# Public Meeting on Prescription Drug User Fee Act (PDUFA) VI:

# Electronic Submissions and Data Standards

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U.S. Food and Drug Administration

April 7, 2021

# PDUFA VI Federal Register Notice*

- FDA announced the public meeting in the Federal Register on January 15, 2021 (FDA-2018-N-4337).

- No comments were submitted to the docket by March 7th cutoff.

- No requests to speak were received by the March 7th cutoff.

*https://www.federalregister.gov/documents/2021/01/15/2021-00831/prescription-drug-user-fee-act-of-2017-electronic-submissions-and-data-standards-public-meeting

# PDUFA VI Commitment Letter

**PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018 THROUGH 2022**

I. ENSURING THE EFFECTIVENESS OF THE HUMAN DRUG REVIEW PROGRAM
- A. Review Performance Goals
- B. Program For Enhanced Review Transparency And Communication For NME NDAs And Original BLAs
- C. First Cycle Revis
- D. Review Of Pr
- E. Major Dispu
- F. Clinical Hol
- G. Special Proto
- H. Meeting Ma
- I. Enhancing R
- J. Enhancing R Review
- K. Enhancemen

II. ENHANCING MAN
- A. Resource Ca
- B. Financial Tra

III. IMPROVING FDA E
- A. Completion O Augmentation Of
- B. Augmentation Of Hiring Staff Capacity And Capability
- C. Complete Establishment Of A Dedicated Function To Ensure Needed Scientific Staffing For Medical Product Review
- D. Set Clear Goals For Drug Review Program Hiring
- E. Comprehensive And Continuous Assessment Of Hiring And Retention

IV. INFORMATION TECHNOLOGY GOALS
- A. Objective
- B. Improve The Predictability And Consistency Of PDUFA Electronic Submission Processes
- C. Enhance Transparency And Accountability Of FDA Electronic Submission And Data Standards Activities

V. IMPROVING FDA PERFORMANCE MANAGEMENT

VI. PROGRESS REPORTING FOR PDUFA VI AND CONTINUING PDUFA V INITIATIVES

VII. DEFINITIONS AND EXPLANATION OF TERMS

**IV. INFORMATION TECHNOLOGY GOALS**
- A. Objective
- B. Improve The Predictability And Consistency Of PDUFA Electronic Submission Processes
- C. Enhance Transparency And Accountability Of FDA Electronic Submission And Data Standards Activities

https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

# PDUFA VI Commitment Letter
# Section IV Information Technology Goals

## Public Meeting Goal

"Beginning no later than *September 30, 2018*, FDA will hold *annual* public meetings to seek stakeholder input related to electronic submission system past performance, future targets, emerging industry needs and technology initiatives to inform the FDA IT Strategic Plan and published targets."

# Today's Meeting

- All will be muted upon entry and during the meeting
- Meeting is being recorded and the slides will be available at the FDA webpage: **PDUFA VI Information Technology Goals and Progress**
- We will progress to the next topic at the scheduled time or when the speakers have finished and there are no further comments.
- Your comments / questions will be captured in the chat. We will try to read them in order of submission. Due to time, we may not be able to read all comments / questions.

# Agenda

## Topic 1

**9:10 – 10:10 am** **Electronic Submissions Gateway**

**Lowell Marshall**
IT Program Manager, ESG
Office of Information Management and Technology (OIMT)
FDA

**Srini Palle**
ESG Program Manager Contractor
Assyst

**Vishu Manegari**
Senior Director, Regulatory Operations
Gilead Sciences

**Peter Goodwin**
Global Team Lead, Regulatory Submissions Group
Roche/Genentech

**John Ferguson**
Director, Regulatory Operations
Novo Nordisk Inc.

**Open Public Comment**

# Agenda

## Topic 2

**10:10 – 11:10 am** **PQ/CMC Data Standards**

**Norman Schmuff**
Associate Director
Office of Pharmaceutical Manufacturing Assessment, Office of Pharmaceutical Quality

**Clarice Hutchen**
Senior Director, GCMC Advisory Office
Pfizer

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

**Rodrigo Palacios**
Associate Director, Global Regulatory Policy
Genentech

**Open Public Comment**

**11:10 – 11:30 pm** **Break**

# Agenda

## Topic 3

**11:30 – 12:30 pm** **Identification of Medicinal Products (IDMP)**

**TJ Chen**
Program Lead, IDMP
Office of Strategic Programs
CDER, FDA

**Larry Callahan**
GSRS Program Lead
Office of Health Informatics
Office of the Commissioner, FDA

**Vada Perkins**
Executive Director, Regulatory Policy & Intelligence (Global)
Bayer Pharmaceuticals

**Deanna Beckett**
Director, Regulatory Lifecycle and RIM
AbbVie

**Vanni Carapetian**
Regulatory Data Capability Lead
Genentech

**Open Public Comment**

**12:30-1:00 pm** **Lunch / Break**

# Agenda

## Topic 4

**1:00 – 1:30 pm** **IND Safety Reporting**

**Suranjan De**
Deputy Director, Regulatory Science Staff,
Office of Surveillance and Epidemiology, CDER, FDA

**Virginia Hussong**
Chief (acting), Data Standards
CBER, FDA

**Nicole Cocuzza**
Senior Manager, Regulatory Submissions
AbbVie

**Teresa Martins**
Senior Director, US Head Regulatory Submissions Management
Bayer Pharmaceuticals

**Open Public Comment**

# Agenda

**Topic 5**

**1:30 – 2:30pm** **eCTD**

**Mark Gray**
Senior Program Manager
Data Standards Staff, CBER, FDA

**David Isom**
Regulatory Policy and Intelligence, Global Regulatory Affairs
Pfizer

**Arvind Ala**
Regulatory Project Management, Global Regulatory Operations
EMD Serono

**Teresa Eastwood-Kiefer**
Regulatory Submission Group
Hoffmann-La Roche Ltd

**Open Public Comment**

**2:30 – 2:45 pm** **Break**

# Agenda

**Topic 6**

| | |
|---|---|
| **2:45 – 3:30 pm** | **Technical Rejection of Study Data** |
| | **Ethan Chen**<br>Director, DDMSS, OBI, OSP, CDER, FDA |
| | **Virginia Hussong**<br>Chief (acting), Data Standards, CBER, FDA |
| | **Open Public Comment** |
| **3:30 pm** | **Meeting Adjourned** |

*Please note that the meeting will progress to the next topic at the scheduled time or when the speakers have finished and there are no further comments.


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# FDA Electronic Submissions Gateway (ESG)

PDUFA VI

Public Meeting on

Electronic Submissions and Data Standards

April 7, 2021

Lowell Marshall, OIMT Program Manager

Srini Palle, Assyst Project Manager

# Agenda

- PDUFA VI Update
- System Enhancements – ESG Cloud

# ESG PDUFA VI Goals

| # | Goal | Target | Status |
|---|---|---|---|
| 1 | Publish target timeframes for the 1) expected submission upload duration(s) and 2) timeframe between key milestones and notifications. | Dec 2017 | Completed |
| 2 | Document and publish the Electronic submission process including key milestones and sponsor notifications . | Dec 2017 | Completed |
| 3 | Invite industry to provide feedback and/or participate in user acceptance testing in advance of implementing significant changes. | Dec 2017 | Completed |
| 4 | Document and implement a process to provide ample advance notification on systems and process changes. | Dec 2017 | Completed |
| 5 | Post, at least annually, historic and current metrics on ESG performance in relation to published targets, characterizations, and volume of submissions. | Dec 2017 | Completed |
| 6 | Publish targets for and measure ESG availability overall (including schedule downtime) and during business hours (8am to 8pm). | Sept 2018 | Completed |
| 7 | Communicate electronic submission milestone notifications, including final submission upload status (Note: Acknowledgements) | Sept 2018 | Completed |
| 8 | Post current ESG operational status on its public website. | Sept 2018 | Completed |
| 9 | Publish submission instructions in the event of an ESG service disruption. | Sept 2018 | Completed |

# ESG Cloud – Introduction

## Phase 1: Account Portal and Virus Scanning

- Enhanced User Experience
- Enhanced Security

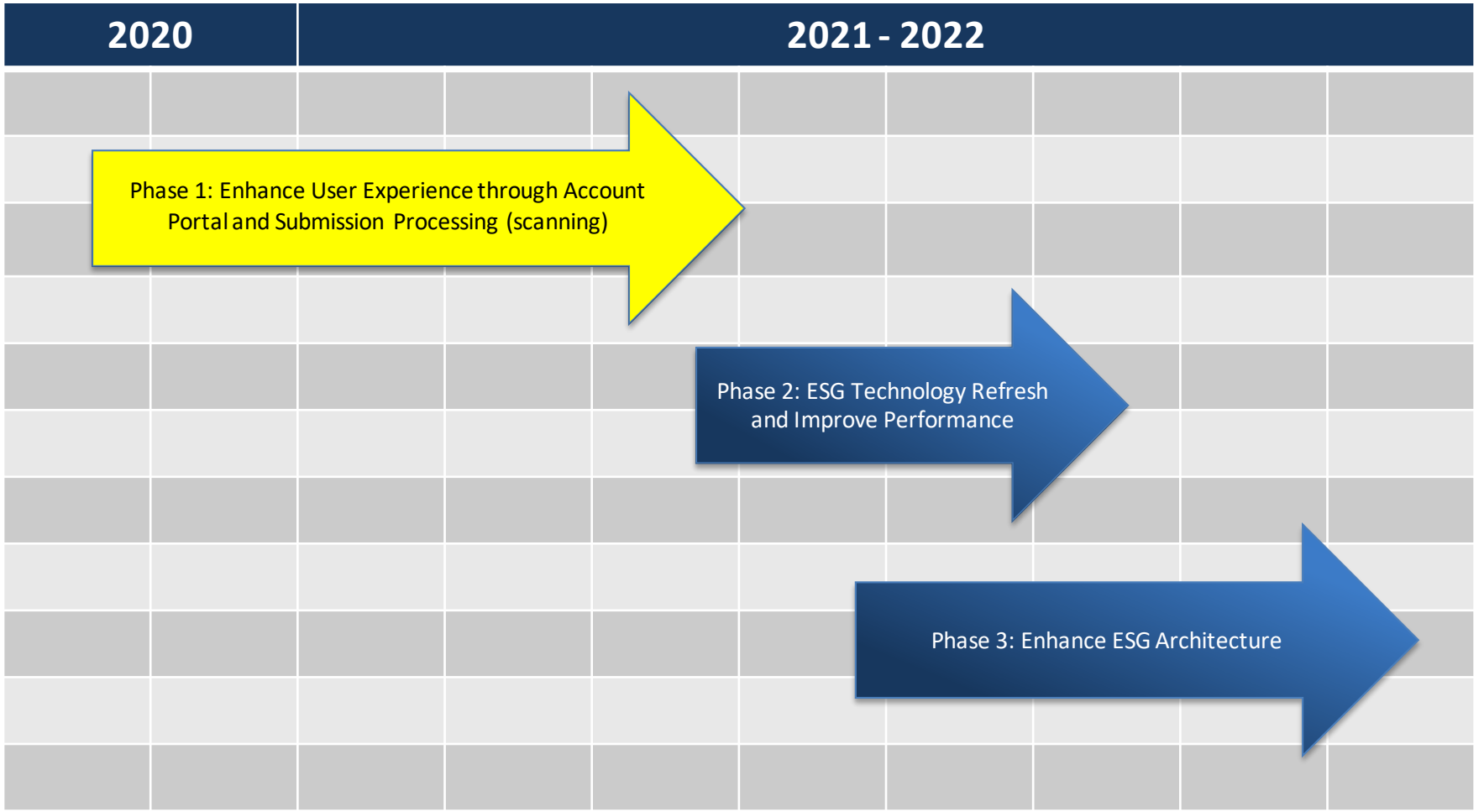
## Phase 2: ESG Core Technology Refresh

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

## Phase 3: Enhanced ESG Architecture

- Streamlined Submission Processing

# ESG Cloud Target State – High Level Timeline



# Phase 1 - Account Portal & Virus Scanning

## ESG 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.

## Virus/Malware Scanning:

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

# Phase 1 - Account Portal & Virus Scanning

## Account Portal 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 Features:

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

# Phase 1 - Account Portal & Virus Scanning: Industry Benefits

## Account Portal

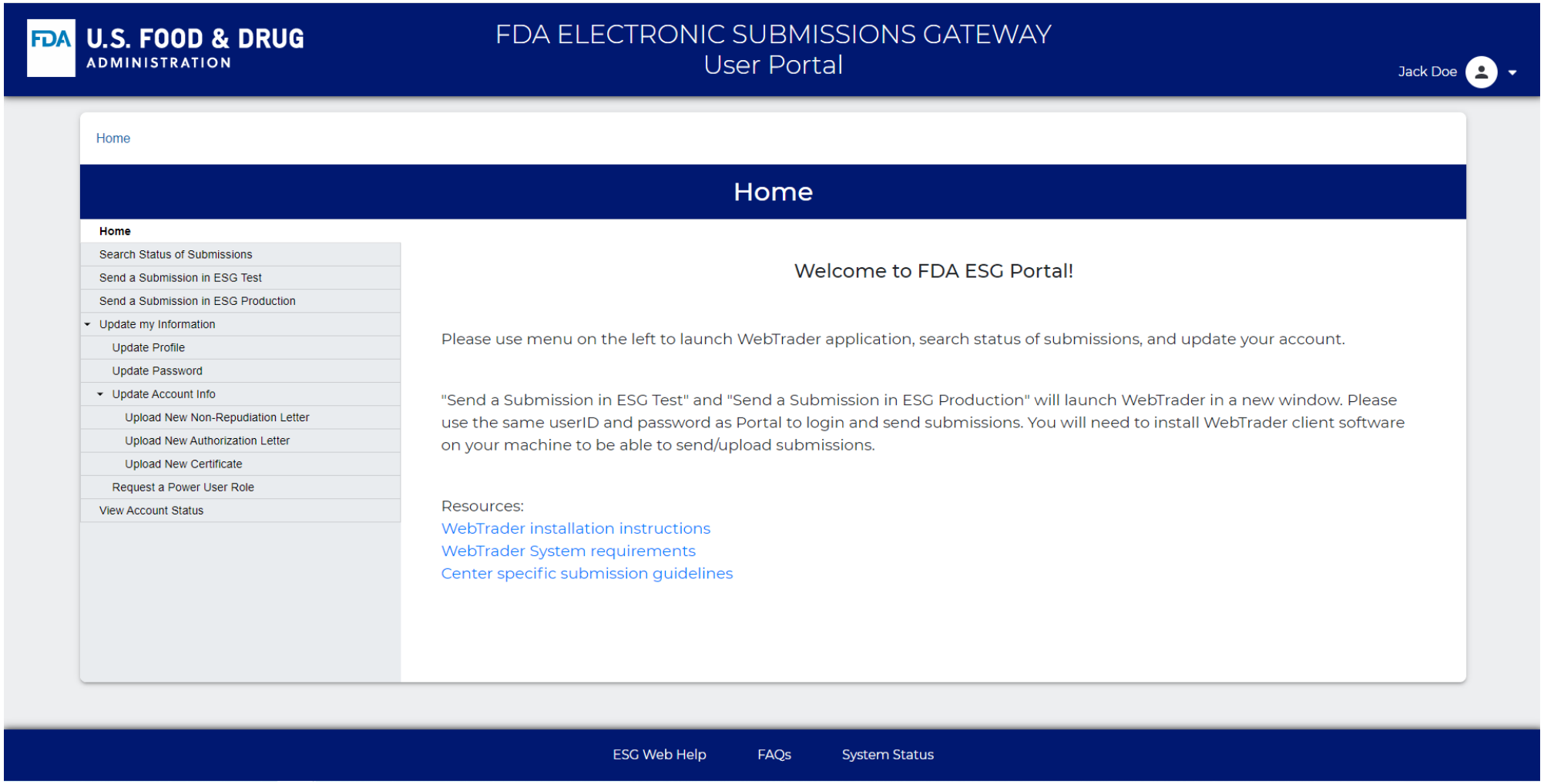
- Automate Industry account registration and approval process aims to reduce onboarding time
- Create ability for users to perform self-service functions such as password reset, unlock accounts, upload and create certificates, and submission tracking
- Industry Power Users allows companies to manage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

## Submission Scanning

- Enhance submission security by adding automated scanning prior to storing in FDA environment

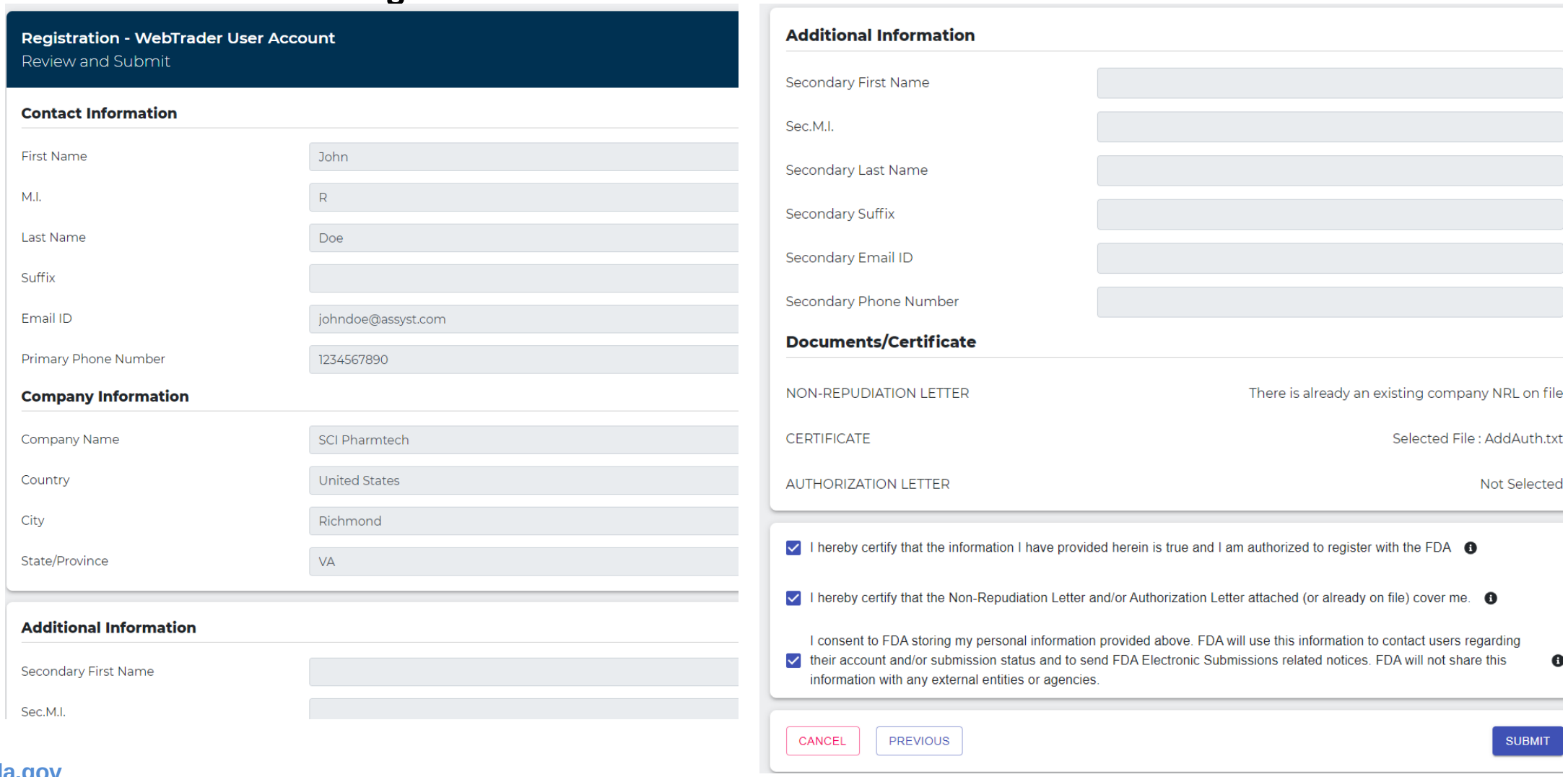
# Phase 1 - Account Portal & Virus Scanning: Industry Benefits

## Account Portal - **WebTrader**



# Phase 1 - Account Portal & Virus Scanning: Industry Benefits

## Account Portal – **WT Registration**



**Registration - WebTrader User Account**
Review and Submit

**Contact Information**

| | |
|---|---|
| First Name | John |
| M.I. | R |
| Last Name | Doe |
| Suffix | |
| Email ID | johndoe@assyst.com |
| Primary Phone Number | 1234567890 |

**Company Information**

| | |
|---|---|
| Company Name | SCI Pharmtech |
| Country | United States |
| City | Richmond |
| State/Province | VA |

**Additional Information**

| | |
|---|---|
| Secondary First Name | |
| Sec.M.I. | |

**Additional Information**

| | |
|---|---|
| Secondary First Name | |
| Sec.M.I. | |
| Secondary Last Name | |
| Secondary Suffix | |
| Secondary Email ID | |
| Secondary Phone Number | |

**Documents/Certificate**

| | |
|---|---|
| NON-REPUDIATION LETTER | There is already an existing company NRL on file |
| CERTIFICATE | Selected File : AddAuth.txt |
| AUTHORIZATION LETTER | Not Selected |

- [x] I hereby certify that the information I have provided herein is true and I am authorized to register with the FDA
- [x] I hereby certify that the Non-Repudiation Letter and/or Authorization Letter attached (or already on file) cover me.
- [x] I consent to FDA storing my personal information provided above. FDA will use this information to contact users regarding their account and/or submission status and to send FDA Electronic Submissions related notices. FDA will not share this information with any external entities or agencies.

CANCEL PREVIOUS SUBMIT

# Phase 1 - Account Portal & Virus Scanning: Industry Test Plan

- FDA ESG will collaborate with PhRMA to test Account Portal and File Scanning
- Multiple users from multiple companies
- A detailed test plan with dates will be shared with PDUFA/UAT group. Industry will have a chance to comment on test plan
- Test schedule will be shared with UAT group for planning
- Thank you for your participation and collaboration!

| UAT Plan | |
|---|---|
| **File Scanning** | **Account Portal Functionality** |
| • Simulate necessary load and capture performance metrics and assess the impact, if any, on file processing times<br>• File scanning from both AS2 and WebTrader account holders | • Validate onboarding functionality<br>• Validate Power-User functionality<br>• Validate Self-Service features |

# Phases 2 and 3 - ESG Cloud Initiative Benefits

## Phase 2 – ESG Technology Refresh and Improved Performance

- Modernize ESG on-prem infrastructure with AWS GovCloud environment
- 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"

*Note: TMAP is available for download at https://www.fda.gov/media/130883/download

# Help Desk and Website Resources

Website: http://www.fda.gov/esg/ Help Desk: ESGHelpDesk@fda.hhs.gov

ESG Submission Times
https://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/AboutESG/ucm590817.htm

ESG Submission Process
https://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/AboutESG/ucm572950.htm

ESG What's New
https://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm

Submission Statistics
https://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/AboutESG/ucm110653.htm

Outage Notification and Disruption Policy
https://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/PoliciesGuidance/ucm610190.htm

Planned Maintenance
https://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/AboutESG/ucm367545.htm

FDA's TMAP
https://www.fda.gov/news-events/fda-voices/fdas-technology-modernization-action-plan-accelerates-path-enhancing-and-promoting-people-first

# ESG Cloud

**Questions**

# Thank you

# FDA's Structured Quality Data: PQ/CMC & KASA Initiatives

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

FDA Public Meeting on Electronic Submissions and Data Standards

Wednesday 7 April 2021 AD

# Outline

- Current/future submission & assessment model
- PQ/CMC*
- Comments on the 2017 Federal Register Notice
- KASA
- ICH
- IDMP
- Current & future activities
- Challenges

*PQ/CMC: Pharmaceutical Quality/Chemistry, Manufacturing and Controls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# Take Away Messages

- PQ/CMC: standardize & structure eCTD **submissions** using XML and HL7 FHIR.
- KASA: structure **assessments** through pre-populated templates, and risk-ranking algorithms
- KASA depends on PQ/CMC for template pre-population


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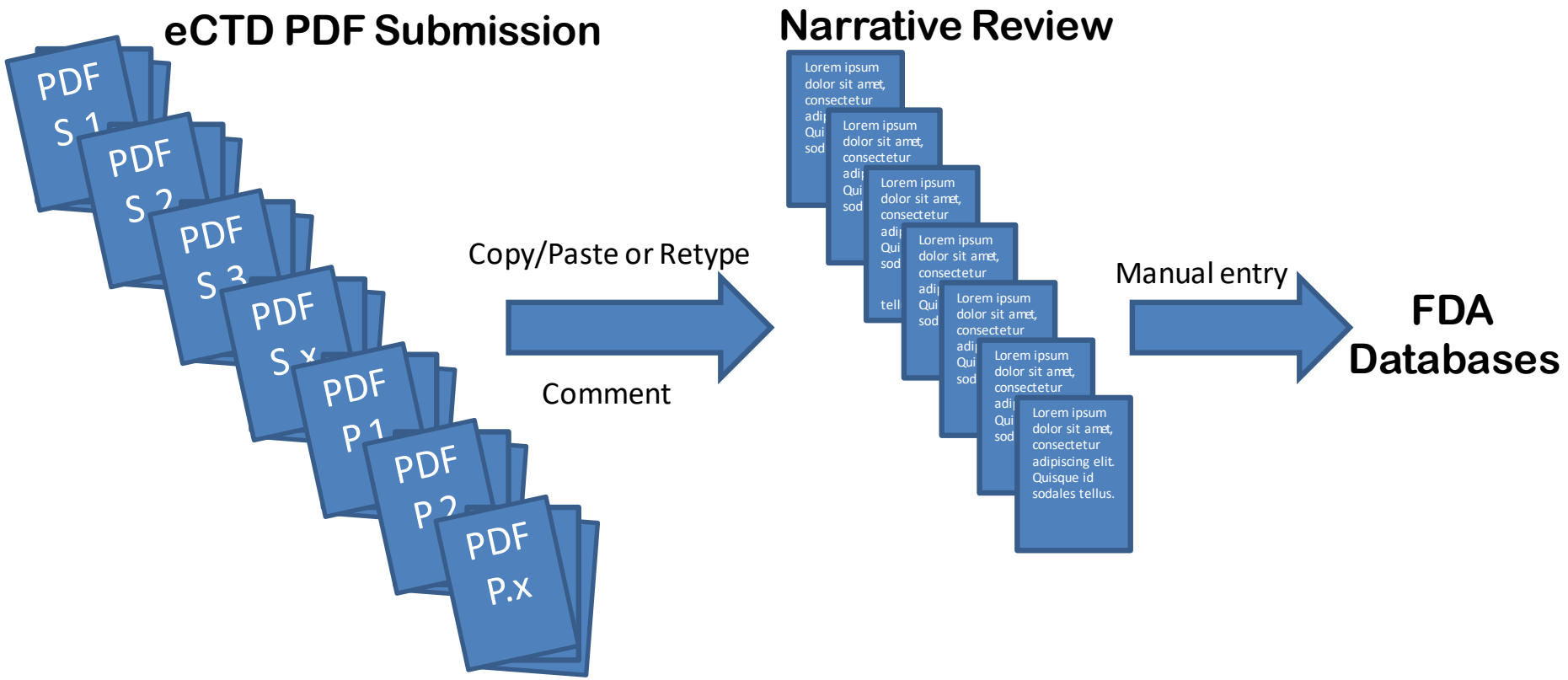
# Current/future submission & assessment model

# Current Module 3 Submission Model



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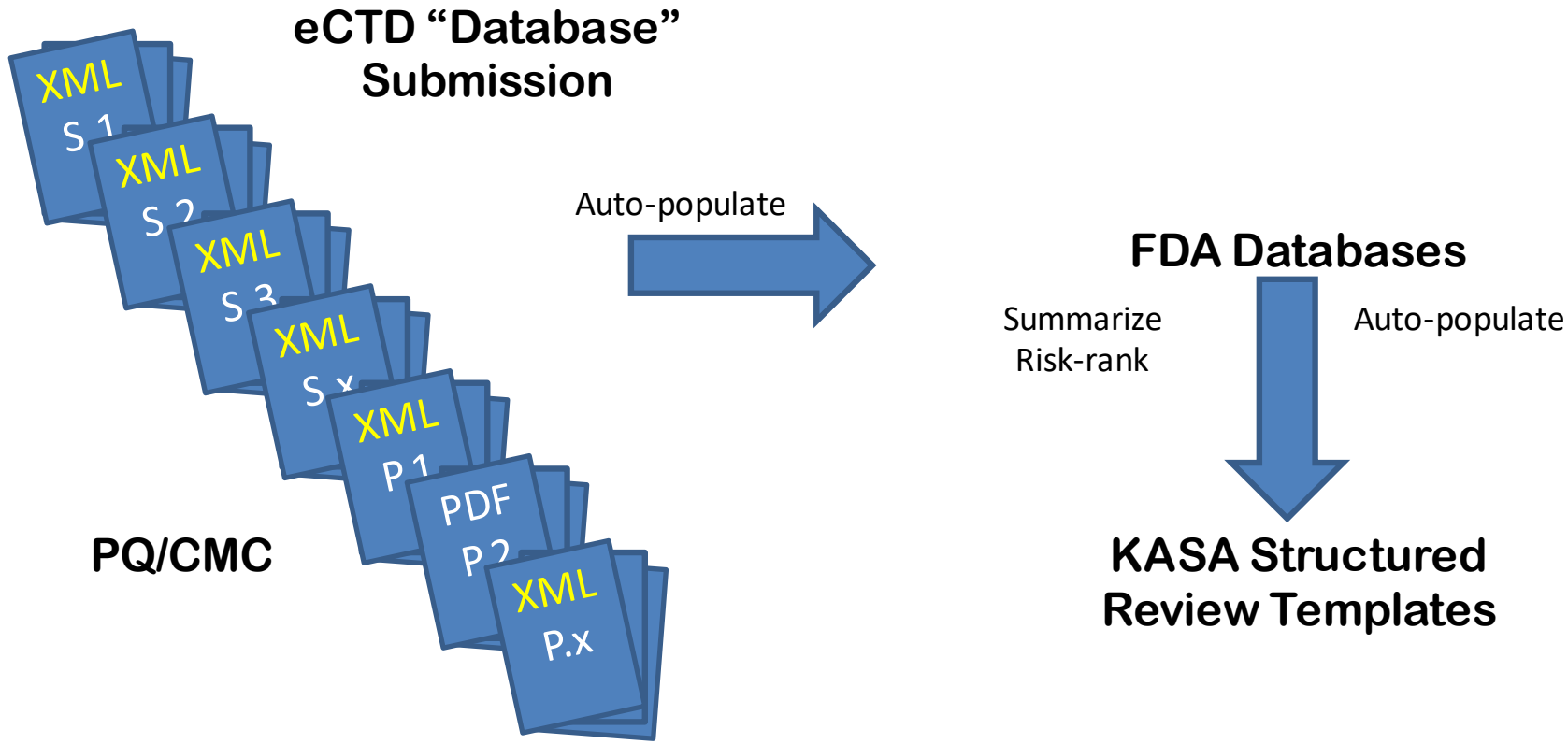
# Possible Future Module 3 Submission Model



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# PQ/CMC

Goal: standardize & structure eCTD submissions using XML and HL7 FHIR



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# PQ/CMC Scope

- Submissions including supplements & amendments
  - Human drugs
    - IND
    - BLA
    - NDA
    - ANDA
    - MF/DMF
  - Veterinary drugs
    - INAD
    - NADA
    - VMF
    - ANADA
    - JINAD

# Draft PQ/CMC Guidance

- Under development, targeted for Q2 2022
- Likely limited to “Specification,” “Batch Analysis” and “Stability”
- Anticipated as a 745A(a) required format
  - Section 745A(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), added by section 1136 of the Food and Drug Administration Safety and Innovation Act (FDASIA) (Public Law 112-144), ***requires*** that submissions under section 505(b), (i), or (j) of the FD&C Act2 and submissions under section 351(a) or (k) of the Public Health Service Act (PHS Act)3 be submitted in electronic format specified by the Food and Drug Administration (FDA or the Agency) beginning no earlier than ***24 months after FDA issues a final guidance*** specifying an electronic submission format. [emphasis added]



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# PQ/CMC data in eCTD Module 3 and Module 2 QOS

- Specification(drug substance/drug product/excipients)
- Batch Analysis (drug substance/drug product)
- Stability(drug substance/drug product)
- Nomenclature of Drug Substance
- Composition of Drug Product
- Batch Formula
- Impurities
- Manufacturing Process
- Annual BLA Lot Distribution Report
- CMC Changes in Annual Report – NDA/ANDA/BLA/NADA/ANADA
- Analytical Procedure Validation
- Facility Information

Note:
- Stability Analysis supported by extant HL7v3 eStability message (currently under revised)
- Deferred to next version of PQ/CMC



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# Proof of Concept Details

- Limited to 7 PhRMA volunteers
- Specification only
- Test of data model and FHIR message
- FDA provided
  - Excel spreadsheet that output FHIR message
  - Validation tool

# Goals for Proof of Concept

- Does the specification data model work?
- Is the structured data an accurate representation of that from the PDF?
- Transport format
  - Is XML FHIR a viable?
  - Suggestions for an alternate model?
  - Compatible with the Electronic Submissions Gateway (ESG)
- Is there extant PhRMA FHIR infrastructure support?
- Does existing PhRMA infrastructure support facile output of a FHIR specification message?

# FHIR Lessons Learned

- Simpler XML than HL7 v3
- More complex than a custom XML Schema
- Validation beyond the Schema is required
- Tools
  - Can be built quickly with competent IT support
  - Currently must be custom built
  - Forthcoming(?) commercial tools may be a better option
- Major new infrastructure and business process changes are needed to support structured documents such as PQ/CMC

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# 2017 Federal Register
# 2018 Public Meeting

FDA U.S. FOOD & DRUG ADMINISTRATION

# KASA

# The KASA Application System

The KASA system is being designed to:


- Capture and manage knowledge during the lifecycle of a drug product;
- Establish rules and algorithms to facilitate risk assessment, control and communication for the drug product, manufacturing process, and facilities;
- Perform computer-aided analyses of applications for a comparison of regulatory standards and quality risk across the repository of approved drug products and facilities;
- Provide a structured assessment that radically eliminates text-based narratives and summarization of information from the applications



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# The Algorithm:

## Failure Modes, Effects and Criticality Analysis (FMECA)

- FMECA algorithm chosen to capture initial inherent risk of CQA
- Initial risk calculated based upon factual information (e.g., basic physicochemical properties and product design) using Risk Priority Number (RPN) for each failure mode for each CQA based upon:
  - Severity of Harm (1-5 scale)
  - Detectability of Failure (1-5 scale)
  - Probability of Occurrence (1-5 scale)

$$RPN = \begin{bmatrix} 5 \\ 4 \\ 3 \\ 2 \\ 1 \end{bmatrix} O \times \begin{bmatrix} 5 \\ 4 \\ 3 \\ 2 \\ 1 \end{bmatrix} S \times \begin{bmatrix} 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{bmatrix} D$$

risk

Risk ranking criteria:

- RPN ≤ 25 considered as **low** risk
- RPN = 26-60 considered as **moderate** risk
- RPN ≥ 61 considered as **high** risk



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# Pre-Approval Assessment

- PAT monitoring
- Design Space
- Process understanding

- Process understanding
- Set process parameters

- Limited development
- Set process parameters

| Application | CQA impacted | Unit Operation | Initial Risk Assessment | Process Control Approach | Facility Control Approach | Updated Risk Assessment |
|---|---|---|---|---|---|---|
| A | Content uniformity | Wet Granulation | High | Approach A | Approach C | **High** → Pre-Approval Inspection |
| B | Content uniformity | Wet Granulation | High | Approach B | Approach A | **Low** |
| C | Content uniformity | Wet Granulation | High | Approach C | Approach C | **High** → Pre-Approval Inspection |

- No inspection history for product or process OR
- Experience with product design and unit operations but
- Poor inspectional history and quality defect signals

- Experience with product design and unit operations with no CGMP issues controlling product/operational risks

CQA: Critical Quality Attribute



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# KASA as a Global System

- KASA is an evolving paradigm involving structured assessment templates, and risk-ranking algorithms
- While KASA per se is ***not*** a proposed ICH topic, it has relevance to other ICH topics
- Although the FDA is still exploring many aspects related to KASA, there is potential for beginning discussions/collaborations with other authorities
- Current program is internal only


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# PQ/CMC & ICH

# PQ/CMC and ICH

- Structured Product Quality Submissions (SPQS) accepted as a topic by the ICH Assembly
- Prioritized as follows:
  - Q13 completes Step1/Step 2
  - New M4-Q (CTD-Q) Expert Working Group formed
  - SPQS work to be determined by new M4-Q EWG
- FDA's PQ/CMC will continue


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# M4Q Revision and SPQS

- M4Q Revision
  - Include new ICH topics, e.g., Q8-Q12 [Q13 & Q14]*
  - Reorganize for modern development practices
  - Anticipate structured submissions
- SPQS
  - Implement M4Q revisions
  - Leverage existing structured content models
  - Previously structured modules will likely still appear somewhere in the revised M4Q (e.g., specification)

*When finalized



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# IDMP AND PQ/CMC

# IDMP Harmonization Efforts

- Attempted to harmonize the specification models of ISO 11238 and PQ/CMC
- Produced & distributed an 82 page “Mapping” report
- Hosted a Webex with some PhRMA members to do further mapping
- Worked with the HL7 FHIR group to incorporate PQ/CMC and IDMP terms into various FHIR resources
- Continue to consider appropriate IDMP terms,
  - E.g. concluded “Ingredient Role” code list (ISO 20443) was adequate for our needs, though somewhat excessive
  - EMA’s SPOR is using a modification of this “Role” code list


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**Table D.1 — Ingredient roles (classCodes)**

| 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 | Active ingredient, where the entire substance is the basis of strength. For example, propranolol hydrochloride quantified as the propranolol hydrochloride salt. |
| ACTIM | Active ingredient, where the active moiety is basis of strength. For example, 287 mg amoxicillin trihydrate equivalent to 250 mg anhydrous amoxicillin. |
| ACTIR | Active ingredient, where another reference substance is the basis of strength. For example, metoprolol succinate quantified by amount of metoprolol tartrate with the equal amount of metoprolol active moiety. |
| ADJV | Adjuvant – an ingredient(s) which augments or promotes the pharmacological effect of the active ingredient(s) without itself being considered active (typically used with vaccines.) |
| IACT | Inactive ingredient, i.e. ingredients added for a purpose other than the intended pharma- |
| COLR | olour appearance. |
| FLVR | taste of the product. |
| PRSV | y the risk of the product's spoiling. |
| STBL | e mixture homogenic (e.g. prevent the |
| MECH | ole, lends a spatial structure to the product, which structure is meaningful to the delivery of the pharmacologically active ingredients near the target site. For example, a collagen matrix used as a base for transplanting skin cells.<br>NOTE Such ingredient has a function other than merely delivering the pharmacologically active substances into a systemic compartment (such as, for example, an ordinary capsule would have.) |
| 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 avoided given the circumstances of the mixture's nature or origin. |

EMA SPOR Ingredient Roles

- Active
- Adjuvant
- Excipient
- Solvent/Diluent

# Current & Future Activities

- Incorporate PQ/CMC, and some IDMP terminology into HL7 FHIR resources
- Refine specification model
- Create implementation guide
- Draft FDA Guidance
- Work with international partners, e.g. EMA, Health Canada
- Define the next M3 sections to model


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# Challenges

- Industry implementation will necessitate:
  - A change in a document-centric business processes
  - Capital investment in IT tools
- No extant IT tools to implement spec. model
- ICH “Structured Product Quality Submissions”
  - May take project in a different direction
- Divergence in data models from KASA & GSRS
- Immaturity of HL7 FHIR
- Alignment with EMA’s SPOR where feasible



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# Future

- PQ/CMC
  - Implementation guide (FHIR)
  - Work with HL7 FHIR
  - Continue structuring other sections
  - Collaborate with internal & external partners
- KASA
  - Refine risk-ranking algorithms
  - Define new controlled vocabulary lists


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# Conclusion

- PQ/CMC & KASA will substantially change the submission process
- Years in the future
  - Required PQ/CMC submission under 745A(a)
  - ICH “Structured Product Quality Submissions”



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# ISO Identification of Medicinal Products (IDMP)

## Global PhPID and Dose Form Harmonization

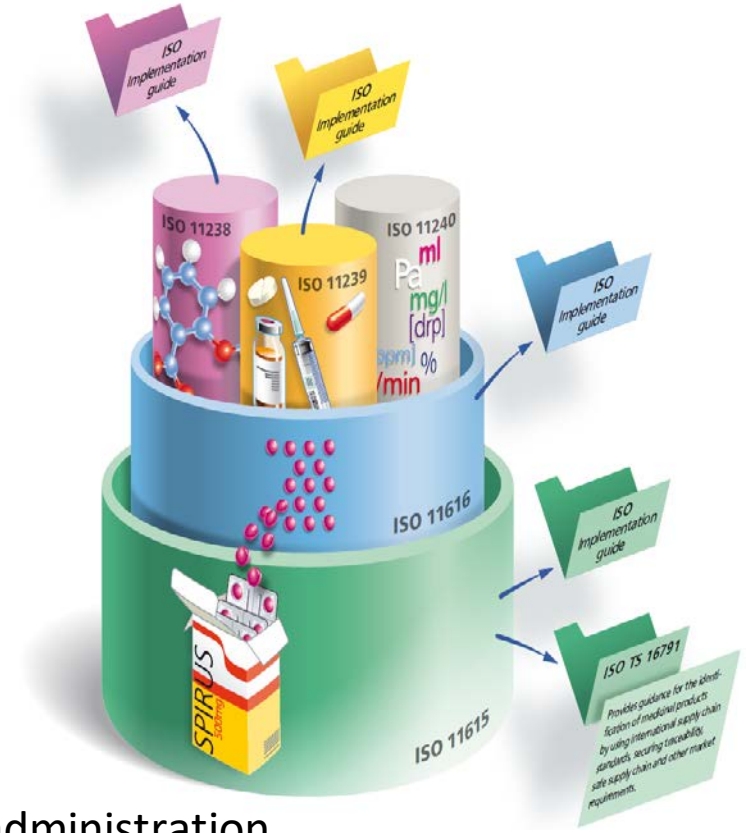
Public Meeting on
Electronic Submissions and Data Standards

April 7, 2021

# What is IDMP

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

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



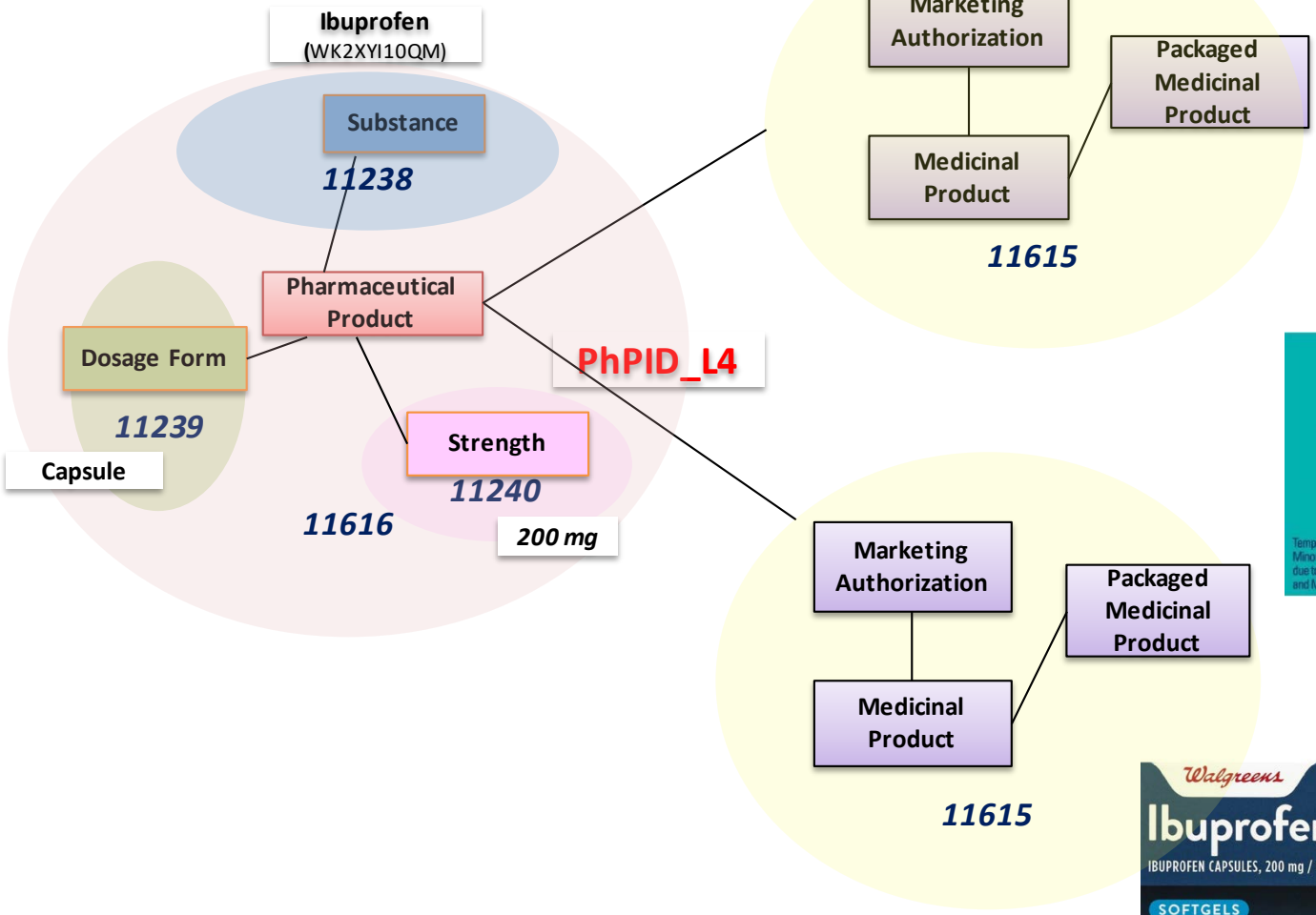

- ISO 11615 – Medicinal Product Identification
- ISO 11616 – Pharmaceutical Product Identification
- ISO 11238 – Substance Identification
- ISO 11239 – Pharmaceutical dose forms, units of presentation and routes of administration
- ISO 11240 – Units of measurement

# Why is it important?

- **PATIENT SAFETY**
  - Safety Surveillance
    - Improve pharmacovigilance by uniquely identifying specific medicinal products through product life cycle
    - Detect safety signals from similar medicinal products referenced in adverse events
  - Support Mitigation of Drug Shortages
    - Identify ***like/similar*** products for replacement to mitigate drug shortages

- Cross-regions or global agreement on common substance ID and dose form is needed for global safety surveillance and drug shortage mitigation

# Connecting Medicinal Products Together









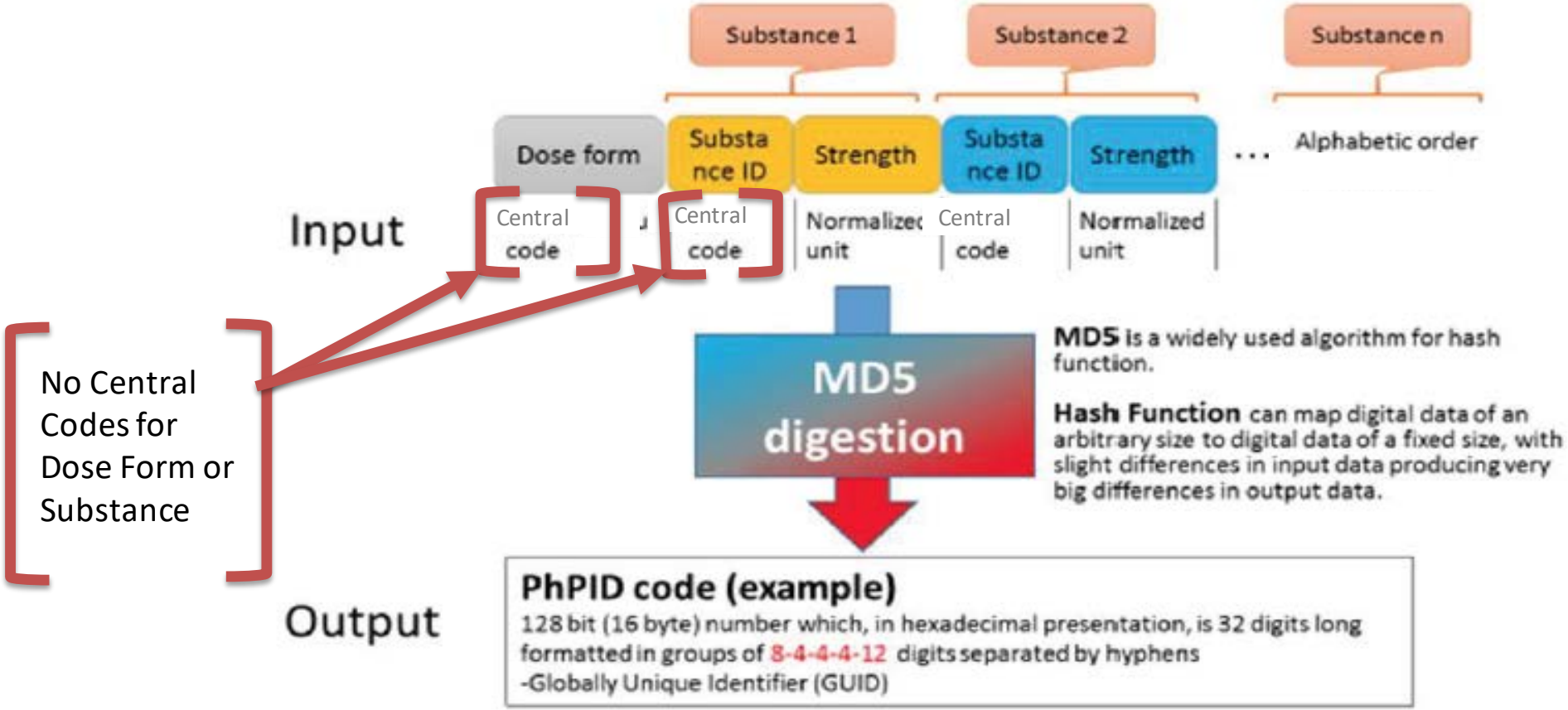
# Concerns with the Current ISO Standard for PhPID

- PhPID Set
  - ❖ 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***

- Substance is the key for all PhPIDs
- A <u>global</u> Level 3 and 4 PhPID is not possible without a global consensus on Dose Form IDs

# Concerns with the Current ISO Standard for Dose Form

## Pharmaceutical Product ID (PhPID)



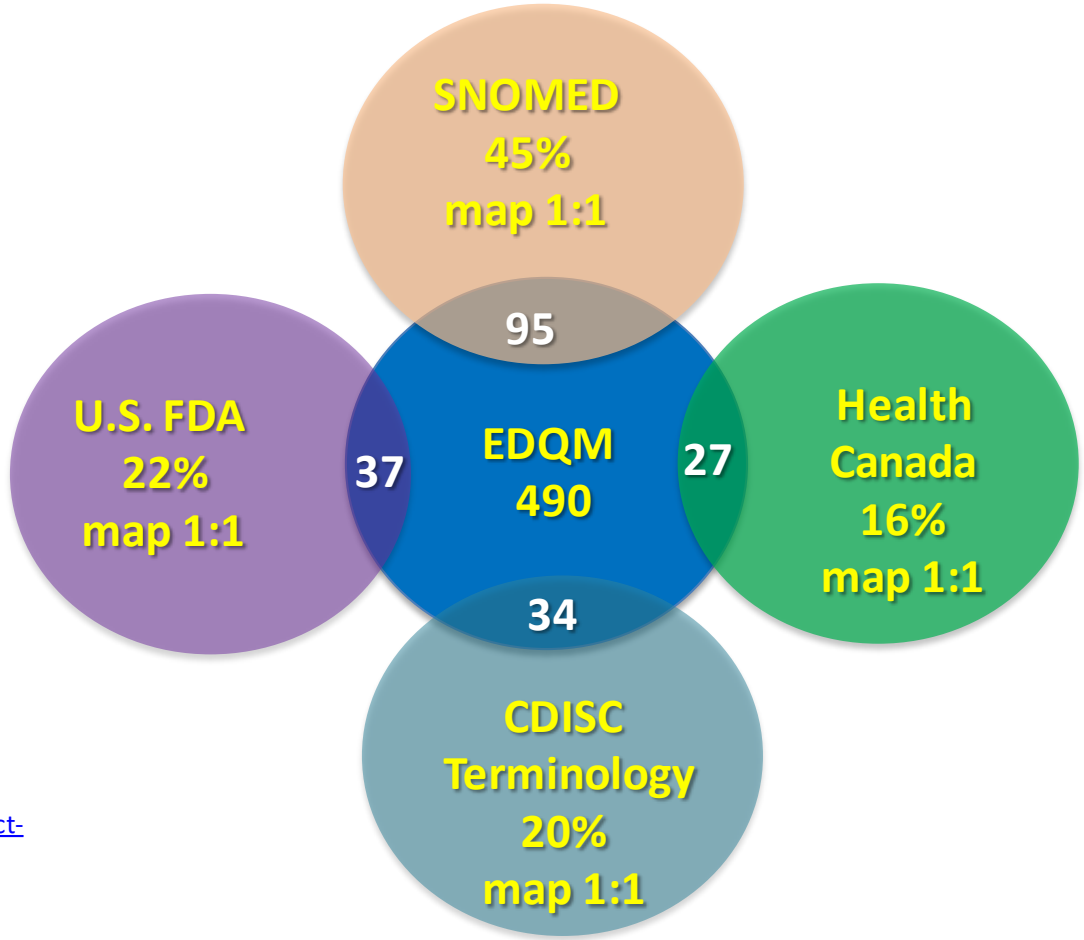

*Conceptual Representation of the Global PhPID Construction**

* Adapted from ISO TS 20451:2017

# Concerns with the Current ISO Standard for Dose Fo

## *Region-to-Region Terminology Mapping is Not a Viable Solution*

- Mapping results are based on a specified set of criteria and may be different region-to-region:
  - EDQM has **490** dosage forms[1]
  - FDA Terminology has **166** dosage forms[2]
  - Health Canada (HC) terminology has **170** dosage forms[3]
  - SNOMED has **213** dosage forms[4]
  - CDISC Terminology has **172** dosage forms[5]




[1] https://standardterms.edqm.eu/).
[2] https://evs.nci.nih.gov/ftp1/FDA/SPL/About.html
[3] https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database/what-data-extract-drug-product-database.html
[4] https://ncim.nci.nih.gov/ncimbrowser/
[5] https://www.cdisc.org/standards/terminology

(Note: HC dosage form dataset for active products was downloaded and analyzed by FDA to determine the extent of 1:1 mapping)

Originally presented January 2020

# Dose Form label can be different in a region and across regions

## Tablet – *Film coated or not?*

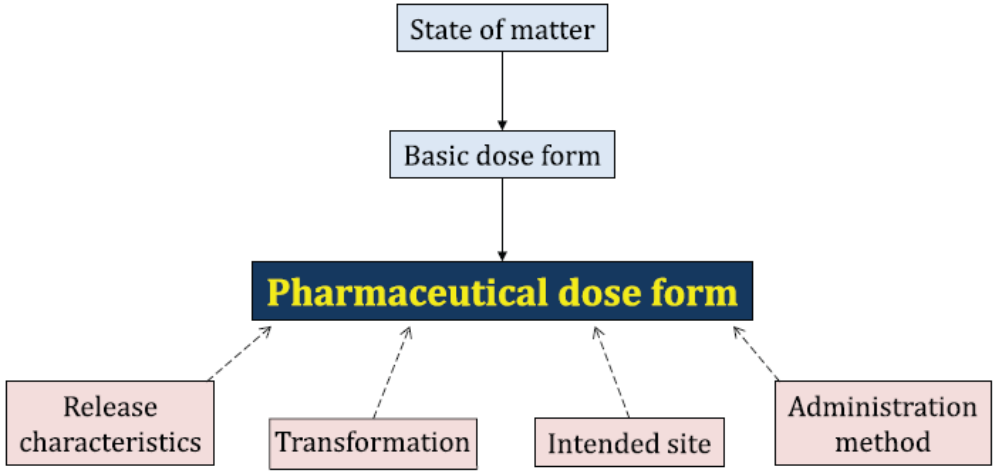


## Capsule – *hard or soft?*



# Dose Form Characteristics Use Case for Global PhPID

- **Overview**
  - **Six** existing EDQM characteristics can be used to describe the pharmaceutical dose forms for use in global IDMP.
    - These include:
      1. State of Matter
      2. Basic Dose Form
      3. Transformation
      4. Release
      5. Intended Site
      6. Administration Method




  - Concerns with central terms, terminology granularity, term definitions, and mapping are virtually eliminated with a centrally-maintained set of coded dose form characteristics.

# Dose Form Characteristics Examples for Global PhPID

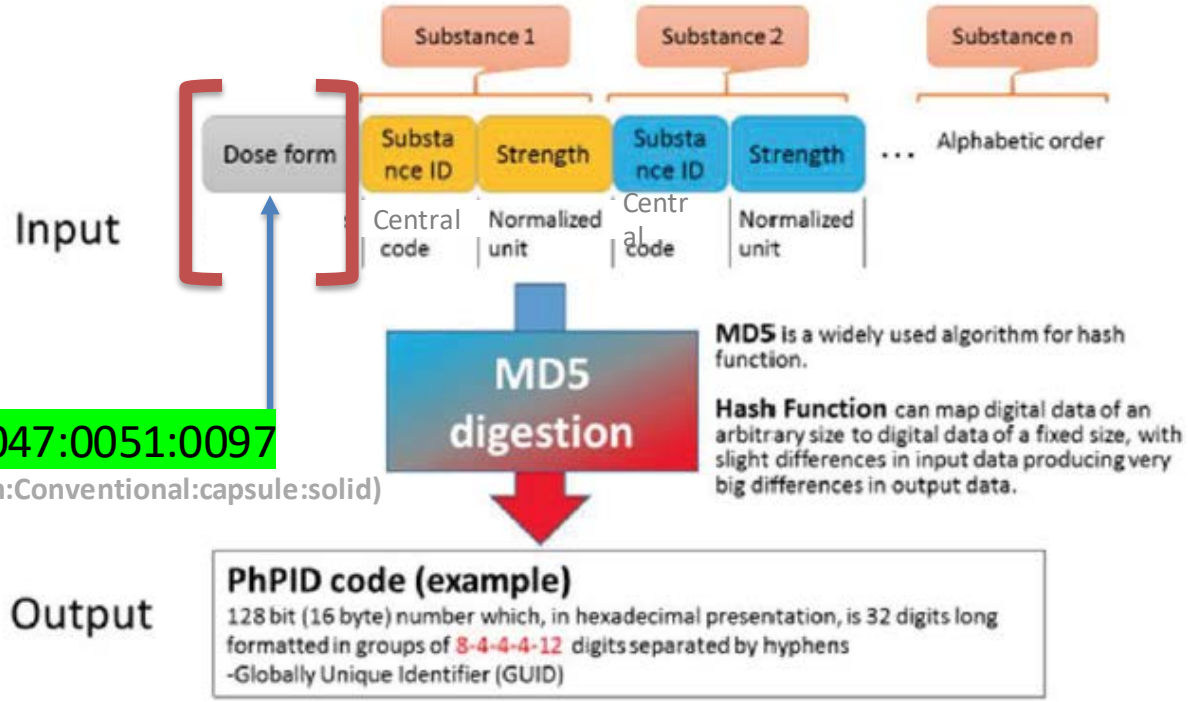
## Tablet – *Film coated or not*

| Pharmaceutical Dose Form | State of Matter | Basic Dose Form | Transformation | Release Characteristics | Intended Site | Administration Method |
|---|---|---|---|---|---|---|
| Coated Tablet | Solid (0097) | Tablet (0069) | No Transformation (0042) | Conventional (0047) | Oral (0031) | Swallowing (0019) |
| Film Coated Tablet | Solid (0097) | Tablet (0069) | No Transformation (0042) | Conventional (0047) | Oral (0031) | Swallowing (0019) |
| Tablet | Solid (0097) | Tablet (0069) | No Transformation (0042) | Conventional (0047) | Oral (0031) | Swallowing (0019) |

## Capsule – *hard or soft*

| Pharmaceutical Dose Form | State of Matter | Basic Dose Form | Transformation | Release Characteristics | Intended Site | Administration Method |
|---|---|---|---|---|---|---|
| Capsule, Hard | Solid (0097) | Capsule (0051) | No Transformation (0042) | Conventional (0047) | Oral (0031) | Swallowing (0019) |
| Capsule, Soft | Solid (0097) | Capsule (0051) | No Transformation (0042) | Conventional (0047) | Oral (0031) | Swallowing (0019) |
| Capsule | Solid (0097) | Capsule (0051) | No Transformation (0042) | Conventional (0047) | Oral (0031) | Swallowing (0019) |

# Dose Form Characteristics Example for Global PhPID

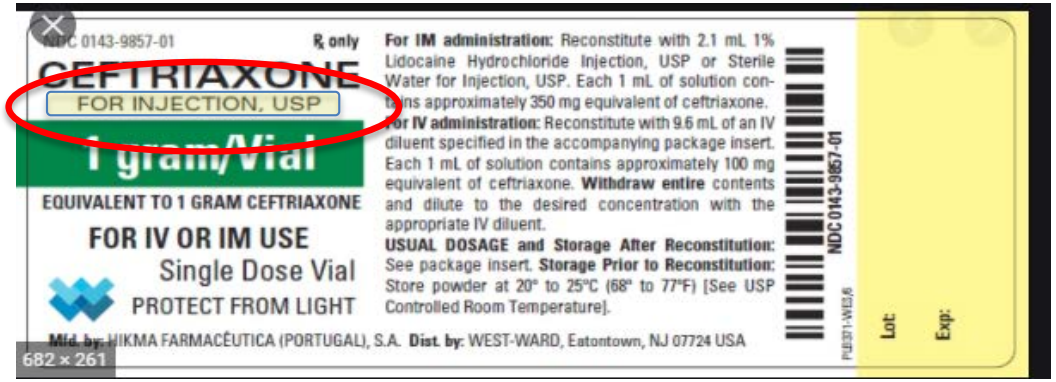



- Group “like” medicinal Products in ‘Capsule’, ‘Capsule, Hard’, ‘Capsule, Soft’ Dose Form.
- This DF characteristics approach will allow the generation of global PhPID for all regions, without a central DF system.

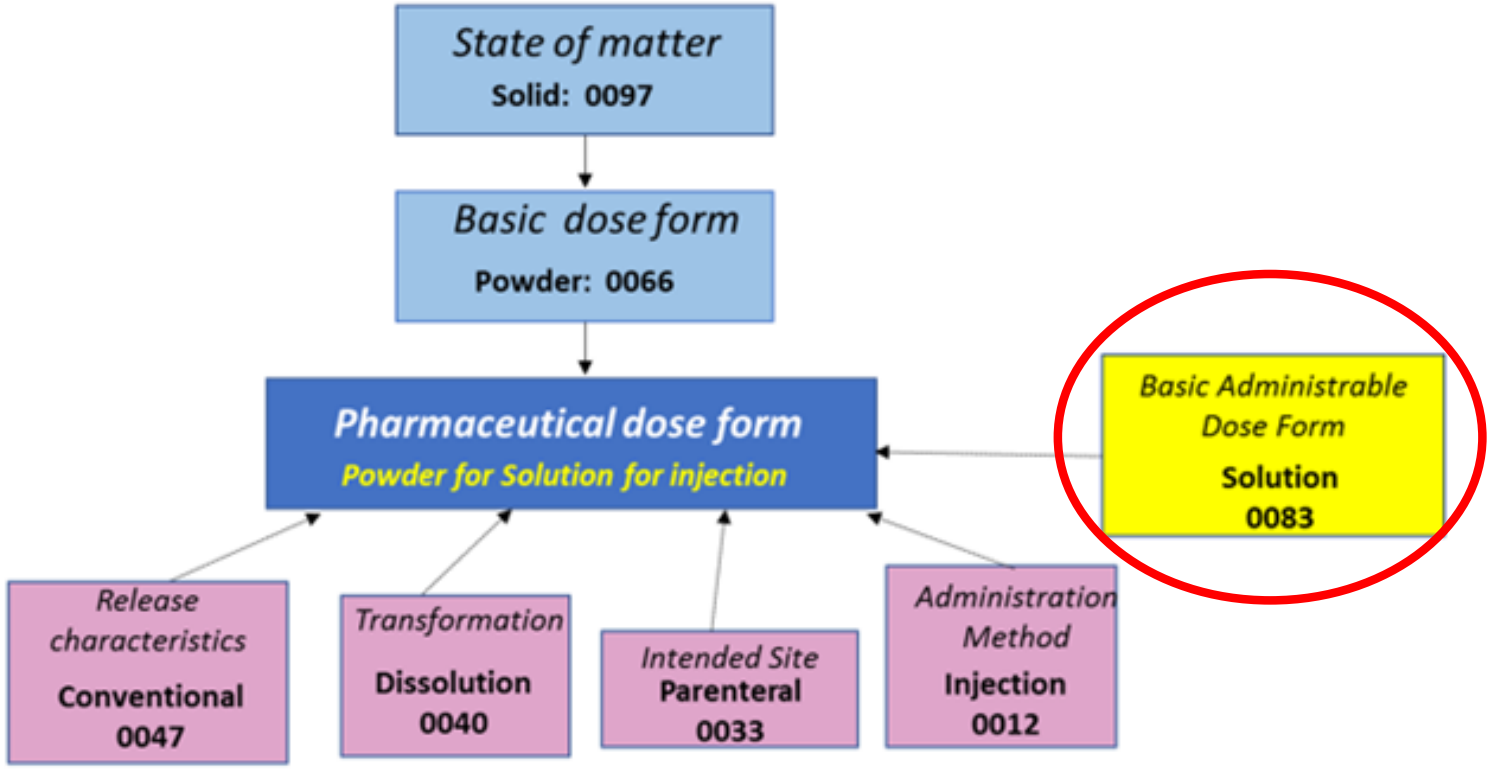
# Dose Form Characteristics Use Case for Global PhPID

## *Medicinal Products that Require Transformation are a Challenge*

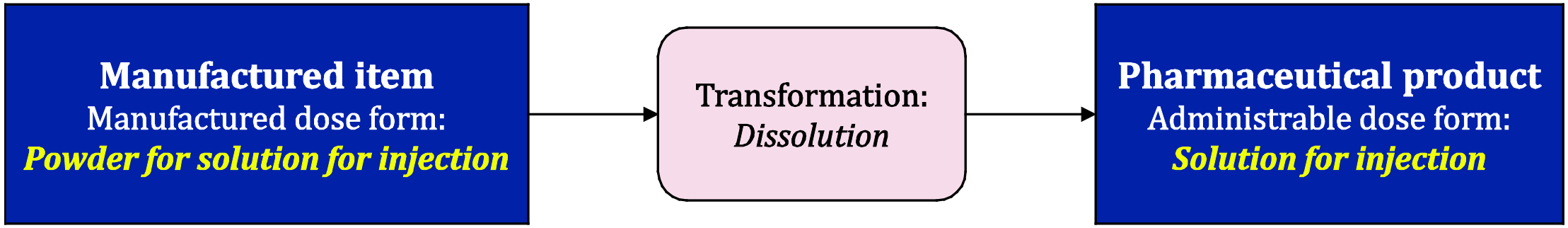




# Dose Form Characteristics Use Case for Global PhPID



# Dose Form Characteristics Use Case for Global PhPID

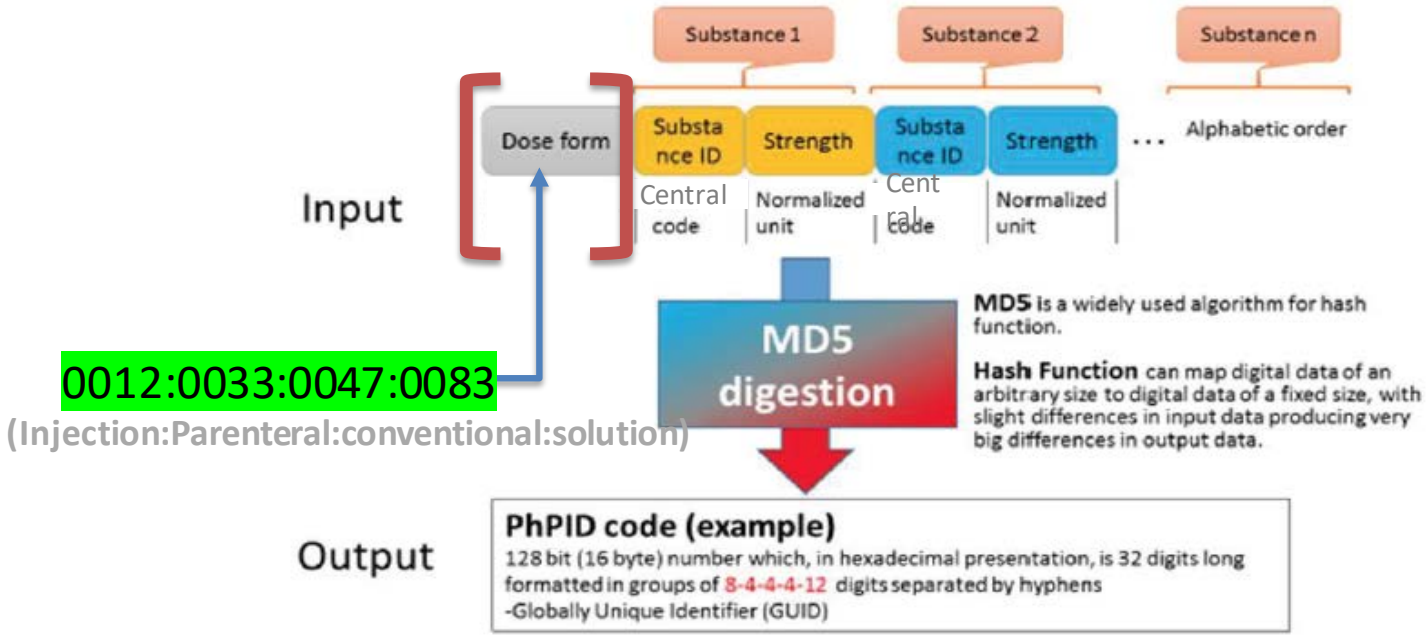



| Pharmaceutical Dose Form | State of Matter | Basic Dose Form | Transformation | Release Characteristics | Intended Site | Administration Method | Basic Admin. Dose Form |
|---|---|---|---|---|---|---|---|
| Powder (for solution) for injection | Solid (0097) | Powder (0066) | Dissolution (0040) | Conventional (0047) | Parenteral (0033) | Injection (0012) | Solution (0083) |
| Concentrate (for solution) for injection | Liquid (0099) | Concentrate (0078) | Dilution (0038) | Conventional (0047) | Parenteral (0033) | Injection (0012) | Solution (0083) |
| (Solution) for injection | Liquid (0099) | Solution (0083) | No Transformation (0042) | Conventional (0047) | Parenteral (0033) | Injection (0012) | Solution (0083) |

Used these 4 characteristics to generate of Global PhPID

# Dose Form Characteristics Use Case for Global PhPID

PhPID for Ceftriaxone 1g



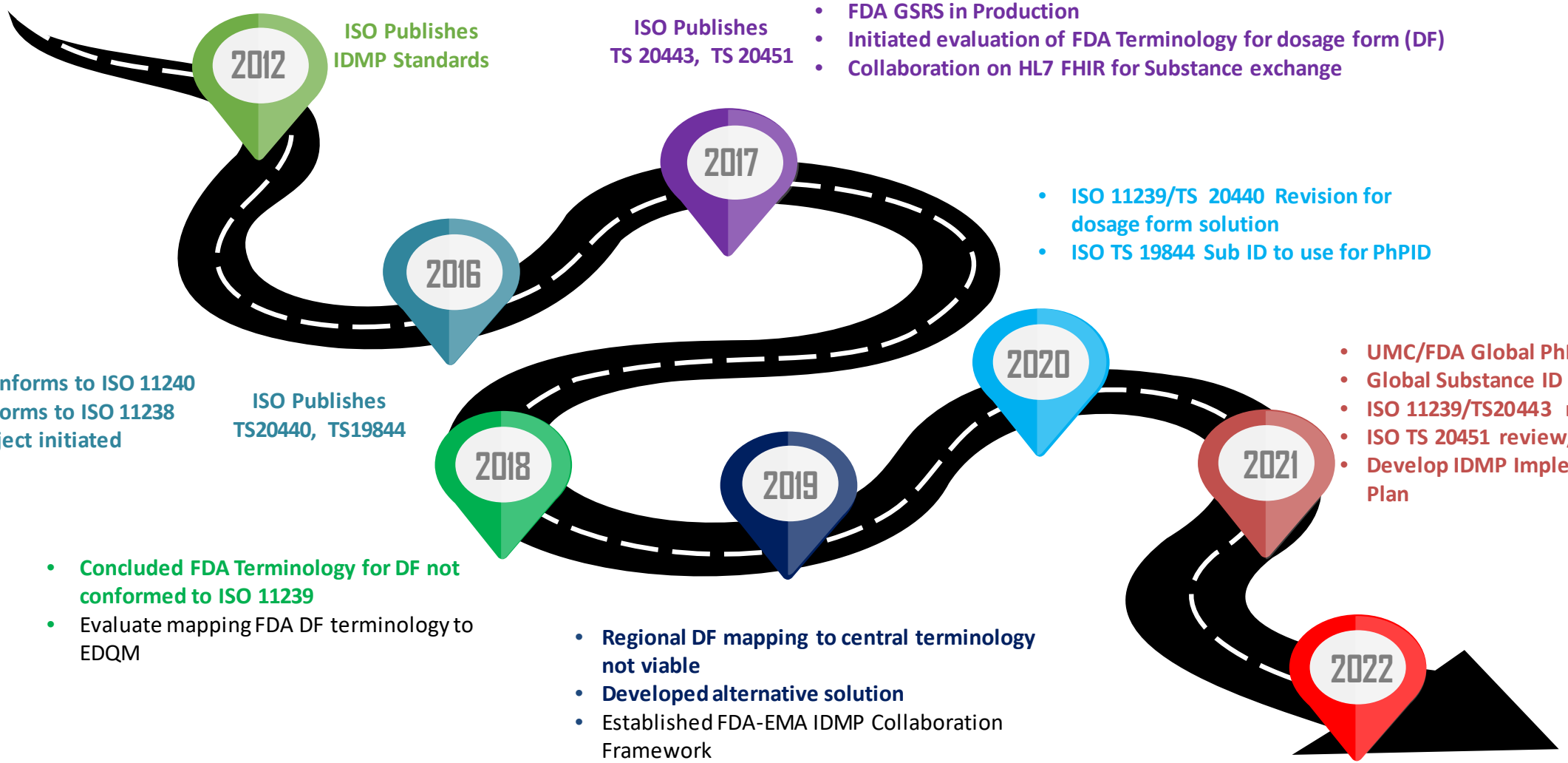

- PhPID groups "like" medicinal Products with same *Administrable Dose Form*; regardless of its' *Manufactured Dose Form*.

* Adapted from ISO TS 20451:2017

# WHO UMC-FDA Global PhPID Pilot

- To evaluate using Pharmaceutical Dose Form Characteristics for Global Pharmaceutical Product Identification (PhPID)
- This pilot is limited to the use of core EDQM dose form characteristics and other potential characteristics for the generation of Global PhPID
- FDA assigns dose form characteristics for US marketed medicinal products base on 34 substances identified in the UNICOM Pilot
- UMC will generate corresponding PhPID using dosage form characteristics together with substance and strength
- FDA and UMC will perform a data equivalency assessment on the use of characteristics for generation of PhPID and present to ISO TC215 WG6
- Prepare a fit-for-purpose report

# FDA IDMP Roadmap 2012-202x




**2012**
- ISO Publishes IDMP Standards

**2016**
- ISO Publishes TS20440, TS19844
- UCUM conforms to ISO 11240
- UNII conforms to ISO 11238
- GSRS Project initiated

**2017**
- ISO Publishes TS 20443, TS 20451
- NDC conforms to ISO 11615
- FDA GSRS in Production
- Initiated evaluation of FDA Terminology for dosage form (DF)
- Collaboration on HL7 FHIR for Substance exchange

**2018**
- Concluded FDA Terminology for DF not conformed to ISO 11239
- Evaluate mapping FDA DF terminology to EDQM

**2019**
- ISO 11239/TS 20440 Revision for dosage form solution
- ISO TS 19844 Sub ID to use for PhPID

**2020**
- Regional DF mapping to central terminology not viable
- Developed alternative solution
- Established FDA-EMA IDMP Collaboration Framework
- Collaboration on HL7 FHIR for MPID exchange
- UNICOM

**2021**
- UMC/FDA Global PhPID Pilot
- Global Substance ID
- ISO 11239/TS20443 revision
- ISO TS 20451 review/revision
- Develop IDMP Implementation Plan

**2022**
- Testing and validate Global PhPID process

# Thank you

U.S. FOOD & DRUG ADMINISTRATION

# ISO 11238 and Global Substance Registration System(GSRS) Update PDUFA Meeting (4/2021

# ISO 11238 Background

- ARISTOTLE (Metaphysics)...the generally recognizable substances... are the sensible substances, and sensible **substances all have matter...,** and in another sense the formula or form..., and thirdly the complex of matter and form, which alone is generated and destroyed, and is, without qualification, **capable of separate existence**

- **A unit of matter that can be quantitatively measured**

- **Five types of substances**
  - Chemicals, Proteins, Nucleic Acids, Polymers, and Structurally Diverse Material
  - Mixtures

- **Substance are not defined based on use**

- **The same substance can be manufactured or isolated using different methods**

# Substances (ISO IDMP)

- Five groups of elements are used to describe single substances.
  - Monodisperse
    - Chemicals
      - Defined primarily by molecular structure (connectivity and stereochemistry)
    - Proteins
      - Amino Acid Sequence, type of glycosylation, modifications
    - Nucleic Acids
      - Sequence, type of sugar and linkage, modifications

# Substances (ISO IDMP)

- Polydisperse
  - Polymers (Synthetic or biopolymers)
    - Structural repeating units, type, geometry, type of copolymer (block or random), ratio of monomers, modifications, molecular weight or properties related to molecular weight, biological source for many biopolymers
  - Structurally Diverse Substances (viruses, cells, tissues, complex materials)
    - Taxonomic, anatomical, fractionation, physical properties, modifications

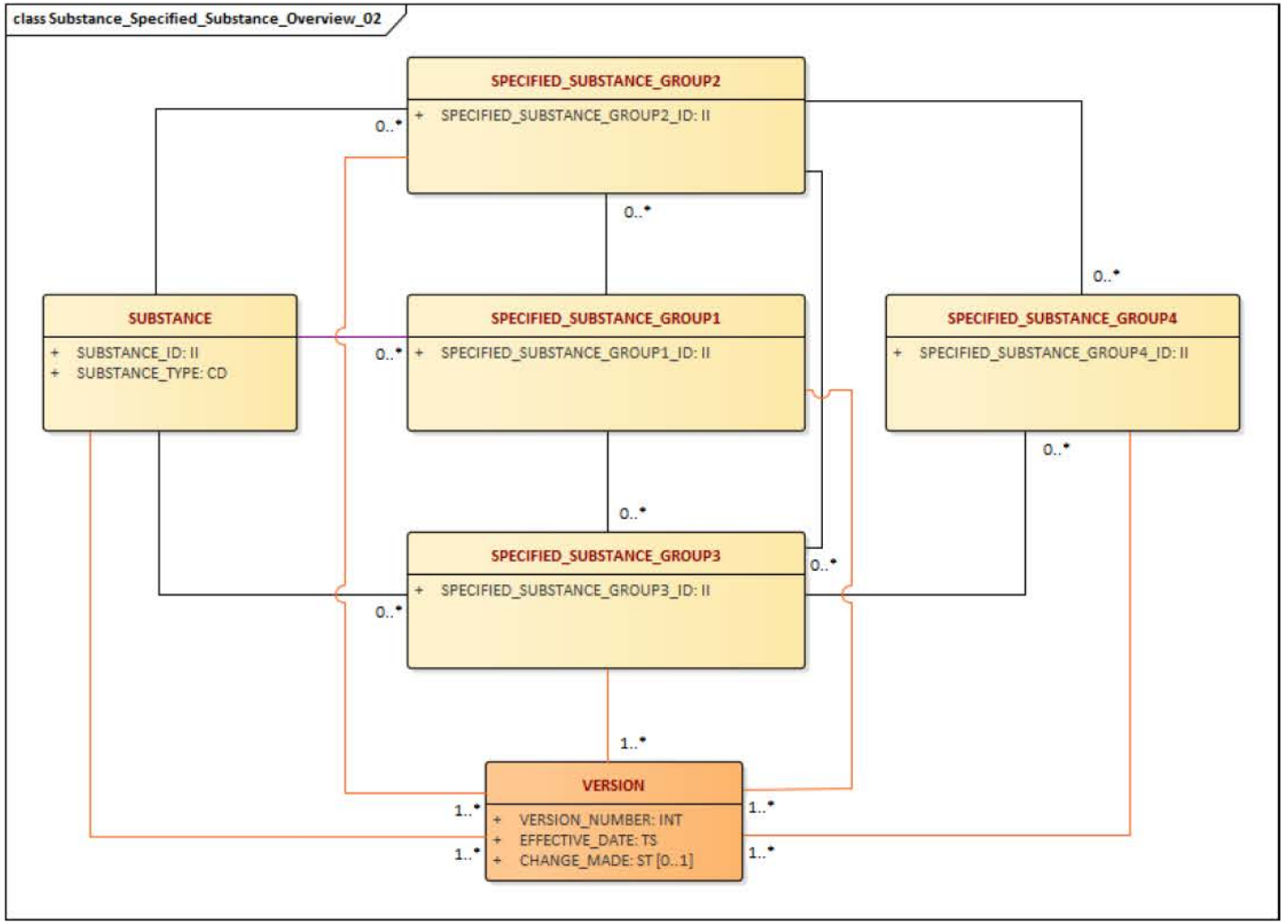
# Need for Specified Substance

- Organize additional information on ingredients (SSG1).
  - Need to describe multiple substance ingredients (Simethicone, Colorants, Flavors)
  - Need to describe extracts (allergenic and herbal extracts, tinctures)
  - Need to distinguish materials that differ by physical form or critical properties (Polymorphs, Flowability, Compressibility)
  - Just starting to implement this at FDA

# Need for Specified Substance

- Need to tie material to a manufacturer and a process (SSG2 and SSG4)
- Need to tie material to a specific grade (SSG3)
- Need to obtain specification information (SSG4)
- Need to obtain information about processing materials (SSG4)
- Need to establish and monitor the supply chain (SSG2)
- Manufacturing and specifications were separated out in ISO version 2

# Specified Substance



# Specified Substance Implementation

- Group 1 implemented will capture cell line data for recombinant proteins.
- Each cell line will get a UNII code
- Still working on how to capture the details of glycosylation at the Group 1 level
- Still have not implemented Group 2 need to agree on a common identifier for companies. (US Duns and FEI; EU:Org database)
- Specification module developed and an impurity module with USP is under development
- Manufacturing prototype has also been developed

# Global Substance Registration System

- Global marketplace for ingredients requires a global system to monitor the global supply chain
- A Global Repository of Regulatory Information and Data on Ingredients (Shortages, substandard and counterfeit ingredients, coordinate inspections)
- Generates a UNII code that can be freely used to identify a substance throughout it's entire lifetime
- Standard is complex, difficult and expensive to implement
- Data abstraction and curation is very expensive
- Global database means better data, less redundancy, more data, less mapping
- Illicit Substances are also often global

# What is the GSRS?

Assigns permanent UNII code to each substance

Compliant with the ISO IDMP Standard

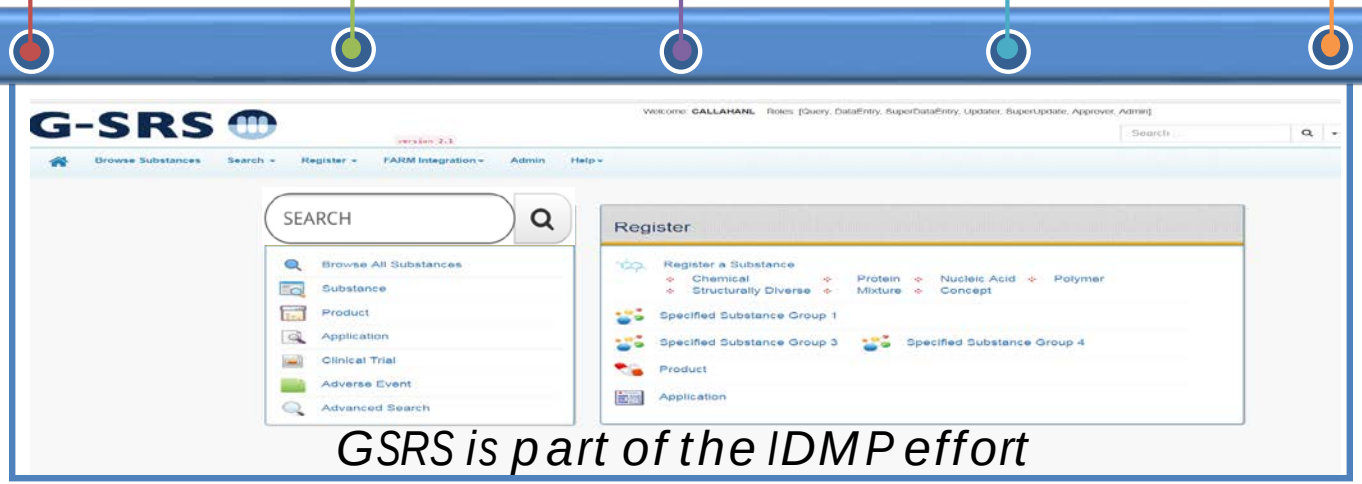
Registers and defines

Ties substances to:

- ✓ Products
- ✓ applications (Integrity, CFSAN and GSRS)
- ✓ clinical trials (CT.gov and EUCT)
- ✓ Adverse events counts
- ✓ Drug targets

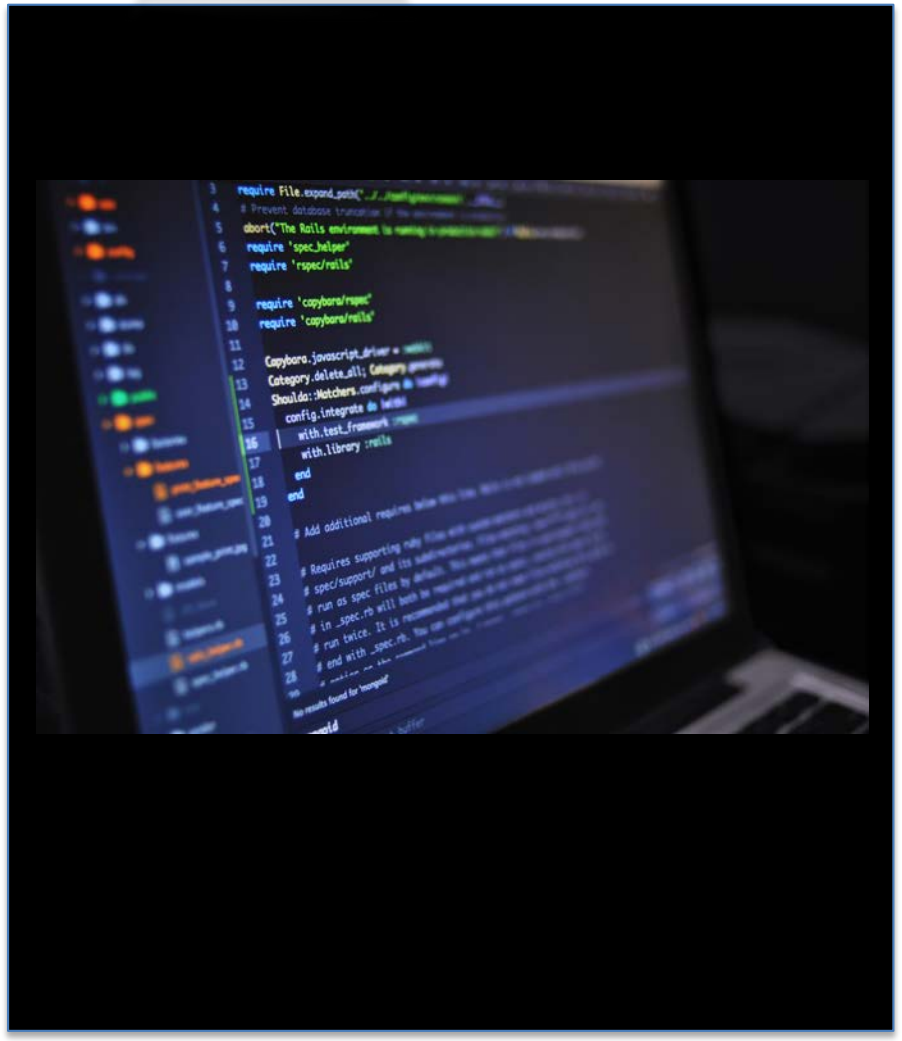
Limited quality information

- ✓ Limited LADMER data (metabolites, cyp, transporter info)




*GSRS is part of the IDMP effort*

# GSRS is a Software Application



- Freely distributable (NCATS version, substance only, FDA version coming in Summer)
- Predominantly open source
- Data accessed and entered through an API
- Backend Java, Oracle (at FDA)
- Works with Oracle, PostgreSQL, MySQL has built-in H2 database
- Has native JSON message can be adapted to HL7-FHIR
- UI development Angular 1.0, Scala, Play framework; Moving to Angular 11
- Extensive use of Lucene Indexes
- Implemented Substance, Specified Substance Group 1, 2, 3 and part of Specified Substance Group 4
- Excel tools for batch updating and queries

# GSRS Software

- Works in all modern browsers: IE, Chrome, and Firefox
- System distributed through NCATS with a large set of curated public domain data and updated periodically
  - Over 120,000 Validated Substances, 200,000 total
  - Over 1,800,000 Names and Codes
  - Over 180,000 relationships between substances (impurities, metabolites, drug targets)
  - Links to many outside resource (Chemid, Pubchem, Drug Bank, Orphan Drug etc)
  - Structure and sequence based searching
  - Faceted and advanced field-based searching
  - Data downloadable in a variety of formats JSON, Text, Excel

# Current Status at FDA

Version 2.8 has been deployed

Rewrite of application has begun

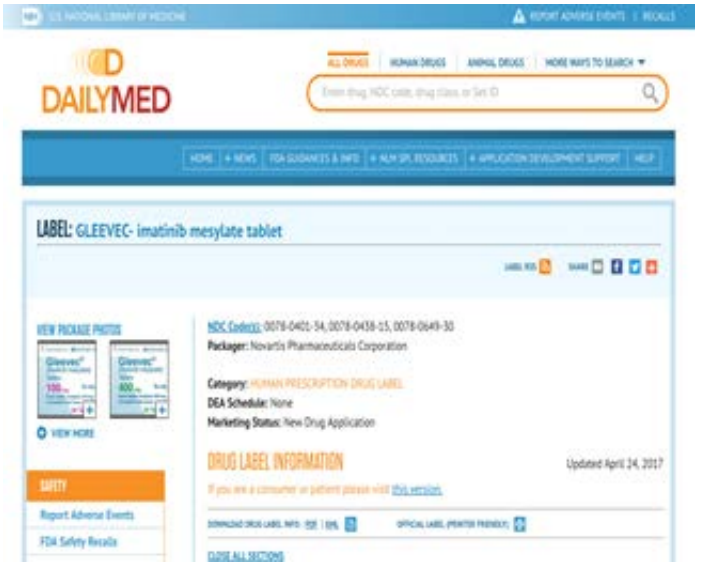
Version 3.0 to be deployed in 2021 (Complete rewrite to eliminate Play framework and Scala, move to Angular 11 and Spring Boot Framework to allow microservices, linking and distribution of other data.

Approximately 200,000 thousand substances registered

Active ingredients, Drug targets, Metabolites, Impurities

# How it's used at FDA

- FDA has adapted GSRS to integrate with existing internal databases and systems.
  - Adverse events
  - Products (SPL)
  - Applications (INDs, NDAs)
  - Clinical Trials
  - In the future, GSRS can be used to facilitate digital submissions of formulation, quality and pharmacology data
  - A number of classification systems
    - CFR DEA Classification

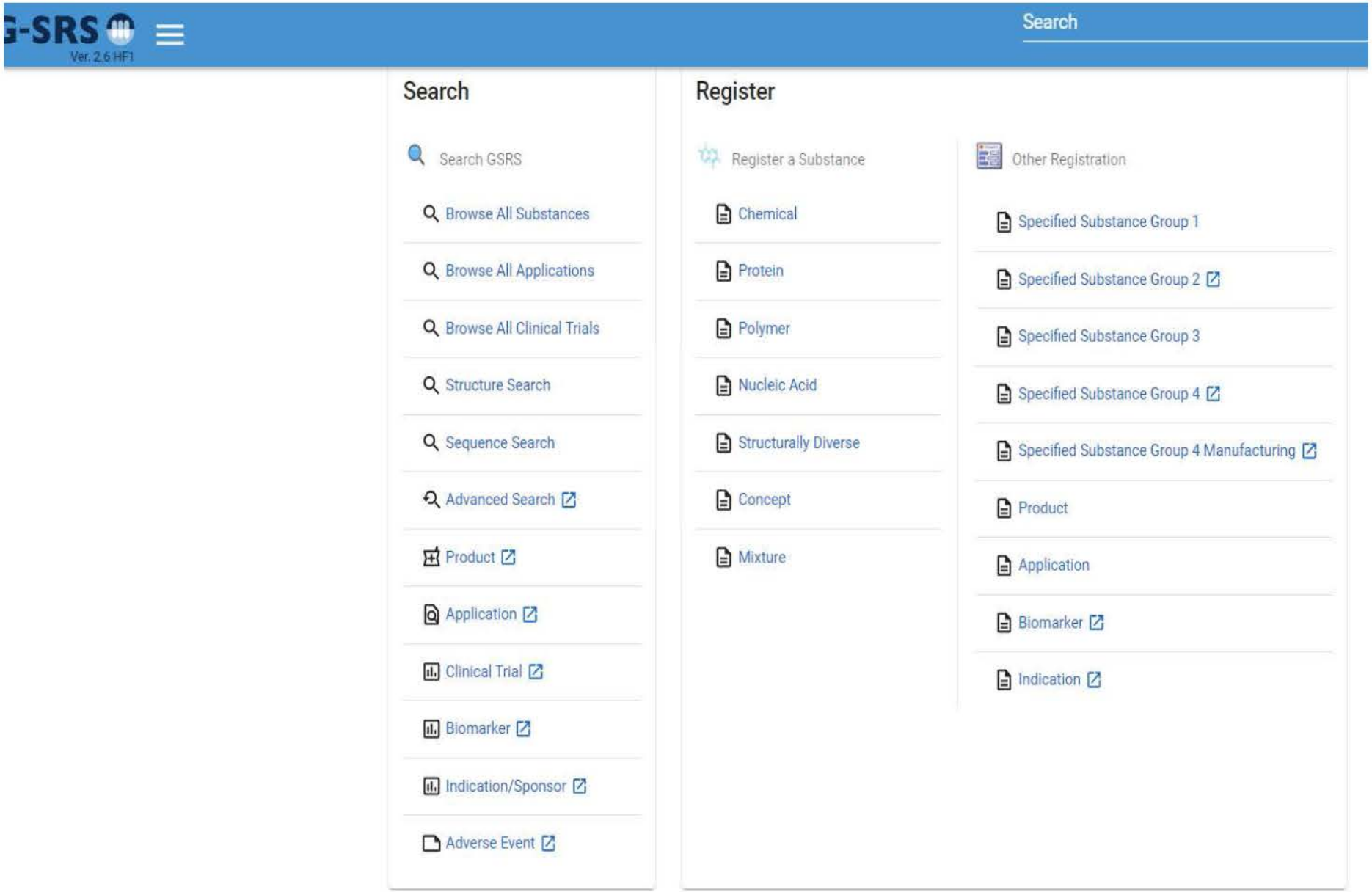


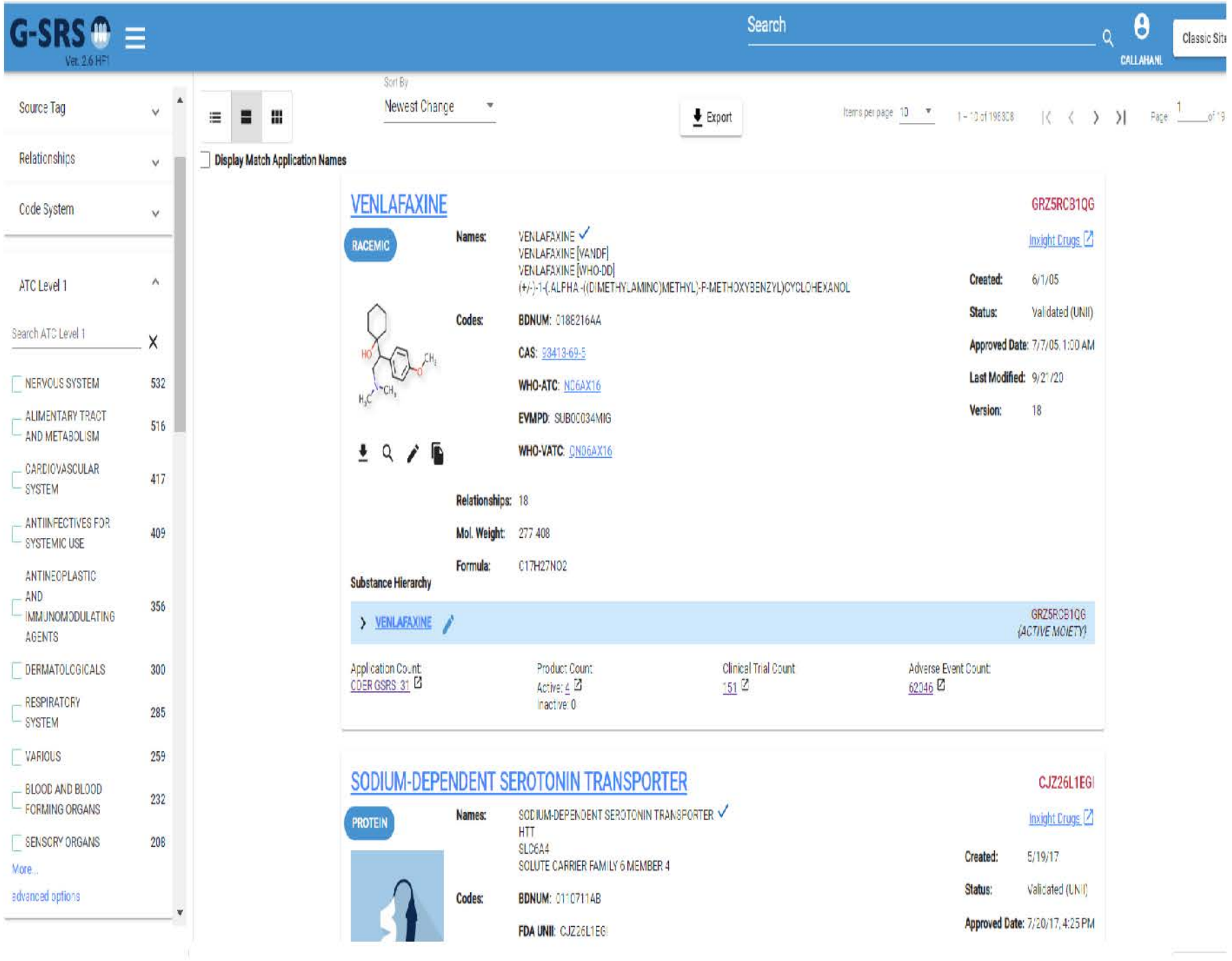
# Vaccine Initiative

- Working with WHO-UMC center to have common identifier for vaccines
- Vaccines are the most important public health tool we have
- No common nomenclature names vary significantly throughout the world
- UMC has set up a site for registration of Vaccine ingredients and related substances
- Used to workout common controlled vocabulary, possible global identifier
- Could be expanded to cover other substances
- US will enter Covid vaccines (phase 3), EU will transfer their vaccines
- Pilot Complete by September
- Industry involvement at some point

# In-vitro Clin Pharm Initiative

- Working with the Pistoia Alliance to develop data standards for in-vitro pharmacology data
- Scope of data determined
  - Metabolites
  - Metabolic Enzymes
  - Transporters
  - Receptors (Safety)
  - Ionic channels
  - Kinases
- Teams being set up
- Quick development in sync with GSRS


G-SRS
Ver. 2.6 HF1
Search
Search
Search GSRS
Browse All Substances
Browse All Applications
Browse All Clinical Trials
Structure Search
Sequence Search
Advanced Search
Product
Application
Clinical Trial
Biomarker
Indication/Sponsor
Adverse Event
Register
Register a Substance
Chemical
Protein
Polymer
Nucleic Acid
Structurally Diverse
Concept
Mixture
Other Registration
Specified Substance Group 1
Specified Substance Group 2
Specified Substance Group 3
Specified Substance Group 4
Specified Substance Group 4 Manufacturing
Product
Application
Biomarker
Indication


G-SRS
Ver. 2.6 HF1
Search
CALLAHANL
Classic Site
Source Tag
Relationships
Code System
ATC Level 1
Search ATC Level 1
NERVOUS SYSTEM 532
ALIMENTARY TRACT AND METABOLISM 516
CARDIOVASCULAR SYSTEM 417
ANTIINFECTIVES FOR SYSTEMIC USE 409
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS 356
DERMATOLOGICALS 300
RESPIRATORY SYSTEM 285
VARIOUS 259
BLOOD AND BLOOD FORMING ORGANS 232
SENSORY ORGANS 208
More...
advanced options
Sort By
Newest Change
Export
Display Match Application Names
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VENLAFAXINE [VANDF]
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Inxight Drugs
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(ACTIVE MOIETY)
Application Count:
CDER GSRS 31
Product Count:
Active: 4
Inactive: 0
Clinical Trial Count
151
Adverse Event Count:
62046
SODIUM-DEPENDENT SEROTONIN TRANSPORTER
CJZ26L1EGI
PROTEIN
Names:
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HTT
SLC6A4
SOLUTE CARRIER FAMILY 6 MEMBER 4
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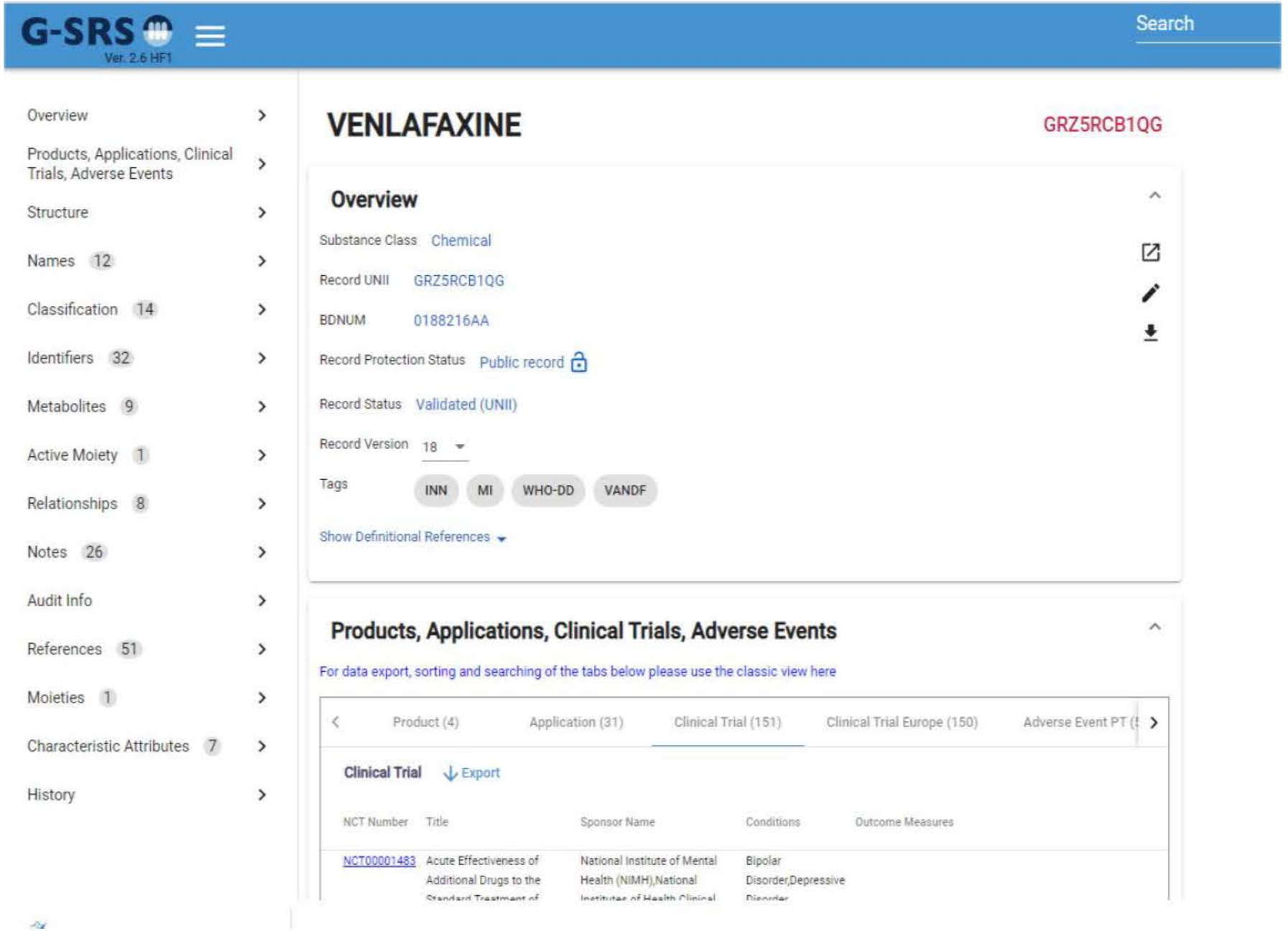
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Ver. 2.6 HF1
Search
Overview
Products, Applications, Clinical Trials, Adverse Events
Structure
Names 12
Classification 14
Identifiers 32
Metabolites 9
Active Moiety 1
Relationships 8
Notes 26
Audit Info
References 51
Moieties 1
Characteristic Attributes 7
History
VENLAFAXINE
GRZ5RCB1QG
Overview
Substance Class Chemical
Record UNII GRZ5RCB1QG
BDNUM 0188216AA
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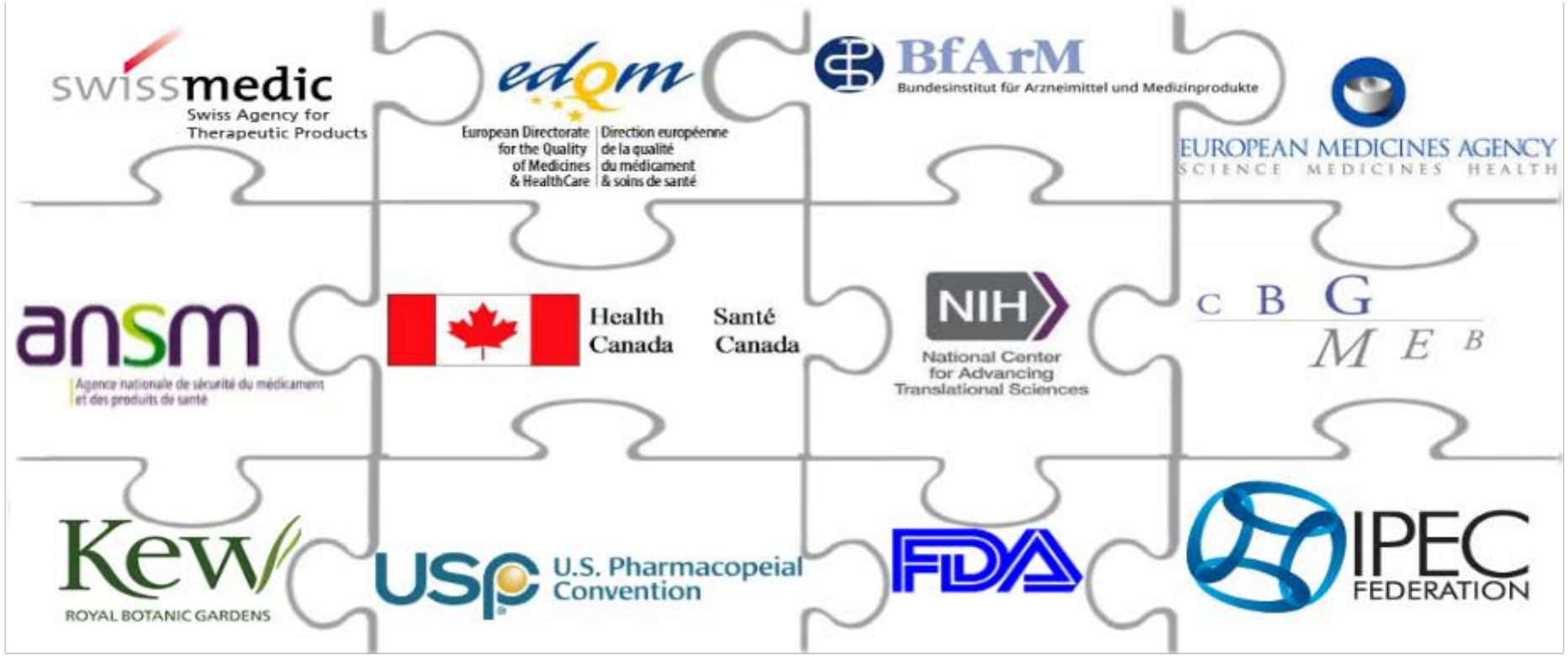
Record Status Validated (UNII)
Record Version 18
Tags INN MI WHO-DD VANDF
Show Definitional References
Products, Applications, Clinical Trials, Adverse Events
For data export, sorting and searching of the tabs below please use the classic view here
Product (4)
Application (31)
Clinical Trial (151)
Clinical Trial Europe (150)
Adverse Event PT
Clinical Trial
Export
NCT Number
Title
Sponsor Name
Conditions
Outcome Measures
NCT00001483
Acute Effectiveness of Additional Drugs to the
National Institute of Mental Health (NIMH),National
Bipolar Disorder,Depressive

# GSRS Public Resources

- To get the software and data from and info from NCATS
  - https://tripod.nih.gov/ginas
- NLM site for a list UNII codes
  - https://fdasis.nlm.nih.gov/srs/srs.jsp
- Paper on the GSRS.
  - Peryea, Tyler, et al. "Global Substance Registration System: consistent scientific descriptions for substances related to health." Nucleic Acids Research 49.D1 (2021): D1179-D1185.
- GInAS Meetings
  - Annual Meeting (USP, WHO-UMC, CBG have hosted)
- To Get on the GInAS Notification List
  - https://tripod.nih.gov/ginas

# Working Collaboratively



# Acknowledgements


**FDA Team**
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Takeshi Misu, Izumi Oba (PMDA)
Vik Srivastava, Craig Anderson (Health Canada)
Philipp Weyerman (Swiss Medic)

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**USP**
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Ta-Jen Chen, Randy Levin, Mary Ann Slack (FDA)
Christian Hay (GS1)
Pam Cafiero, Surenda Gokhale, William Gregory, Barry Hammond, Manabu Inoue; Kostas Kidos, Andrew Marr, Vada Perkins, Wolfgang Spiegl (Industry)
Paul Houston (EMA/CDISC)

**EDQM**
Claude Coune, Chris Jarvis (EDQM)

**Excipient Industry**
Dave Schonecker, Katherine Ulman


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# 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(R2)

# IND Safety Reports

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

| **Current Process:**<br><br>**PDFs in eCTD format** | **New Process:**<br><br>**ICH E2B XML files to FAERS** |
|---|---|
| • Inefficient and labor intensive review<br>  • ~50,000/yr<br><br>• Lack of universal tracking system | • Allows for use of data visualization and analytic tools for review and tracking<br><br>• Leverages existing processes in use for postmarket safety reporting (ICH E2B data standards & FDA gateway)<br><br>• 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

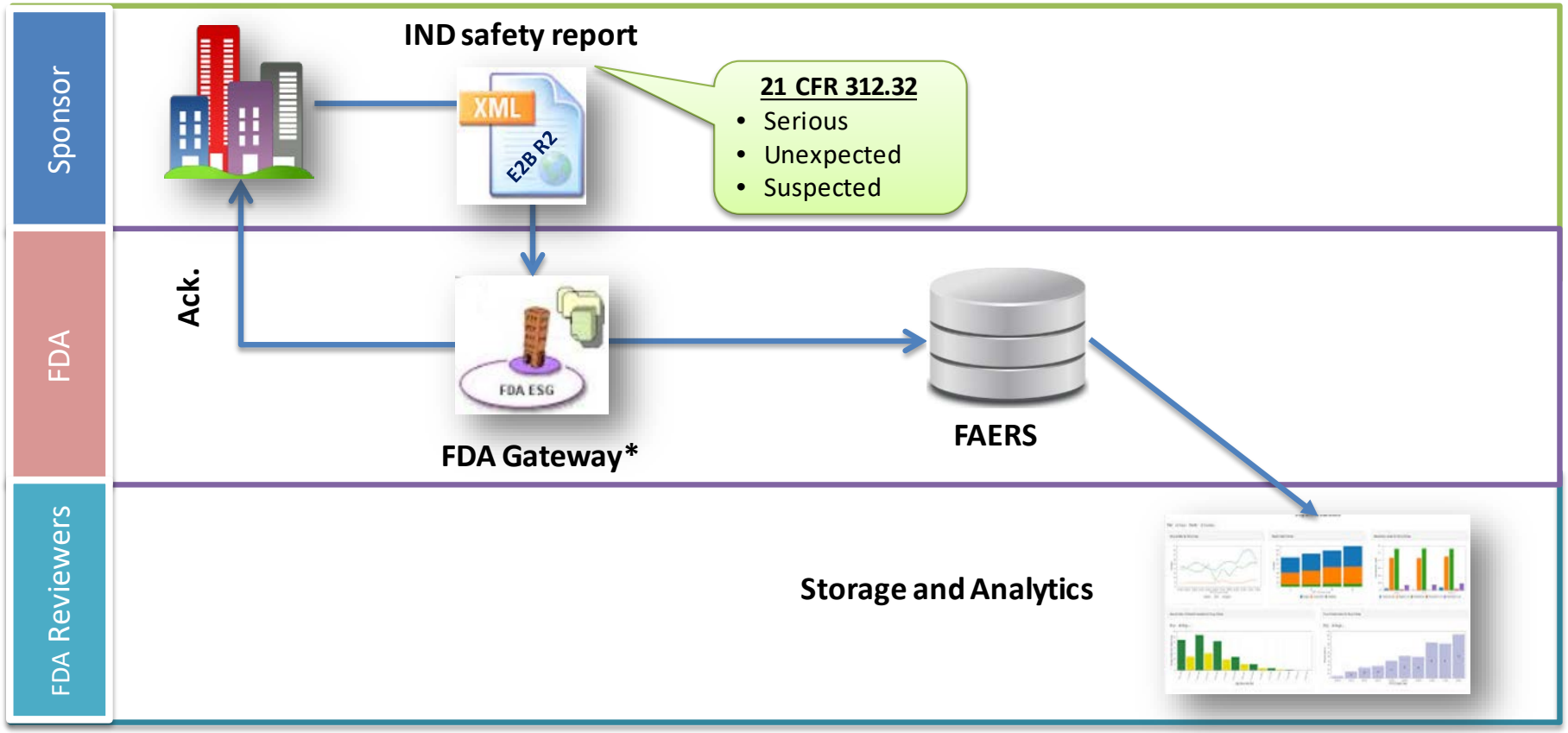
FDA will announce when the voluntary submission process will begin

*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)*
- *Electronic Submission of IND Safety Reports - Technical Conformance Guide (October 2019)*
- *Revised Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments (September 2019)*
- FAERS website updated with links 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<br>(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<br>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.<br>(21 CFR 312.32(c)(1)(i)(C) | X | |
| Findings from other studies<br>(21 CFR 312.32(c)(1)(ii)) | | X |
| Findings from animal or in vitro testing<br>(21 CFR 312.32(c)(1)(iii)) | | X |
| Increased rate of occurrence of serious suspected adverse reactions<br>(21 CFR 312.32(c)(1)(iv)) | | X |

# Technical Specifications

- *Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments* has been updated with information for IND reporting

- ICH E2B(R2) elements specific to IND safety reporting
  - IND numbers
  - Cross-reporting
  - Reports from aggregate analysis

# Technical specifications

- **IND numbers**
  - Data elements for IND number(s)
  - IND number where the event occurred (A.2.3.2)
  - *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(s) for cross-reported IND(s) placed in repeated block A.2
    - Repeat block A.2, only A.2.3.2 and A.2.3.3, 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 study ID field - 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
- The pre-market (IND) ICSR submission would include the study name and the study number

# Routing Mechanism - Triage of ICSRs

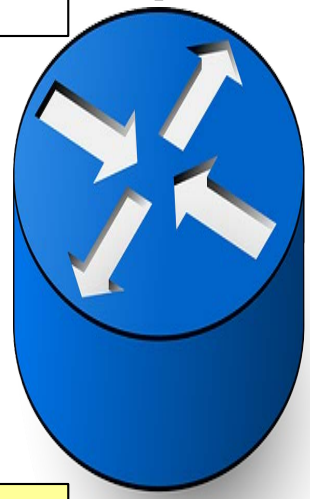
## Sponsor Submission

## FDA Adverse Event Reporting System

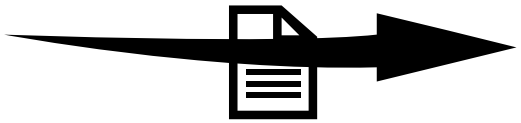
Pre-Market ICSR Submission

AS2* Header: AERS_PREMKT_CDER or
AS2 Routing ID: FDA_AERS_PREMKT_CDER

A.1.01: Sender's Report ID
A.1.4: 2
A.2.3.1: NCT+name
A.2.3.2: IND number
A.2.3.3: accordingly
…



A.1.01: Sender's Report ID + "-IND"
…
…
…



Post-Market ICSR Submission

AS2 Header: AERS or
AS2 Routing ID: FDA_AERS

A.1.01: Sender's Report ID
A.1.4: 1
A.2.3.1: empty
A.2.3.2: empty
A.2.3.3: empty
B.4.k.4.1: NDA 07852
…

A.1.01: 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 Data Elements are re-purposed and designated specifically for pre-market

# Routing Mechanism - Method 1

- **AS2 Header Attributes**
  - Current State: Post market reports (does not apply to pre-market)
    - Destination: "CDER" or "CBER"
    - Attribute values: "**AERS**" for XML's and "**AERS_ATTACHMENTS**" for PDF's
  - Future State: For IND reports, new header attributes setup/configure to route the files into the new folders (apply to pre market ICSRs based on Center)
    - Destination remains the same ("CDER" or "CBER)
    - Attribute values: "**AERS_PREMKT_CDER**" for XML's and "**AERS_ATTACHMENTS_PREMKT_CDER**" for PDF's
    - Attribute values: "**AERS_PREMKT_CBER**" for XML's and "**AERS_ATTACHMENTS_PREMKT_CBER**" for PDF's

*Note: Attribute value for PDF's is applicable only for E2B (R2) submissions. For E2B (R3) documents are embedded*

# Routing Mechanism - Method 2

- **AS2 Routing ID's** – using unique routing ID's
  - Current State: Post market reports (does not apply to premarket)
    - Routing ID's: "**FDA_AERS**" for XML's and "**FDA_AERS_ATTACHMENTS**" for PDF's
  - Future State: For IND reports, new Routing ID's setup/configure (apply to premarket ICSRs based on Center)
    - CDER Routing ID's: "**FDA_AERS_PREMKT_CDER**" for XML's and "**FDA_AERS_ATTACHMENTS_PREMKT_CDER**" for PDF's
    - CBER Routing ID's: "**FDA_AERS_PREMKT_CBER**" for XML's and "**FDA_AERS_ATTACHMENTS_PREMKT_CBER**" for PDF's

*Note: Routing ID's for PDF's is applicable only for E2B (R2) submissions. For E2B (R3) documents are embedded*

# Validate E2B Submission

- Provide a mechanism for industry to: i) Validate the regional E2B R2 and regional E2B R3 data files; ii) Convert regional E2B R2 to regional E2B R3 data file
- Mechanism can be used before production submission
- Mechanism available for use via a public URL
- Uploaded file are not stored
- Update FAERS Electronic Submission web page to provide this information

# Findings from the Pilot

- Logically designed, easy to use
- Ensures XML is formatted per FDA's technical specifications; sponsor does not have to learn XML and AS2
- Confirmation emails are sent to the person who submitted the report per email in registration form. If multiple individuals submit reports, make sure working as expected
- Data entry can be labor-intensive as there is no tool for uploading (e.g., from spreadsheet)
- May not match internal process currently in place (e.g., for collecting data from investigators) – could add time

# 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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# FDA Electronic Common Technical Document (eCTD) Update

PDUFA VI
Public Meeting on
Electronic Submissions and Data Standards

April 07, 2021

Mark Gray, Senior Project Manager CBER/DSS

# Agenda

- eCTD Guidance Updates
- eCTD Module 1 Specification Notice
- eCTD v4.0 Update



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# eCTD 745A(a) Guidance

Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (Revision 7)

- Published February 21, 2020
- https://www.fda.gov/media/135373/download
- Updates
  - Exemption for DMF Type III submissions
  - Long-term Waivers
    - 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
    - Granted waivers are valid for 5-years



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# eCTD 745A(a) Guidance (continued)

- Short-term Waivers: FDA will grant short-term waivers from the eCTD requirement only in unique and rare circumstances and for a limited duration
  - Extraordinary events or circumstances beyond the control of the submitter that justify a waiver, including but not limited to, natural disasters that impact computer operations.
  - An unplanned long-term internet disruption or other unplanned event that would preclude the sponsor from submitting in eCTD format (e.g., malware attacks).
- Waiver Process
  - CDER: email esub@fda.hhs.gov
  - CBER: email esubprep@fda.hhs.gov
  - *Please review the guidance for waiver criteria and process requirements; all details are not included in this presentation*



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# Important Notice about eCTD Module 1 Specification

- *Starting March 1, 2022*, the older version of M1, utilizing DTD 2.01, will no longer be supported. The current version of M1, utilizing DTD 3.3, will be required to pass validation.

- For more information, please see
  - Federal Register Notice located here: https://www.regulations.gov/document?D=FDA-2018-D-1216-0017
  - eCTD Submission Standards located here: https://www.fda.gov/media/93301/download



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# eCTD v4.0 Update – ICH M8 Activities

- Q&A Updates
  - Keywords
    - Business rules and validation
    - Document Type keywords to facilitate the transition to eCTD v4.0
  - Specification for Submission Format
- ICH M8 finalizing an update to the ICH eCTD v4.0 Implementation Package
- Regional Implementation Information posted on the ICH eCTD v4.0 webpage
  - Regional planned Technical Pilots & Implementation Dates
  - Links to regional Implementation Documents



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# 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
- Changes include
  - Removal of the following:
    - Two-way communications and associated data elements
    - Regulatory Review Time
    - Applicant DUNS Number
    - Document media type (future use)
    - Category Event
  - Submission folder structure update
  - Additional instructions for grouped submissions


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# eCTD v4.0 Update – FDA Implementation Strategy

- FDA is working with our vendor to incorporate eCTD v4.0 functionality
  - Initial release October 2021
  - FDA plans to engage with a limited number of industry stakeholders in 2022 to plan and carryout testing
- Initial release/acceptance for new applications in eCTD v4.0
  - Allows for development of eCTD v4.0 applications across regions
- Future phases
  - Transition of current applications
  - Two-way communication



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# eCTD v4.0 Enhancements

- ***Enhanced control of dossier***
  - Enhanced Life-cycle control: one-to-one, one-to-many, many-to-one
  - Simple reuse of previously submitted documents
  - Keyword/attribute modifications
  - Document Ordering: explicitly define display order for documents in a specific section
  - New eCTD v4 Keyword "Group Title"
    - Sponsors can use group titles based on M4 Granularity Document where "One or multiple documents can be submitted"
- ***Message structure & flexibility***
  - Harmonized design for regional and ICH requirements
  - One xml message (no more STFs)
  - Message is managed through the use of controlled vocabularies
    - For example, heading/section changes will not require modification of the standard
- ***Support for two-way communication (Regional)***
  - The regulatory authority can use eCTD v4.0 to send correspondence to the submitter



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# 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



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# 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/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm309911.htm)
  - FDA eCTD v4.0 M1 Implementation Package
  - eCTD v4.0 Technical Conformance Guide
  - Link to ICH eCTD v4.0 webpage



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# Thank you

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# FDA Study Data Technical Rejection Update

PDUFA VI

Public Meeting

April 7, 2021

# Agenda

- Technical Rejection Criteria for Study Data (TRC) – What's New
- FDA's Study Data Guidance and Requirements
- TRC Conformance Statistics and Trends
- Addressing the Most Common TRC Errors
- Summary

# Technical Rejection Criteria for Study Data (TRC) – What's New

# Technical Rejection Criteria for Study Data – What's New

- TRC effective date published on FDA's *Electronic Common Technical Document (eCTD)* web page and within TRC document
- Warning notice if submission contained study information and failed eCTD validations in TRC
  - CDER sending notice in ESG 3rd acknowledgement
  - CBER sending notice from CBER-edata account
- Starting Sept 15th, 2021, if submission contains study information and fails eCTD validations in TRC, CDER and CBER will reject

# FDA's Electronic Common Technical Document (eCTD) web page was updated on March 5th 2021

## Study Data Standards Resources

Subscribe to Email Updates | Share | Tweet | Linkedin | Email | Print

Study data standards describe a standard way to exchange clinical and nonclinical study data. These standards provide a consistent general framework for organizing study data, including templates for datasets, standard names for variables, identify appropriate controlled terminology and standard ways of doing calculations with common variables. Data standards also help FDA receive, process, review, and archive submissions more efficiently and effectively.

**Quick Links**

- Data Standards Catalog v7.0 (March 15, 2021)
- Study Data Technical Conformance Guide v4.6 (November 2020)

This Study Data Resources page includes required items and helpful tools for submission of study data to FDA's Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), and Center for Devices and Radiological Health (CDRH).

**1. FDA Data Standards Catalog**

FDA accepts electronic submissions that provide study data using the standards, formats, and terminologies described in the FDA Data Standards Catalog.

- FDA Data Standards Catalog v7.0 (XLS -71KB) (March 15, 2021)

## Electronic Common Technical Document (eCTD)

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The eCTD is the standard format for submitting applications, amendments, supplements, and reports to FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).

### Important Dates

Reminder: Per Providing Regulatory Submissions In Electronic Format — Standardized Study Data, Guidance for Industry, electronic submission of standardized study data is required for NDA, BLA, ANDA, and Commercial IND. FDA plans to implement eCTD validation checks when submissions contain content under modules 4 and 5 beginning **September 15, 2021**. Submissions which fail this validation will be subject to rejection. Please see the Technical Rejection Criteria for Study Data and the eCTD Validation Criteria (error code 1734, 1735, 1736, 1789) for details.

After the dates listed below, eCTD requirements for submissions to CDER and CBER will go into effect and submissions that do not use eCTD will not be filed or

**Quick Links**

- NDA to BLA eCTD Transition Instruction to Industry (PDF - 90 KB)
- eCTD Guidance (Final, Rev 7) (PDF -11 KB)
- eCTD Submission Standards (PDF - 91KB)
- FDA Data Standards Catalog
- eCTD Technical Conformance Guide (PDF - 303KB)
- Drug Master Files (DMFs)
- Technical Rejection Criteria for Study Data Information
- eCTD Submission Types and Sub-Types (PDF - 630 KB)

**Notices**

- FDA announces effective date for study data information NEW

# Technical Rejection Criteria updated on March 15th, 2021

The Technical Rejection Criteria (Revised 03/15/21) was updated to reflect the effective dates for implementation of the criteria and published to FDA's website on the *Study Data for Submission to CDER and CBER* web page.

**Technical Rejection Criteria for Study Data**

**Study data standards are required in clinical and nonclinical studies that start after December 17, 2016.[1] Technical rejection criteria have been added to the existing electronic common technical document (eCTD) validation criteria to enforce the deadlines below[2] and will become effective on September 15, 2021.**

## Study Data for Submission to CDER and CBER

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Data standards enable FDA to modernize and streamline the review process. They also enable more consistent use of analysis tools to better view drug data and highlight areas of concern.

Study data standards describe a standard way to exchange clinical and nonclinical research data between computer systems. These standards provide a consistent general framework for organizing study data, including templates for datasets, standard names for variables, and standard ways of doing calculations with common variables.

FDA is instituting new requirements for data standards that will apply to most study data submitted to FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).

**Stay Connected**

If you have study data questions for CDER, please contact the CDER eDATA Team at cder-edata@fda.hhs.gov.

For electronic submissions, contact the CDER Electronic Submission (ESUB) Support Team at esub@fda.hhs.gov.

If you have study data questions for CBER, please contact CBER-edata@fda.hhs.gov.

For electronic submissions, contact CBER ESUB at esubprep@fda.hhs.gov.

Beginning after the dates specified below, FDA may refuse to file for New Drug Applications (NDAs) and Biologics License Applications (BLAs) or refuse to receive for Abbreviated NDAs (ANDAs) any electronic submission whose study data do not conform to the required standards specified in the FDA Data Standards Catalog. See the Technical Rejection Criteria for Study Data (PDF) for more information. FDA conducted an analysis of study data conformance on submissions received during a

# Where to Find the TRC Effective Date

The Effective Dates for validation criteria 1734, 1735, 1736, and 1789 have been added to the "Technical Rejection Criteria for Study Data" and the "Specifications for eCTD Validation Criteria" documents.

| | |
|---|---|
| **Number:** | 1734 |
| **Group:** | General |
| **Description:** | A dataset named ts.xpt with information on study start date must be present for each study in Module 4, sections 4.2.3.1, 4.2.3.2, 4.2.3.4, and in 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 |
| **Severity Description:** | High |
| **US DTD Version** | 2.01 and 3.3 |
| **Effective Date:** | 9/15/2021 |

| | |
|---|---|
| **Number:** | 1735 |
| **Group:** | STF |
| **Description:** | The correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in Module 4, sections 4.2.3.1, 4.2.3.2, 4.2.3.4, and in 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 |
| **Severity Description:** | High |
| **US DTD Version** | 2.01 and 3.3 |
| **Effective Date:** | 9/15/2021 |

| | |
|---|---|
| **Number:** | 1736 |
| **Group:** | General |
| **Description:** | For Standard for Exchange of Nonclinical Data (SEND) data, a Demographic (DM) dataset and define.xml must be submitted in Module 4, sections 4.2.3.1, 4.2.3.2, 4.2.3.4<br><br>For Study Data Tabulation Model (SDTM) data, a DM dataset and define.xml must be submitted in 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<br><br>For Analysis Data Model (ADaM) data, an ADaM Subject level analysis dataset (ADSL) dataset and define.xml must be submitted in 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 |
| **Severity Description:** | High |
| **US DTD Version** | 2.01 and 3.3 |
| **Effective Date:** | 9/15/2021 |

| | |
|---|---|
| **Number:** | 1789 |
| **Group:** | STF |
| **Description:** | 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 |
| **Severity Description:** | High |
| **US DTD Version** | 2.01 and 3.3 |
| **Effective Date:** | 9/15/2021 |

# TRC Warnings

Sponsors will receive warnings from FDA when a TRC error is identified in submissions received between March 15 and September 15, 2021. Warning notices will specify each error and provide: Error Code; Error Reason; STF Study ID; eCTD Section (if applicable)

## CDER Notice included in the ESG 3rd Acknowledgement

ASR Successful and 3rd Acknowledgement PDF notification with
▼SPECIAL WARNING▼

Your submission has been successfully processed, however, during eCTD validation it was noted that this submission contains the following error information listed in the table below:

▼Warning: Per the 'Specifications for eCTD Validation Criteria', the severity level of the following error codes will be effective as a High error as of 09/15/2021

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

Note: If a study for this submission received validation error code 1734, the given study was not validated for other error codes 1735 and 1736

Warning: Per the 'Specifications for eCTD Validation Criteria', the severity level of the following error codes will be effective as a High error as of 09/15/2021

| Error Code | Reason | Findings |
|---|---|---|
| 1789 | Files in study sections without STF reference | m5/53-clin-stud-rep/535-rep-effic-safety-stud/confusion/5351-stud-rep-contr/uat-1/rptamnd-1.pdf [a5] |

This is an informational notice that after 09/15/2021 submissions with an error code, where the error code corresponds to a particular study data format requirement, will be rejected per the published Technical Rejection Criteria for Study Data/Specifications for eCTD Validation Criteria (https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd), as discussed in the eCTD guidance, Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.

**Application Type/Number:** NDA444493
**eCTD Sequence Number:** 0006
**CoreID:** ci1613111075001.2641324_Test@fdsuv08654_te1

## CBER Warnings sent from the CBER-edata account

Dear XXXXX,

Your submission below was successfully processed on MM/DD/YYYY.

**Application Type/Number:** BLA XXXXXX
**eCTD Sequence Number:** XXXX

However, during eCTD validation it was noted that this submission contains the following error information listed in the table below:

▼Warning: future High error for study data as specified in the Study Data Technical Rejection Criteria

1734, 1735, 1736 Template Table

| Error Code | STF Study ID | eCTD section | Error Reason |
|---|---|---|---|
| 1734 | YHTEST1 | 5.3.5.2 | Invalid Start Date format in ts.xpt |

Note: If a study for this submission received validation error code 1734, the given study was not validated for other error codes such as 1735 and 1736

1789 Template Table

| Error Code | Reason | eCTD section | Findings |
|---|---|---|---|
| 1789 | A file has been submitted in a study section without providing an STF file. | 5.3.5.1 | m5/53-clin-stud-rep/531-rep-biopharm-stud/5312-compar-ba-be-stud-rep/ome-rm02-001/stf-ome-rm02-001.xml [N4765450c17914e3fa2e5314c71db1459STF] |
| 1789 | A file has been submitted in a study section without providing an STF file. | 5.3.5.1 | m5/53-clin-stud-rep/531-rep-biopharm-stud/5312-compar-ba-be-stud-rep/ome-rm02-001/stf-ome-rm22222-001.xml [N4765450c17914e3fdfdfg45dfgdgd5314c71db1459STF] |

This is an informational notice that after *September 15, 2021* submissions with an error code, where the error code corresponds to a particular study data format requirement, will be rejected per the published Technical Rejection Criteria for Study Data/Specifications for eCTD Validation Criteria (https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd), as discussed in the eCTD guidance, Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.

# FDA's Study Data Guidance and Requirements

# Purpose of eCTD and Study Data Requirements

- Reviewing study data in a timely manner is critical for FDA's review process (e.g. Reviewers have 30 days to review an IND application)
- When sponsors submit data to the FDA in a reliable and accessible format, it improves efficiency and consistency of review decisions
- CDISC Standards enable FDA to streamline the review process:
  - Reduce time for reviewers to locate and identify study data
  - Reduce the burden on sponsors and reviewers from IRs (Information Requests)
  - Reduce review time by enabling the use of COTS reviewer's tools such as JReview, JMP Clinical, etc. to automate review analyses
  - Support data driven decisions by applying data mining and data analytic techniques

**"The agreement to assemble all the Quality, Safety and Efficacy information in a common format (called CTD - Common Technical Document ) has revolutionized the regulatory review processes, led to harmonized electronic submission that, in turn, enabled implementation of good review practices. For industries, it has eliminated the need to reformat the information for submission to the different ICH regulatory authorities."**

Source: https://www.ich.org/products/ctd.html

# FDA Guidance and Data Standards Catalog

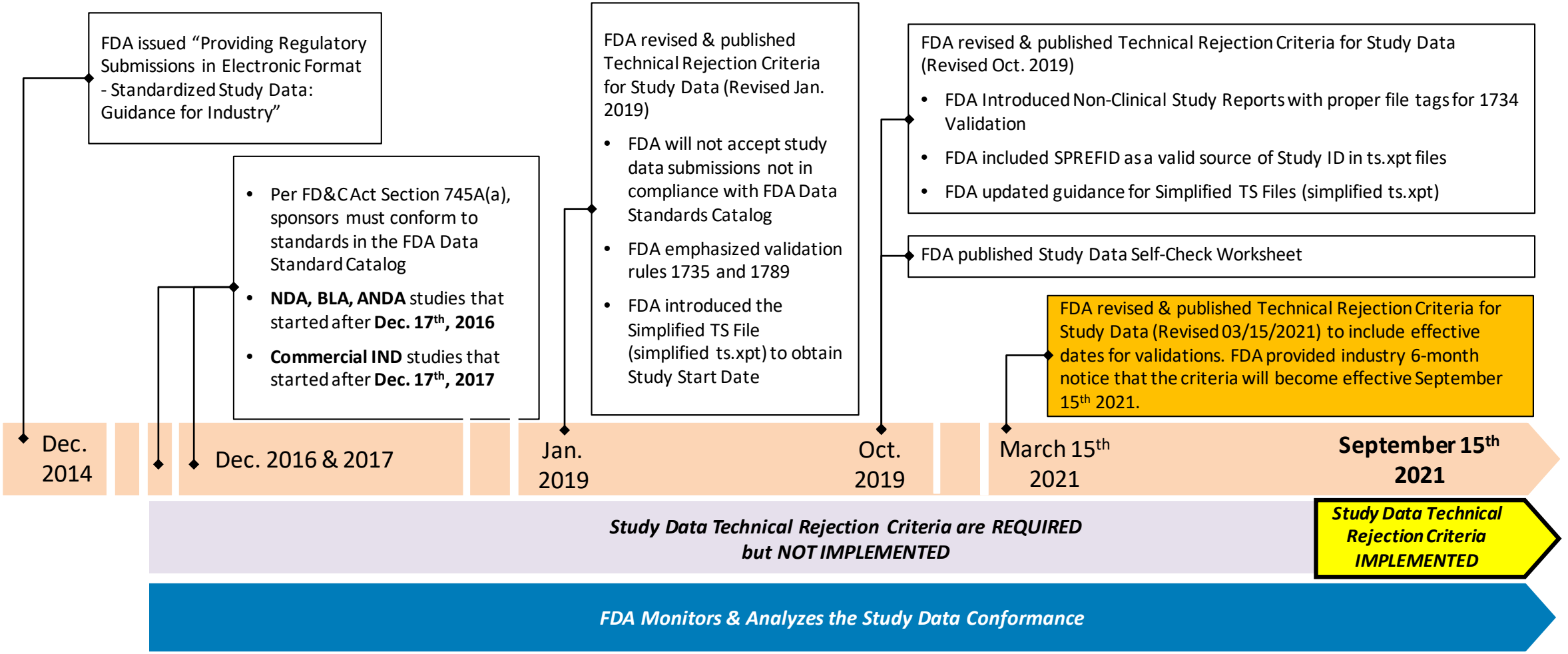
- Per FD&C Act Section 745A(a), drug application sponsors must use the standards defined in the FDA Data Standards Catalog starting 24 months after final guidance for a specific submission type
- FDA issued "Providing Regulatory Submissions in Electronic Format - Standardized Study Data: Guidance for Industry" in December 2014 (updated in October 2020)
- Sponsors must conform to standards in the FDA Data Standards Catalog:
  - NDA, BLA, ANDA studies that started after December 17th, 2016
  - Commercial IND studies started after December 17th, 2017
- Sponsors are obligated to meet Technical Rejection Criteria for Study Data which determine whether a submission complies with FDA's standards for study data



**Even if your study started prior to the dates above, it will need to include a trial summary file (contains the study start date and/or reason code for standardized data not applicable) if files are submitted under sections listed in the Technical Rejection Criteria for Study Data**

# Technical Rejection Criteria Revisions Timeline

**September 15th 2021:** The eCTD validations listed in the Technical Rejection Criteria become effective. FDA will reject submissions that fail these validations.



# FDA Technical Rejection Criteria for Study Data (SDTRC)

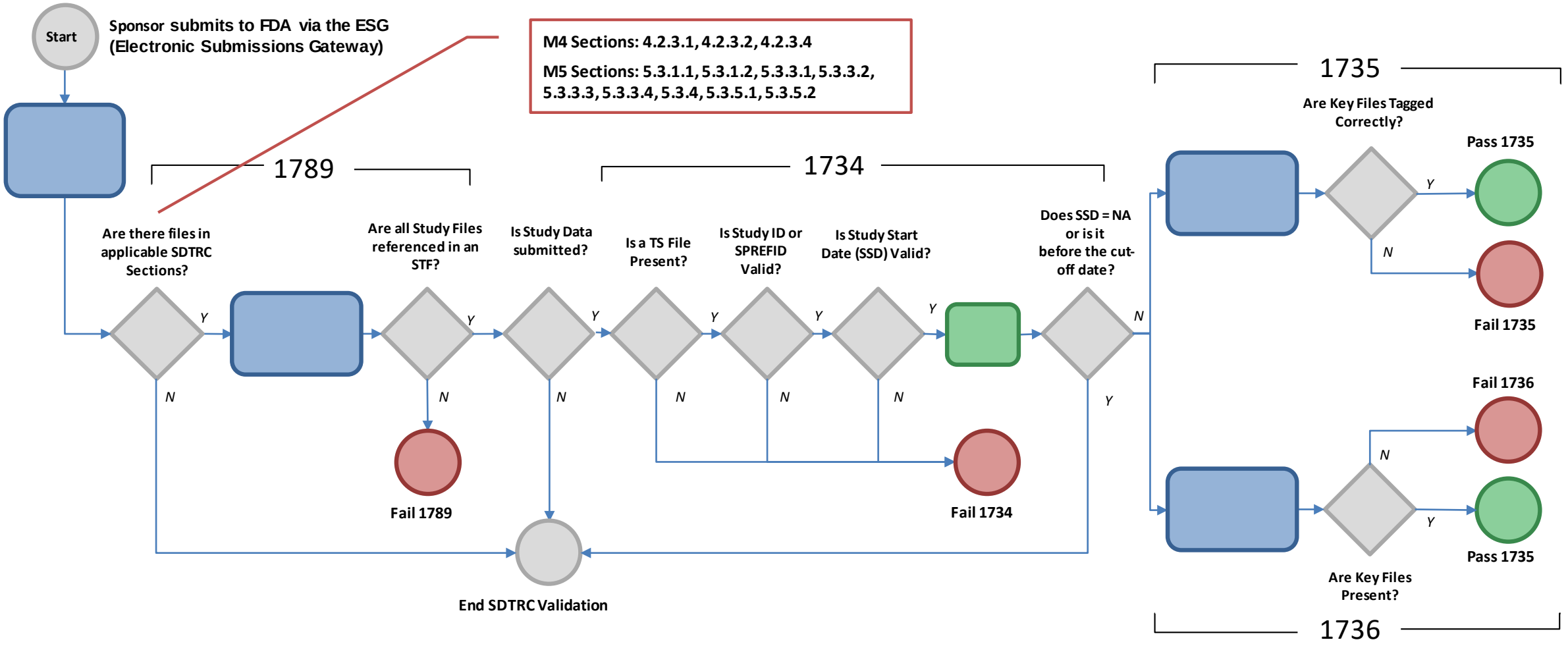
- Study Data Technical Conformance Guide provides technical recommendations for submitting study data according to CDISC standards

- Technical Rejection Criteria for Study Data provides the conditions under which FDA will not accept submissions with study data

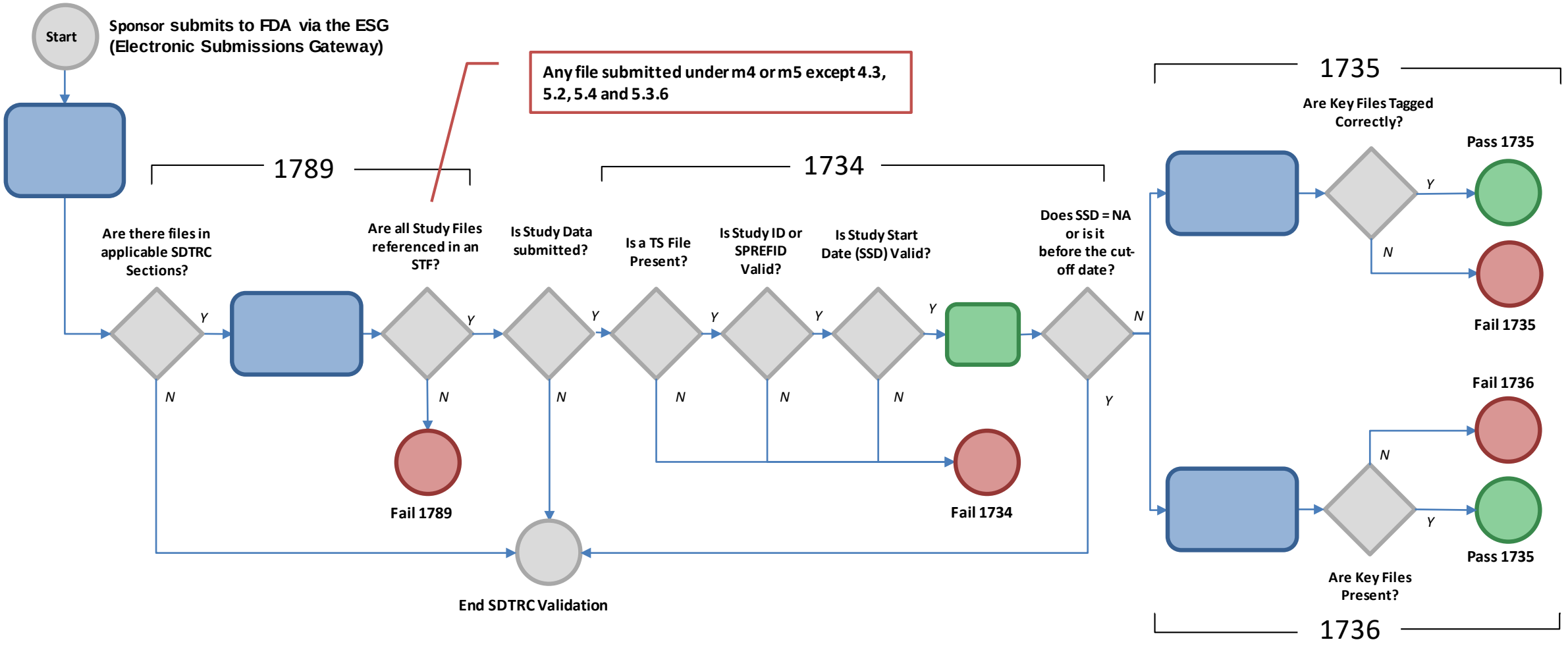
| Error | Description (Reference to FDA Study Data Technical Rejection Criteria March 2021 version) | Severity Level |
|---|---|---|
| 1734 | A dataset named ts.xpt with information on study start date must be present for each study in required sections* | High |
| 1735 | The correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections* | High |
| 1736 | For Standard for Exchange of Nonclinical Data (SEND) data, a Demographic (DM) dataset and define.xml must be submitted in Module 4 required sections*<br>For Study Data Tabulation Model (SDTM) data, a DM dataset and define.xml must be submitted in Module 5 required sections*<br>For Analysis Data Model (ADaM) data, an ADaM Subject level analysis dataset (ADSL) dataset and define.xml must be submitted in Module 5 required sections* | High |
| 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 | High |

** 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*

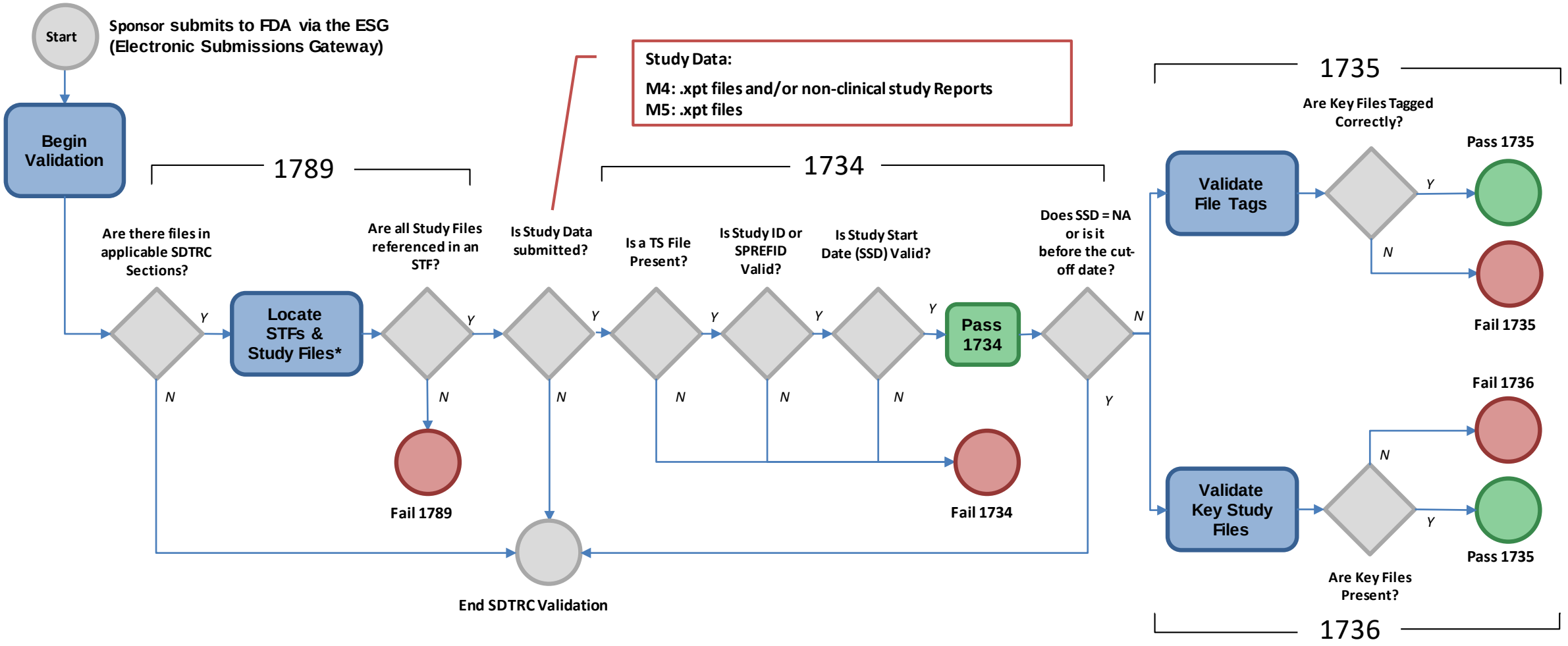
# TRC Validation Rule Testing



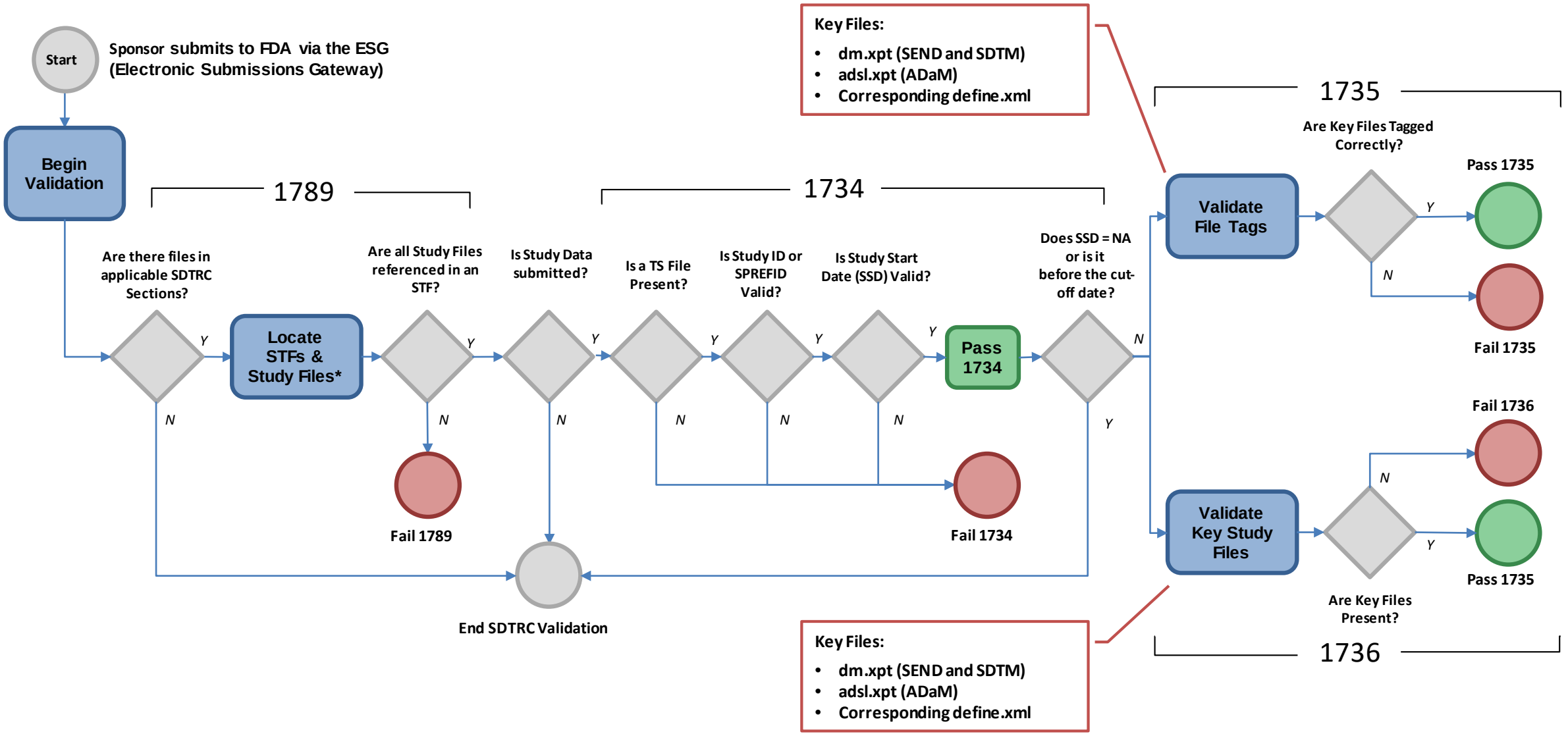
# TRC Validation Rule Testing



# TRC Validation Rule Testing



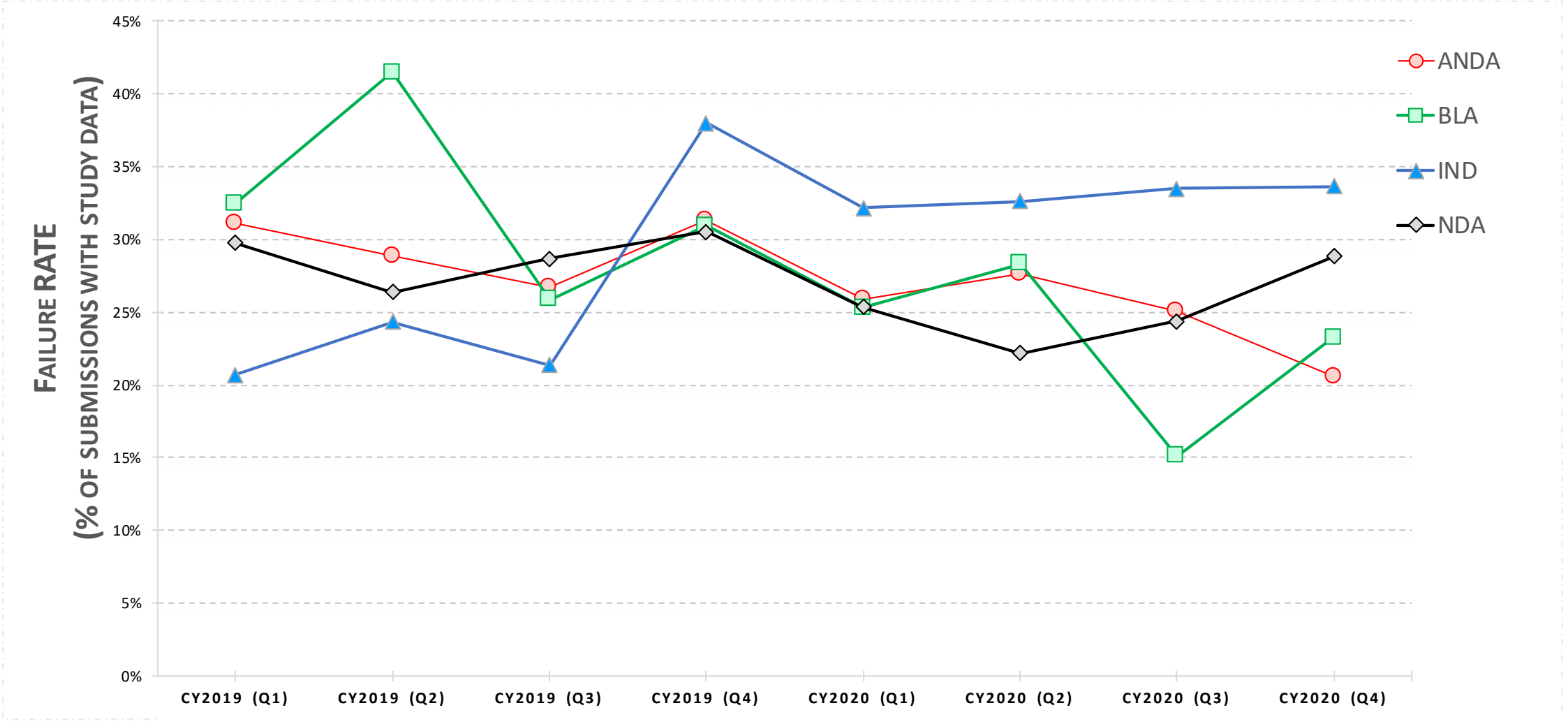
# TRC Validation Rule Testing



# TRC Conformance Statistics and Trends

# CDER CY2019 & CY2020 Conformance Trend:

## TRC Validation Errors 1734 & 1736




**Notes:**

1) CY2019 and CY2020 analysis was conducted according to the TRC (Revised Oct. 2019)
2) Analysis includes NDA, BLA, ANDA and Commercial IND Sequence received by CDER between 1/1/2019 and 12/31/2020
3) Validation of error 1736 is not performed if a study has error 1734
4) M4 Definition of Study Data - .xpt files and/or a Study Report tagged as pre-clinical-study-report, legacy-clinical-study-report, or study-report-body present in eCTD module 4
5) M5 Definition of Study Data - .xpt files present in eCTD module 5

# CDER CY2020 Submission Level Conformance:
## Validation Errors 1734 & 1736

ANDA, NDA, BLA, and Commercial IND Submissions received by CDER between 1/1/2020 and 12/31/2020, were assessed for conformance to the two high-level errors as revised in the Technical Rejection Criteria for Study Data (Revised March 2021)

| | | ANDA | BLA | NDA | Comm. IND** | All |
|---|---|---|---|---|---|---|
| a | **Total Number of Submissions** | 61,525 | 19,808 | 55,817 | 95,222 | 232,372 |
| b | **Total Number of Submissions with Study Data*** | 704 | 388 | 1073 | 3291 | 5456 |
| c | **Total Number of Submissions with Study Data* in TRC Applicable Sections** | 635 | 268 | 693 | 1907 | 3503 |
| d | **Total Number Submissions with Critical Errors (e or f)** | **175** | **90** | **271** | **1086** | **1622** |
| e | **Error 1734** | 164 | 87 | 263 | 1045 | 1559 |
| f | **Error 1736** | 28 | 7 | 21 | 62 | 118 |
| g | **Failure Rate (% among submissions with Study Data* in TRC Applicable Sections) [d/c]** | 27.56% | 33.58% | 39.11% | 56.95% | 46.30% |
| h | **Failure Rate (% among submissions with Study Data*) [d/b]** | **24.86%** | **23.20%** | **25.26%** | **33.00%** | **29.73%** |
| I | **Failure Rate (% among all submissions) [d/a]** | 0.28% | 0.45% | 0.49% | 1.14% | 0.70% |

**Notes:**

1) CY2020 analysis was conducted according to the TRC (Revised Oct. 2019)
2) Analysis includes NDA, BLA, ANDA and Commercial IND Sequence received by CDER between 1/1/2020 and 12/31/2020
3) Validation of error 1736 is not performed if a study has Error 1734
4) * M4 Definition of Study Data - .xpt files and/or a Study Report tagged as pre-clinical-study-report, legacy-clinical-study-report, or study-report-body present in eCTD module 4
5) * M5 Definition of Study Data - .xpt files present in eCTD module 5
6) **Comm. IND Clinical studies are included in this analysis which constitutes a very small fraction of the total submissions with critical errors. Comm. IND clinical studies are not subject to errors 1734, 1735, 1736, or 1737

# CDER CY2020 Study Level Conformance for Validation Errors 1734 & 1736

- A high number of non-clinical (m4) studies fail Validation Rule 1734 because of a missing trial summary dataset
- A trial summary dataset (ts.xpt) is required when a non-clinical study report is submitted (TRC Revised March 2021)

| | | ANDA | | BLA | | NDA | | Comm. IND | Total | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| | | m4 | m5 | m4 | m5 | m4 | m5 | m4 | m4 | m5 |
| a | **Total Number of Studies*** | 45 | 1398 | 1041 | 796 | 5477 | 2556 | 33534 | 40097 | 4750 |
| b | **Total Number of Studies* in TRC Applicable Sections** | 15 | 1222 | 136 | 453 | 868 | 1645 | 5619 | 6638 | 3320 |
| c | **Total Number Studies with Critical Errors (d or f)** | **12** | **342** | **82** | **109** | **349** | **334** | **3272** | 3715 | 785 |
| d | **Error 1734** | 12 | 277 | 82 | 104 | 348 | 333 | 3173 | 3615 | 714 |
| f | **Error 1736** | 0 | 65 | 0 | 5 | 1 | 24 | 99 | 100 | 94 |
| g | **Error Rate (% among failed studies with Study Data* Data in TRC Applicable Sections**) [c/b]** | 80.0% | 28.0% | 60.3% | 24.1% | 40.2% | 20.3% | 58.2% | 55.97% | 23.64% |
| h | **Error Rate (% among Total Number of Studies) [c/a]** | **26.7%** | **24.5%** | **7.9%** | **13.7%** | **6.4%** | **13.1%** | **9.8%** | 9.27% | 16.53% |

**Notes:**

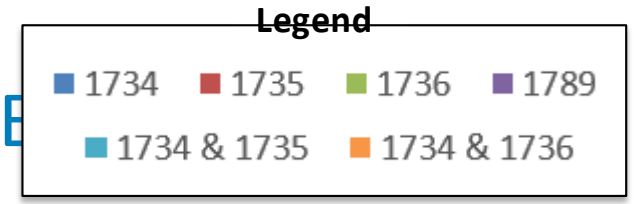
(1) CY2020 analysis was conducted according to the TRC (Revised Oct. 2019)

(2) Validation of errors 1736 is not performed if a study has Error 1734

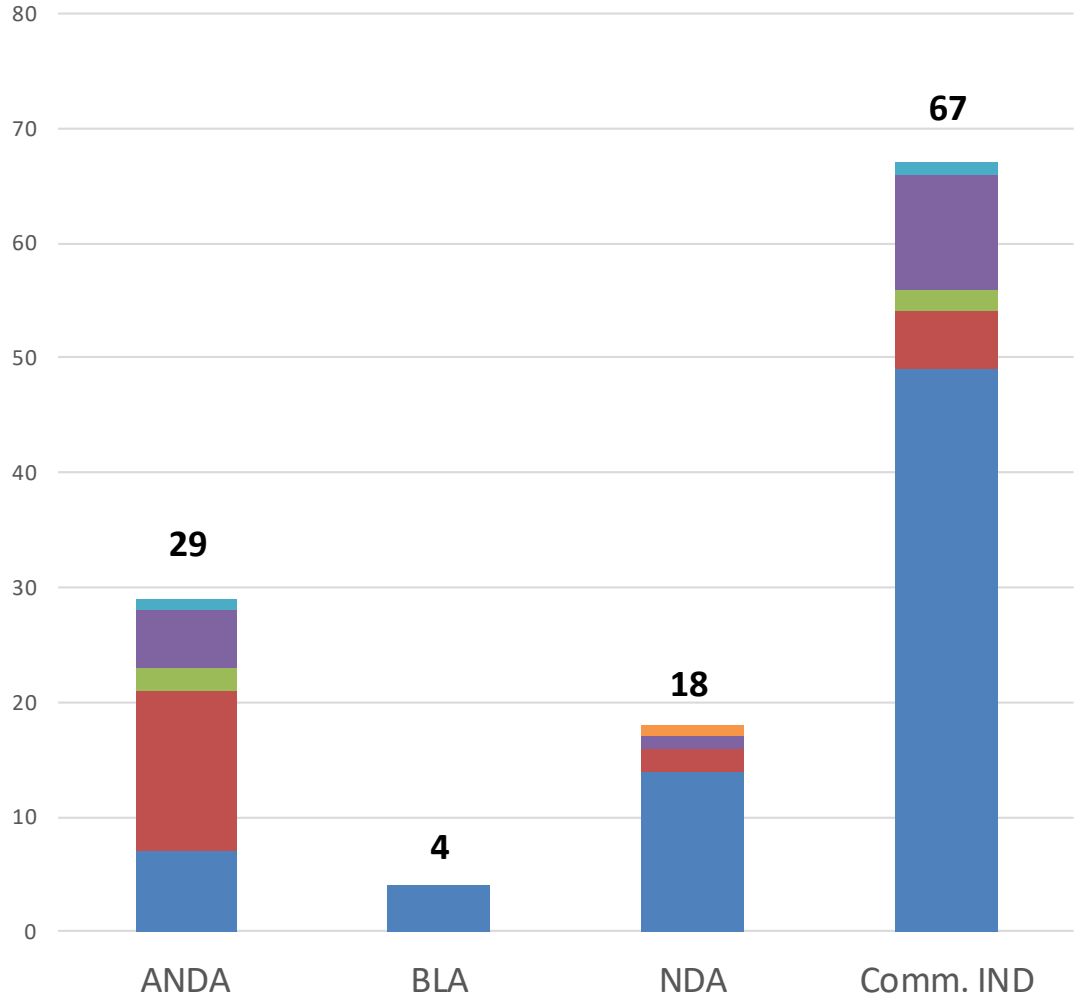
(3) *M4 Definition of Study - .xpt files and/or a Study Report tagged as pre-clinical-study-report, legacy-clinical-study-report, or study-report-body present in TRC applicable sections

(4) *M5 Definition of Study - .xpt files present in TRC applicable sections

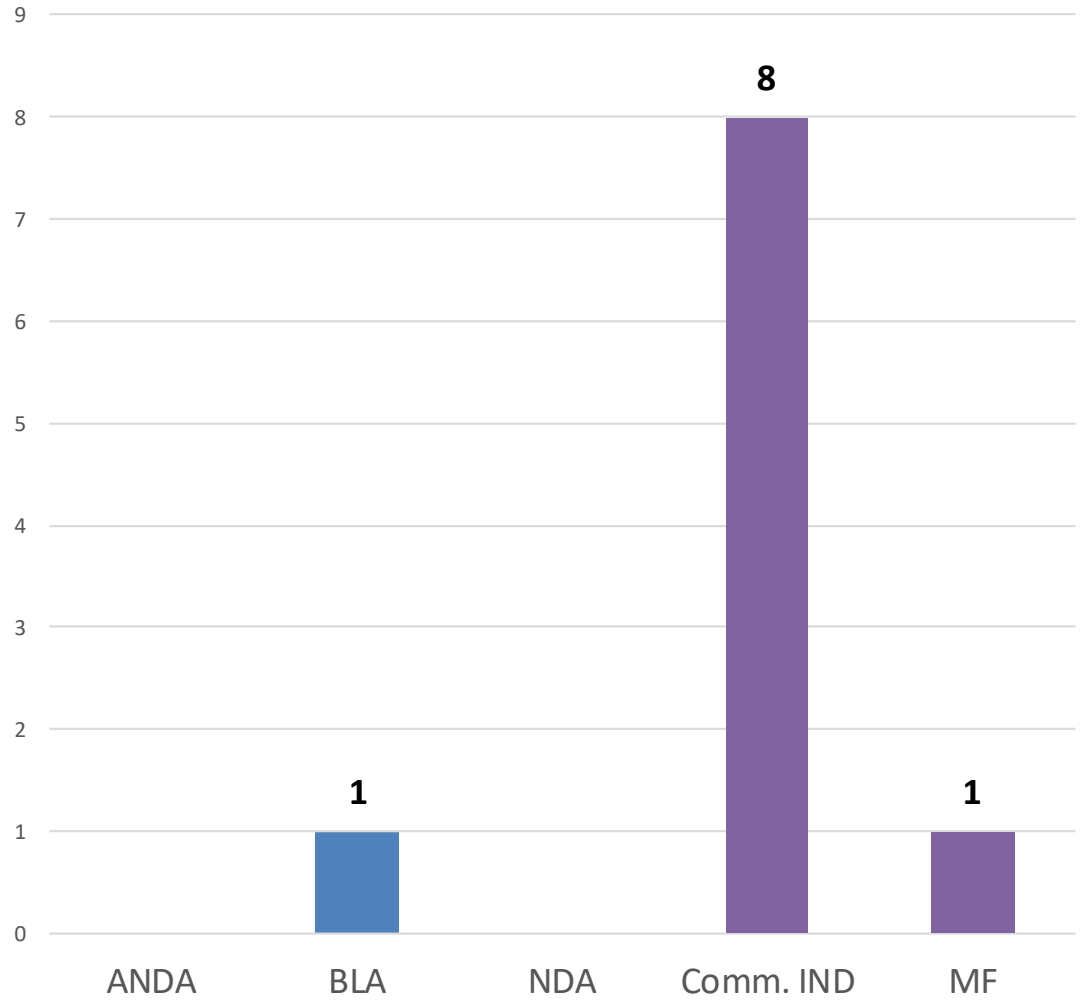
# Warnings from CDER & CE




## CDER 3rd Acknowledgement Warnings




## CBER Warnings




***Notes:*** *Metrics generated from data between March 15, 2021 and March 30, 2021*
*CBER SEND mandatory requirement starts March 15, 2023*
*Error 1789 applies to all application types*

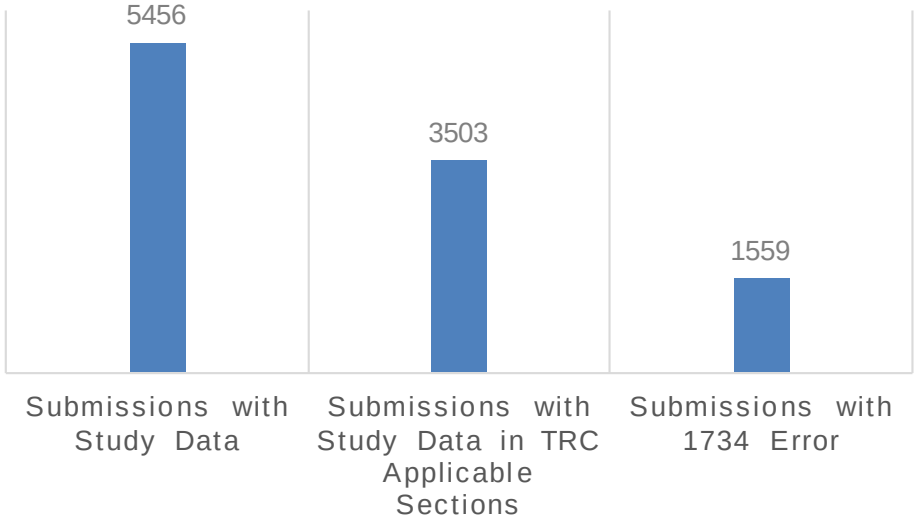
# Addressing the Most Common TRC Errors

# Most Common Error Reasons for Validation Rule 1734

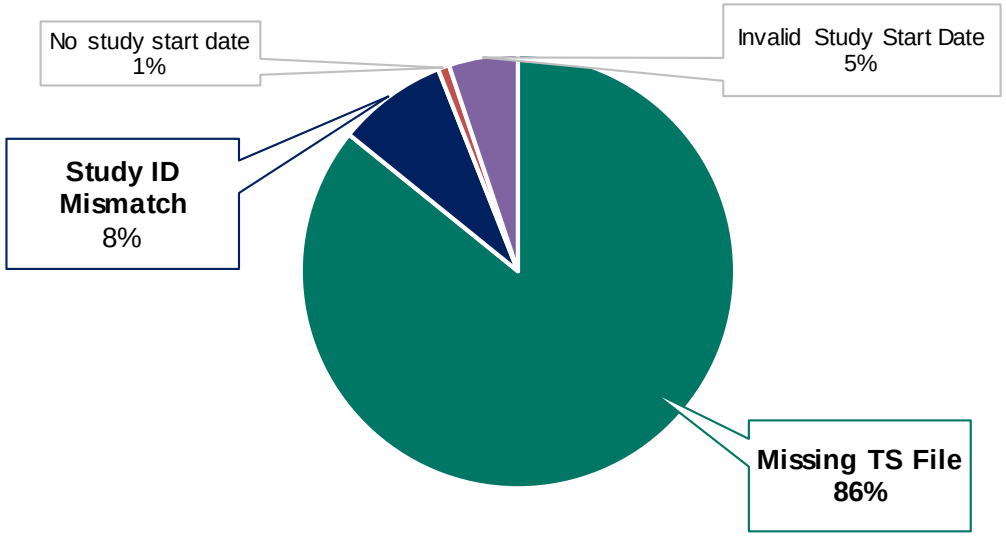
| Error | Description |
|---|---|
| **1734** | Trial Summary (TS) dataset (ts.xpt) with information on study start date must be present for required sections* |

- Common error reasons for all application types:
  - A missing ts.xpt file
  - Study ID Mismatch between TS and STF

**All Applications (Jan – Dec 2020)**




**4369 Studies with Error 1734****




** 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*

*** 4369 studies within 1559 different submissions*

# Missing TS Files for Non-Clinical Studies

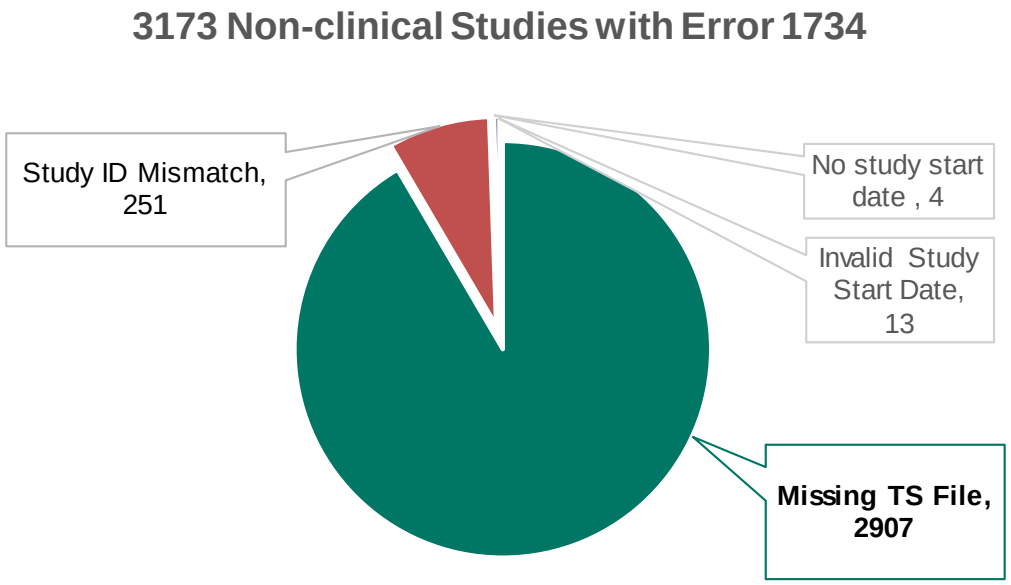
- 3,173 IND non-clinical studies fail for TRC rule 1734
- 2,907 of those studies fail due to a missing ts.xpt

| | Count |
|---|---|
| Studies with study data or reports | 2,907 |
| Studies with only study reports | 2,807 |

**2,907 IND non-clinical studies were missing the ts.xpt**

| Toxicology Sections | Count |
|---|---|
| Repeat dose toxicology (m4.2.3.2) | 2,115 |
| Single dose toxicology (m4.2.3.1) | 621 |
| Carcinogenicity (m4.2.3.4) | 171 |

**72.8% of the 2907 non-clinical studies with missing ts.xpt are in the repeat dose toxicology eCTD section**




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

# Missing TS File

| Study Report File Tag Criteria | | | | | |
|---|---|---|---|---|---|
| Study Start Date | Application Type | Data Type | Study Sections | Expectation by Center | |
| | | | | CDER | CBER |
| Prior to or on 17-Dec-2017 | Commercial INDs | Nonclinical | 4.2.3.1, 4.2.3.2, 4.2.3.4 | 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) | Rejection criteria will not be applied |
| | | Clinical | 5.3.1.1, 5.3.1.2, 5.3.3.1z, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2 | Rejection criteria will not be applied | |
| After 17-Dec-2017 | Commercial INDs | Nonclinical | 4.2.3.1, 4.2.3.2, 4.2.3.4 | Rejection criteria will be applied; submit a full TS | Rejection criteria will not be applied |
| | | 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 | Rejection criteria will not be applied | |
| Prior to or on 17-Dec-2016 | NDA, BLA, ANDA | Nonclinical | 4.2.3.1, 4.2.3.2, 4.2.3.4 | 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) | Rejection criteria will not be applied |
| | | 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 | Rejection criteria will be applied; submit a simplified TS if the study contains an xpt dataset (other than the ts.xpt) | |

# Missing TS File

- A Simplified ts.xpt file would be expected when a non-clinical study report is submitted but SEND datasets are not required
- Simplified ts.xpt:
  - Sponsors should submit a dataset named 'ts.xpt' with four variables: STUDYID, TSPARMCD, TSVAL, and TSVALNF
- Example of Simplified ts.xpt Dataset:

| STUDYID | TSPARMCD | TSVAL | TSVALNF |
|---|---|---|---|
| • Study ID in STF File | • SSTDTC for a clinical study<br>• STSTDTC for a nonclinical study | • Format: yyyy-mm-dd<br>• Left blank when study start date is not available or relevant | • Left blank when study start date is provided in TSVAL<br>• "NA" |

***References:***

*FDA Study Data Technical Conformance Guide (Version 4.6, November 2020)*

*FDA Technical Rejection Criteria for Study Data (Revised March 2021)*

# Tools for Industry

FDA has provided tools to help sponsors meet study data standard requirements and provide more transparency on the validation process.

**www.fda.gov**

**Sponsor reviews Study Data Standards & Resources:**

1. **Study Data Technical Rejection Criteria**
2. **Simplified TS File Generator Utility (PHUSE) & Simplified TS File Creation Guide**
3. **Study Data Self-Check Worksheet**

**Prepare Submission**

4. **Sponsor submits an eCTD and/or Standardized Data Sample to the FDA to receive feedback, highlighting errors found during processing of the sample**

**Gateway**

**Sponsor submits an application with study data**

1. **Technical Rejection Criteria for Study Data (Revised March 2021)**
   - Clarifies the requirements for eCTD Validation of submissions with study data
   - Provides a validation table and examples in Appendix 1 and Appendix 2 to illustrate the requirements
2. **Simplified TS File Generator Utility (PHUSE) & Simplified TS File Creation Guide**
   - Helps sponsors easily generate a Simplified TS file to provide a Study Start Date for a study

**3. Study Data Self-Check Worksheet**

- Helps sponsors understand criteria for submissions with study data to pass TRC validations
- Dynamically guides sponsors to prepare study data files according to TRC requirements

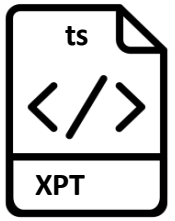
**4. eCTD and/or Standardized Data Sample Validation**

- Allows sponsors to validate sample submissions and receive feedback prior to submission

# Example: Simplified TS Files

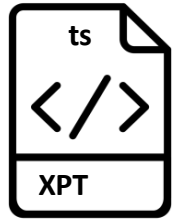
**Example of a Simplified TS file submitted for a non-clinical study with study-id "S107" in the STF file:**

| | STUDYID | TSPARMCD | TSVAL | TSVALNF |
|---|---|---|---|---|
| 1 | S107 | STSTDTC | 2014-10-26 | |




**Example of a Simplified TS file submitted for a non-clinical study with study-id "S107" in the STF file without a study start date:**

| | STUDYID | TSPARMCD | TSVAL | TSVALNF |
|---|---|---|---|---|
| 1 | S107 | STSTDTC | | NA |



# Summary

- Overall Error rate of TRC rule 1734 and 1736 has not significantly reduced from CY2019 to CY2020
- FR Notice was published (March 3rd, 2021) and announced an update to FDA Data Standards Catalog. Catalog contains a footnote stating TS.XPT file is required for studies
- TRC effective date published on FDA's *Electronic Common Technical Document (eCTD)* web page and in the TRC document
- ESG 3rd Acknowledgement from CDER now includes warning if submission contained study information and failed eCTD validations in TRC
- Starting Sept 15th, 2021, if submission contains study information and fails eCTD validations in TRC, CDER and CBER will reject

# References

## ❖ Study Data Standards Resources

- Providing Regulatory Submissions In Electronic Format - Standardized Study Data: Guidance For Industry [Oct 2020]
- Study Data Technical Conformance Guide [Nov 2020]
- FDA Data Standards Catalog [March 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 For Study Data [March 2021]
- 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

## ❖ 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

# Acknowledgments

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