021]
  - Link: https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources

- **Study Data for Submission to CDER and CBER**
  - Technical Rejection Criteria Self-Check Worksheet
  - Technical Rejection Criteria Self-Check Worksheet Instructions
  - Link: https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

- **Electronic Common Technical Document (eCTD)**
  - Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications: Guidance for Industry [February 2020]
  - eCTD Submission Standards [March 2022]
  - Specifications for eCTD Validation Criteria [March 2022]
  - Link: https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd

- **Providing Regulatory Submissions In Electronic Format - Submissions Under Section 745a(a) Of The FD&C Act: Guidance For Industry**
  - Link: https://www.fda.gov/regulatory-information/search-fda-guidance-documents

INDUSTRY COMMENT

PUBLIC COMMENT


Thank
You