Identification of Medicinal Products: Path to Global Implementation

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ISO Identification of Medicinal Products (IDMP)

Global PhPID and Dose Form Harmonization

SBIA

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What is IDMP

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

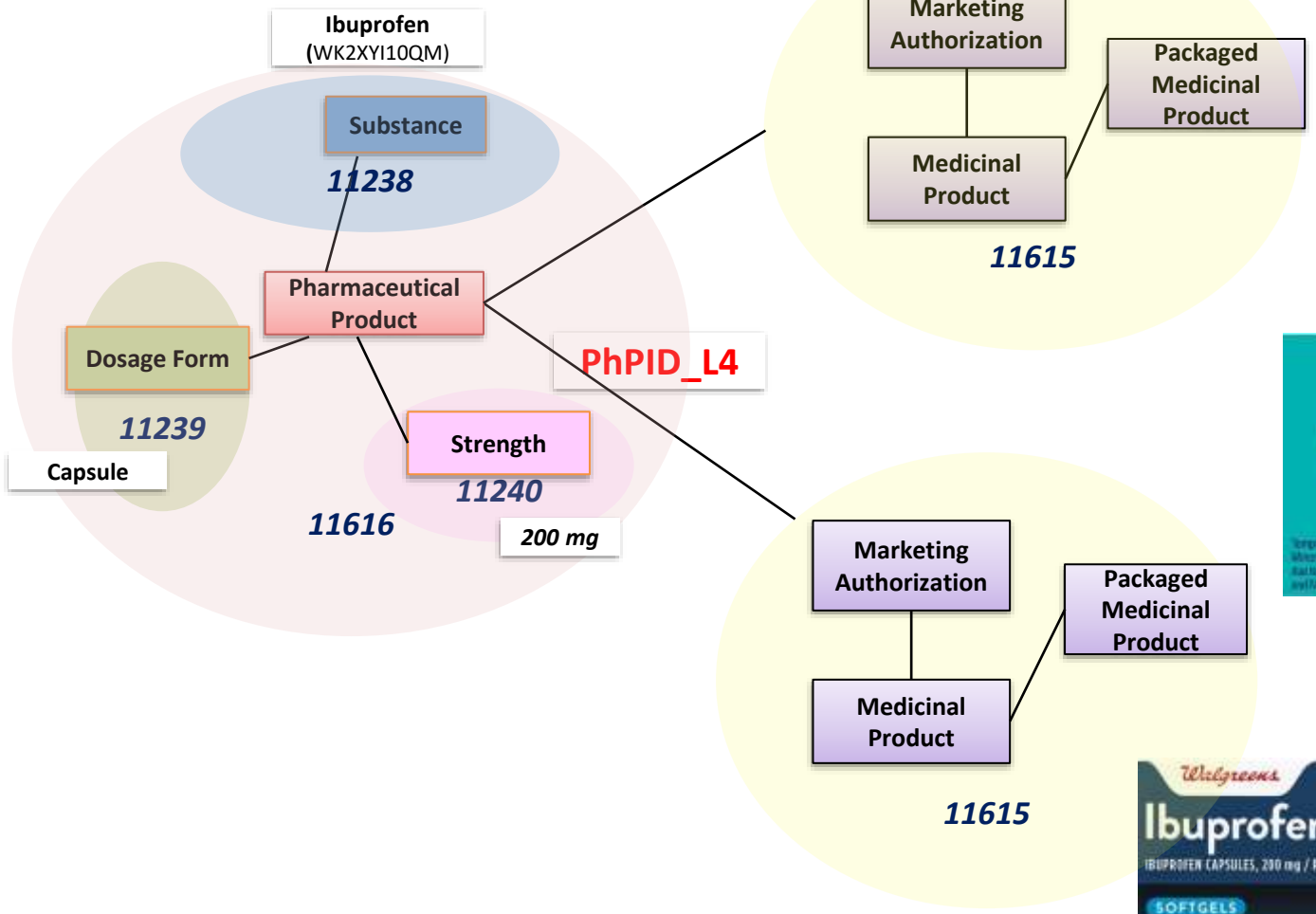
- Data elements and structure to **uniquely** and **unambiguously** identify medicinal product, Pharmaceutical Product, and substance
- **common vocabularies** for improved people communication
- **common message standards** for improved IT system communication

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

Key Benefits of IDMP

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

Connecting Medicinal Products Together



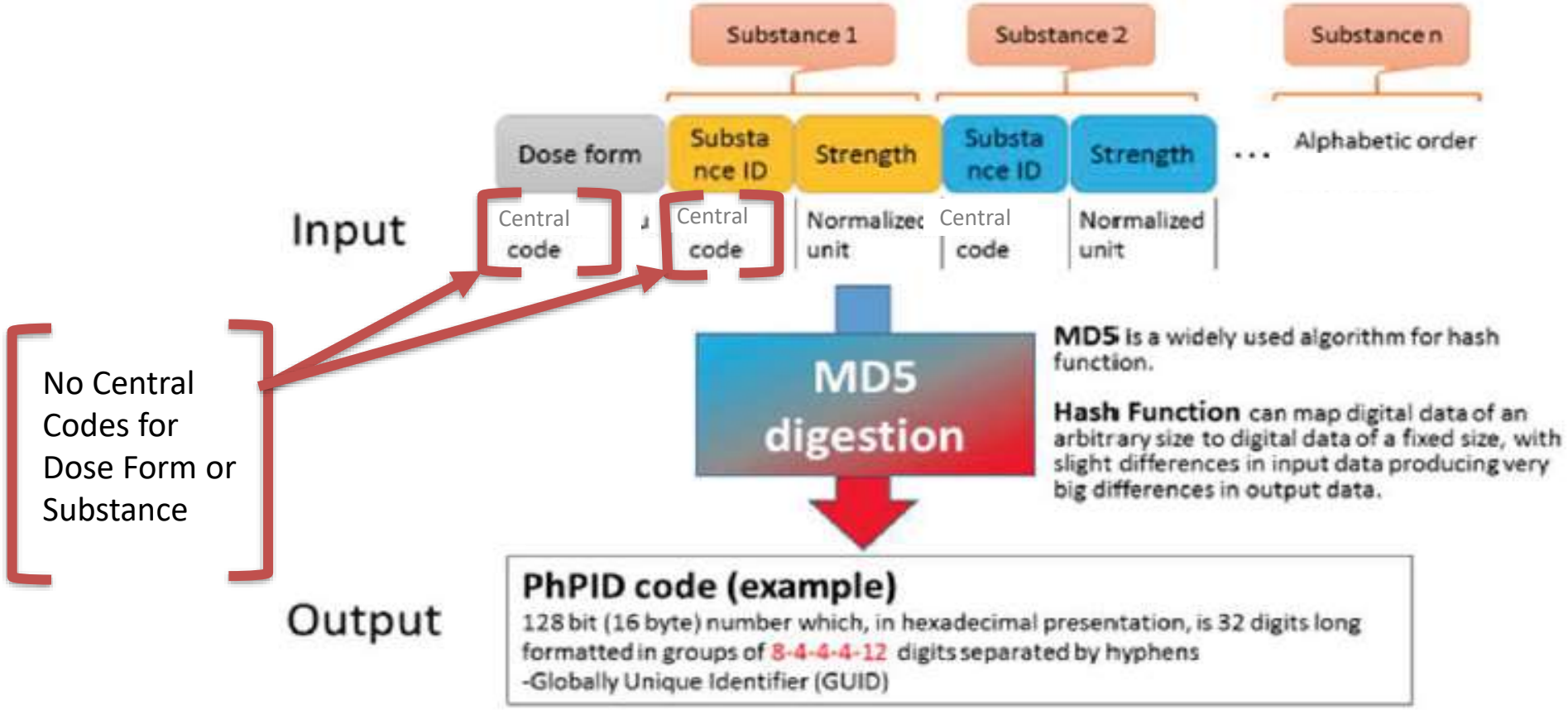
Concerns with the Current ISO Standard for PhPID

- 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 global 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)



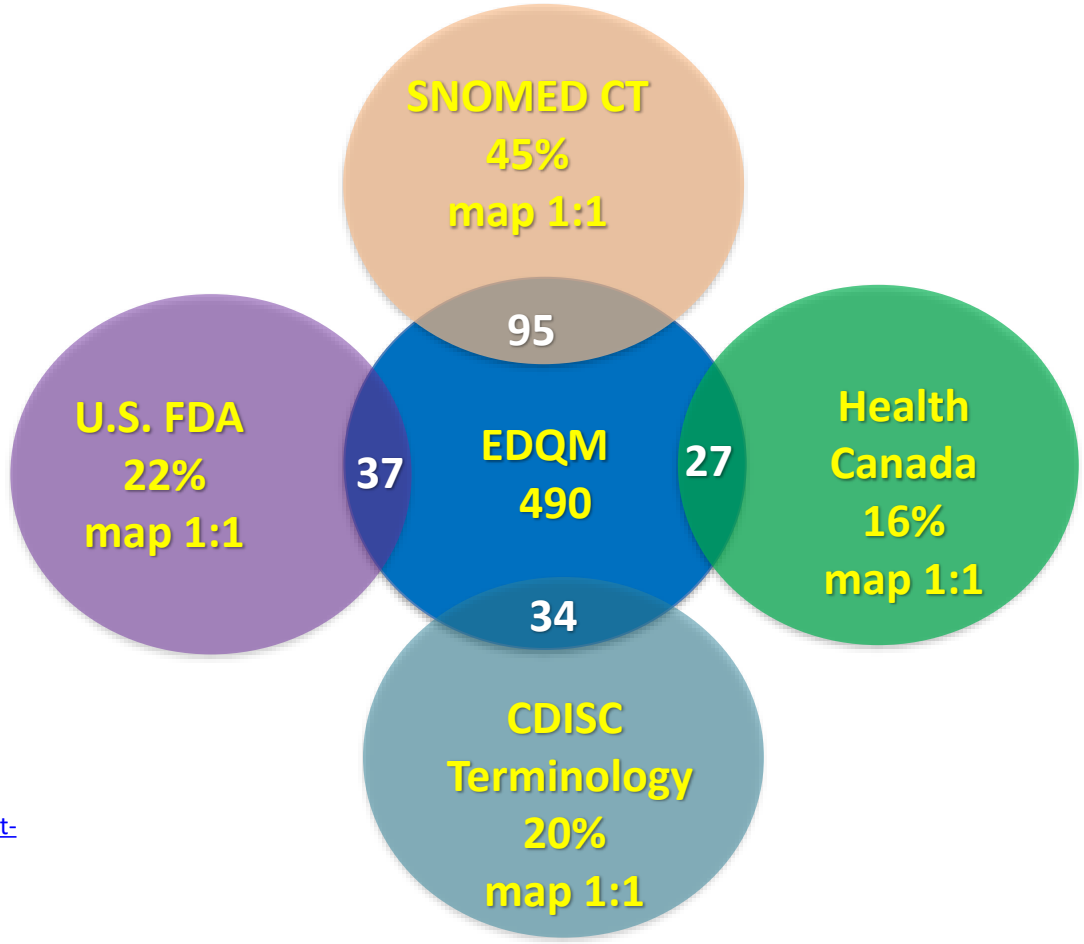
*Conceptual Representation of the Global PhPID Construction**

* Adapted from ISO TS 20451:2017

Concerns with the Current ISO Standard for Dose Fori

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

UNICOM Gap Analysis Report

4 Workshop results and suggesting gaps

4.1 Dose forms

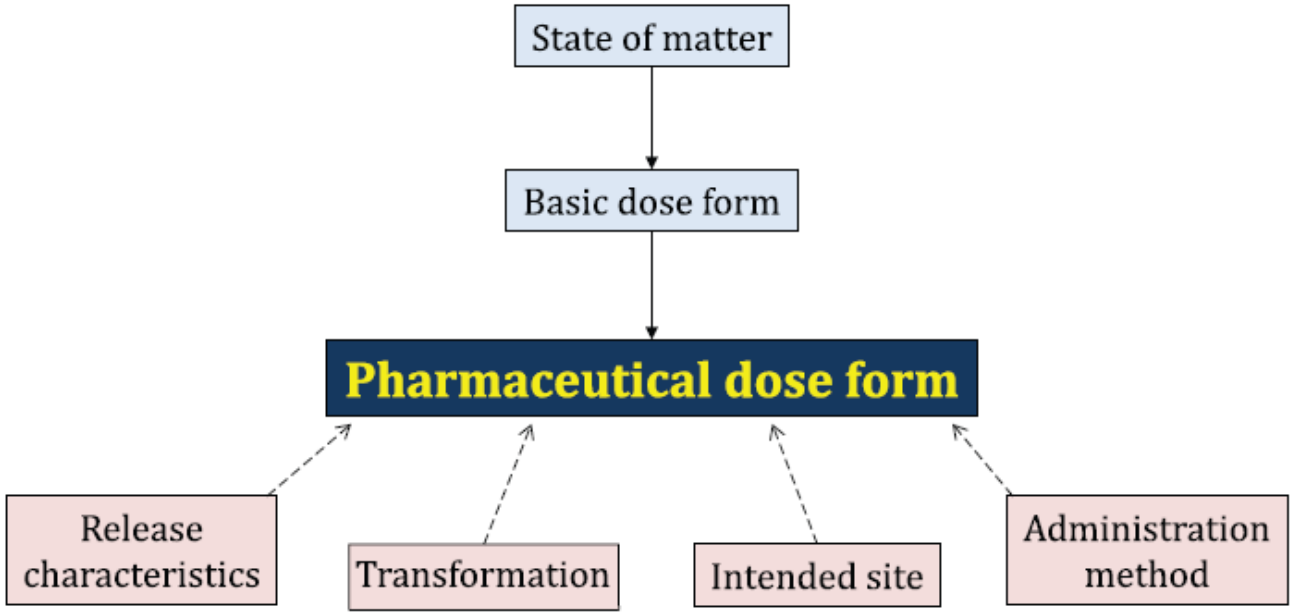
… The adoption of this IDMP standard has been **difficult**, at times.

- NCAs are in the process of implementing the standard in their own processes and **are facing backward compatibility issues, because the granularity of terminologies varies frequently from EDQM**.
- The US FDA has shared its implementation difficulties, which are similar to those of the NCAs.

Source: Unicom - https://unicom-project.eu/wp-content/uploads/2020/09/UNICOM_Gap-Analysis.draft_.v12-1.pdf

Dose Form Characteristics Use Case for Global PhPID

- **ISO 11239**
  - –**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

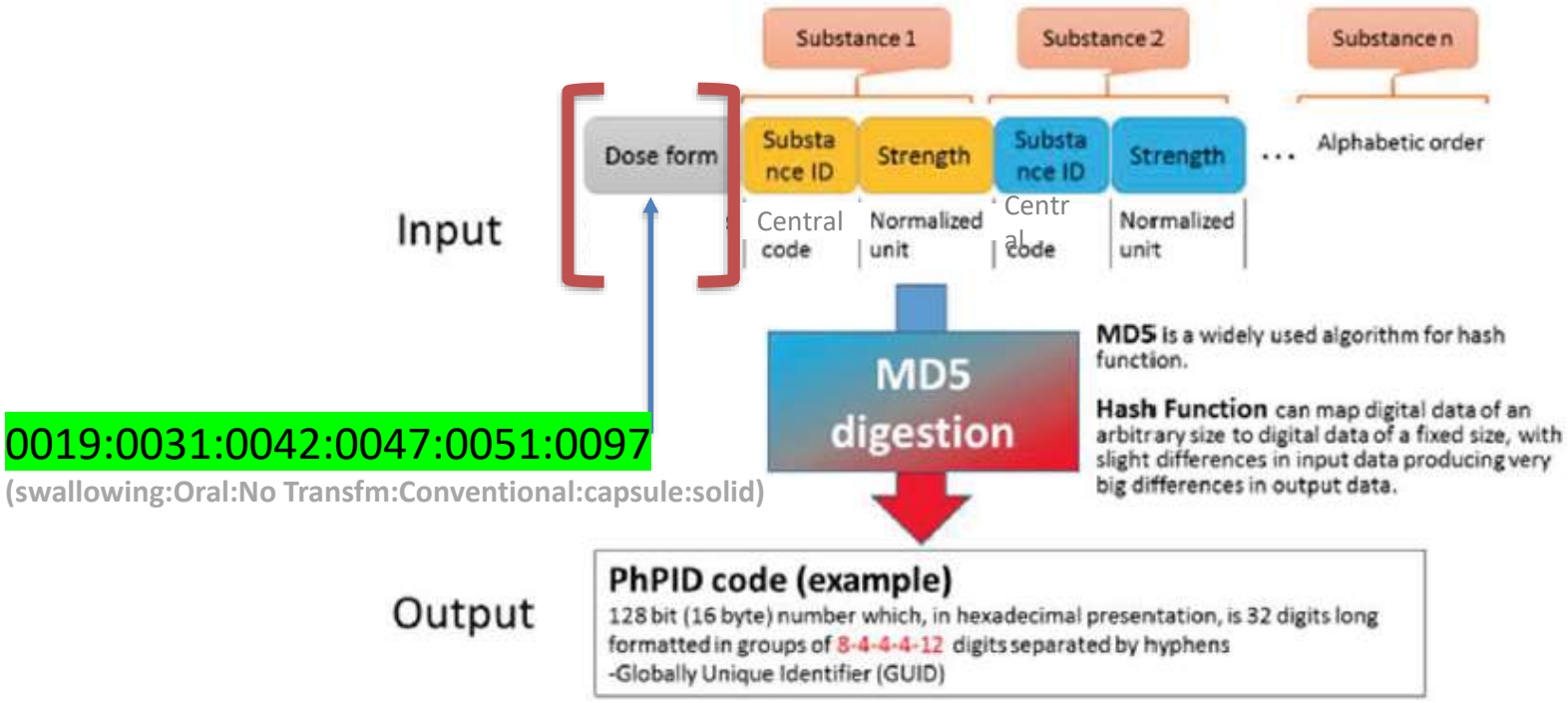


Dose Form Characteristics Examples for Global PhPID

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)
Capsule, Gelatin Coated	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.

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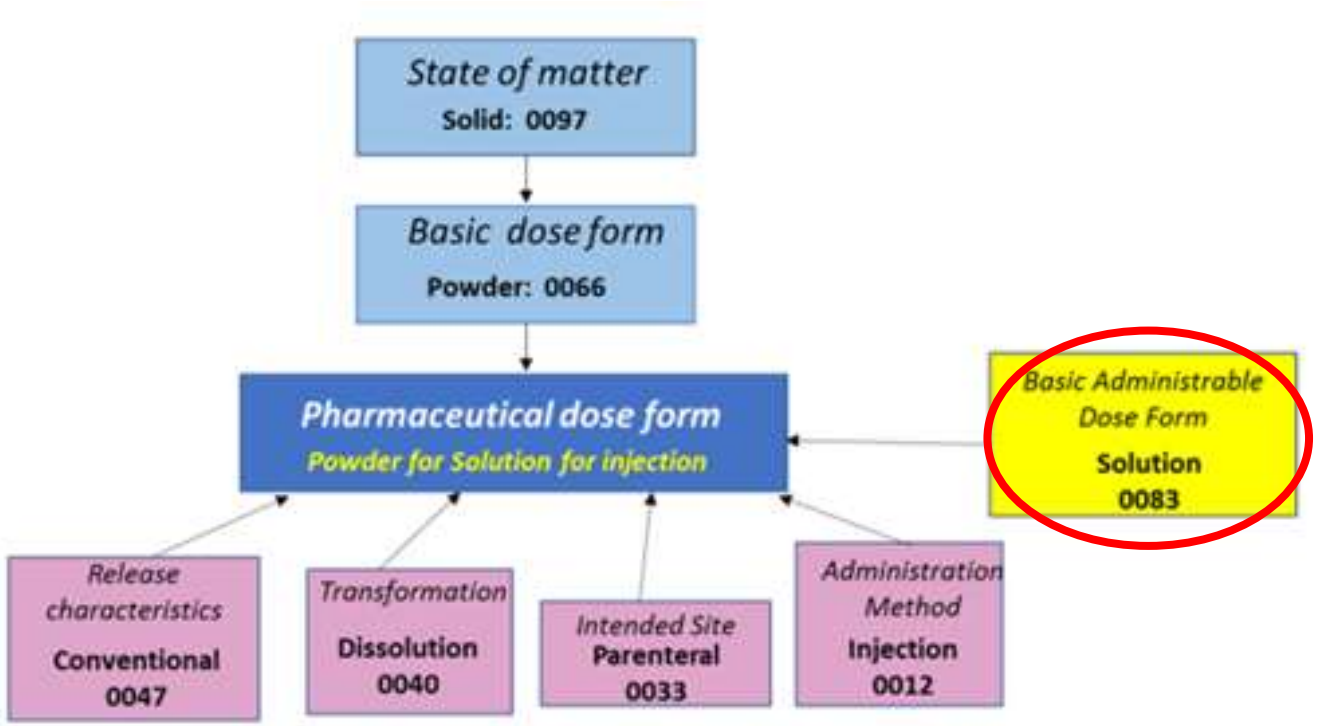
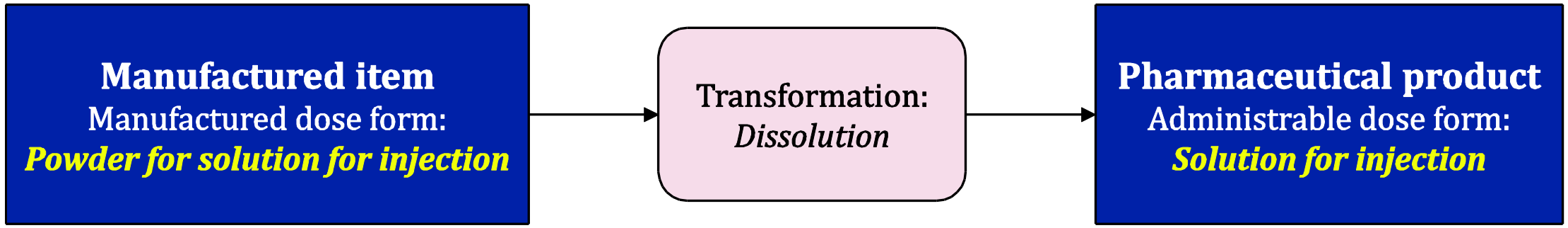
Dose Form Characteristics for Global PhPID

Medicinal Products that Require Transformation are a Challenge



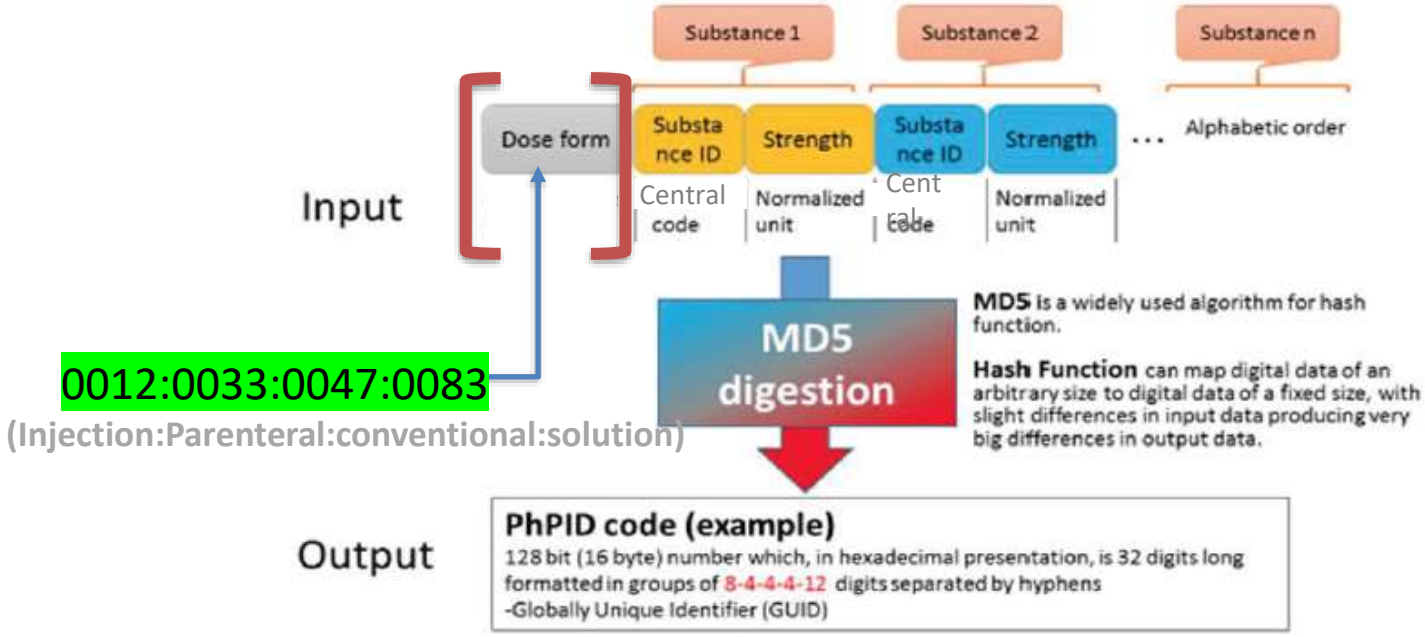
Dose Form Characteristics Use Case for Global PhPID



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

* Adapted from ISO TS 20451:2017

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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 based 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 perform a data equivalency assessment on the use of characteristics for generation of PhPID and present to ISO TC215 WG6 in June 2021

Pilot Identified Some Challenges

❖ Dose Form expression variations

❖ Pfizer Covid-19 vaccine

- EMA – ***Dispersion*** for Injection
- FDA – ***Suspension*** for Injection
- UK – ***Solution*** for Injection

❖ **Strength expression variations** – different units

- %, IU, mg/g or mg/mL

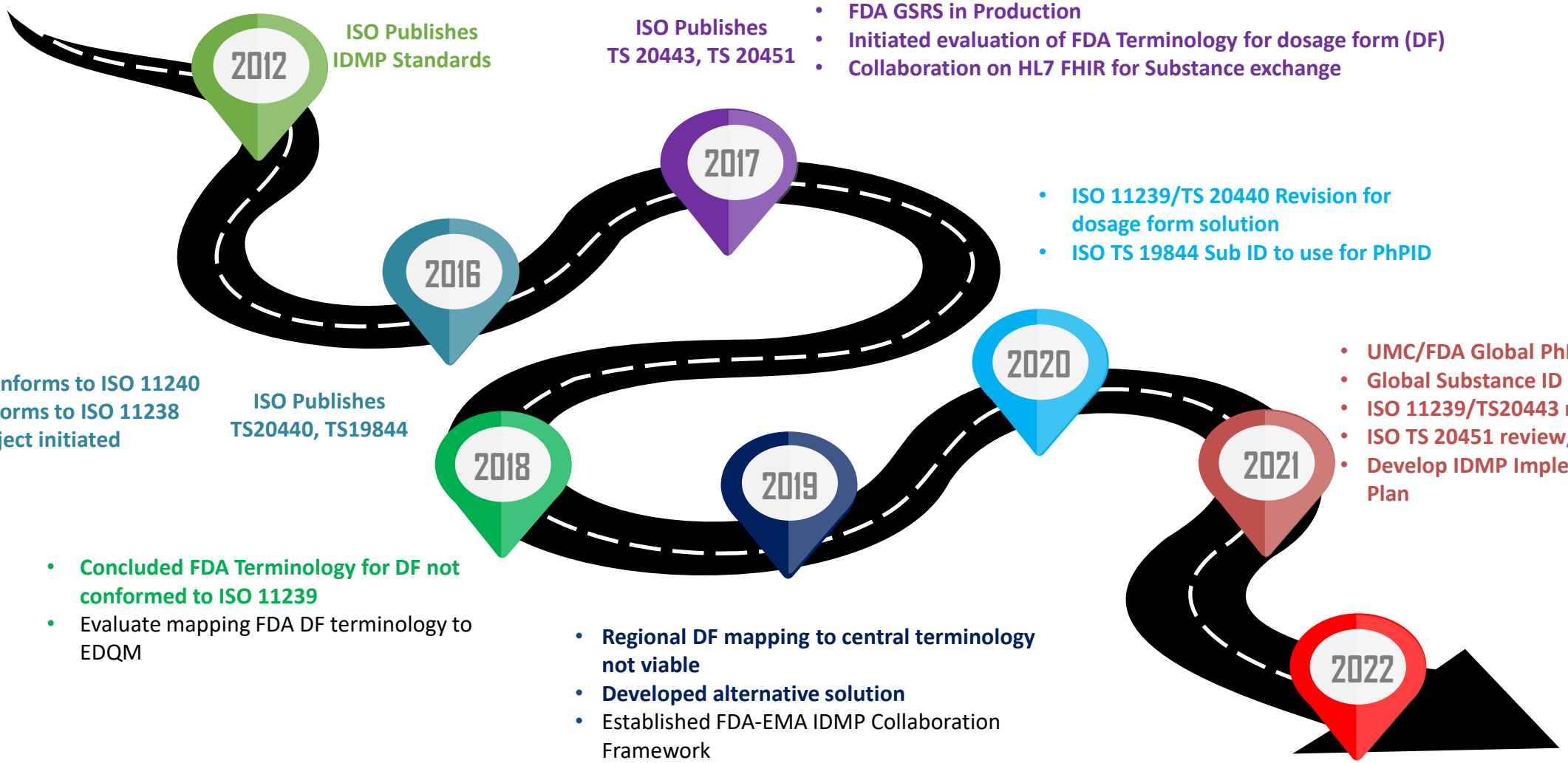
❖ AstraZeneca Covid-19 vaccine

- EMA – 2.5×10^8 ***infectious units***
- UK – 5×10^{10} ***viral particles***
- Australia – 5×10^{10} ***viral particles***

Preliminary Results and Next Steps

- Generally, dose form characteristics as input to generation of PhPID is a viable solution.
- A single organization, with global prospective, to consistently assign Dose Form Characteristics, strength, and substance ID may be important for global IDMP implementation
- Proceed with the revision of ISO 11239/TS20440 and related IDMP standards with ISO TC215 WG6

FDA IDMP Roadmap 2012-202x



2012
- ISO Publishes IDMP Standards

2016
- UCUM conforms to ISO 11240
- UNII conforms to ISO 11238
- GSRS Project initiated

2017
- ISO Publishes TS 20443, TS 20451

2018
- 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

2019
- ISO Publishes TS20440, TS19844

2020
- ISO 11239/TS 20440 Revision for dosage form solution
- ISO TS 19844 Sub ID to use for PhPID

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

2022
- Concluded FDA Terminology for DF not conformed to ISO 11239
- Evaluate mapping FDA DF terminology to EDQM

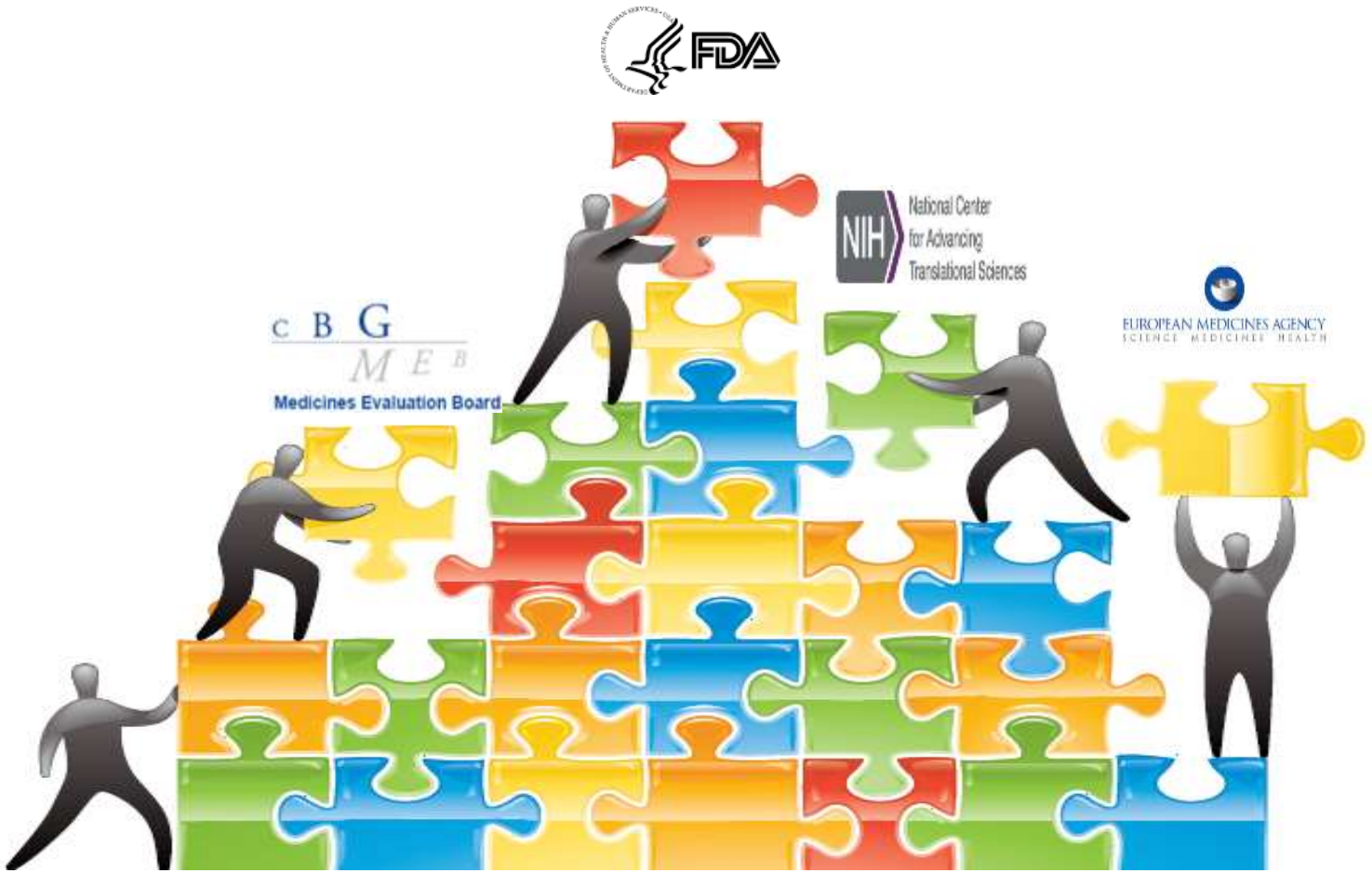
- Regional DF mapping to central terminology not viable
- Developed alternative solution
- Established FDA-EMA IDMP Collaboration Framework
- Collaboration on HL7 FHIR for MPID exchange
- UNICOM

- Testing and validate Global PhPID process

Thank you

U.S. FOOD & DRUG ADMINISTRATION

ISO 11238 and Global Substance Registration System(GSRS) SBIA Webinar (06/11/2021)



Organizing Information

- FDA has the most important/valuable repository of human biological and product data but limited integration.
  - Submission process
  - Paper
  - PDF's
- IDMP is an effort to organize information on a global scale

Organizing Information

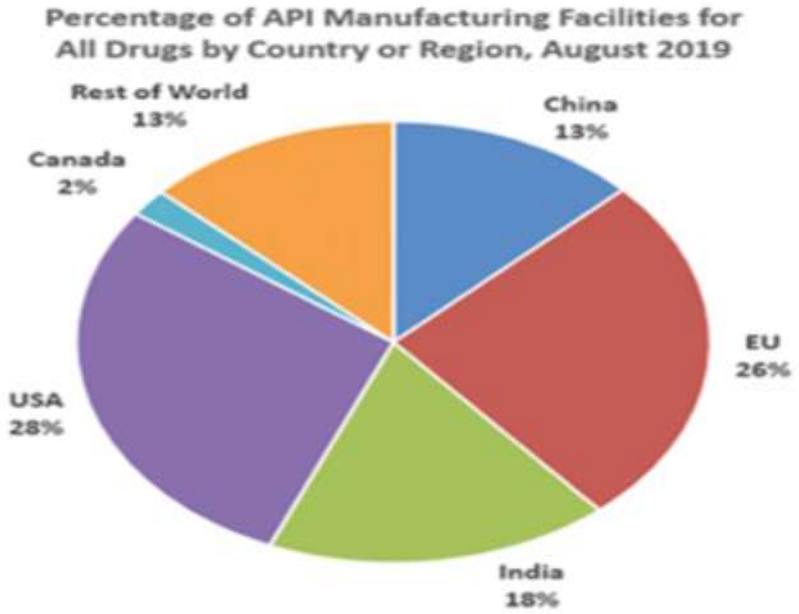
- The amount of information is increasing
  - More drugs and vaccines on a global scale
  - Rapid Screening Methods
  - Enzyme and Receptor Profiling
  - CYP , Transporter and Receptor
  - Genomics
  - Epigenomics
  - Electronic Health Records
  - Many CMC changes

Global Medicinal Products

- Medicinal/Pharmaceutical Product Marketplace is the most Global Marketplace
  - Highest Value Products
  - Highly regulated
  - Small Amounts of Material
    - Excipients often only a small proportion of market
  - Relatively Low Shipping Costs
  - Multiple ingredients from a variety of companies
    - Active
    - Excipients
    - Starting Materials
    - Packaging
    - Testing (Reference Standards)
    - Reagents

Global Pharmaceutical Manufacturing

Figure 1: Manufacturing Sites of APIs for US Market by Country or Region (August 2019)



Source: Center for Drug Evaluation and Research, US Food and Drug Administration

https://www.dcatvci.org/6213-global-api-sourcing-which-countries-lead

Pharmaceutical Supply Chain

Figure 1

Organizing Information

- Substances are one of the key lynchpins for organizing information
- Names are insufficient to describe substances
  - Same name different substances
    - Lime (fruit)
    - Lime (chemical)
  - Different names same substance
    - Acetaminophen
    - Paracetamol
- Define substances based on core scientific principles and assign a permanent Unique Ingredient Identifier (UNII)

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

Substances Scope

- Active ingredients
- “Inactive” ingredients
- Impurities
- Metabolites
- Targets
- Off-targets
- Processing materials

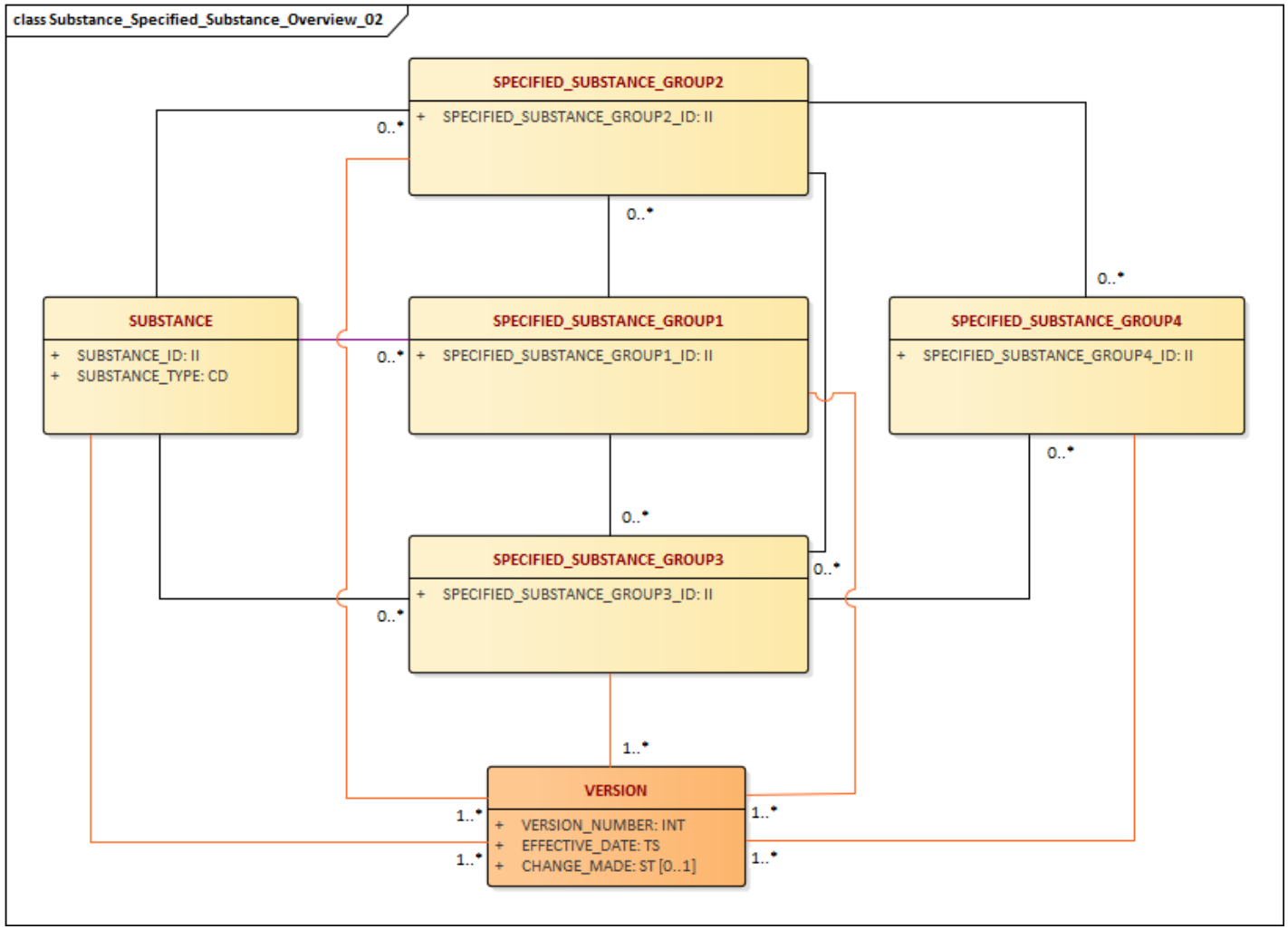
Need for Specified Substance

- 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.
- Still working on how to capture the details of glycosylation at the Group 1 level
- Group 2 needs 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
- Help address shortages, substandard and counterfeit ingredients, coordinate inspections
- FDA with NIH has developed a software system that can be used by regulatory agencies throughout the world to register substances
- System being used by EMA, other European agencies and WHO-UMC
- Common system will make it easier to transfer data and allow international implementation

GSRS

Global Substance Identifier

- IDMP specified the need for a global substance ID
- Global substance ID has not yet been agreed on
- Need a single organization needed to maintain a global substance
- Work with WHO-UMC underway for global substance ID
- Needed to implement PHPID
- Single organization to handle all of the Global Ids or a federated approach?

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

Registers and defines

Limited quality information

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

GSRS is part of the IDMP effort

FDA

GSRS

GSRS Software

- Works in all modern browsers: IE, Chrome, and Firefox
- System freely distributed through NCATS with a large set of curated public domain data and updated periodically
  - 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
- Being used by EMA. Bfarm, WHO-UMC and CBG in Europe

Current Status at FDA

Approximately 200,000 thousand substances registered

120,000 Substances curated most publicly available

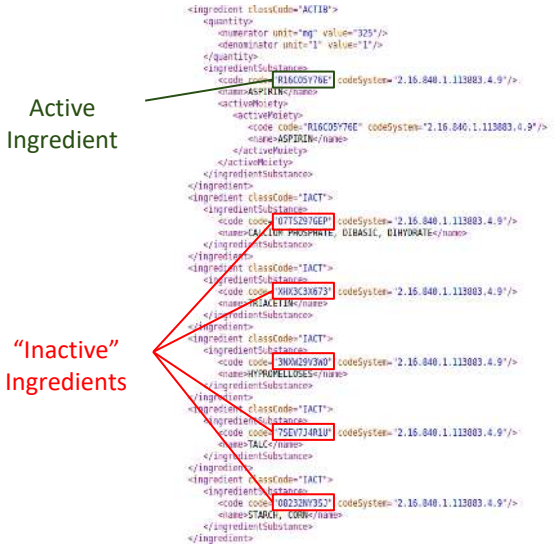
Over 2,000,000 Names and Codes

Nearly 200,000 Relationships Drug targets, Metabolites, Impurities

Much of the data is public domain

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
  - Several classification systems
    - CFR DEA Classification



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

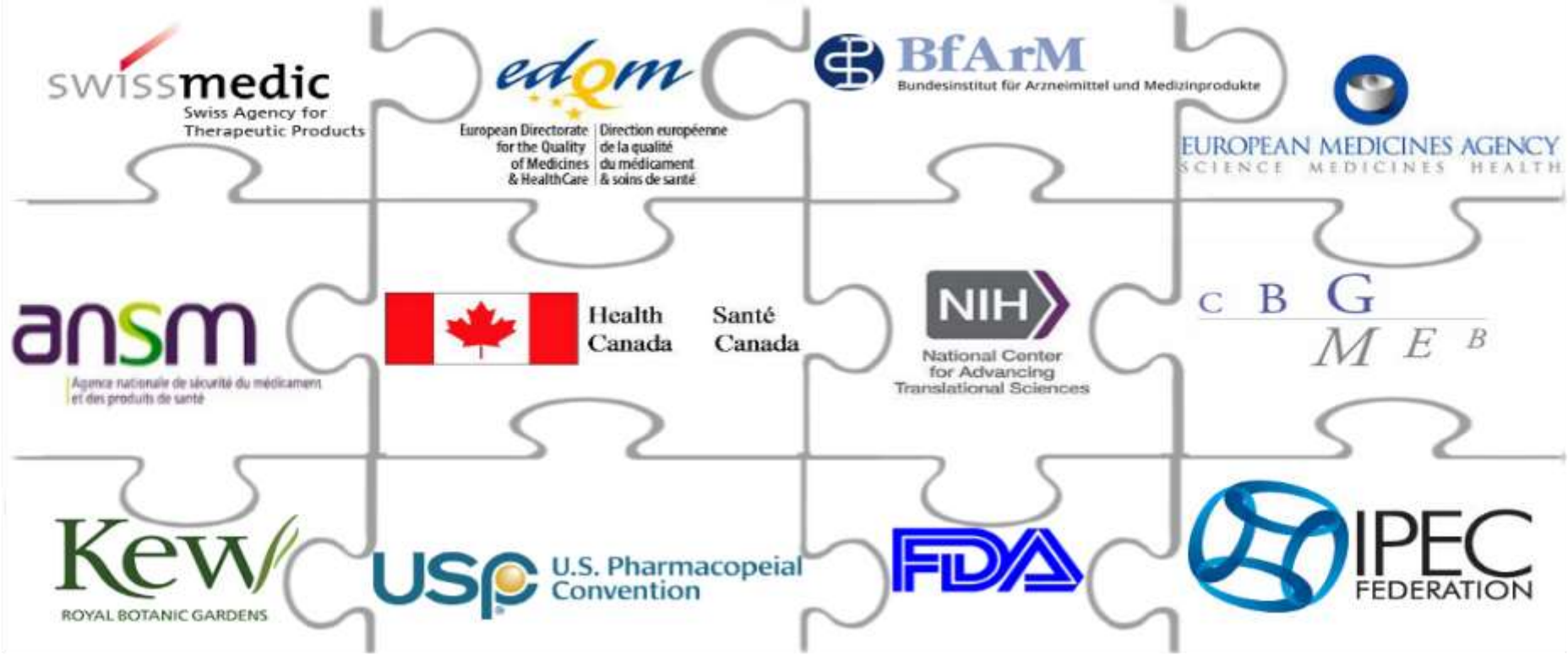
Vaccine Initiative

- Vaccines are the most important public health tool we have
- No international nomenclature names vary significantly throughout the world
- WHO-UMC has set up a site for registration of Vaccine ingredients and related substances
- Used to workout common controlled vocabulary, possible global identifier
- Pilot Complete by September
- Industry involvement at some point

GSRS Public Resources

- To get the software and data from and info from NCATS
  - https://gsrs.ncats.nih.gov
- NLM site for a list UNII codes
  - https://fdasis.nlm.nih.gov/srs/srs.jsp
- GInAS Meetings
  - Annual Meeting (USP, WHO-UMC, CBG have hosted)
- To Get on the GInAS Notification List
  - https://gsrs.ncats.nih.gov

Working Collaboratively



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EDQM
Claude Coune, Chris Jarvis (EDQM)

Excipient Industry
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FDA
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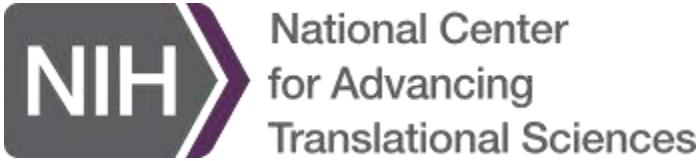
ADMINISTRATION

GSRS Open Software

SBIA Webinar (06/11/2021)

Tyler Peryea
Cheminformatician
FDA/OC/OCS/OHI

Collaboration With

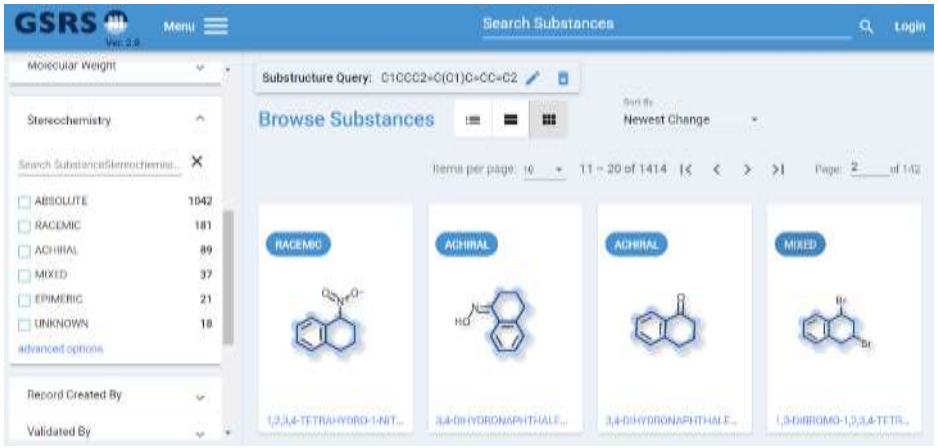


GSRS Software

- Outline
  - What is it?
  - How does it work?
  - Where is it used?
  - Where is it going?
  - How to get involved?

GSRS Software

- Freely distributable and open-source software
- Implementation of ISO 11238 standard
- Created and maintained by NIH/NCATS in collaboration with FDA and several other organizations



GSRS Software

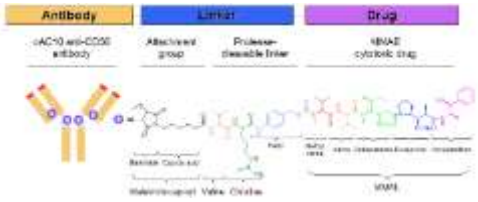
- What is it for?

  GSRS Software is a self-contained **web application and database** for registering, storing, searching and exchanging substance information in a machine-readable form in compliance with the **ISO IDMP 11238** standard.

  It is freely distributable and can be used as a local substance registration system by regulators, researchers and industry.

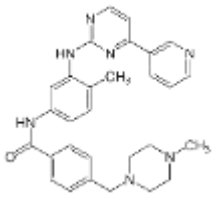
GSRS Software

Substances



Complex Macromolecules

Plant and Animal derived substances and extracts



Small Molecules

Vaccines

Exploration of Substance Space

Systematic Definition and Curation

Regulatory Tracking

Pharmacovigilance

Metabolism

Systematic Use

Organizing Biological Data

Inventory

Nomenclature

Links to Other Databases

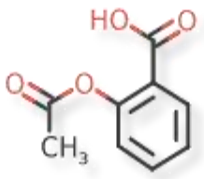
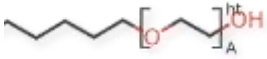
Manufacturing Information

Agreeing on Fundamentals Makes Everything Easier!

GSRS Software

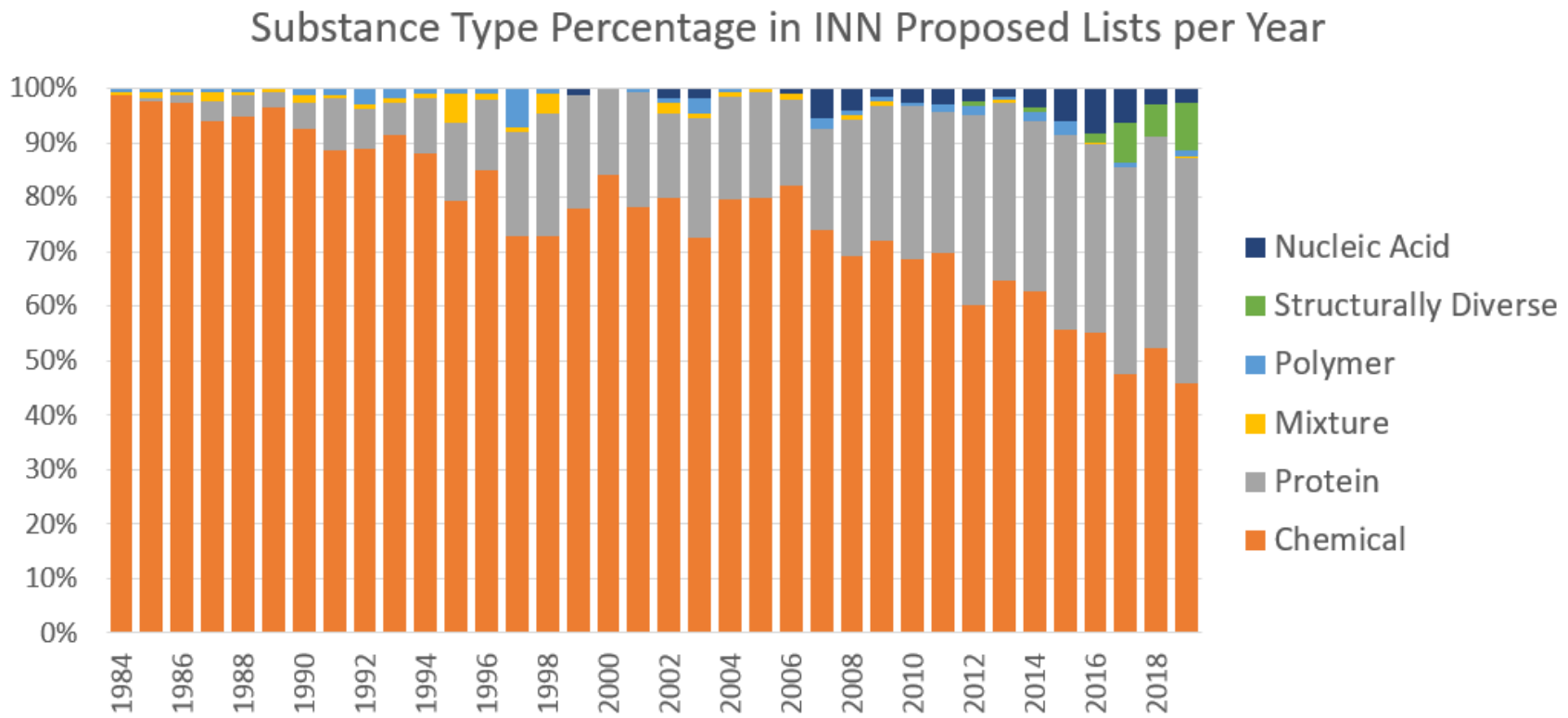
What is a substance?

A substance is a conceptual physical entity, which is capable of separate existence, and is uniquely definable based on its immutable chemical, physical and/or taxonomic properties.

Substance Type	Chemical	Polymer	Protein	Nucleic Acid	Structurally Diverse
Defined By	Chemical Structure	Structural Repeat Unit(s)	Amino Acid Sequence(s)	Nucleobase Sequence	Taxonomic Information + Part
Example			>A35X00TA2K RCPGCGQGVQAGCPGGCVEE EDGGSPAEGCAEAEGCLRRE GQECGVYTPNCAPGLQCHPP ...	>303159CVH9 TAAACGTTATAACGTT ATGACGTCAT	

Organism Family	CANNABACEAE
Organism Genus	CANNABIS
Organism Species	SATIVA
Author	L.
Infraspecific Type	SUBSPECIES
Infraspecific Name	SUBSP. SATIVA

GSRS Software



The *kinds* of substances being made as APIs are changing

GSRS Software

- Registering a Substance

GSRS

- Systematic
- Structured
- Machine-Readable
- Searchable
- Exchangeable

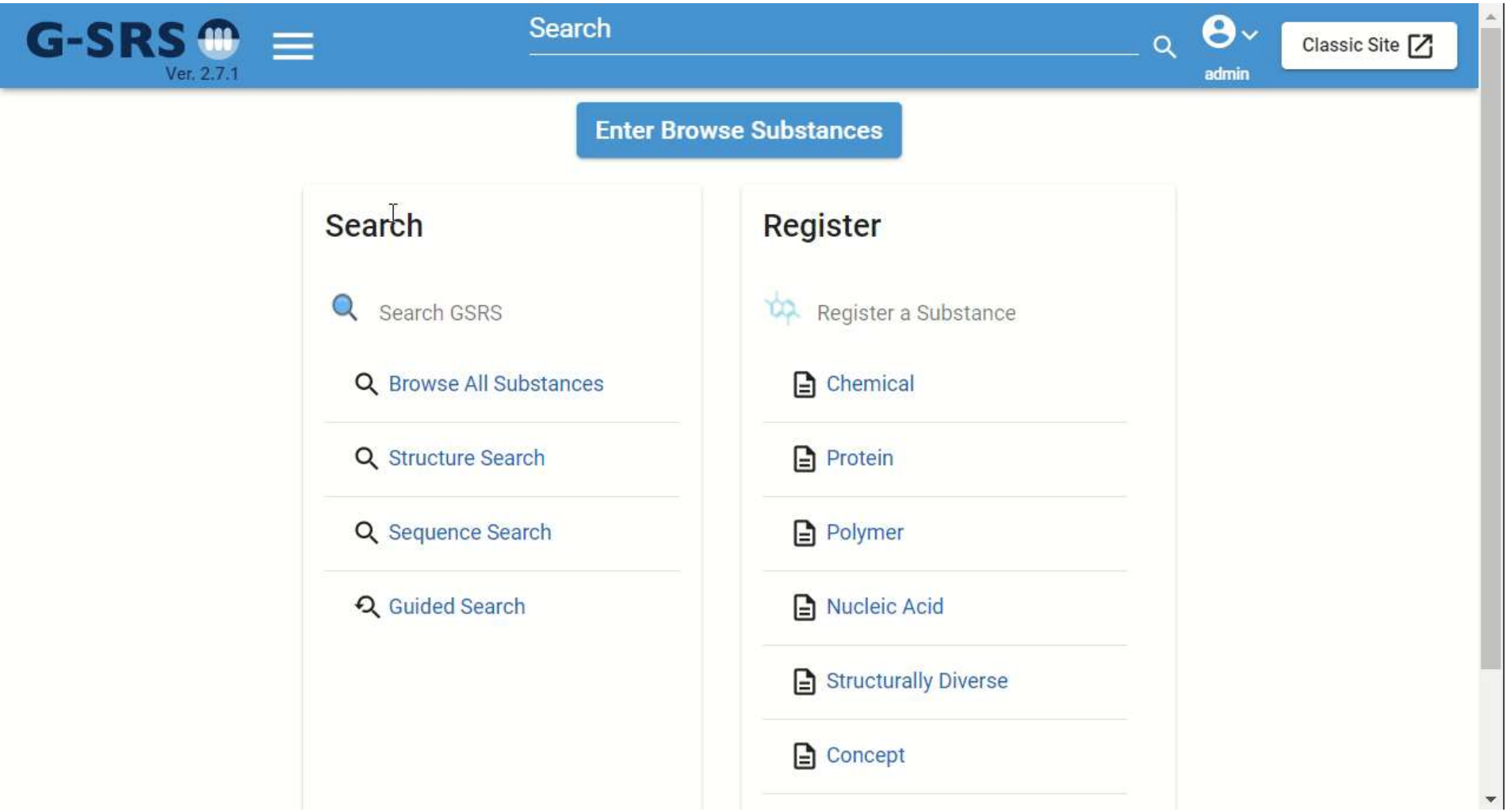
GSRS Software

- Registration Tools
  - Data Entry Forms
  - Name-to-chemical structure tool
  - Image-to-chemical structure tool
  - Configurable validation rules
  - Uniqueness check algorithm
  - Audits and edit history

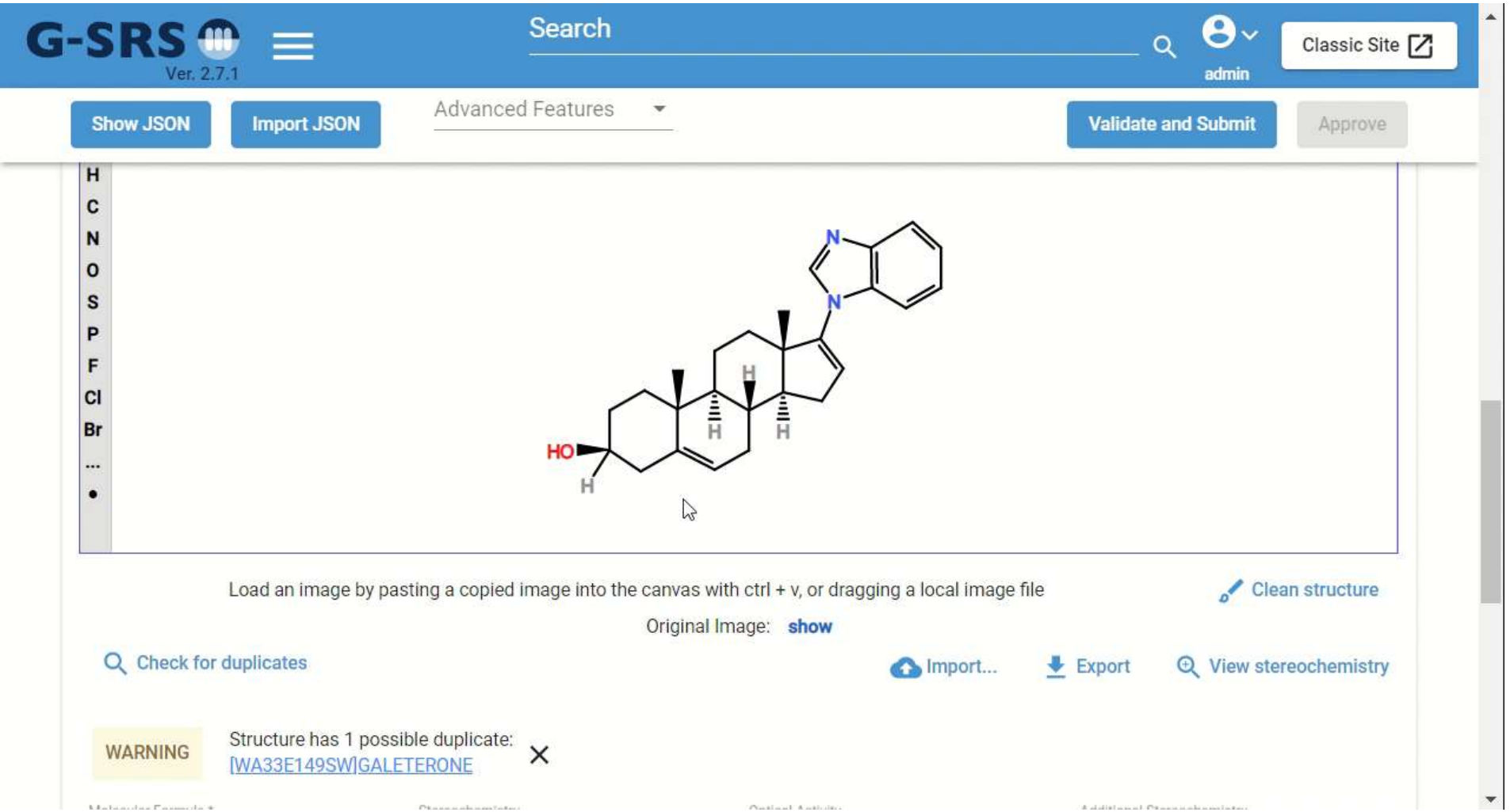
GSRS Software

DEMO

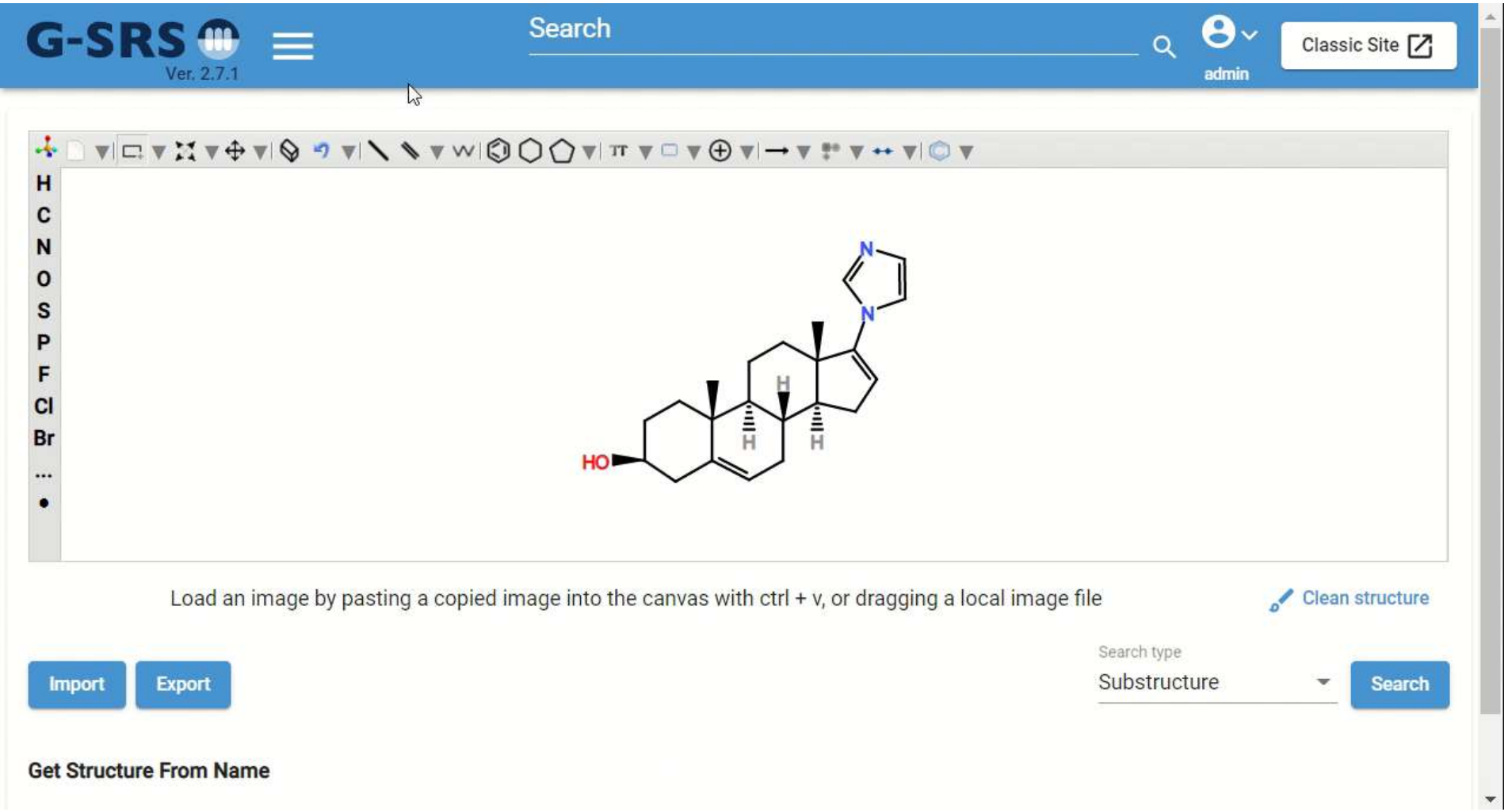
GSRS Software



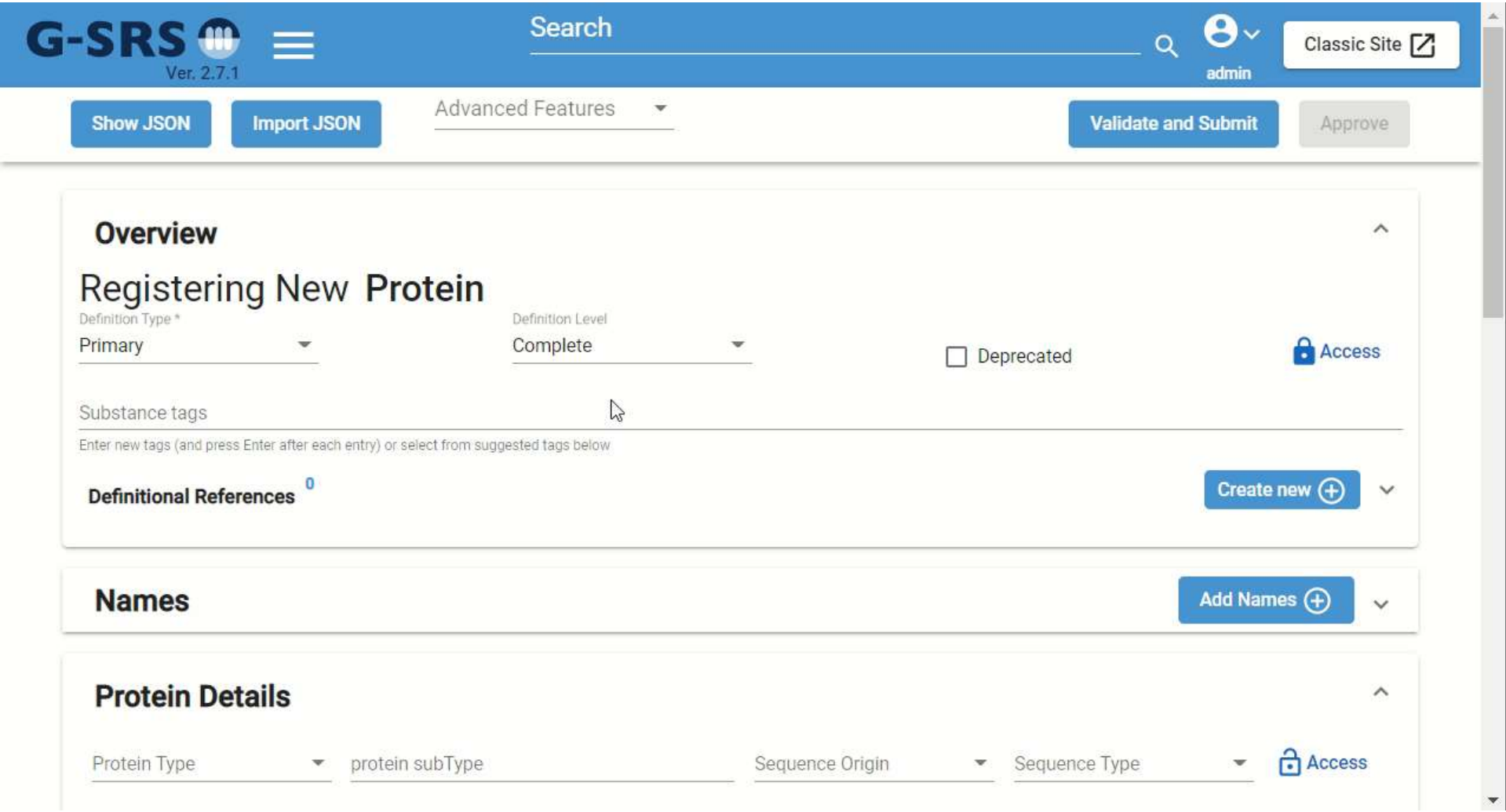
GSRS Software



GSRS Software

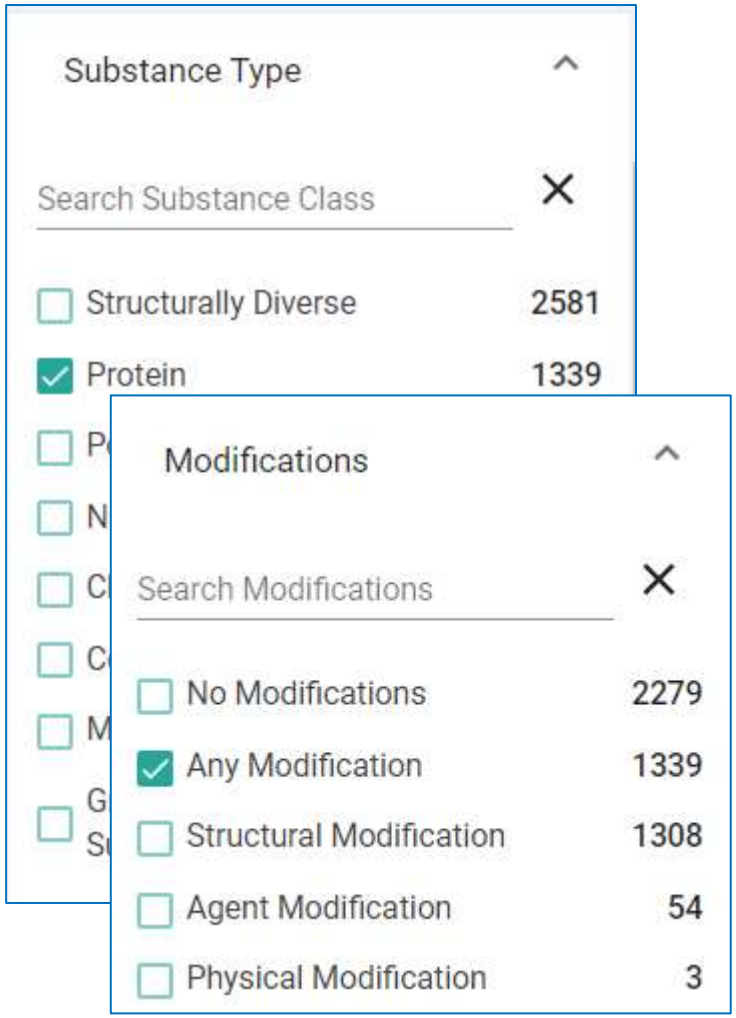


GSRS Software



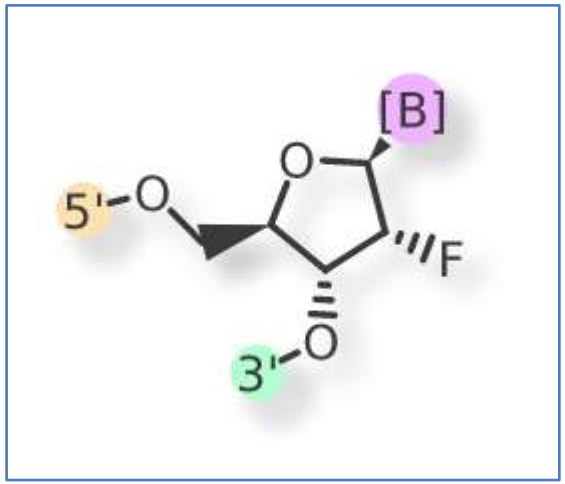
GSRS Software

- Browse & Search
  - Rich fielded text searches
  - Structure-based searching
  - RNA/Protein sequence-based searching
  - Customizable “facet” filters
  - Customizable data exports



GSRS Software

- Other Tools
  - User Management
  - CV Management
  - Full REST API
  - Scheduled Jobs
  - Custom Triggers
  - Custom Reports

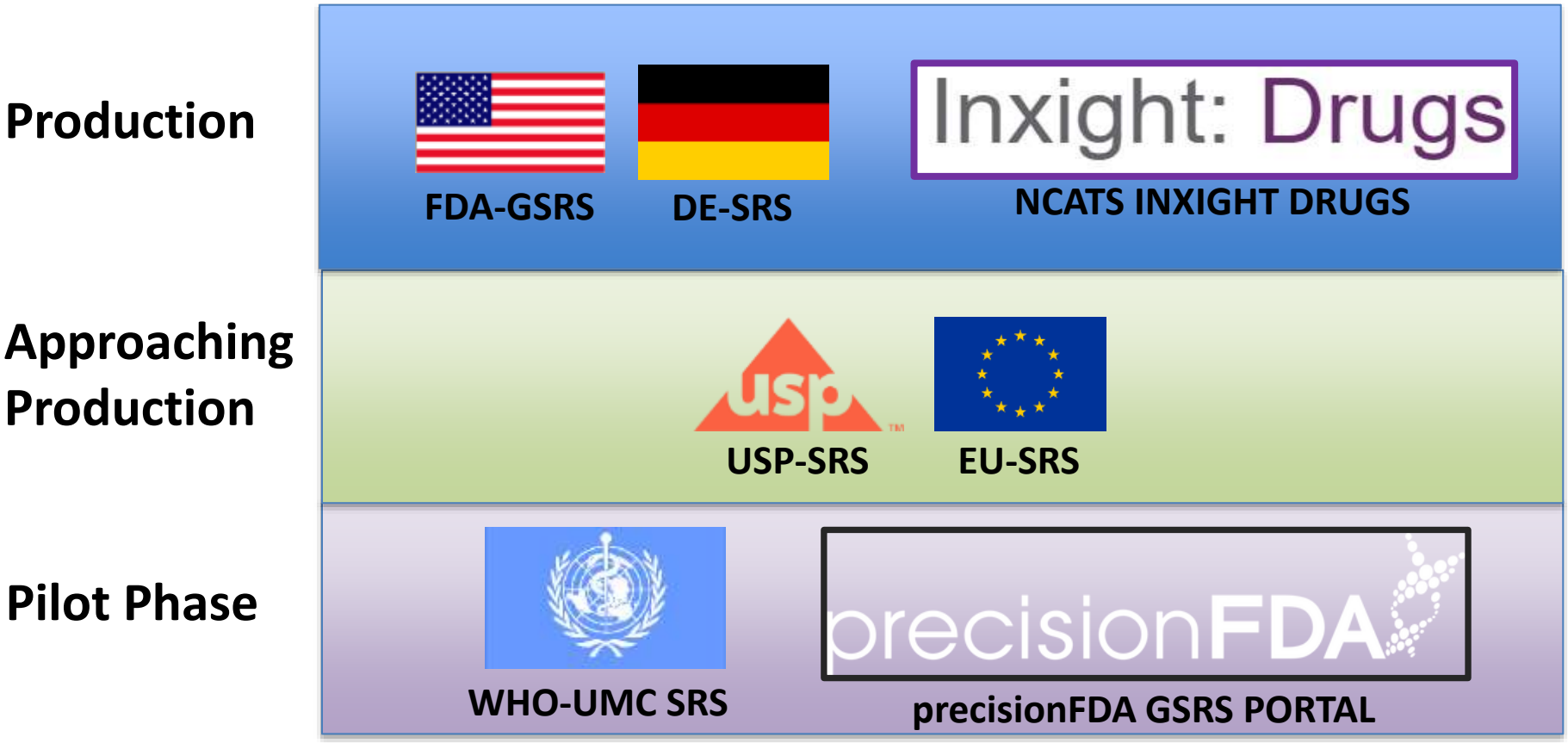


Other Downloads

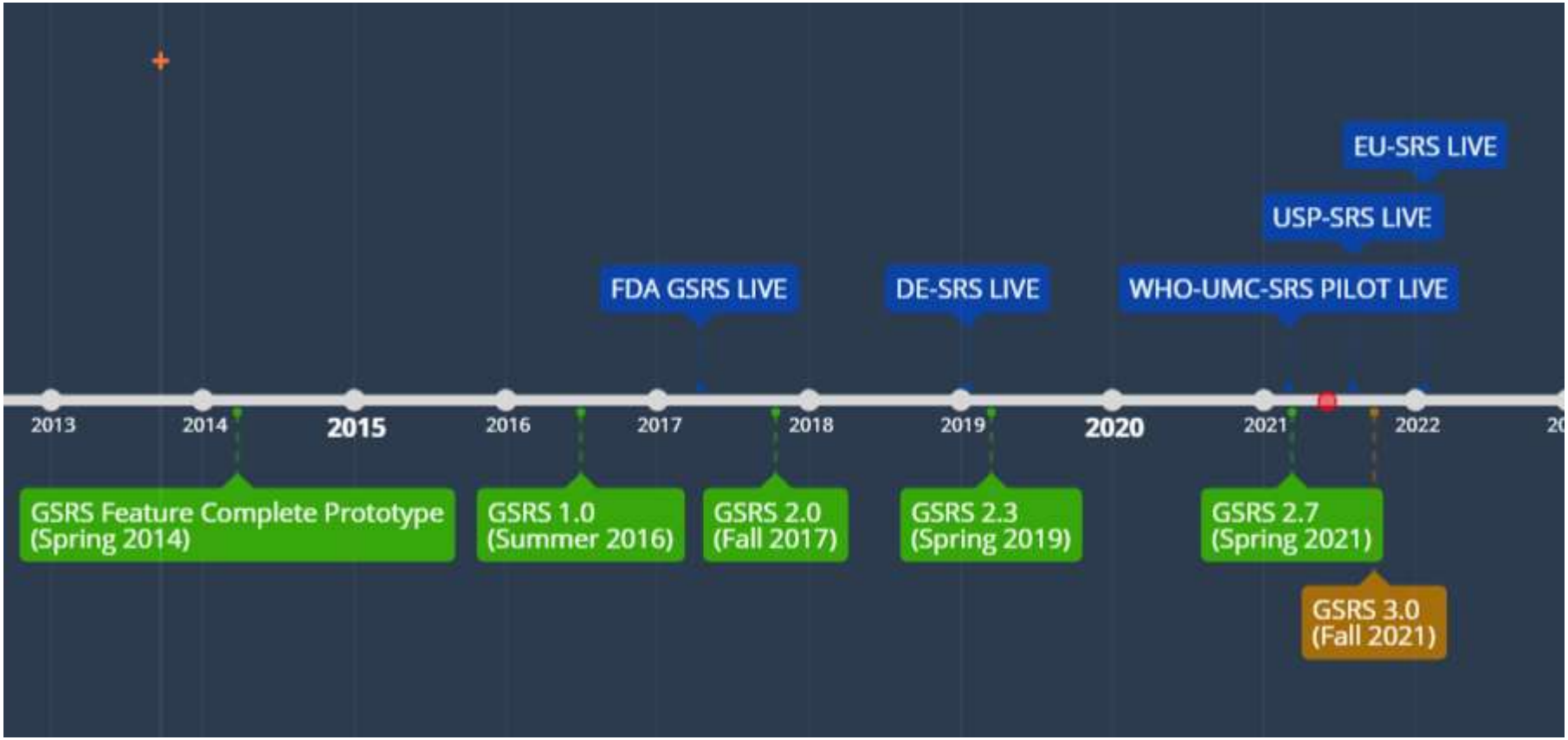
- Ginas Excel Tools

GSRS Software

Projects based on GSRS Open-Source Software

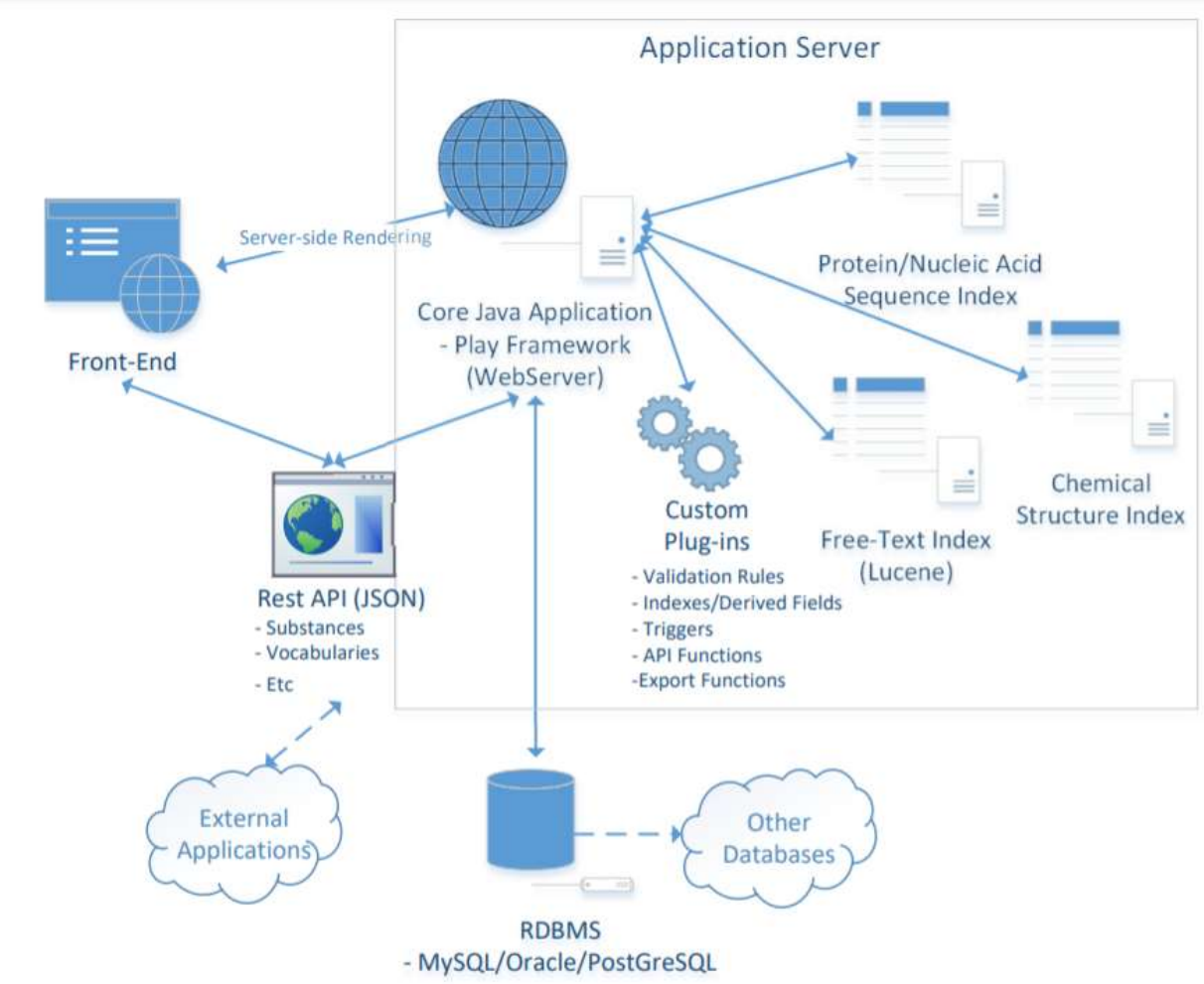


GSRS Software



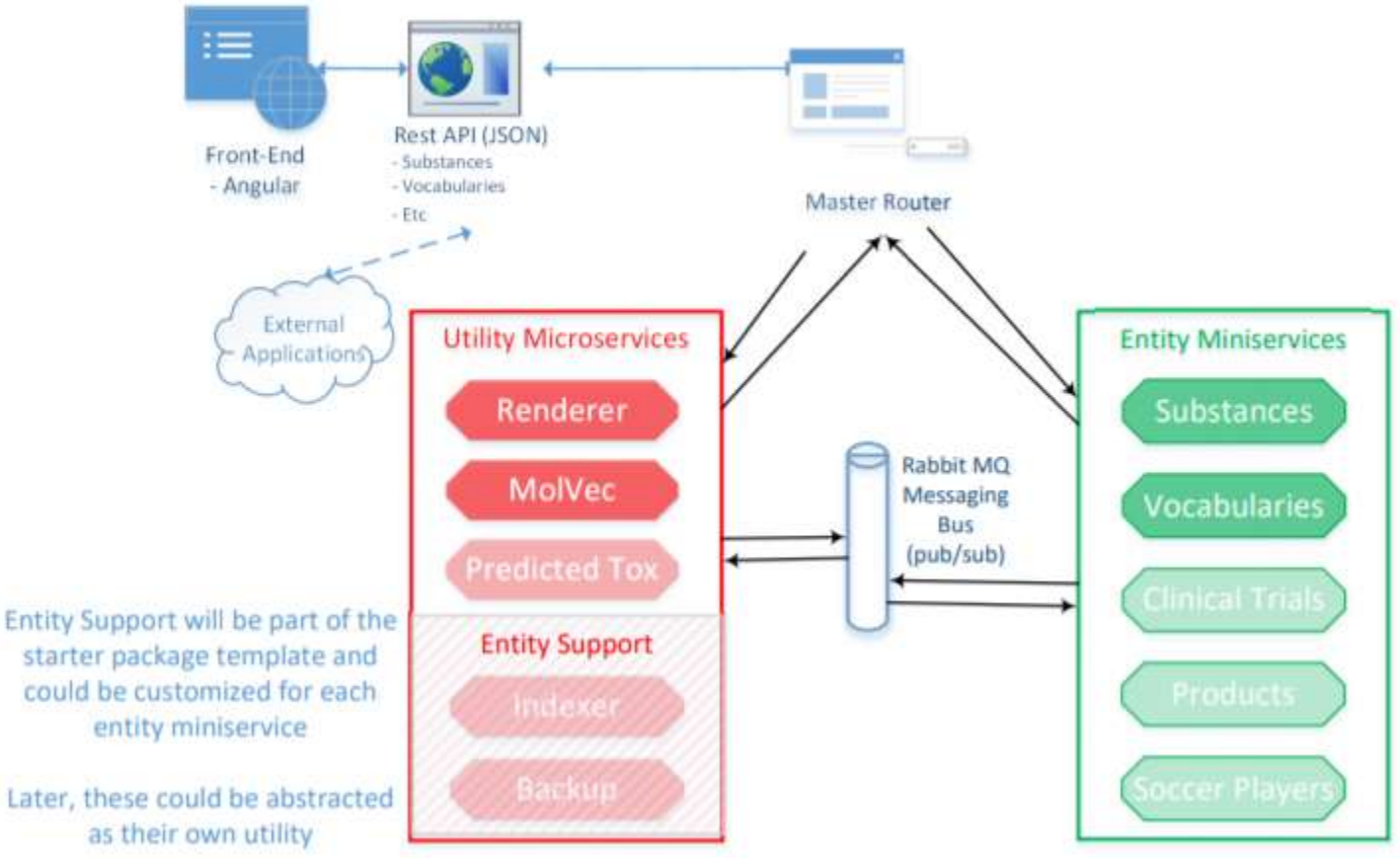
Development Timeline

GSRS Software



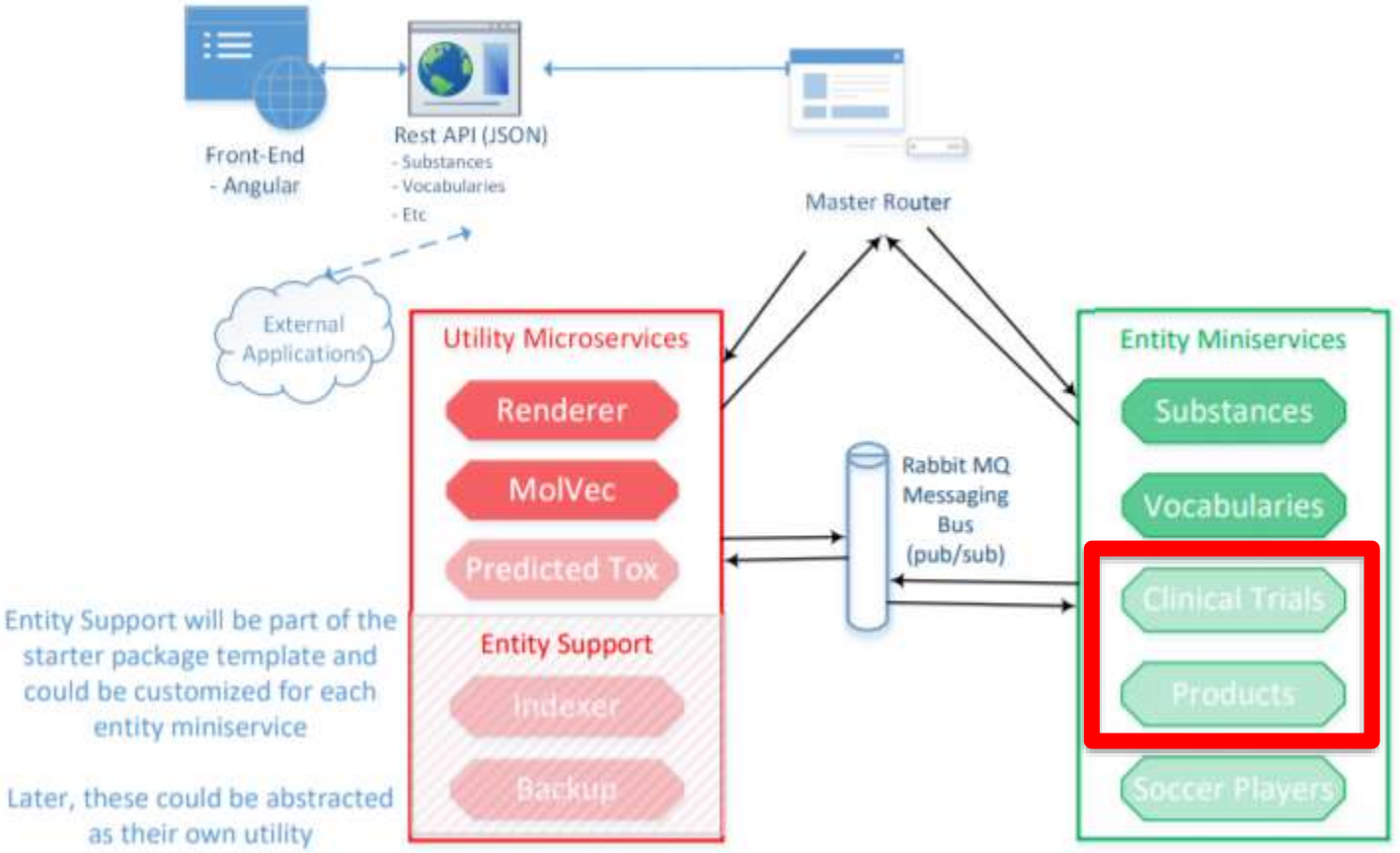
GSRS 2.X Software Architecture

GSRS Software



GSRS 3.X Software Architecture

GSRS Software



GSRS 3.X Software Architecture

GSRS Public Resources

- Software Project site:
  - https://gsrs.ncats.nih.gov/
- GitHub Source Code:
  - https://github.com/ncats/gsrs-play
- To get on notification list:
  - https://gsrs.ncats.nih.gov/

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