U.S. Food and Drug Administration
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Substance Registration: Considerations for Maintenance and Governance

Vada A. Perkins

Chief, Business Operations Staff

FDA/CBER/OD

Mary Ann Slack

Deputy Director

FDA/CDER/OSP

Understanding the Internal/External Interface: Current Practice

- Substance registration and use maintained internally
  - Within the FDA firewall
  - Protection of confidential/trade secret information
- Updates from internal to external sources (public information) based on internationally accepted "sources of truth" and confidentiality/trade secret requirements
  - Potential for two-way communication
- To the extent it is public, regulators with legal requirements can publish once information is publicly available
  - Potentially GInAS (future state)

Substance Identification: In Regulatory Practice

- Regulators/Industry must understand and be provided with the defining elements and criteria associated with substance identification

- Industry/regulators should evaluate the substance information following established criteria
  - ***EN ISO 11238:2012(E)-***Data elements and structures for the unique identification and exchange of regulated information on substances
    - ISO DTS 19844 (substances implementation guide)

Substance Identification: Regulatory Use Cases (Product Lifecycle)

- **Investigational**
  - Clinical trials
    - Tracking formulation/dose changes throughout the investigational process
    - Goal: Associating substance to ***ALL*** investigational and marketed products throughout the FDA
  - Clinical trial registration requirements (Industry)
    - Repurpose
- **Pre-Market**
  - New drug/biologic review
  - Pre-approval inspections
- **Post-Market**
  - Pharmacovigilance
    - Adverse events/adverse drug reaction reporting
  - Compliance
    - Product-Establishment relationship
      - Supply chain
      - Counterfeiting
    - Import/export
    - Voluntary recalls

Regulatory Review Process for Product-Substance Association (US)

High Level Procedures

1. After an application is accepted from Industry, a request for a Unique Ingredient Identifier (UNII) is submitted by the FDA product office to FDA-SRS with the following information:
   a. Draft labeling
   b. List of ingredients (active and inactive)
   c. Additional information may be required

Note: Target timeframe for receipt of UNII Code assignment from FDA-SRS is ***4-6 weeks***

2. Forward the completed initial UNII Code assignment recommendation to the FDA product reviewer

Process within the US (cont.)

3. FDA product reviewer concurs with the identifying description based on his/her review of the application
   - If discrepancies are identified, consultation is initiated with the FDA-SRS team and/or the company to resolve any issues

4. FDA notifies the company through official regulatory communication of the UNII code assignment

Note: Information is validated once the electronic labeling file (HL7 SPL) is resubmitted to FDA for public posting via validation business rules. Files are rejected and submitted back to sender to address any deficiencies

Ensures that substance information associated with product(s) is verified and accurate to the greatest extent possible.

Fundamental Maintenance Organization (MO) Criteria

- ***Initial creation*** of the controlled vocabulary, including associated controlled sub-vocabularies;
- Change requests for both ***new and existing terms, non-preferred terms and synonyms***
- Process/procedure for handling multiple ***translations***
- Change requests for both ***new and existing underlying definitions***
- ***Up-to-date publication*** of change release documentation reflecting significant updates and additions
- Maintenance of the ***technical implementation of the structures*** in response to changes

ISO Draft Technical Report (DTR) 14872

- ISO is developing a draft technical report that describes the maintenance model and core principles for implementation and use of the suite of ISO Identification of Medicinal Products (IDMP) standards.
- ISO TR 14872 identifies fundamental requirements that an ISO IDMP MO should address:
  - Receiving requests for change
  - Categorization of changes
  - Authorization of changes
  - Producing change schedules
  - Planning/testing changes
  - Implementing changes
  - Reviewing the changes to ensure successful adoption/integration

***ISO ballot cycle complete with comment resolution underway**
2nd version of DTS 14872 for ballot due to ISO on 22 Aug 2014*

Working in Parallel…

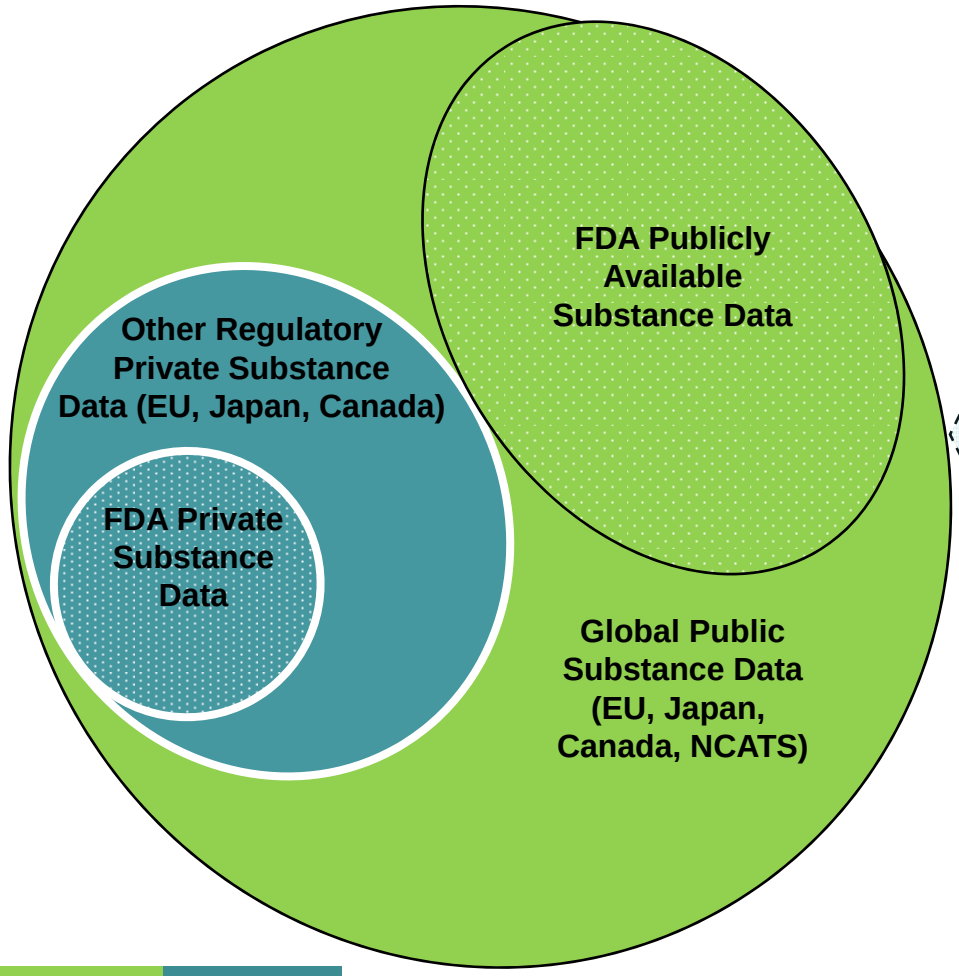
- FDA internal activities
  - Update FDA/SRS
    - *ISO 11238/DTS 19844 compliant

- GInAS activities
  - Provide an open source systems solution (NCATS) for substance identification
    - *ISO 11238/DTS 19844 compliant

**Important to ensure a universally accepted scientific approach (ISO TS 19844) for substance identification and term/ID assignment*

GInAS Potential – FDA's Perspective

Global Substance Data Landscape



Why ISO 11238?

- Facilitate harmonization of substance data across geographical boundaries
- To enable product information exchange
- Important element for interoperability across healthcare systems (requires consistent use of standard)

Benefits of an ISO-Compliant SRS

ISO 11238 based SRS satisfies the FDA's internal regulatory needs and external commitments

Agency Benefits (internal; private data)

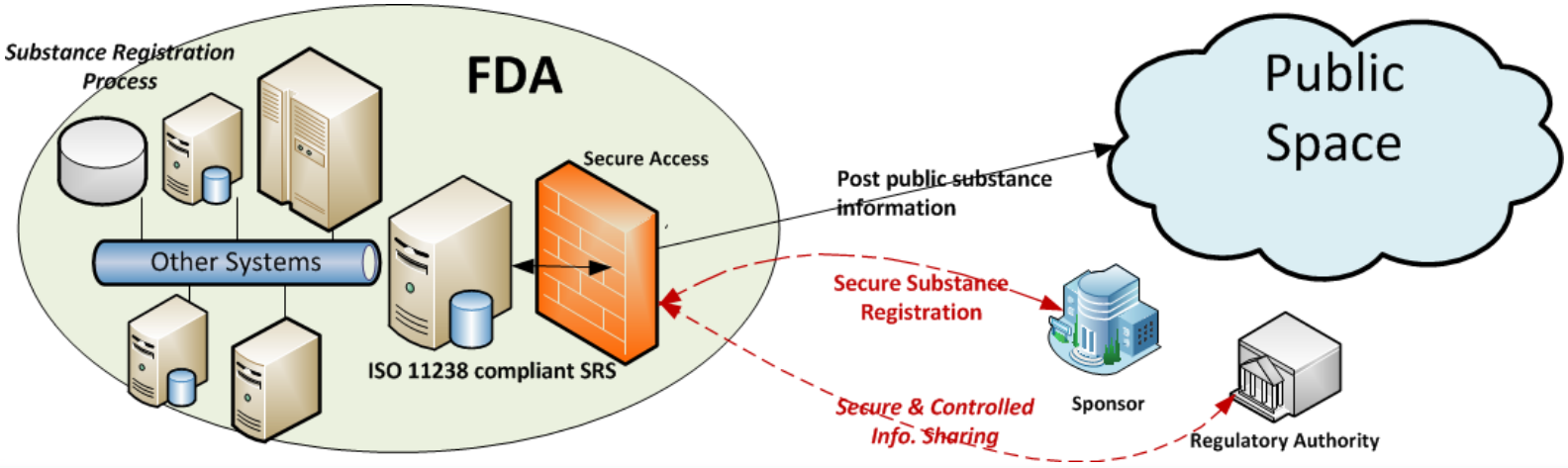
Investigational	• Helps track formulation/dose changes through the investigational process • Assists in monitoring constituent substances
Pre-Market	• Facilitate product review by detailing specific constituent substances • Enables better regulatory control
Post-Market	• Provides robust analytics capabilities in adverse events/drug reaction reporting • Provides stronger regulatory power for recalls, counterfeiting, and import/export

Collaboration Benefits (external; public data)

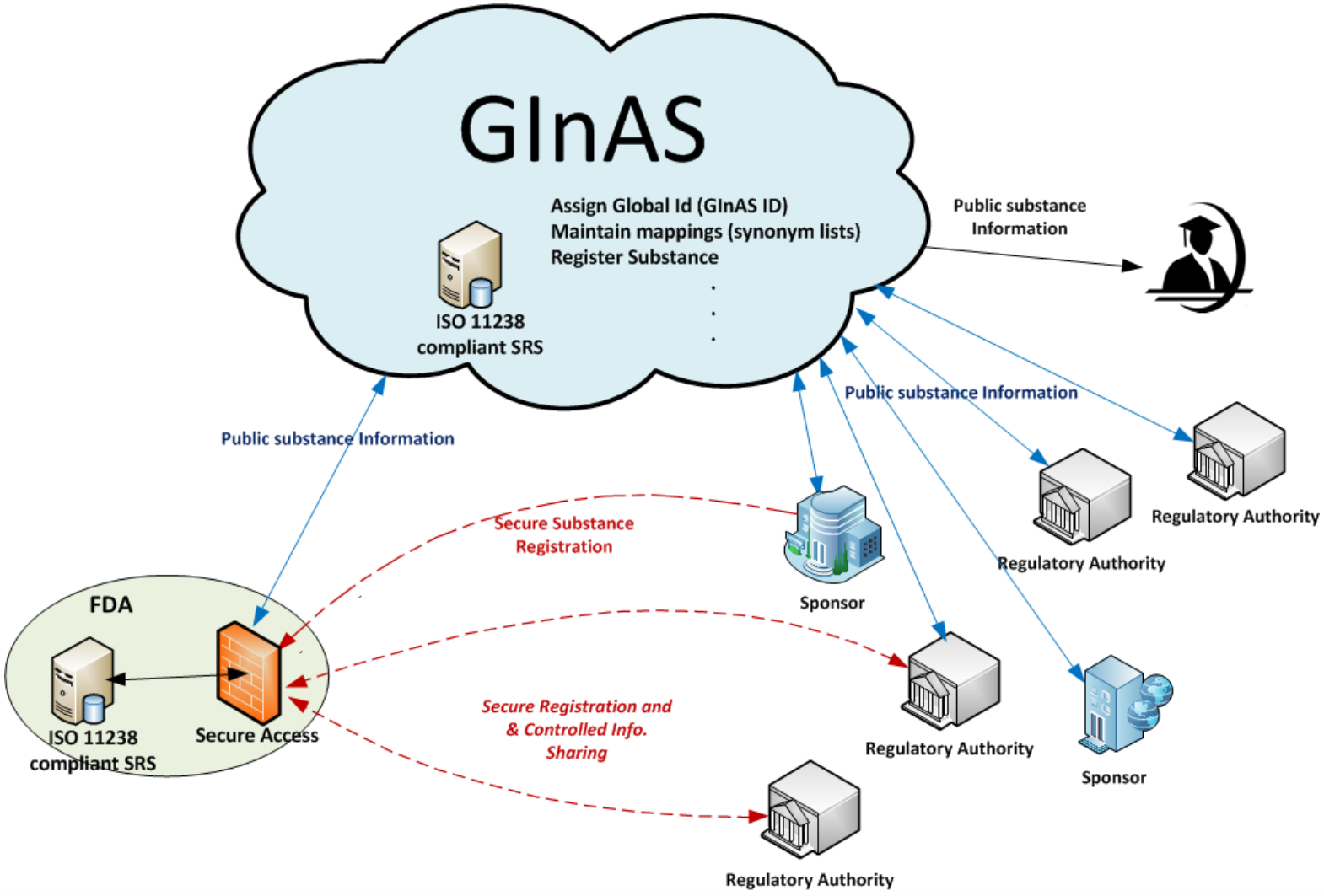
Investigational	• Standardized concept definitions and structures are needed to uniquely identify products across regional boundaries • Many clinical trials have an international component
Post-Market	• More robust analytics capabilities in adverse events/drug reaction reporting • Better regulatory control in reporting and enforcing recalls- many international manufacturers, packagers & distributors in supply chain

FDA Requirements for Substance ID Maintenance

- Must Maintain Substance ID For Pre And Post Market Substances
- Must Support Confidential/Trade Secret Information
  - Safeguard against unauthorized access
  - Post online only after information is publicly available
  - Not ALL defining elements that describe a substance may be in the Public Domain
- Authoritative Source
  - Safeguard data integrity
  - Safeguard against improper/inappropriate data
    - No automatic acceptance of substance information
    - Information must be verified and validated before acceptance

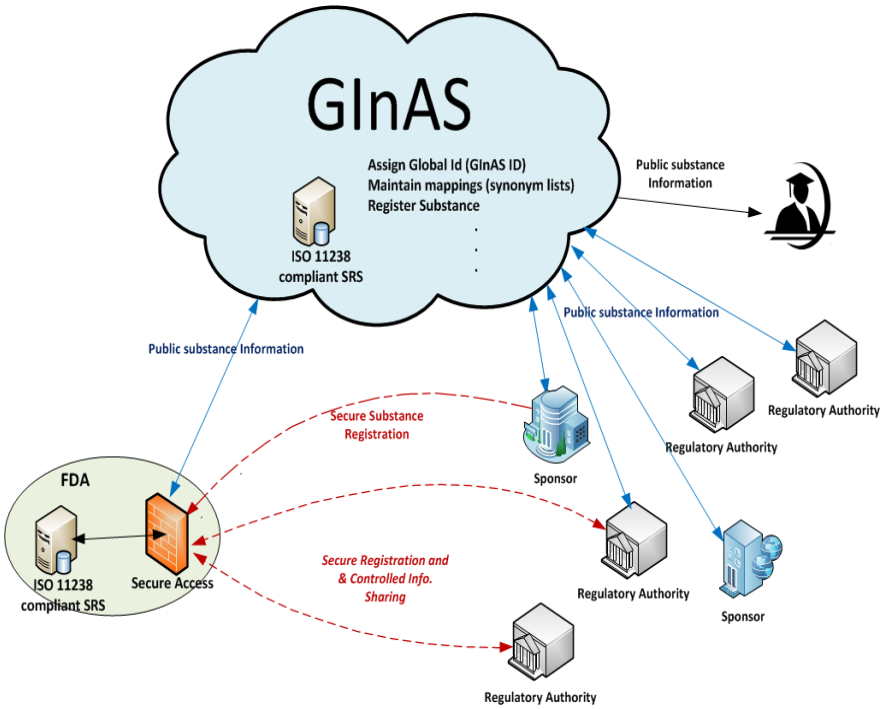


GInAS and Substance Identification -- Possibilities



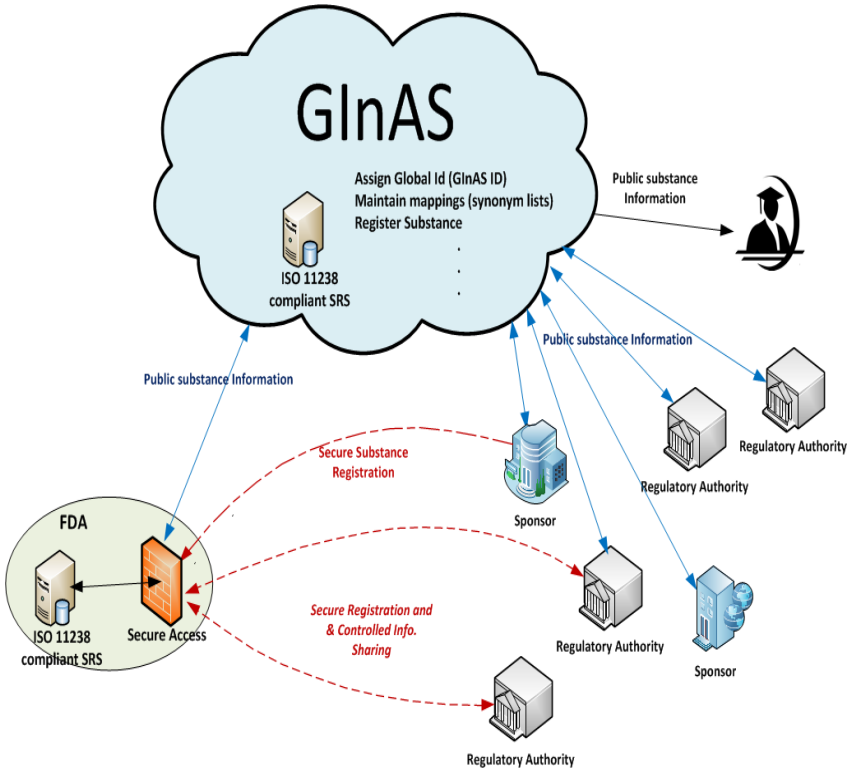
Minimal Requirements

- All GInAS participants comply with ISO 11238 standard and DTS 19844 (implementation guide) for Substance Identification
- Each Regulatory Authority can maintain its own Substance Registration (minimum impact to its regulatory process)
- Regulatory Authorities can establish agreements with each other for substance registration & maintenance if they choose
- GInAS provides a source of public data to stakeholders

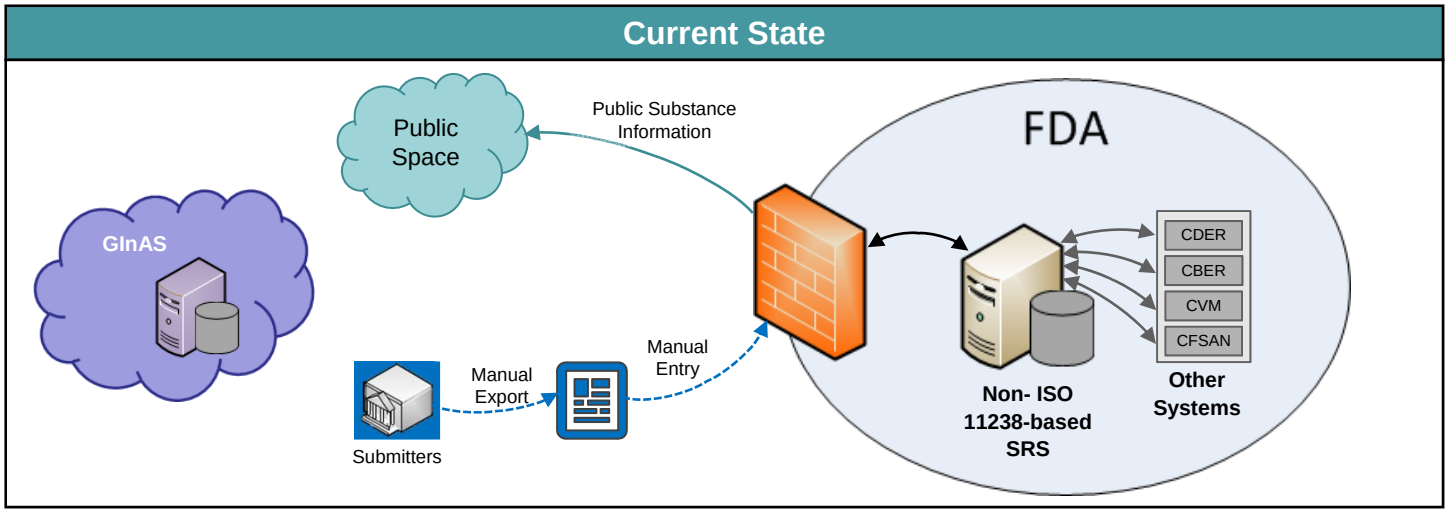


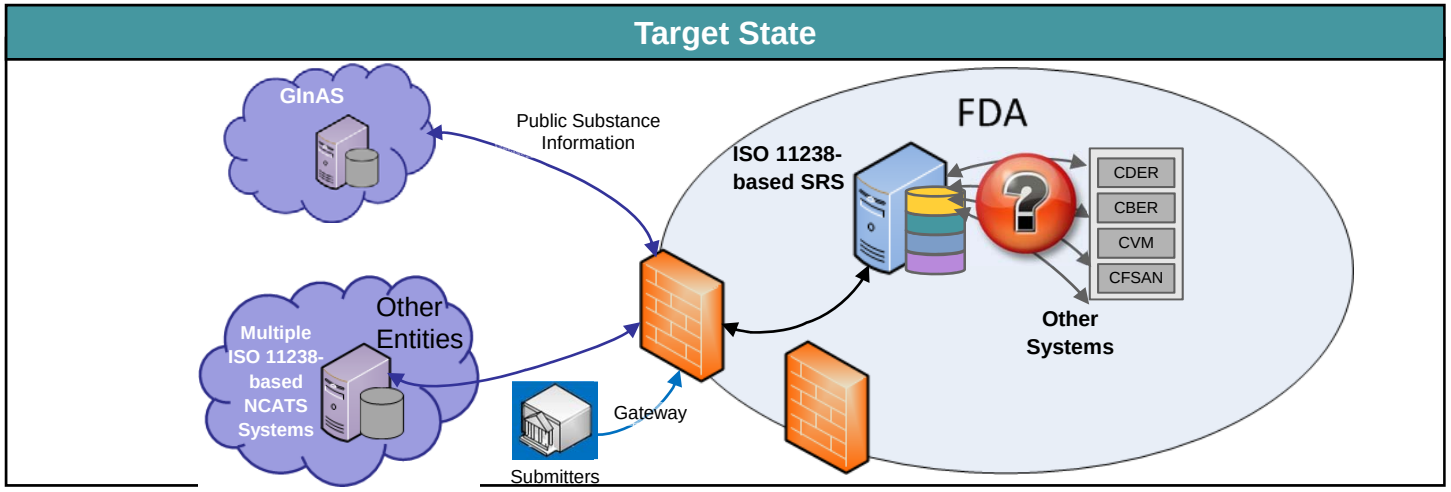
Possible GInAS Roles

- Repository of publicly available substance information and IDs
- Resource for Global Substance ID that maps to Regional IDs (Harmonization)
- Registration & Maintenance Organization for Unique Substance IDs
- Others?



For FDA – Current State vs. Envisioned Target State





In Summary

1. All of this is made possible only if we implement the ISO SRS standard and follow the IG
2. Consistent implementation is made easier (but not required) through use of a common system for registration such as NCATS' system
3. Each regulatory authority may continue its current process of registering substances and assigning unique IDs
4. For those who desire to share regulatory information, it would be valuable for an entity to host and maintain public substance information
   - Significant value (but more complex) if the entity would assign global IDs to unique substances, and identify and maintain mappings of regional IDs to the global IDs for unique substances

How Do We Get There?