Identification of Medicinal Products (IDMP): What is IDMP and Why Should I Care?

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FDA Webinar  
June 13, 2019
Identification of Medicinal Products (IDMP) Update:

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What is IDMP?

• IDMP is a suite of five standards developed (2012) within the International Organization for Standardization (ISO) which will create an internationally-accepted framework to uniquely identify and describe medicinal products.

• FDA is a member of ISO and has participated in the development of these five standards.

• The 5 Standards include data elements and structures for identification for
  – ISO 11615 - medicinal product information (MPID)
  – ISO 11616 - pharmaceutical product information (PhPID)
  – ISO 11238 - substances (Substance ID)
  – ISO 11239 - pharmaceutical dose forms, units of presentation and routes of administration
  – ISO 11240 - unique identification and exchange of units of measurement
Potential Benefits of IDMP

**Safety Surveillance**
- Unambiguous global identification will improve pharmacovigilance by uniquely identifying specific medicinal products in ICSRs.
- Globally detect safety signals from medicinal products referenced in adverse events.

**Transparency**
- Communicate medicinal product data globally.
- Opportunity to communicate and build trust with the public and other stakeholders about medicinal product quality and safety.

**Mitigation of Drug Shortages**
- Standard allows us to identify pharmaceutically equivalent products across regions, to support mitigation of drug shortages.

**Interoperability**
- Harmonized source for product information based on globally controlled vocabularies and standards
- Support the exchange of medicinal product information between companies and regulators.
FDA’s Approach to ISO IDMP Standards
## FDA IDMP Roadmap (1)

<table>
<thead>
<tr>
<th>ISO 11615</th>
<th>ISO 11238</th>
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</thead>
<tbody>
<tr>
<td><strong>Medicinal Product ID</strong></td>
<td><strong>Substance ID</strong></td>
<td><strong>Units of Measure</strong></td>
<td><strong>Dosage Form &amp; Route of Administration</strong></td>
<td><strong>Pharmaceutical Product ID</strong></td>
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<tr>
<td>2012</td>
<td>• ISO publishes Standard</td>
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</tr>
<tr>
<td>2016</td>
<td>• GSRS Project Initiated</td>
<td>• UNII conforms to ISO 11238</td>
<td>• UCUM conforms to ISO 11240</td>
<td>• Test FDA / Regional PhPIDs</td>
</tr>
<tr>
<td>2017</td>
<td>• Initiate evaluation of NDC conformance</td>
<td>• GSRS in production</td>
<td>• Initiate evaluation of FDA Terminology for SPL conformance</td>
<td></td>
</tr>
<tr>
<td>2018</td>
<td>• NDC Conforms to ISO 11615</td>
<td>• Collaborate on FHIR Exchange Standard</td>
<td>• Determined FDA Terminology does not conform to ISO 11239</td>
<td></td>
</tr>
<tr>
<td>2019</td>
<td>• Collaboration with EMA on MPID FHIR (development)</td>
<td>• Continue collaboration with EMA on GSRS and FHIR</td>
<td>• Determined mapping must be to a central terminology</td>
<td></td>
</tr>
</tbody>
</table>

### Key Terms:
- ISO: International Organization Standardization
- UNII: Unique Ingredient Identifier
- GSRS: Global Substance Registration System
- UCUM: Unified Code for Units of Measure
- NDC: National Drug Code
- FHIR: Fast Healthcare Interoperability Resources
- EDQM: European Directorate for Quality of Medicines
- ISO 11238
- ISO 11239
- ISO 11240
- ISO 11615

### Notes:
- GSRS: Global Substance Registration System
- UNII: Unique Ingredient Identifier
- UCUM: Unified Code for Units of Measure
- NDC: National Drug Code
- FHIR: Fast Healthcare Interoperability Resources
- EDQM: European Directorate for Quality of Medicines

**9 June 2019**

- ISO: International Organization Standardization
- UNII: Unique Ingredient Identifier
- UCUM: Unified Code for Units of Measure
- FHIR: Fast Healthcare Interoperability Resources
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</tr>
<tr>
<td>2020</td>
<td>• Continue collaboration with EMA on MPID FHIR (expect balloted in Jan)</td>
<td>• Periodic GSRS updates</td>
<td>• Develop / identify central terminology</td>
<td>• Continue collaboration with EMA on GSRS &amp; FHIR</td>
<td>• ISO publishes Standard</td>
</tr>
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</table>

9 June 2019

- ISO: International Organization Standardization
- UNII: Unique Ingredient Identifier
- GSRS: Global Substance Registration System
- UCUM: Unified Code for Units of Measure
- NDC: National Drug Code
- FHIR: Fast Healthcare Interoperability Resources
- EDQM: European Directorate for Quality of Medicines
Identification of Medicinal Products (IDMP): Update on MPID, PhPID, SubID & Units

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FDA Webinar
June 13, 2019
• **MPID Description**
  – Data elements and structures for unique identification and exchange of regulated medicinal product information

• **U.S. National Drug Code (NDC)** is FDA’s regional MPID
  – First two segments of the NDC code will be used to represent MPID
  
  – The full NDC will be used to represent the medicinal product at the **package** level (known as the PCID)

  – Example:

  ![Image of National Drug Code (NDC)]

  ```
  FDA: 61414 - 1234 - 1
  ```

  **MPID = Labeler and Product Codes**

  **US FDA Identifiers**
8.2.1 General considerations

For each authorized Medicinal Product, a unique MPID shall be assigned. The MPID ... supplementary to any existing authorization number as ascribed by a Medicines Regulatory Agency in a region. This is ... and to contribute to improving patient safety by allowing for the unique identification of Medicinal Products worldwide.

The MPID shall use a common segment pattern ... define a specific MPID concept. The pattern is:

a) country code segment (ISO 3166-1 alpha-2 code elements);

b) marketing authorization holder (organization identifier) code segment; Labeler Code

c) Medicinal Product code segment. Product Code

Any change of the values related to these three code segments shall result in the assignment of a new MPID.
• ISO 11615:2017

3.1.41 marketing authorisation holder
– organisation that holds the authorisation for marketing a Medicinal Product (3.1.50) in a region (3.1.73)

• CFR 21 Part 207 Subpart C—National Drug Code

§207.33 (c) Who must obtain an NDC labeler code ...
– (1) Each person who engages in manufacturing, repacking, relabeling, or private label distribution of a drug subject to listing under this part must apply for an NDC labeler code, by providing ...
8.2.2.4 Medicinal Product code segment
This code segment shall reflect a Medicinal Product code assigned to the Medicinal Product. It utilises defining attributes to determine a single Medicinal Product to which a code is assigned. A different Medicinal Product code segment shall be assigned, leading to a unique MPID, (subject also to the notes below) whenever any of the following items of information for a Medicinal Product are modified, as applicable, per a Medicines Regulatory Agency process(es):

a) marketing authorization in relation to the jurisdiction;

b) legal status of supply (e.g. prescription only or “over the counter” sale);

c) Medicinal Product name;

d) pharmaceutical dose form;

e) active ingredient(s)/active moieties and their corresponding strength;

f) device(s) where a Medicinal Product is combined with a medical Device;

g) therapeutic indication(s) as authorized for the Medicinal Product
CFR 21 Part 207 Subpart C—National Drug Code

§207.35 What changes require a new NDC?

(b) The proposed new NDC must include a new product code when there is a change to any of the following information:

1. The drug’s established name or proprietary name, if any;
2. Any active pharmaceutical ingredient or the strength of any active pharmaceutical ingredient;
3. The dosage form;
4. A change in the drug’s status, between prescription and nonprescription;
5. A change in the drug’s intended use between human and animal;
6. The drug’s distinguishing characteristics such as size, shape, color, code imprint, flavor, and scoring (if any).

(c) When there is a change only to the package size or type, including the immediate unit-of-use container the proposed new NDC must include only a new package code and retain the existing product code unless all available package codes have already been combined with the existing product code in NDCs assigned by FDA.
• **MPID Exchange Standard (ISO/TS20443)**
  – ISO 11615:2017
    • “This document has been developed in conjunction with the Common Product Model (CPM) and Structured Product Labelling (SPL) in HL7.”
  – FDA uses SPL (HL7 v3 message) for labeling and drug listing and registration submissions, and does not currently have plans to change
    • FDA determined that the MPID required components are captured in the SPL label
    • Indication will be captured prospectively via regulatory submissions

  – FDA is collaborating with EMA to develop and test HL7 Fast Healthcare Interoperability Resource (FHIR) for information exchange
    • Test will ensure adherence to the ISO (TS20443) technical specification, *and*
    • FDA will evaluate and determine steps necessary to accept FHIR messages as well as SPL
**PhPID Description** - *PhPID is a code generated by an algorithm based on substance, strength, and dose form. PhPID can be used to associate products with same or similar pharmaceutical composition.*

PhPID_SUB_L1 → Substance Term(s)
PhPID_SUB_L2 → Substance Term(s) + Strength + reference strength
PhPID_SUB_L3 → Substance Term(s) + Dose Form
PhPID_SUB_L4 → Substance Term(s) + Strength + reference strength + Dose Form

• FDA is currently testing the generation of regional PhPIDs
• In May 2018, WHO/UMC presented a conceptual proposal for validation and maintenance of global PhPIDs.
• Planning to participate at a technical and policy working group meeting in August 2019.

**NOTE 1** The substance(s) within the ingredient role “active” and “adjuvant” is utilised to define the PhPID.
• **SubID Description**
  – Data elements and structures for unique identification and exchange of regulated information on substances

• **Unique Ingredient Identifier (UNII)**, ISO 11238 compatible, used by FDA for many years to uniquely and unambiguously identify substances

• The Open Source Global Substance Registration System (GSRS) has been developed and is available at [https://tripod.nih.gov/ginasi/](https://tripod.nih.gov/ginasi/)
  – FDA-GSRS is in production (approx. 180,000 entries)
IDMP on FHIR

• In January 2018, the EU endorsed* using FHIR as the basis for the API for the Product Management Service
  – Makes FHIR the data standard that supports the exchange of information about medicinal products, substances, and related reference data in the EU

• HL7’s BR&R workgroup presently sponsors the development of ISO IDMP 11238 (Substance Specification) and IDMP 11615 (Medicinal Product) resources
  – Medicinal Product resource development takes place in collaboration with HL7’s Pharmacy work group
  – IDMP resources are expected to be balloted by January 2020 meeting

• **Units of Measurement Definition**
  – Data elements and structures for unique identification and exchange of units of measurement

• **The *Unified Code for Units of Measure (UCUM)* was selected as the ISO 11240 compliant standard**
  – UCUM is a system intended to include all units of measures being contemporarily used in international science, engineering, and business
  – Currently, FDA receives submissions that use the UCUM syntax standard for dosage strength in both content of product labeling and drug establishment registration and drug listing.
Identification of Medicinal Products (IDMP): Update on Dosage Form and Route of Administration

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• DF & RoA Description
  – Data elements and structures for unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration and packaging

• Based on review of ISO 11239’s technical specification (20440:2016), the terminology of the European Directorate for the Quality of Medicines (EDQM) conforms to the ISO 11239 standard.
  – European Directorate for the Quality of Medicines, under the authority of the Council of Europe, maintains the terminology.
  – EDQM terminology can be found at: https://standardterms.edqm.eu/
• **FDA Terminology for SPL is used in**
  – Content of drug and biologics labeling
  – Drug establishment registration and listing
  – CDISC controlled terminology for SDTM used in clinical trials

• **National Cancer Institute / Enterprise Vocabulary Service (NCI /EVS) maintains the FDA terminology as part of the larger NCI terminology**

• Based on review of TS20440:2016 and analysis of EDQM, the **FDA Terminology for SPL does not** conform to the ISO 11239 standard for international IDMP.
Mapping Results of FDA Terminology to EDQM PDFs

- FDA Terminology has **166** Pharmaceutical Dosage Forms (PDF)
- EDQM has ~**484** PDFs
- FDA Terminology & EDQM share **36** common / mapped dose forms
FDA Terminology Capsule Types Without a 1:1 Map to EDQM Standard Term Capsule Types

<table>
<thead>
<tr>
<th>Source PT</th>
<th>NCIt Conc</th>
<th>EDQM-HC Preferred Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>capsule</td>
<td>C149582</td>
<td>Inhalation vapour, capsule</td>
</tr>
<tr>
<td>capsule, COATED</td>
<td>C149872</td>
<td>Prolonged-release capsule, soft</td>
</tr>
<tr>
<td>capsule, COATED PELLETS</td>
<td>C150008</td>
<td>Vaginal capsule, soft</td>
</tr>
<tr>
<td>capsule, COATED, EXTENDED RELEASE</td>
<td>C149882</td>
<td>Rectal capsule</td>
</tr>
<tr>
<td>capsule, DELAYED RELEASE</td>
<td>C149664</td>
<td>Modified-release capsule, soft</td>
</tr>
<tr>
<td>capsule, DELAYED RELEASE PELLETS</td>
<td>C64904</td>
<td>capsule, hard</td>
</tr>
<tr>
<td>capsule, EXTENDED RELEASE</td>
<td>C64909</td>
<td>capsule, soft</td>
</tr>
<tr>
<td>capsule, FILM COATED, EXTENDED RELEASE</td>
<td>C149531</td>
<td>Gastro-resistant capsule, hard</td>
</tr>
<tr>
<td>capsule, FILM COATED, EXTENDED RELEASE</td>
<td>C149613</td>
<td>Intrauterine capsule</td>
</tr>
<tr>
<td>capsule, GELATIN COATED</td>
<td>C149368</td>
<td>Chewable capsule, soft</td>
</tr>
<tr>
<td>capsule, LIQUID FILLED</td>
<td>C149732</td>
<td>Oromucosal capsule</td>
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<tr>
<td></td>
<td>C149663</td>
<td>Modified-release capsule, hard</td>
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<tr>
<td></td>
<td>C149871</td>
<td>Prolonged-release capsule, hard</td>
</tr>
<tr>
<td></td>
<td>C149532</td>
<td>Gastro-resistant capsule, soft</td>
</tr>
<tr>
<td></td>
<td>C150007</td>
<td>Vaginal capsule, hard</td>
</tr>
</tbody>
</table>
• If EDQM (standard terms) is considered the IDMP central terminology, international PhPID Levels 3 and 4 may not be possible for some regions.

• For FDA, using EDQM, an international PhPID may not be possible for the highlighted levels below:

  1. PhPID_Substance Level \_L1 \rightarrow \text{Substance(s) Term}

  2. PhPID_Substance Level \_L2 \rightarrow \text{Substance Term(s) +Strength+ reference strength}

  3. PhPID_Substance Level \_L3 \rightarrow \text{Substance Term(s) + Administrable Dose Form}

  4. PhPID_Substance Level \_L4 \rightarrow \text{Substance(s) Term + Strength + reference strength + Administrable Dose Form}
• **ISO TS 20440 Systematic Review Cycle**
  – As of 15 April, TS 20440 is scheduled for systematic review cycle
  – ISO ballot process underway to open for review: August 2019
  – If approved for systematic review, working group formed to update the Technical Specification 20440.
  – Goal: to ensure all parties can conform to a central set of dosage form terms.
Examples of EMA - FDA IDMP Collaboration

- Related to IDMP activities:
  - EWG E2B, ICH M2/M8
  - eCTD
  - CTD M2.3, 3 /PQ/CMC
- Develop & disseminate information on conformance to IDMP standards
- ISO IDMP underlying messaging infrastructure. FHIR resources for substance and medicinal product via HL7 Biomedical Research & Regulation workgroup (BR&R).

- Implementation of the EU Substance Registration System and Integration of GSRS and data exchange between regions to support EMA and FDA applications.
- Implementation of the ISO IDMP suite and information exchange between the regions.
- Proposed maintenance of IDMP global identifiers and terminology (substance IDs, PhPIDs, Org IDs, etc.).
Identification of Medicinal Products (IDMP)

IDMP is a suite of five standards developed within the International Organization for Standardization (ISO) which provides an internationally-accepted framework to uniquely identify and describe medicinal products with consistent documentation, coding and exchange of product information between global regulators, manufacturers, suppliers and distributors.

An FDA focus on the challenges of the global supply chain and foreign sourcing of medicinal products, we continue to participate and promote the adoption of international harmonized IDMP to ensure the safety of medications throughout the world.

The five IDMP standards are:

**Medicinal Product Identification (MPID)**
- ISO 11615 [disclaimer icon]: Data elements and structures for unique identification and exchange of regulated medicinal product information

**Pharmaceutical Product Identifier (PnPID)**
- ISO 11616 [disclaimer icon]: Data elements and structures for unique identification and exchange of regulated pharmaceutical product information

**Substance Identification (SubID)**
- ISO 11238 [disclaimer icon]: Data elements and structures for unique identification and exchange of regulated information on substances

**Dosage Form and Routes of Administration (DF & RoA)**
- ISO 11239 [disclaimer icon]: Data elements and structures for unique identification and exchange of regulated information on pharmaceutical dosage forms, units of presentation, routes of administration and packaging

**Units of Measurement (UoM)**
- ISO 11240 [disclaimer icon]: Data elements and structures for unique identification and exchange of units of measurement

**Technical specifications - Implementation guide for relevant IDMP standards:**

**Medicinal Product Identification (MPID)**
- ISO TS20443 [disclaimer icon]: Implementation technical specification for ISO 11615

**Pharmaceutical Product Identification**
- ISO TS20451 [disclaimer icon]: Implementation technical specification ISO 11616

**Substance Identification (SubID)**
- ISO TS19844 [disclaimer icon]: Implementation technical specification for ISO 11238

**Dosage Form and Routes of Administration (DF & RoA)**
- ISO TS20440 [disclaimer icon]: Implementation technical specification for ISO 11239

https://www.fda.gov/industry/fda-resources-data-standards/identification-medicinal-products-idmp
Identification of Medicinal Products

The Identification of Medicinal Products Working Group (Identification of Medicinal Products: IDMPWG)’s work is to ensure the awareness and understanding of the IDMP standards by regulatory authorities, to clarify how and why these standards can add value to regulatory business processes; to improve the quality and effectiveness of shared regulatory functions, and to share strategies and experiences for their successful and consistent implementation.

Mandate

1. General considerations

The international community, in the form of a domain for implementation of International standards, has the International Organization for Standardization (ISO) for the global Identification of medicinal products (IDMP). This includes the development of both ISO standards and corresponding ISO Technical Specifications for use as implementation guides. The standards provide definitions and concept models for the unique identification of medicinal products throughout the product lifecycle for improved regulatory and clinical activities. This enhances the application of the standards’ broader: that is, the regulatory domain, to encompass unique identifier registration in implementing the standards’ potential value not only to regulatory business processes, but more broadly in healthcare systems.

To optimize the utility of the standards in the regulatory domain, broader regulatory uptake is desirable. However, outside of the early adopters of the standards, there is minimal awareness of what the standards are, what the regulatory use cases are (the value of the standards to regulatory), and what measures exist to facilitate the implementation of the standards. There is a need for a venue in which regulators can exchange information around the implementation of the standards. The IDMP Working Group provides such a venue for regulators to learn about the ISO standards.

2. Objectives

Objectives of the IDMP Working Group are to ensure the awareness and understanding of the standards of the IDMP standards more globally by the pharmaceutical regulators to clarify how and why these standards can add value to regulatory business processes; to improve the quality and effectiveness of shared regulatory functions, and to share strategies and experiences for their successful and consistent implementation.

3. Scope

Provide an understanding of the ISO IDMP standards and their implementation by:
- Sharing strategies around implementation approaches such as linked, shared, or modular across the product lifecycle
- Clarifying use cases (e.g., the regulatory and public health value, e.g., in the areas of pharmaceutical compliance, clinical information support, prescribing, dispensing, risk management and lifecycle management activities from investigational phases through product registration)
- Updating members on the status, progress, and challenges of implementation activities by early adopters
Overview of Global Substance Registration System (GSRS), Identification of Medicinal Products (IDMP)

Larry Callahan, PhD
Global Substance Registration System (G-SRS)
Office of Health Informatics
Office of Chief Scientist (OCS)FDA
Outline of Talk

• Organizing Information
• IDMP Standard
• What is a substance
• GInAS/GSRS
• Status of Development
• Adverse Event Data
Organizing Information

- FDA has the most important/valuable repository of human biological and product data but limited integration.
  - Submission process
    - Paper
    - PDF’s
  - Organizational
    - Different Centers
    - Different Contractors
    - Business Process
- The amount of information is increasing
  - Rapid Screening Methods
  - Enzyme and Receptor Profiling
    - Cyp, Transporter and Receptor
  - Genomics
  - Epigenomics
  - Electronic Health Records
  - Many CMC changes
- Substances
  - A key lynchpin for organizing scientific and regulatory information
  - GSRS attempts to define substances consistently and unambiguously based on scientific principles
  - UNII permanently assigned ties an identifier to actual entities independently of nomenclature
Organizing Information

• Identification of Medicinal Products (IDMP)
  – ISO project; 5 standards

• Approach of the IDMP to organizing information
  – Goal is to get data organized prior to submission
  – Fielded data is better than non-fielded Data
  – Controlled vocabulary is better than non-controlled vocabulary
  – Codes are better than names in electronic systems particularly relevant to substances
  – Substance terminology on definitions (truth) not hierarchy
  – All substances in medicinal products should be defined and assigned a permanent unique ID
Goals of IDMP Project

• Develop a common data structure and terminology for the description of medicinal products
  – Facilitate data exchange
    • Pharmacovigilance
    • Quality of pharmaceutics/detect/prevent counterfeiting
    • Predict/prevent drug-drug food-drug interactions
    • Incorporation of diverse data into databases
    • Prevent drug shortages
    • Promote Drug Development
  – Consistent review
  – Enter once use many (substances, organizations)
  – Assist in mining of EHRs (Effectiveness. Safety, Better Dosing)
  – Global ID for substances and pharmaceutical products (ie 200 mg ibuprofen tablets)
Global Health Benefits of IDMP

- **Improve Pharmacovigilance**
  - Globally detect safety signals from medicinal products referenced in adverse events

- **Support Mitigation of Drug Shortages**
  - Allows the identification of pharmaceutically equivalent products across regions

- **Promote Greater Understanding and Sharing**
  - Supports the exchange of post-market medicinal product information between companies and regulators
What is a Substance: ISO 11238

- 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 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
Why Register Substances

Need to tie substances to regulatory submissions

- Enhance review and drug development
  - Active substance and inactive substances under review
  - Biomarkers can be defined and tracked
  - Use substances and related substance information to structure submissions
    - Quality
    - Manufacturing
    - In-vitro data
    - Clinical Information
      - Clinical trial registration
      - ICSR
  - Starting materials
  - Processing materials
  - Impurities

Need to tie substances to other substances

- Relationships between substances
  - Active Moiety
  - Salt/Solvate-> Parent relationships
  - Metabolites
  - Impurities
  - Drug target
  - Metabolic Enzymes (substrate, inhibitor, inducer)
  - Transporters (substrate, inhibitor, inducer)
  - Off target enzymes and receptors
Why Register Substances?

Need to tie substances to products

- Quality perspective
  - Change in substance can lead to a change in product
  - Find all products that could contain a “bad” ingredient (heparin, diethylene glycol)
  - Consistent specifications
- Safety perspective
  - Track adverse events based on substances
  - Tie substances to targets and pathways
- Drug Utilization
  - Predict and prevent shortages
  - Global marketplace need a global systems

Need to tie substances to manufacturer

- Quality
  - Who makes it
  - Where they make it
  - How they make it
  - Coordinate Inspections and testing
Tie Substances to other Information

Need to tie substances to other information

- Quality
  - Characterization
  - Specifications
  - Stability
- Physical Properties
  - Molecular weight
  - Solubility
  - pKa or pKb
  - Partition coefficients
  - Polymorph (crystal, amorphous)
- Toxicology and Animal Pharmacology
  - Genotoxicity
  - Cellular Cytotoxicity
  - Summary Animal Toxicology
- Acute, Subchronic and Chronic
  - NOAEL, tissue distribution
  - Environmental Fate
  - Lab on a Chip results

- Clinical Pharmacology (LADMER)
  - Dissolution Data
  - Pharmacokinetics (Cmax, Tmax, Half-life, Vd, etc.)
  - Metabolism
  - Excretion
  - Pharmacodynamics
- Health and Disease
  - Indications (treatment, prevention, causative)
  - Adverse Events
  - Drug-Drug Interactions
  - Drug-Food Interactions
  - Health Outcomes
  - - omics
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
UNII, SPL, Orange Book, Purple Book, Green Book, INDs

- GSRS currently implemented at FDA at the substance level
- UNII is required for all ingredients listed in SPL
- Nearly all drug targets have UNII codes
- UNII codes assigned when INDs come in (CDER)
- Companies will eventually preregister or obtain UNII shortly after submission
- UNII is not explicitly listed in Orange Book, Purple Book or Green Book
What is the GSRS?

Assigns permanent UNII code to each substance

Compliant with the ISO IDMP Standard

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

Registers and defines
- Products
- applications
- clinical trials
- Adverse events counts
- Drug targets

Compliant with the ISO IDMP Standard
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)

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
GSR is a Software Application

- Freely distributable (NCATS version, substance only)
- Predominantly open source
- Data accessed and entered through an API
- Backend Java, Oracle
- 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, upgrading to angular 2.6
- Extensive use of Lucene Indexes
- Implemented Substance, Specified Substance Groups 1, 2, 3 and part of Specified Substance Group 4
- Excel tools for batch updating and queries

www.fda.gov
How it’s used at FDA

• FDA has adapted GSRS to integrate with existing internal databases and systems.
  – Adverse events
  – Products
  – Applications (INDs, NDAs)
  – Clinical Trials
• Industry uses the data from GSRS to find the UNII codes for their substances, which are submitted to the FDA.
  – In the future, they will be able to create a JSON message defining their substance to the FDA
  – Change submission process and eCTD
• Works in all modern browsers: IE, Chrome, and Firefox
• System will be distributed with a large set of curated public domain data and updated periodically
  – Over 180,000 substances or concepts
  – Over 900,000 names, 800,000 codes (CAS numbers, WHO-ATC, etc), 150,000 relationships between substances (targets, metabolites, metabolic enzymes, transporters)
  – Links to many outside resource (Chemid, Pubchem, Drug Bank, Orphan Drug etc)
  – Mapped to both CTGOV and EUCT
  – Structure and sequence based searching
  – Faceted and advanced field-based searching
  – Data downloadable in a variety of formats JSON, Text, Excel
  – Attempts to tie indication-target-intervention
Where we are going?

Develop and deploy R applications for substance based analysis

Dec 2018
Decommission FDA software

Communication Procedures

Develop portal for direct substance registration for industry and other regulators

Oct 2019

Begin entering SSG1 data

Jan 2020 – Nov 2020

Deploy portal for direct substance registration for industry and other regulators

Nov 2020

NCATS to distribute

Jun 2019

Modify internal process for substance communication

Oct 2019

Begin entering SSG1 data

Jan 2020 – Nov 2020

Modify w/Integrity & FAERS product Dictionary

Jan 2020

Software updates to current version of SOLR

Oct 2020

Ul development angular 6

Jan 2021

Create robust communications procedures

Oct 2018

Develop distributable Version of FDA software

Oct 2018

Modify w/Integrity & FAERS product Dictionary

Nov 2019

Begin entering SSG1 data

Jan 2020 – Nov 2020

Software updates to current version of SOLR

Oct 2020

Ul development angular 6

Jan 2021
LISINOPRIL ANHYDROUS

ABSOLUTE

Names:
- LISINOPRIL ANHYDROUS
- L-PROLINE, 1-(N(SUP 2)-H1-CARBOXY-3-PHENYLPROPAN-1-YL)-(S)-1-CARBOXY-3-PHENYLPROPAN-1-YL)
- LISINOPRIL [INN]
- LISINOPRIL [MI]

Codes:
- BDNUM: 0335557AA
- CAS: 76547-98-3
- WHO-ATC: C09AA03
- EVMPD: SUB23348 SUB08533MIG

Date validated: 10 years ago
Created: 14 years ago
Last modified: a minute ago
Status: Validated (UNII)
Version: 8

Relationships: 4

Formula: C21H131N3O5
Mol Weight: 405.49

Substance Hierarchy
- LISINOPRIL ANHYDROUS

Product Count: Active: 0
Inactive: 0
Application Count: CDER: 0
SRS: 0
Clinical Trial Count: 0
Adverse Event Count: 47533
**Lisinopril Anhydrous**

**Names:**
- Lisinopril anhydrous
- L-proline
- 1-(N(SUP 2)-(1-carboxy-3-phenylpropyl)amino)-L-proline

**Codes:**
- BNUM: 0335557AA
- CAS: 76547-98-3
- WHO-ATC: C09AA03
- EVMPD: SUB23348 SUB08533MIG

**Formula:** C21H31N3O5

**Mol Weight:** 405.49

**Date validated:** 10 years ago

**Created:** 14 years ago

**Last modified:** 13 hours ago

**Status:** Validated (UNII)

**Version:** 8
**Classification**

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### ZIDOVUDINE

**Overview**

Product, Application, Clinical Trial, Adverse Event

**Structure**

Names

Classification

Identifiers

Relationships

Metabolites

**Impurities**

Characteristic Attributes

Notes

Audit Info

---

**3'-CHLORO-3'-DEOXYTHYMIDINE**

**Mediator Substance**

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**Index** | **Source Text / Citation** | **Source Type** | **Tags** | **Document** | **Date Accessed** |
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Clinical Trial Europe Details

EudraCT Number: 2004-000390-30-GE
Title: Safety and Efficacy of SCH-417690 in HIV-infected Treatment-Naive Subjects
Sponsor Name: Schering Plough Research Institute

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**Show 10 entries**

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**Title**

Title

**External Title**

External Title

**Indication**

Indication

---

**Total Products:** 1  
Add Additional Product

## Product 1

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GInAS Meetings

• To get the software and data from NCATS
  – https://tripod.nih.gov/ginahas

• Meetings and Teleconferences
  – Free and Open to Public

• To Get on the GInAS Notification List
  – Sign-up at https://tripod.nih.gov/ginahas

• NCATS Inxight Link
  – https://drugs.ncats.io/

• NLM-FDA Link