Overview of ISO IDMP, Substances and HL7 Patient Care WG (allergy-intolerance)

Joint HL7 Biomedical Research & Regulation WG and Patient Care WG Meeting, May 10, Madrid, Spain

Panagiotis Telonis (EMA), Christian Hay (ISO/GS1), Herman Diederik (EMA/CBG), Larry Callahan (FDA), Frank Switzer (FDA), Tyler Peryea (NCATS/NIH), Noel Southall (NCATS/NIH)

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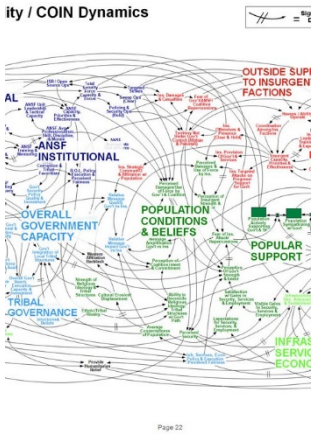
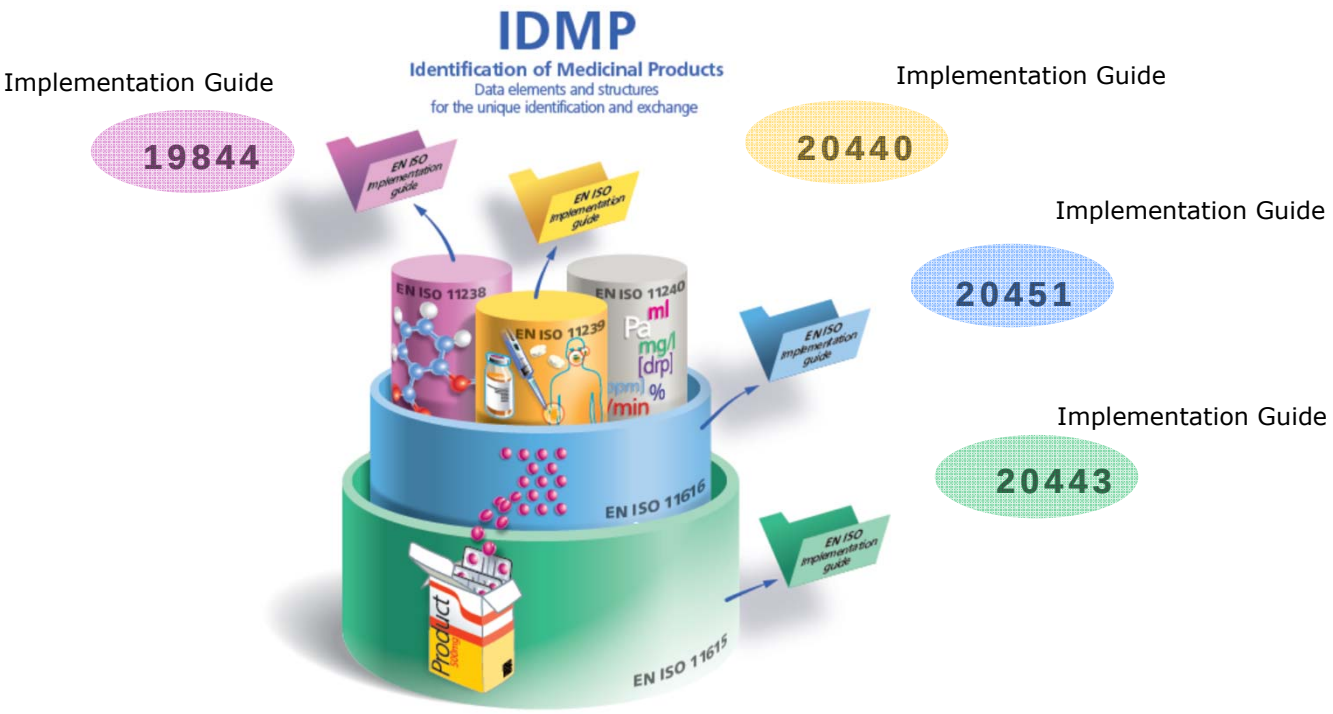
1. High Level Overview of IDMP
2. Substances/ISO 11238/19844/G-SRS
3. HL7 PC - Allergy & Intolerance
4. Q&A and examples

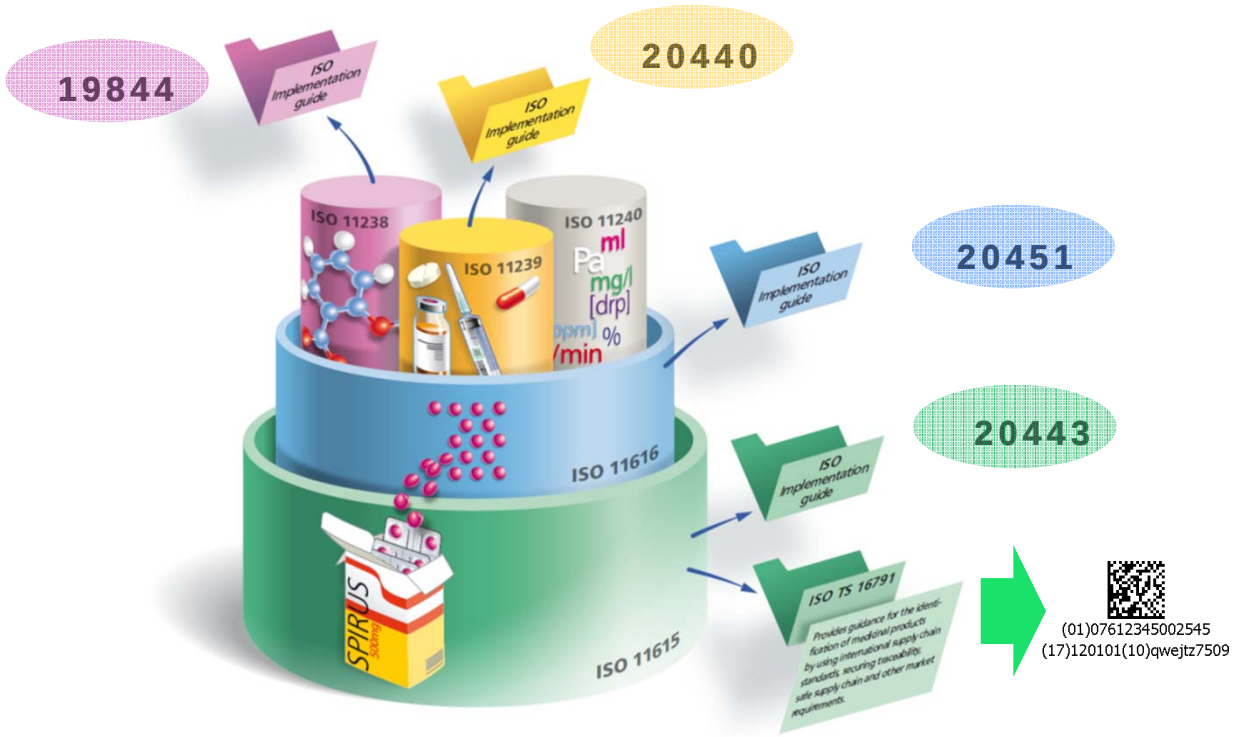
Overview of IDMP
…to introduce the discussion about allergies



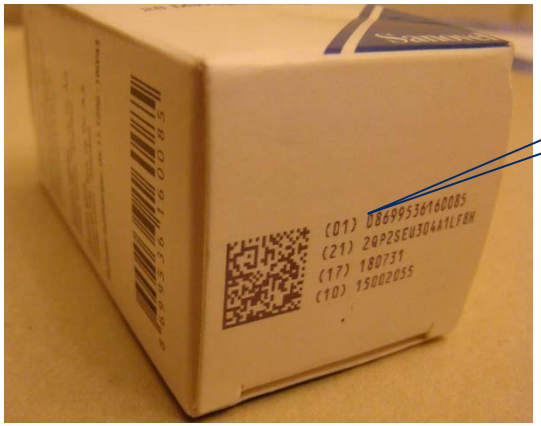
IDMP in a graphical representation



IDMP – the link to Supply Chain



DataMatrix, the preferred carrier

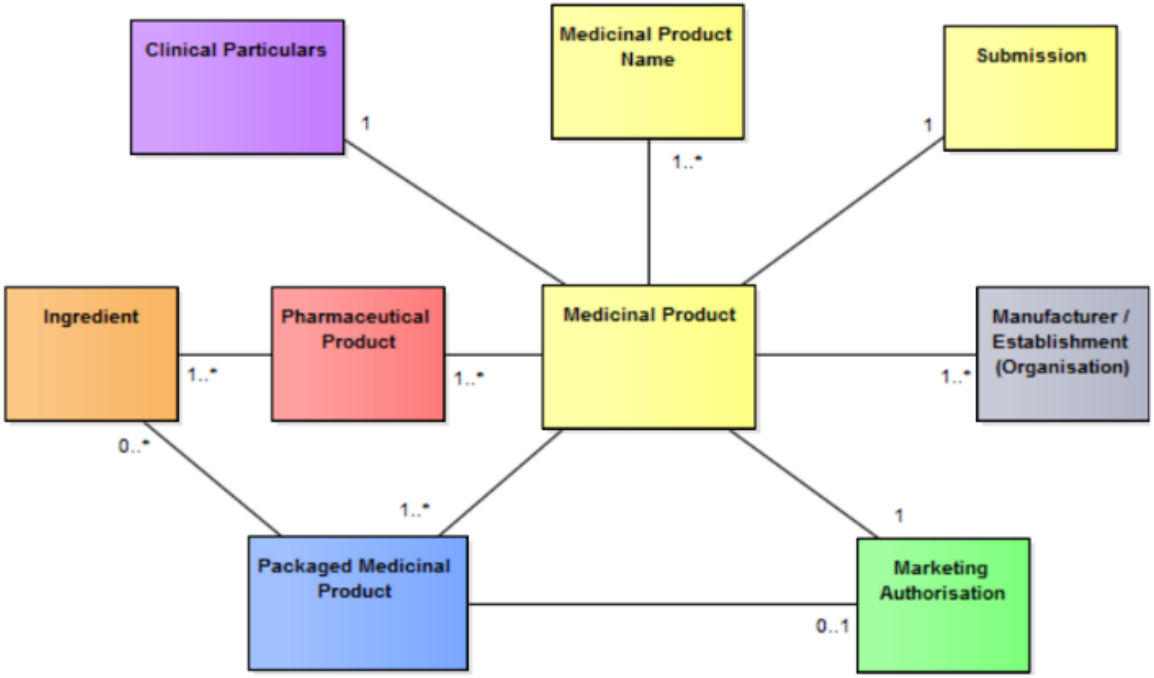


Product identifier (GTIN)

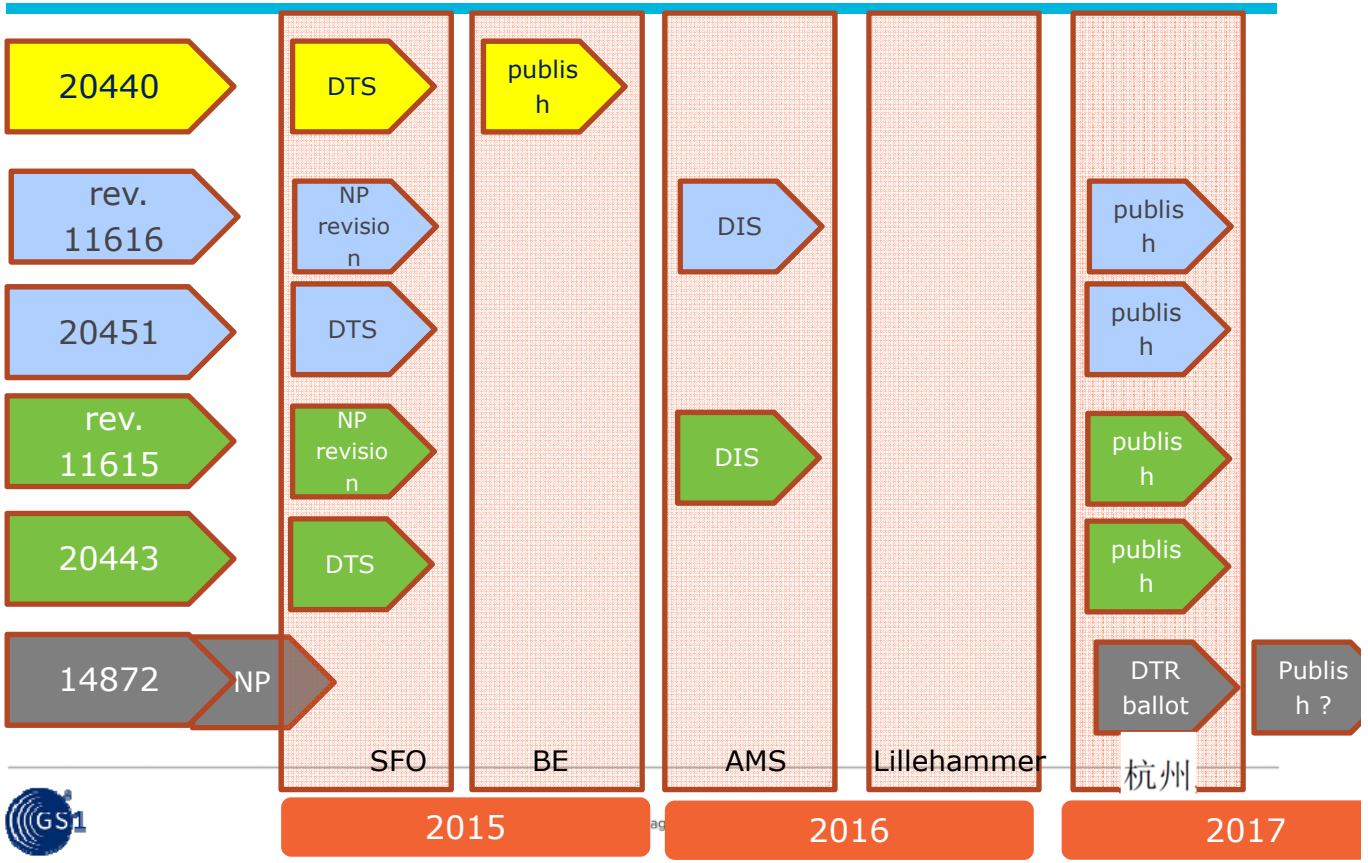
IDMP:
Packaged Item
Data Carrier Identifier
Code System* : 2.51.1.1
Value: 08699536160085

* OID for GS1 GTIN

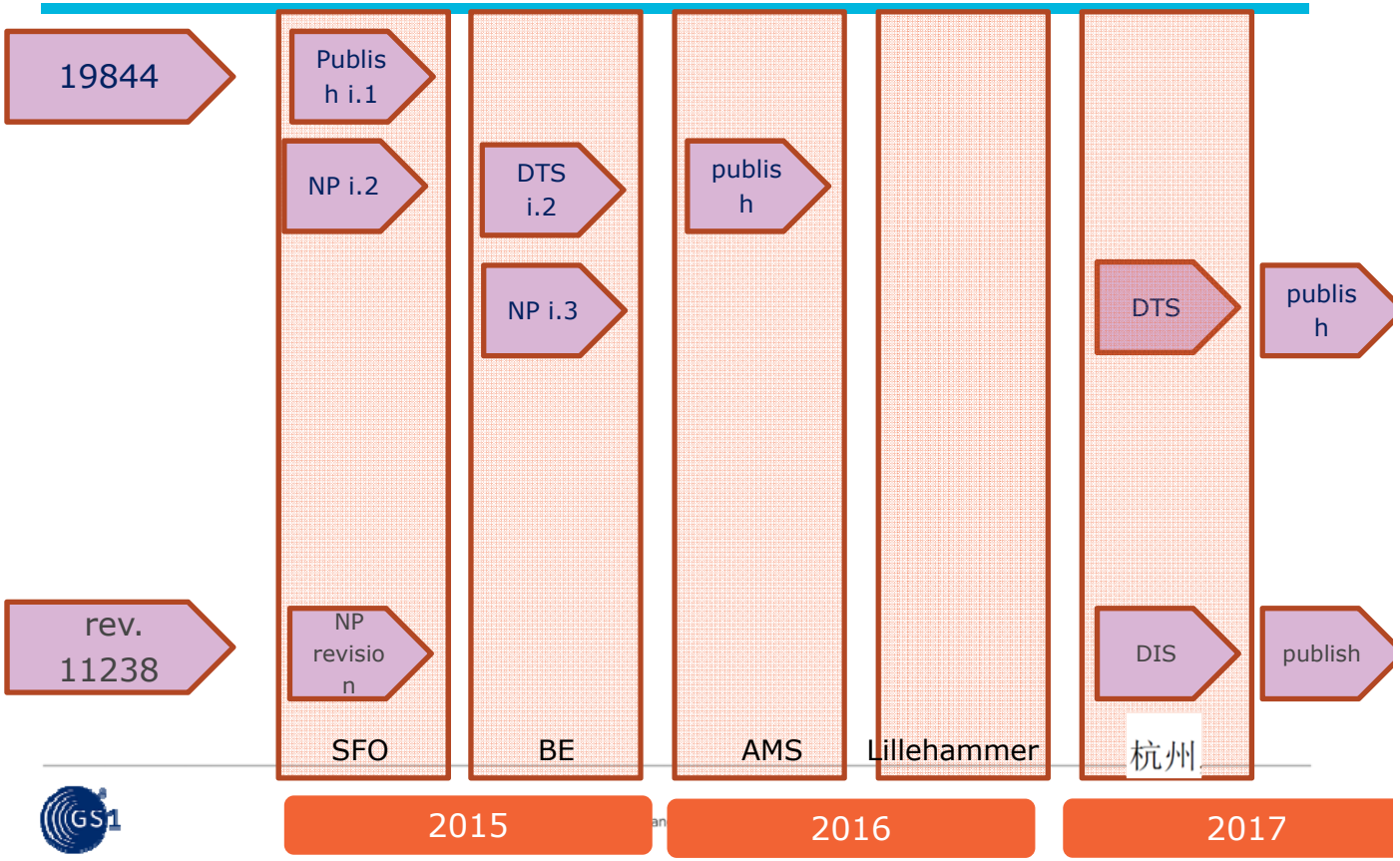
Medicinal Product overarching model



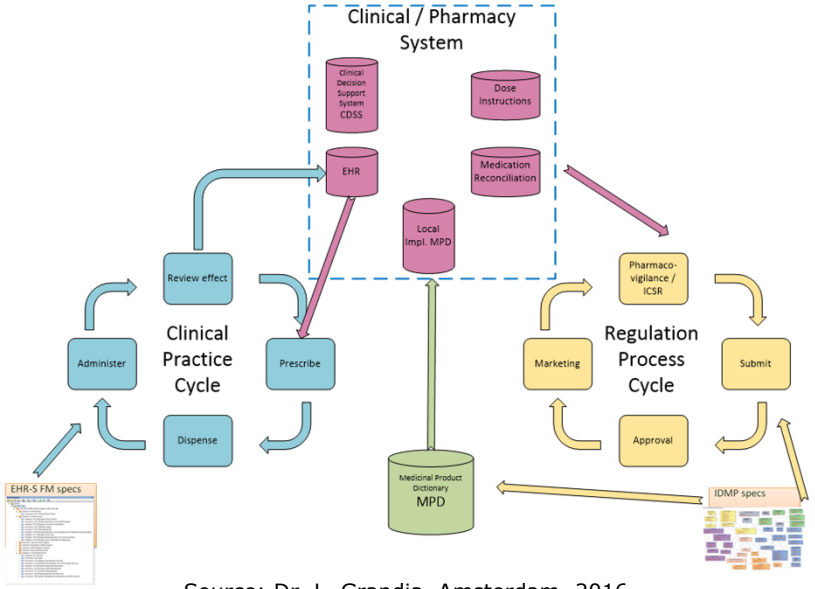
IDMP roadmap



IDMP roadmap

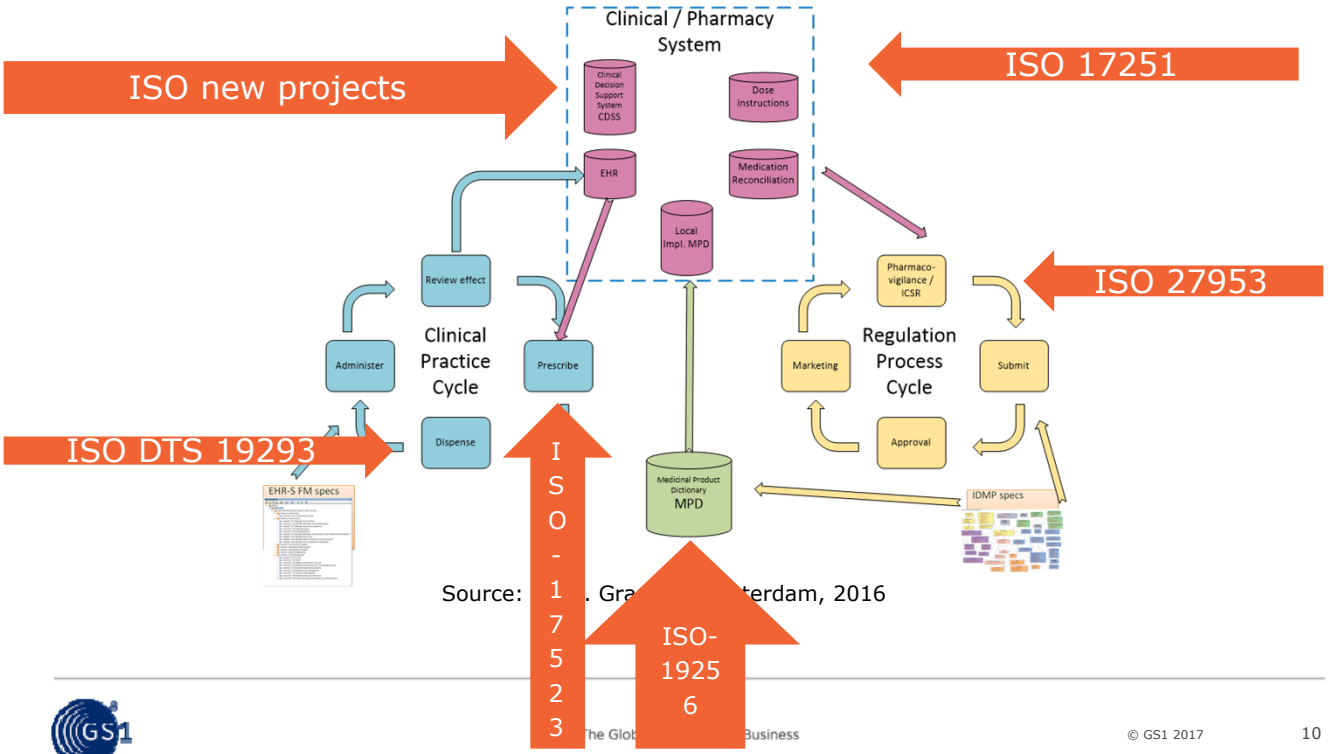


IDMP impact on Clinical Processes



Source: Dr. L. Grandia, Amsterdam, 2016

IDMP impact on Clinical Processes



Source: . Gra terdam, 2016

Main IDMP identifiers

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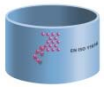
ISO IDMP Global Harmonisation

Medicinal Product ID (MPID)

- *Regional Identification*

Pharmaceutical Product ID (PhPID) *(algorithm)*



- Based on core elements for identification of medicinal products

Substances

- Global Substance Registration System *(G-SRS)*

Dosage forms and Routes of Administration

- European Directorate for the Quality of Medicines *(EDQM)*

Units of measurement

- Unified Code for Units of Measure *(UCUM)*

Why is substance (ID) important

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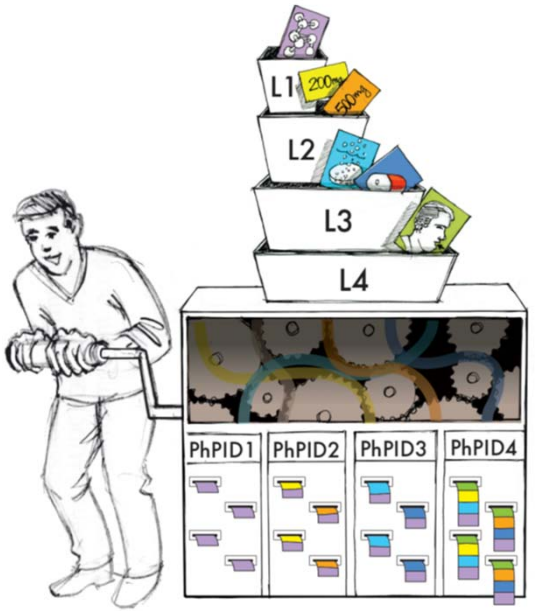
Example: Paracetamol/Acetaminophen

• **PhPID_SUB_L1 →** paracetamol	• **PhPID_SUB_L1 →** paracetamol	• **PhPID_SUB_L1 →** paracetamol
• **PhPID_SUB_L2 →** paracetamol, **500 mg**	• **PhPID_SUB_L2 →** paracetamol, **500 mg**	• **PhPID_SUB_L2 →** paracetamol, **500 mg**
• **PhPID_ SUB _L3 →** paracetamol, **tablet**	• **PhPID_ SUB _L3 →** paracetamol, **caplet**	• **PhPID_ SUB _L3 →** paracetamol, **capsule**
• **PhPID_ SUB _L4 →** paracetamol, **500 mg, tablet**	• **PhPID_ SUB _L4 →** paracetamol, **500 mg, caplet**	• **PhPID_ SUB _L4 →** paracetamol, **500 mg, capsule**

Substance ID as food for PhPID generation



- **PhPID_SUB_L1 →** paracetamol
- **PhPID_SUB_L2 →** paracetamol, **500 mg**
- **PhPID_ SUB _L3 →** paracetamol, **tablet**
- **PhPID_ SUB _L4 →** paracetamol, **500 mg, tablet**

IDMP (high level wrap-up)

Four levels of Information

- Substance (Global Unique identifier)
- Specified Substance (Global/can be implemented per Jurisdiction Regional)
- Pharmaceutical Product (Global Identifier) substance, strength, dosage form
- Medicinal Product (Regional per Jurisdiction)

NOTE: ISO 11238 standard and ISO/TS 19844 within ISO IDMP suite address both Substances and Specified Substances

ISO/DIS 11238 (revision of ISO 11238:2012)
ISO/TS 19844 (revision of ISO/TS 19844:2016)

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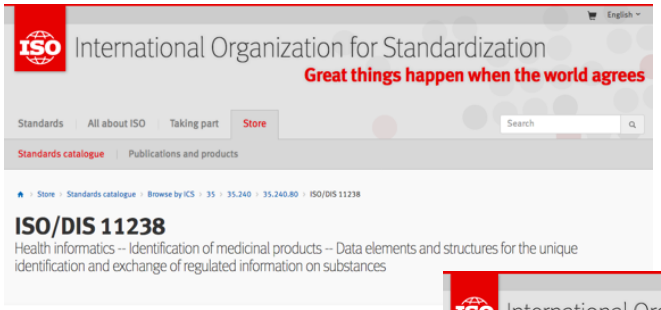

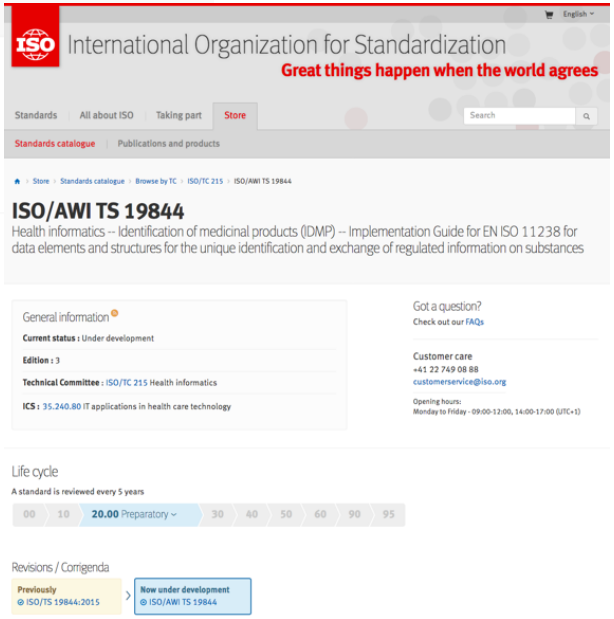

Substances/Specified Substances - the most challenging aspect of the IDMP

ISO 11238 - ISO/TS 19844: Substances/Specified Substances

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Substance

- Is defined on what the substance is (*e.g.* its main and general characteristics).
- Can have different roles e.g. active, adjuvant, basis of strength, excipient

Specified Substance

- More granular, specific description of a substance and may have defining elements e.g. including manufacturing information, purity, grade
- Allows for the specification of multiple substances ("Intermediate Products" e.g. AS03 - adjuvant composed of squalene (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams)

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G-SRS (open source)

- Provides a common tool and a repository of definitional substance information
- Will be linked to other information related to product/clinical trials/applications /quality /pharmacology
- It is freely distributable with bonus public domain information

Instead of relying on drug or chemical names which vary across countries, regions, jurisdictions, IDMP enables substances to be defined by standardised scientific descriptions. The substance is registered per type, as defined in the standard (e.g. chemicals, proteins, polymers, structurally diverse, nucleic acid, etc.) and then, certain criteria apply to distinguish substances in each category from one another (e.g., chemical structure, DNA sequence etc.). When enough information is available and validated, a substance is assigned a unique identification code, which can be used as a quick way to refer to that substance in the future.

What is a Substance: ISO 11238 Definition

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- A Substance is defined based on **what something is** and not on how it is made or, used
  - Recombinant Salmon Calcitonin is the same substance as Synthetic Salmon Calcitonin
- A Substance is defined based on **immutable** properties independent of physical form, grade or level or purity
  - Most chemicals are defined by molecular structure
  - Proteins by their sequence and type of glycosylation
  - Complex materials from biological matrices that cannot be defined by a limited number of related chemical structures are defined based on taxonomic, anatomical and limited fractionation information

What is a Substance: Example

- Processes that irreversibly change the molecular structure results in a new substance
  - Hydrogenated castor oil is different from castor oil
  - An irreversibly-modification of a protein will be a different substance from a non-covalently modified protein
- Ambiguity will be limited
  - Vegetable oil would not be a substance need to specify the vegetable
  - Degree of polymerization or molecular weight needs to be specified for a polymer
    - Macrogol is not a substance but Macrogol 8000 is
  - Stereochemistry should be completely defined
- Materials that are defined as the same substance are not necessarily bioequivalent or pharmaceutical equivalents (Biosimilars are defined having the same amino acid sequence, but may differ for their Glycans).

What is a Substance: Example (cont.)

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❖ Five groups of elements are used to describe single substances.

- Monodisperse*
  - ➢ Chemicals
    - o Defined primarily by molecular structure (connectivity and stereochemistry)
  - ➢ Proteins
    - o Amino Sequence, type of glycosylation, modifications
  - ➢ Nucleic Acids
    - o Sequence, type of sugar and linkage, modifications

(*) Monodisperse substances are substances that can be described as a single molecular entity

What is a Substance: Example (cont.)

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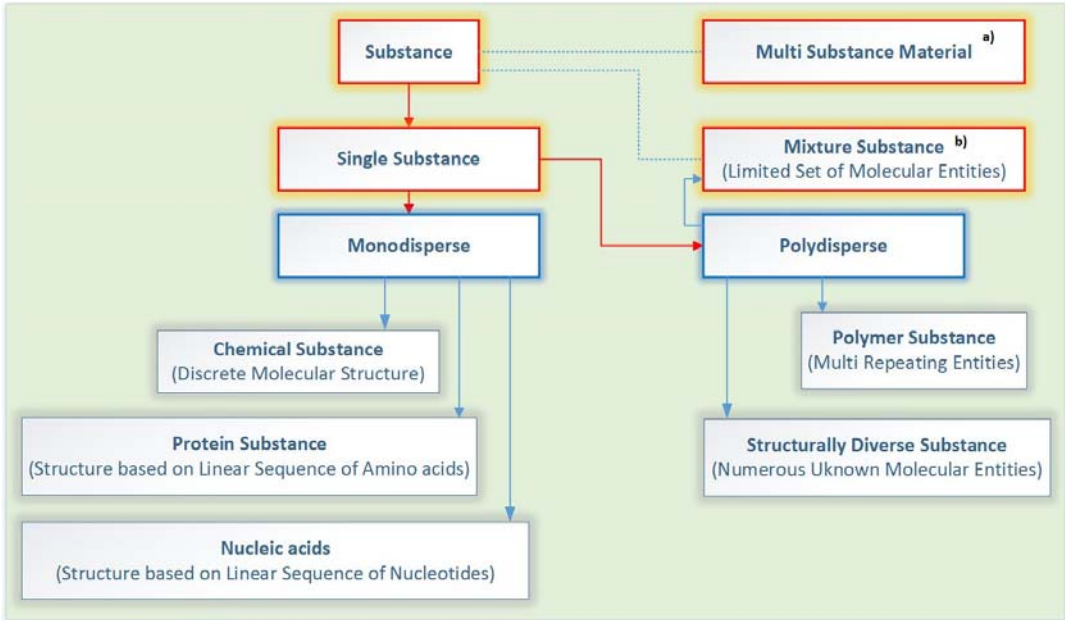
❖ Five groups of elements are used to describe single substances (cont.)

- Polydisperse*
  - ➢ Polymers (Synthetic or biopolymers)
    - o 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
    - o Taxonomic, anatomical, fractionation, physical properties, modifications

(*) Polydisperse substances are substances that typically have multiple molecular entities that are too numerous or too diverse to be captured as a mixture (e.g. cells or tissues) or where the production of the substance inherently results in polydispersity (e.g. polymers).

Decision tree or process by which the type of substance is determined



a Multi-substance material: Multi Substances and/or Specified Substances of diverse origin.

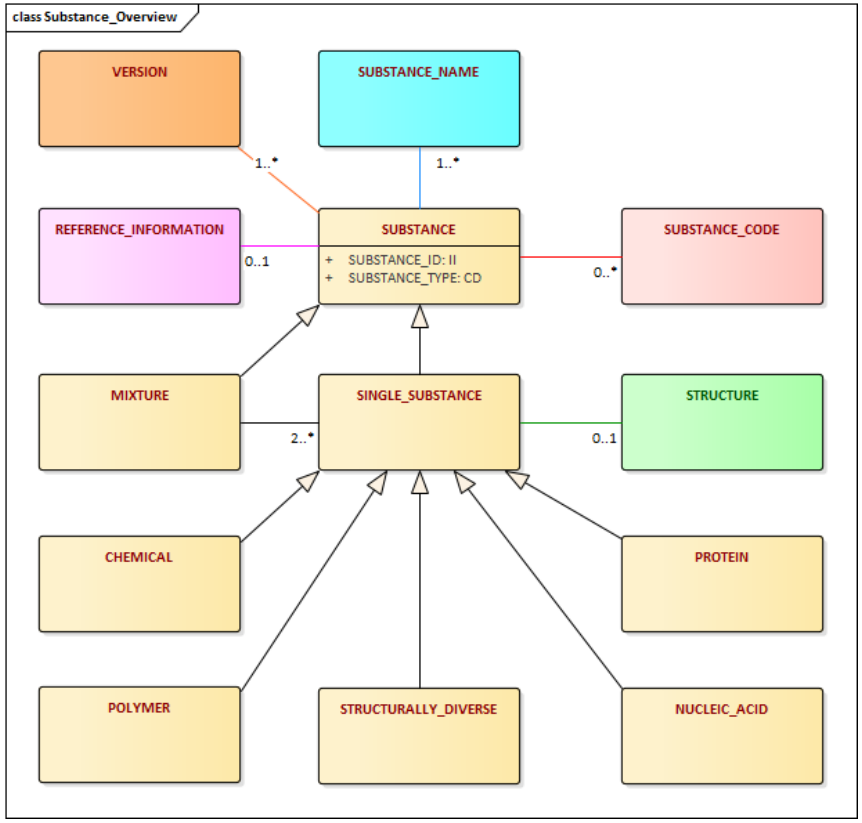
b Mixture: Type of polydisperse substance that is either a combination of single substances isolated together or synthesised/obtained or produced in the same process or an extract of a homologous group of substances (multi-substance starting material) resulting from the same synthetic process.

Source: ISO/TS 19844

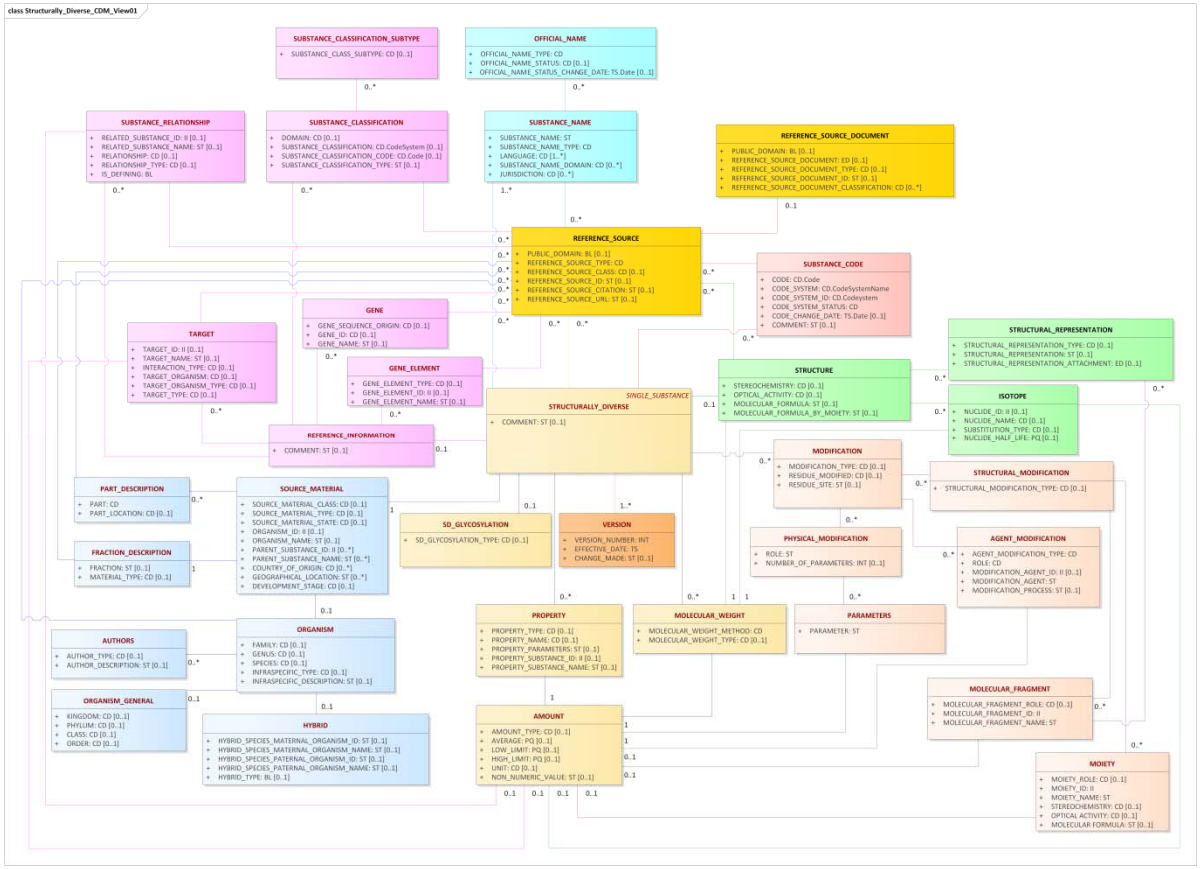
Mixtures

- Mixture substances are described as simple combinations of related single substances that are either isolated together or are the result of the same synthetic process.
  - Proportions are not captured
    - Variations in amounts can be significant.
    - Specifications would be captured the specified substance level.
    - All single entities typically present in amounts greater than 1% either by weight or mole percent could be part of the mixture
- Diverse material that is brought together to form a product or intermediate product is not defined as a substance. (Simethicone is not a substance)

High level Substance model



Single Substance/Structurally Diverse Model



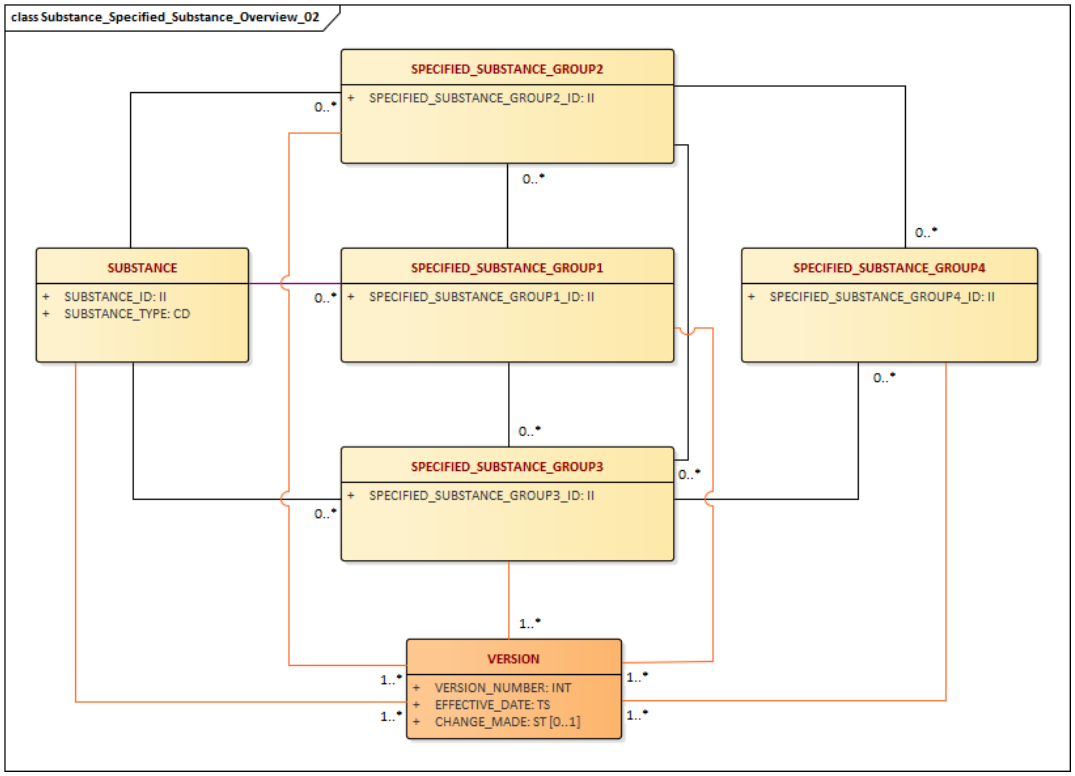
Why Specified Substance (high level)

- Need to link material to a manufacturer and a process
- Need to tie material to a specific grade
- Need to obtain specification information
- Need to obtain information about processing materials
- Need to establish and monitor the supply chain

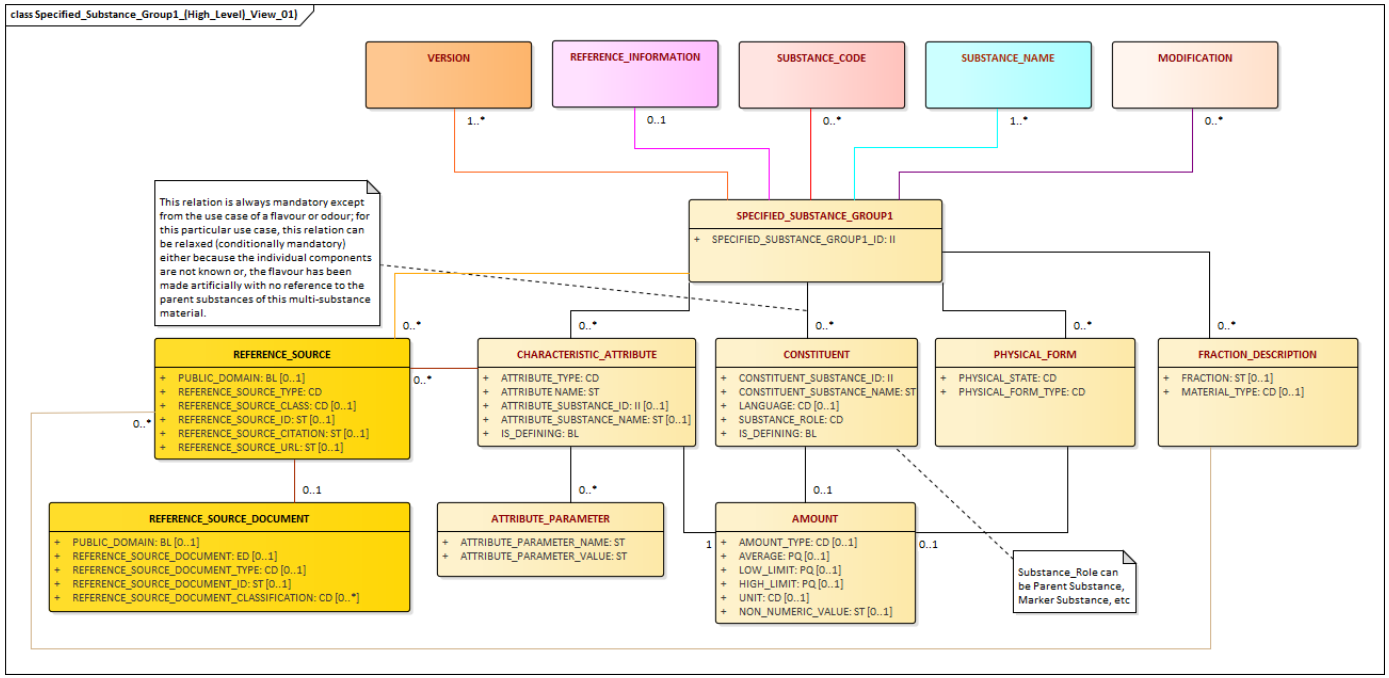
Specified Substance Groups (in brief)

- Specified Group 1: Multiple substance materials (Coatings, Colorants, Flavorants); Physical Form; Extracts
- Specified Group 2: Manufacturer and minimal manufacturing information
- Specified Group 3: Grade of material (USP, EP, technical, standardized etc.)
- Specified Group 4:
  - Detailed manufacturing information
  - Specifications

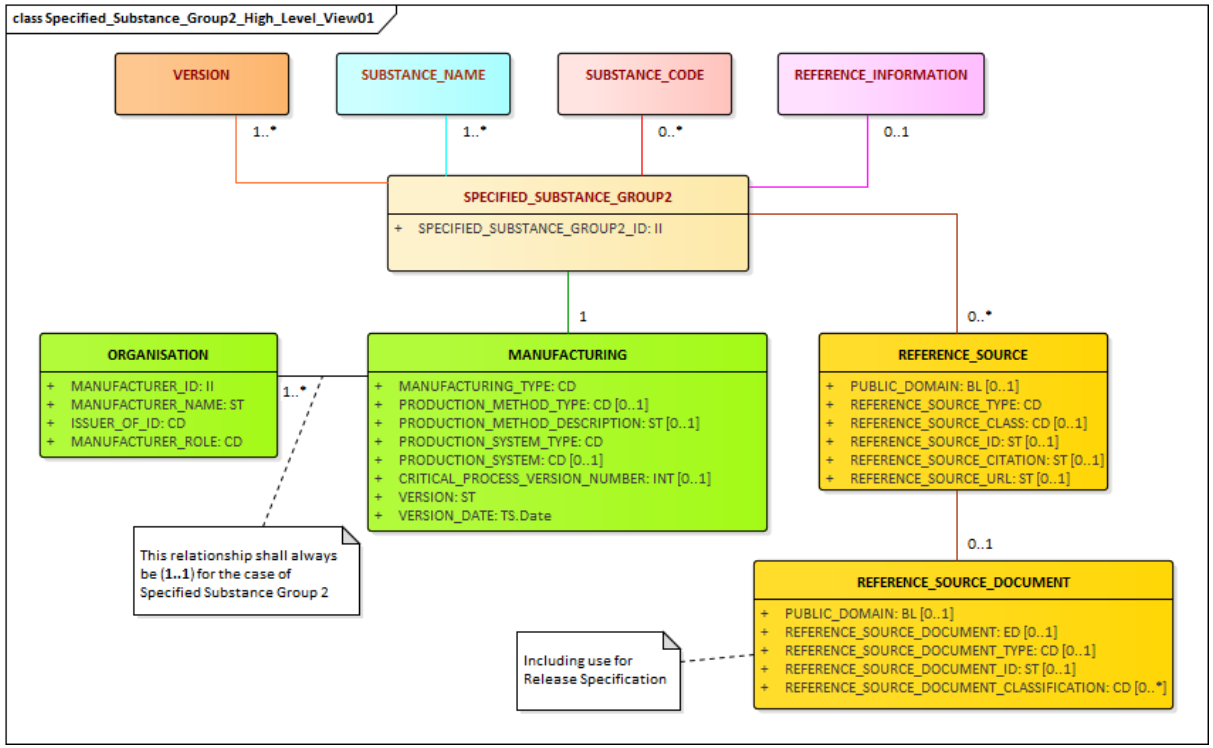
Specified Substance (high level)



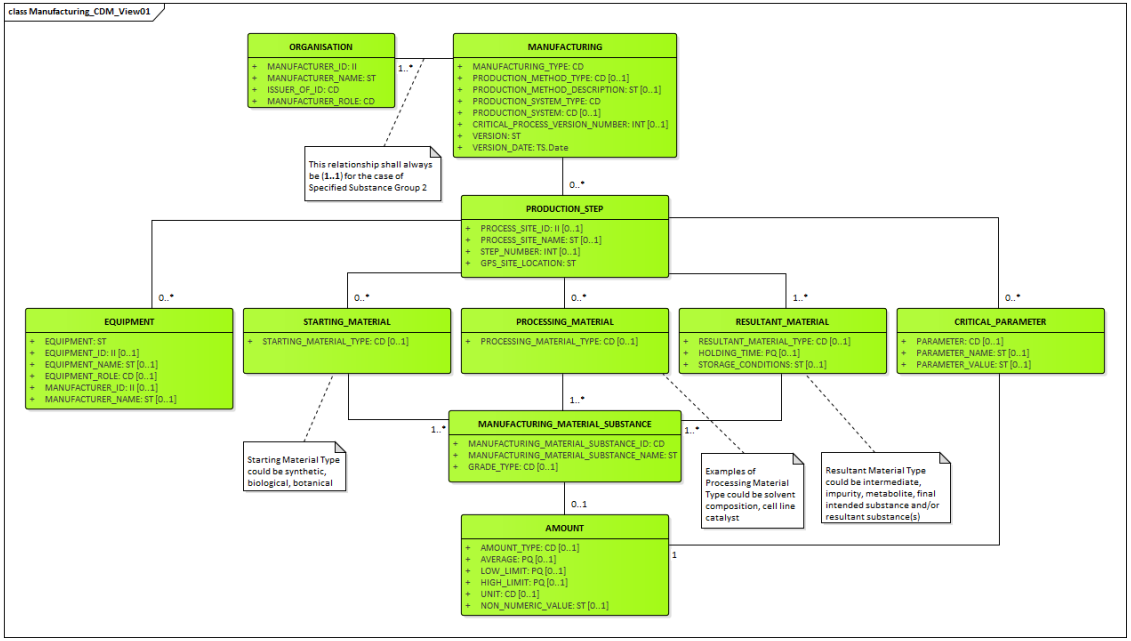
Specified Substance Group 1



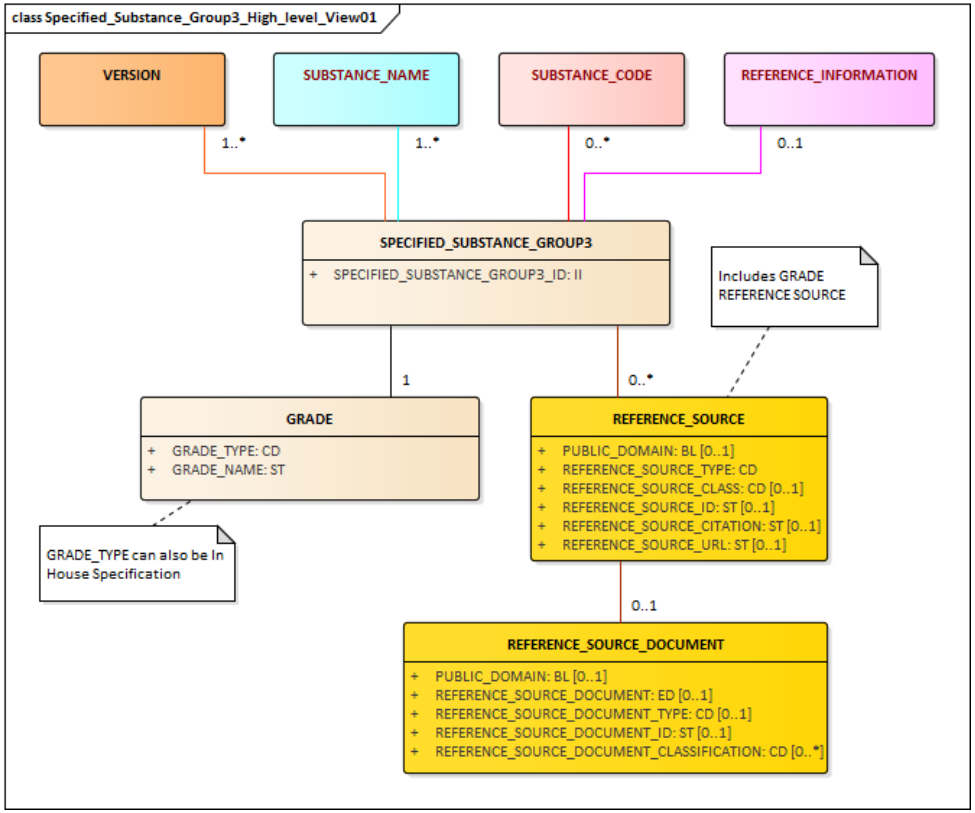
Specified Substance Group 2



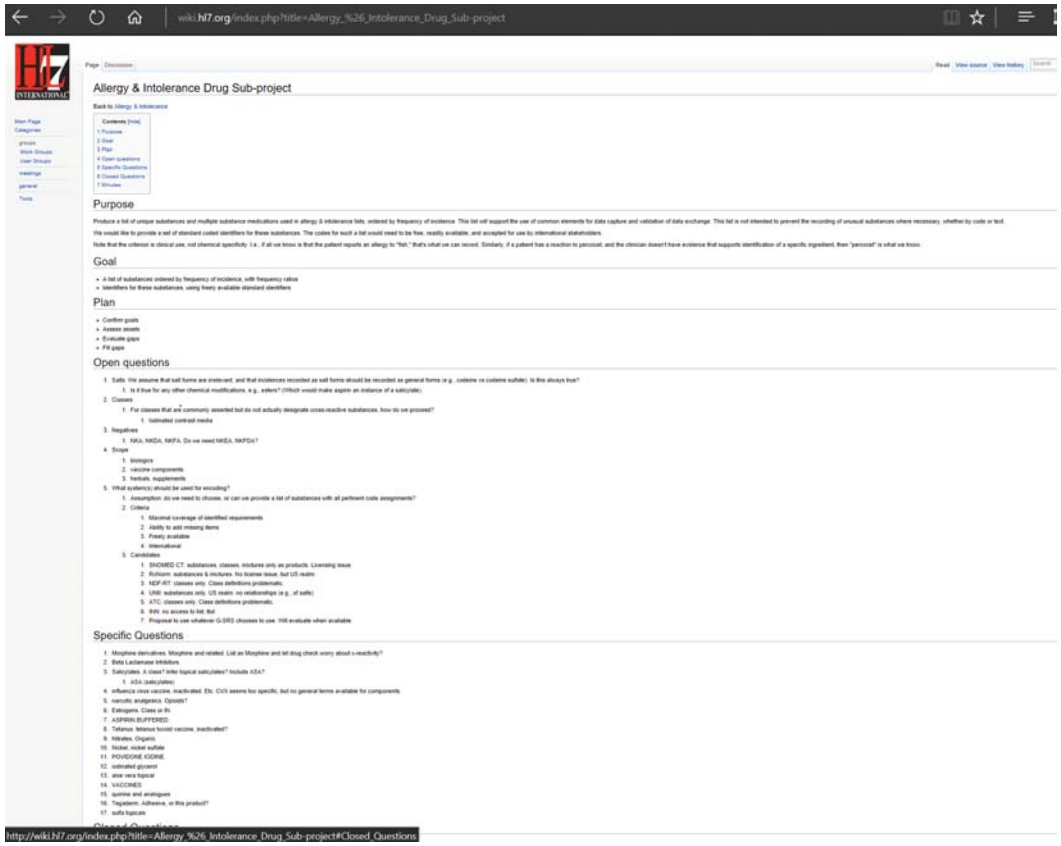
Manufacturing Model



Specified Substance Group 3



HL7 Patient Care - Allergy & Intolerance Drug Sub-project



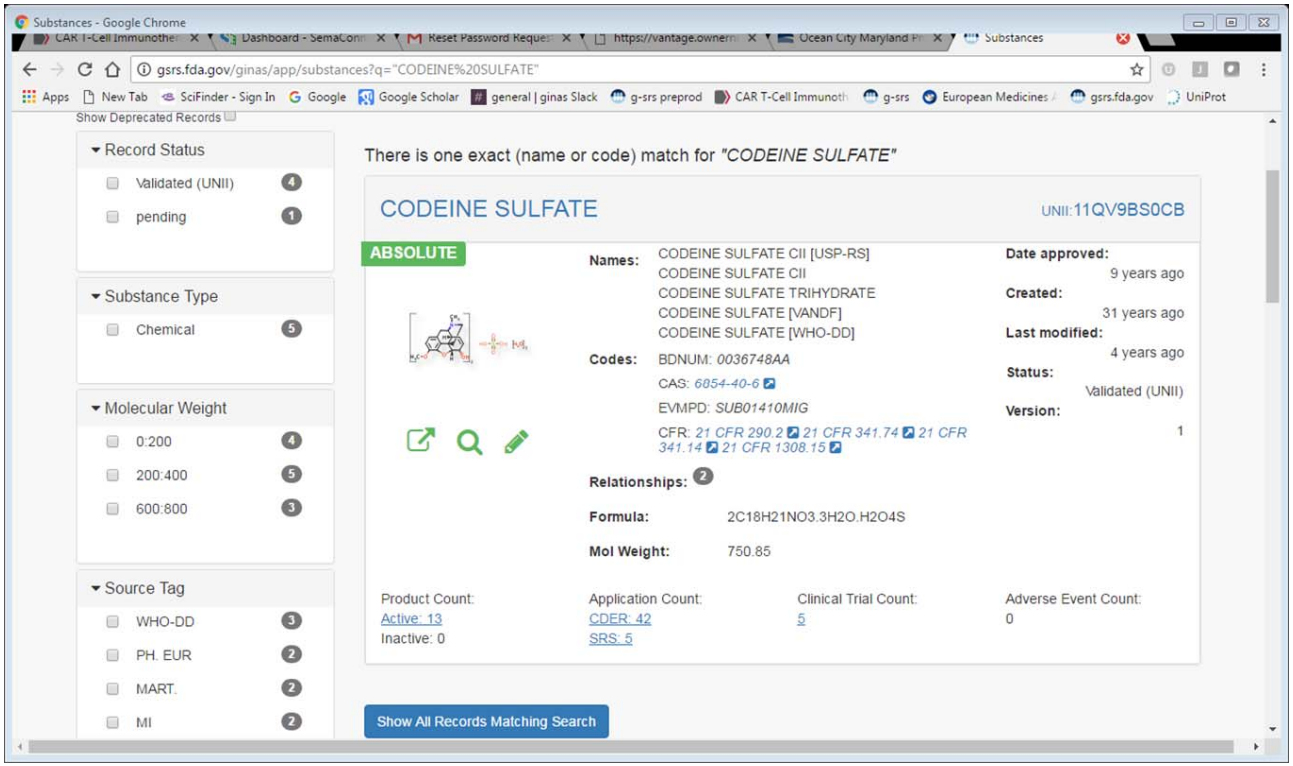
http://wiki.hl7.org/index.php?title=Allergy_%26_Intolerance_Drug_Sub-project

Question: Salts: We assume that salt forms are irrelevant, and that incidences recorded as salt forms should be recorded as general forms (e.g., codeine vs codeine sulfate). Is this always true?

Answer: This is not always true:

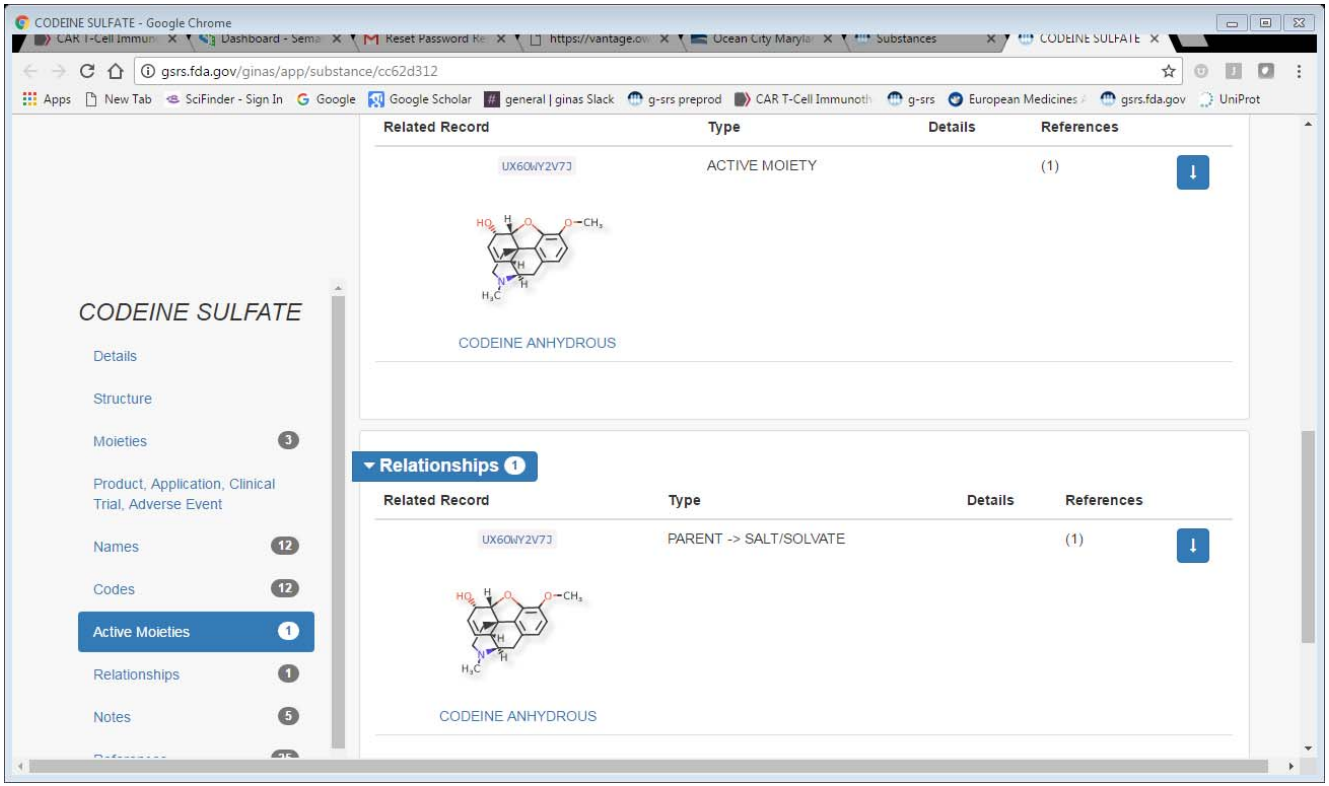
- *Different salt forms can dramatically change the performance of a medicine*
- *Some salts will dramatically delay the absorption of a drug or change where a drug may be absorbed, the stability of a drug.*
- *Some drug allergies are not necessarily due to the drug but the impurities in the drugs and the salt form can have an effect on the impurities that will form over the lifetime of the drug.*
- *In the IDMP/G-SRS we always have an explicit relationship between the salt form and the parent (non-salt) as well as the active moiety*

Dashboard for Codeine Sulfate in G-SRS

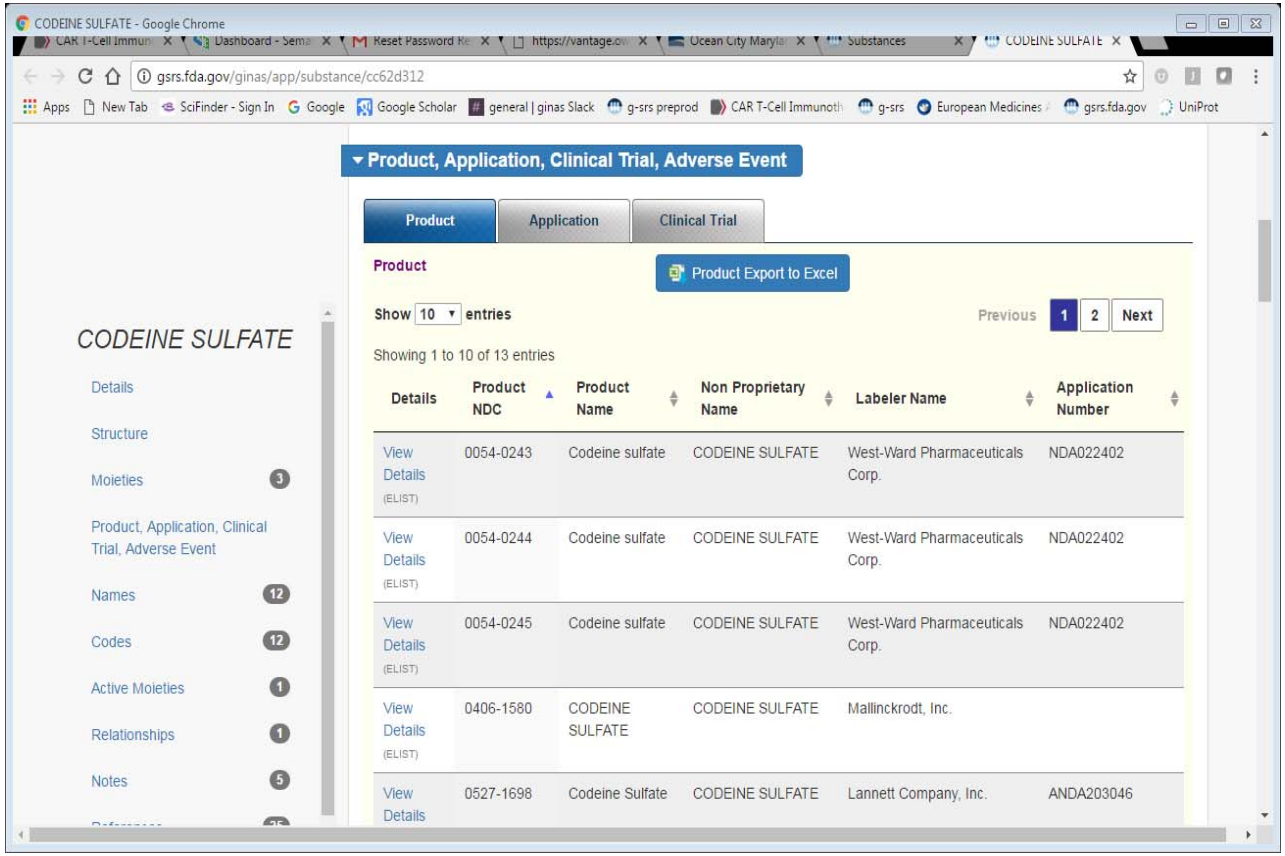


A Codeine Sulfate Trihydrate = Preferred term US. Actually the Preferred term should be Codeine hemisulfate sesquihydrate (1:0.5: 1.5). Per ISO definition we only use stoichimetric complete values, the mol. formula 2: 1: 3. and therefore the mol. weight = 750.85 refers to two molecules codeine as base.

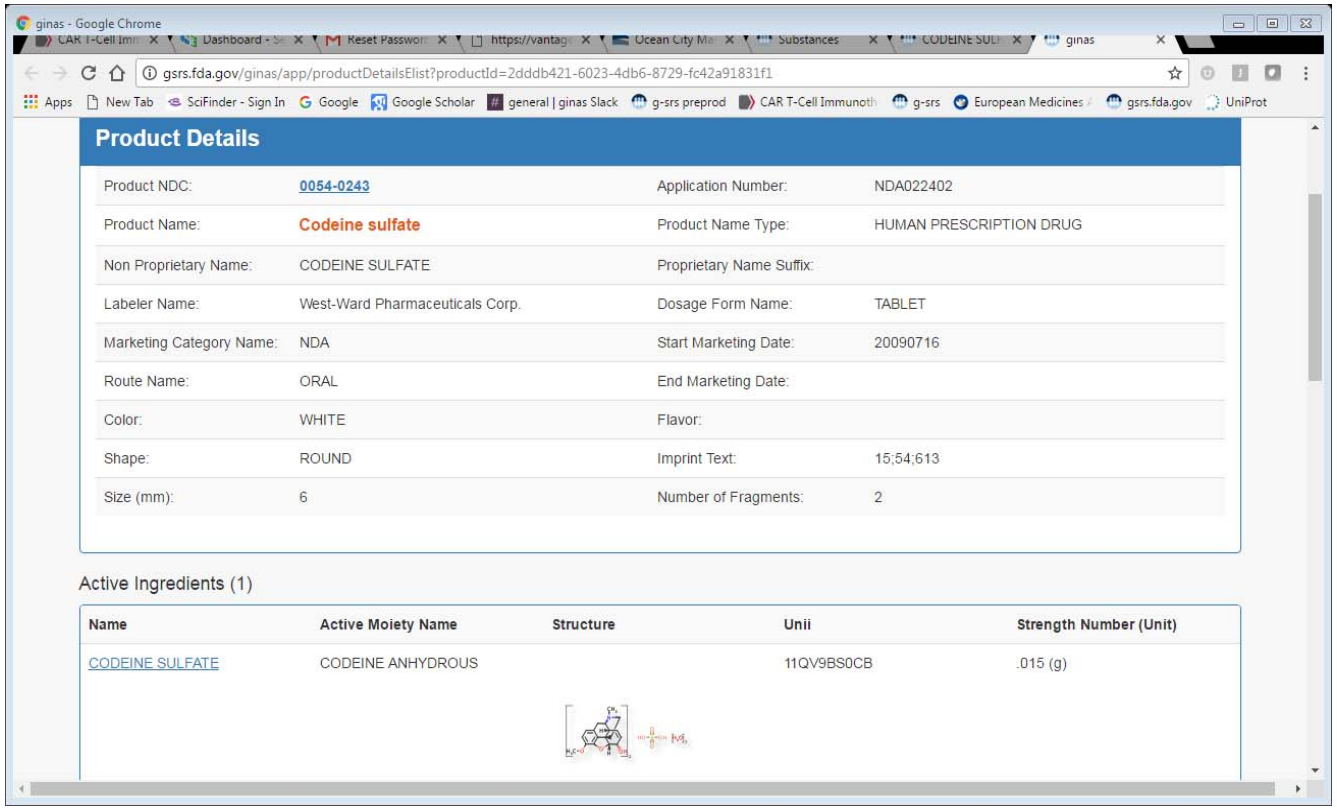
Parent-Salt Relationship



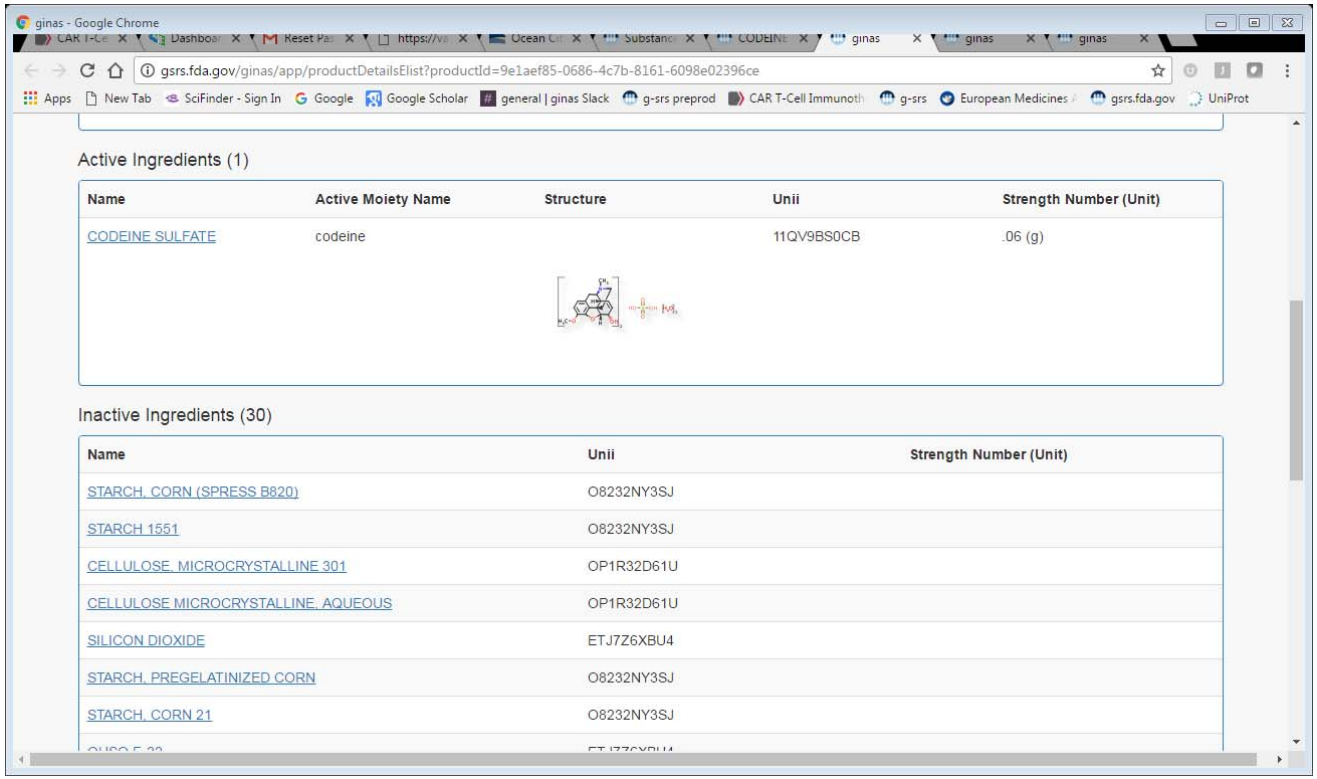
Products that Contain Codeine Sulfate



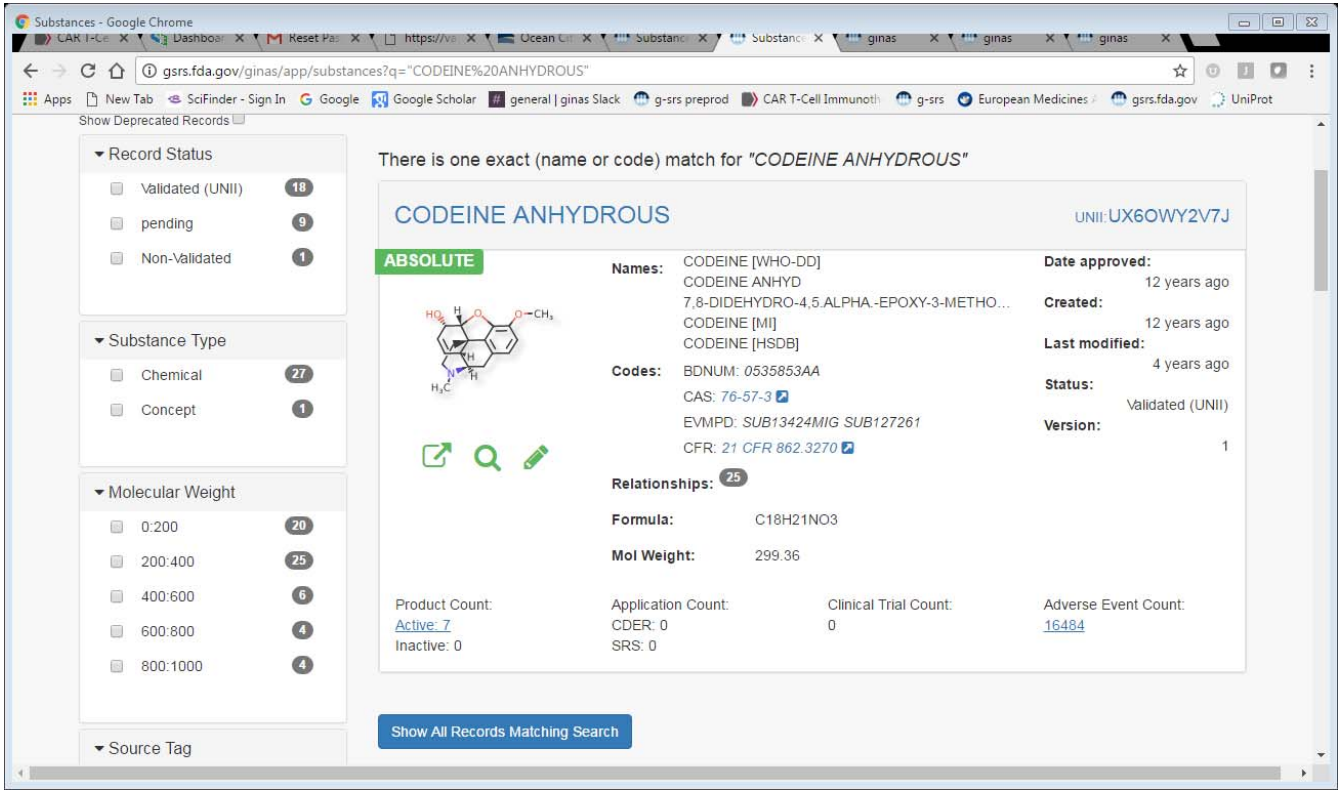
Product Details



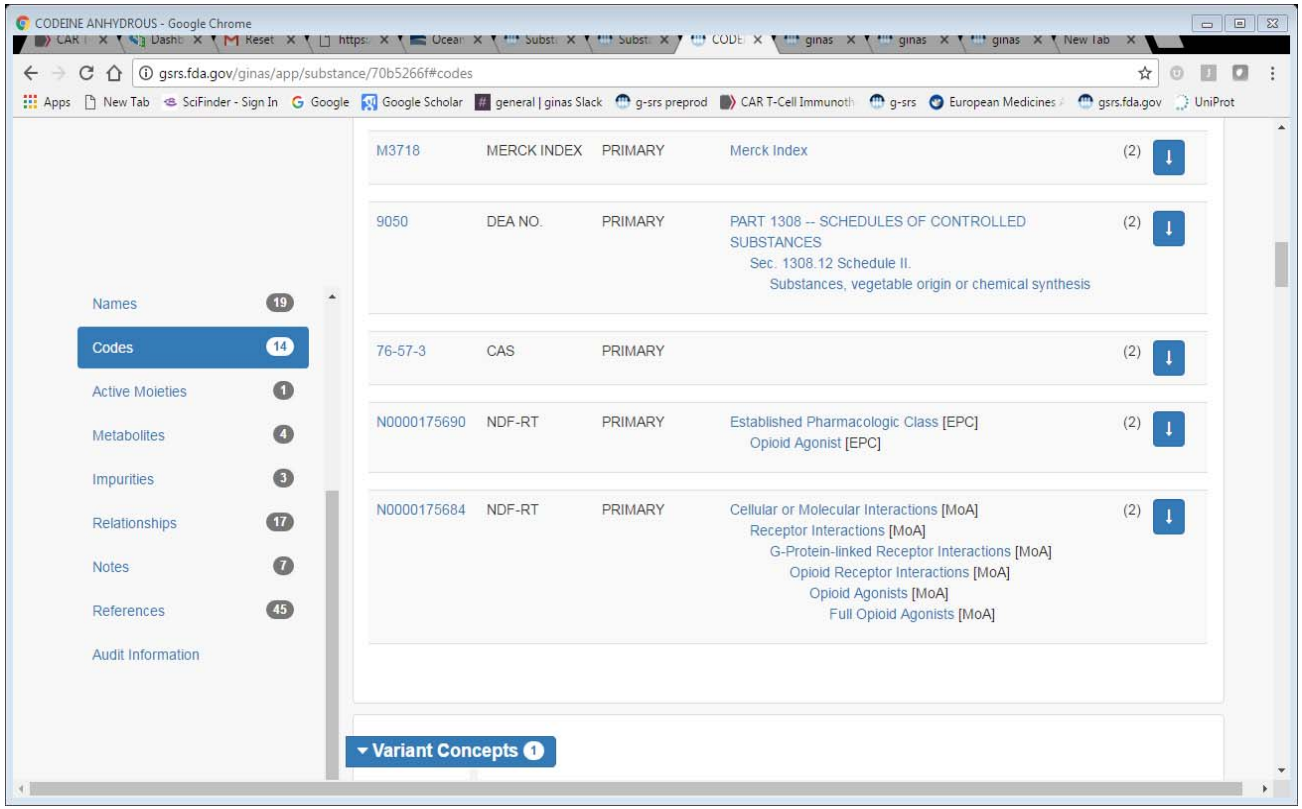
Product Details cont.



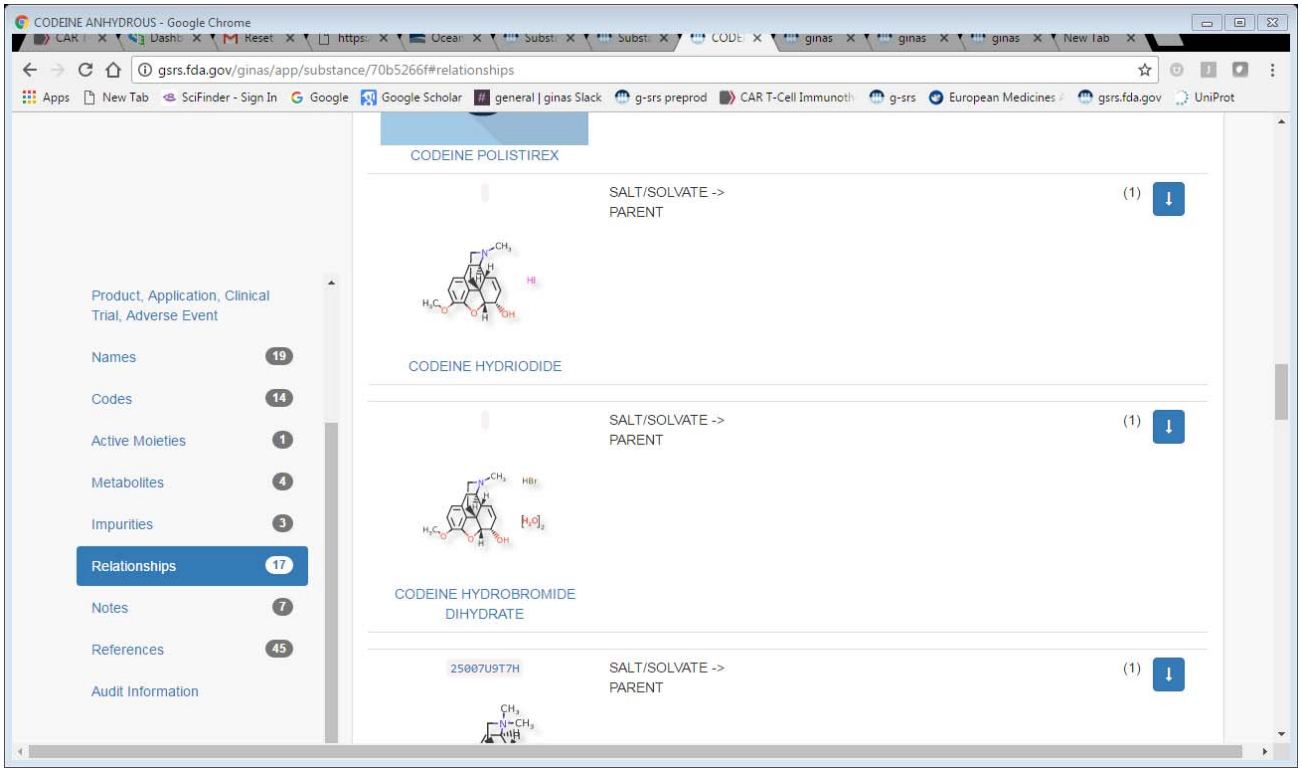
Codeine Dashboard



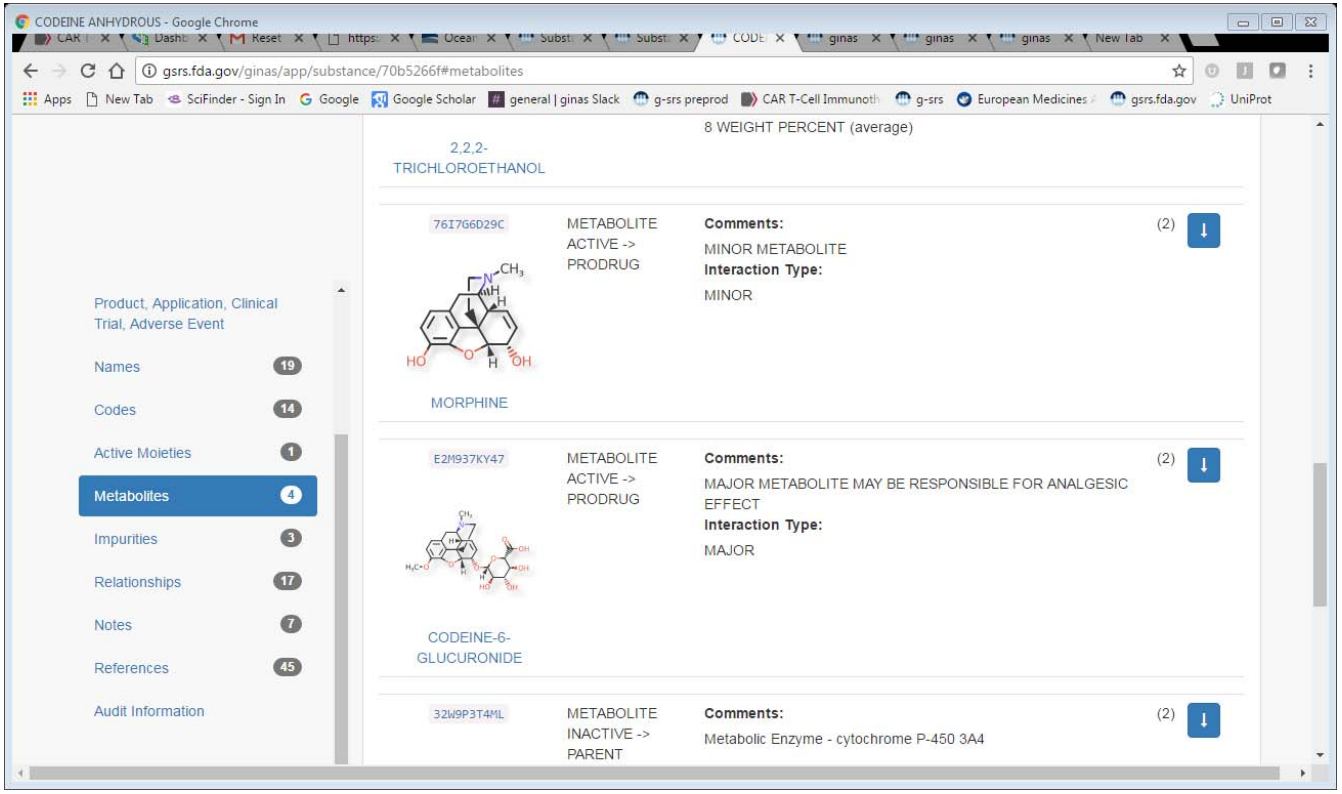
Codeine Codes and Classification



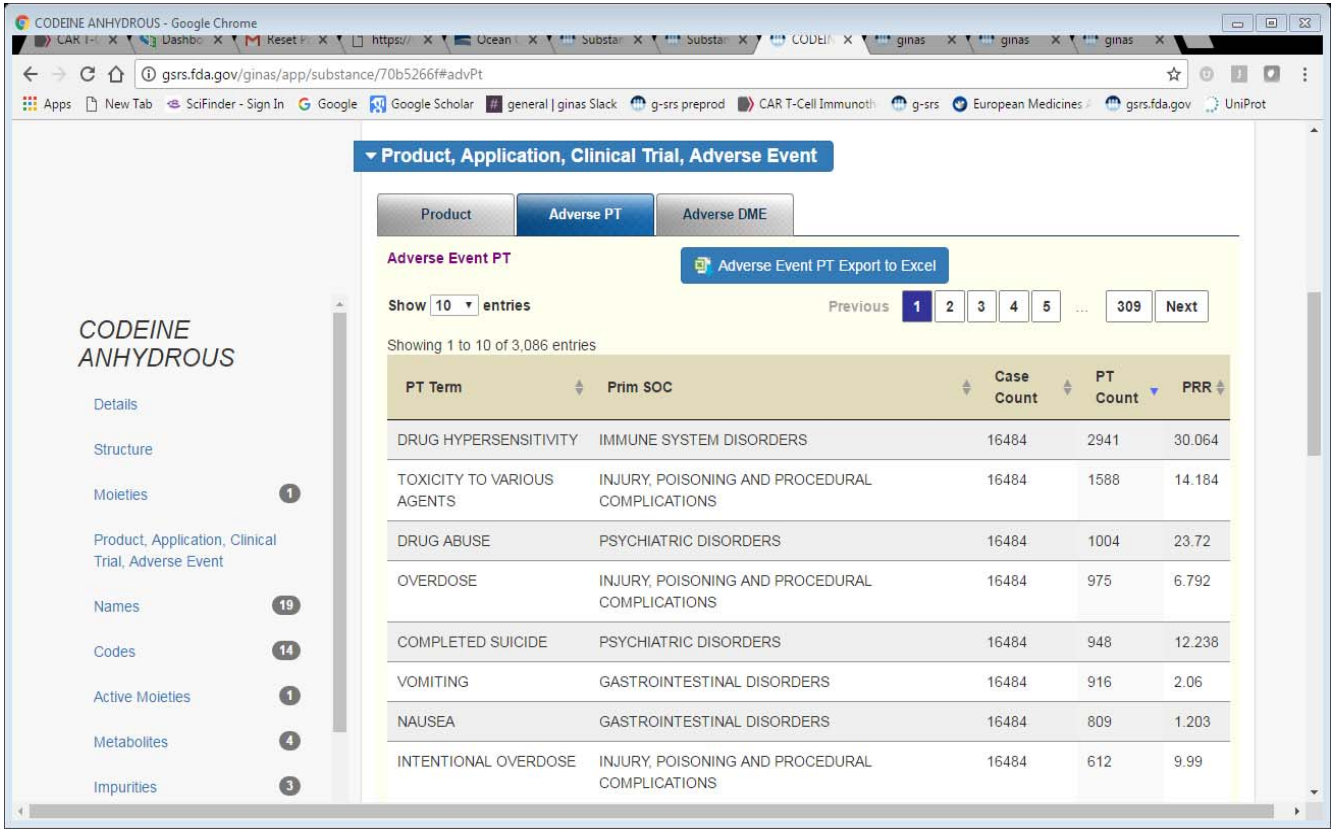
Codeine Relationships



Codeine Relationships



Adverse Events to Active Moiety



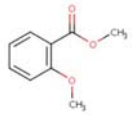
PT Term	Prim SOC	Case Count	PT Count	PRR
DRUG HYPERSENSITIVITY	IMMUNE SYSTEM DISORDERS	16484	2941	30.064
TOXICITY TO VARIOUS AGENTS	INJURY, POISONING AND PROCEDURAL COMPLICATIONS	16484	1588	14.184
DRUG ABUSE	PSYCHIATRIC DISORDERS	16484	1004	23.72
OVERDOSE	INJURY, POISONING AND PROCEDURAL COMPLICATIONS	16484	975	6.792
COMPLETED SUICIDE	PSYCHIATRIC DISORDERS	16484	948	12.238
VOMITING	GASTROINTESTINAL DISORDERS	16484	916	2.06
NAUSEA	GASTROINTESTINAL DISORDERS	16484	809	1.203
INTENTIONAL OVERDOSE	INJURY, POISONING AND PROCEDURAL COMPLICATIONS	16484	612	9.99

JSON message for Codeine

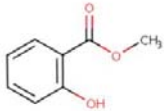
Object
uuid: "70b5266f-4706-49ae-85cd-0ef23b9e50f8"
created: 1116478800000
createdBy: "EAH"
lastEdited: 1373642375000
lastEditedBy: "SWITZERF"
deprecated: false
definitionType: "PRIMARY"
definitionLevel: "COMPLETE"
substanceClass: "chemical"
status: "approved"
version: "1"
approvedBy: "J4"
approved: 1121662800000
 names: Array [19]
 0: Object
uuid: "78e88acd-0f64-4914-bdf8-2f81d7b0fcbc"
created: 1405635086001
createdBy: "SWITZERF"
lastEdited: 1405635086001
lastEditedBy: "SWITZERF"
deprecated: false
name: "CODEINE [WHO-DD]"
type: "cn"
 domains: Array [0]
 languages: Array [1]
0: "en"
 nameJurisdiction: Array [0]
 nameOrgs: Array [0]
preferred: false
displayName: false

Question (cont.): Is it true for any other chemical modifications, e.g., esters? (Which would make aspirin an instance of a salicylate)?

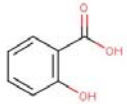
Answer: No, esters are different substances from their parent substances e.g. Methylsalicylate



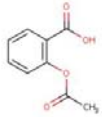
2-methoxy-methyl salicylate



Methyl salicylate



Salicylic acid (parent)



'Aspirin' Acetylsalicylic acid

Side effects:

Salicylic acid: contact dermatitis, penetration of the skin can be increased

Methyl salicylate: Methyl salicylate/menthol cream is a topical analgesic, interaction with coumarins. It is aggressive on the skin.

Dimethyl salicylate (2-methoxy-methyl salicylate, Benzoic acid, 2-methoxy, methylester, Methyl o-anisate): Causes serious eye irritation

Acetylsalicylic acid: Salicylic acid intolerance, since the substance can be metabolized into salicylic acid.

So differences per ester, some adverse effects in common.

Question: What system(s) should be used for encoding?

… UNII: substances only. US realm. no relationships (e.g., of salts)

Answer: This is not true:

- *extensive relationships, relationship to active moieties, metabolites, metabolic enzymes, extensively curated, capture, defines substances not just hierarchy.*
- *Realm is increasing, Europe will use and, perhaps Canada, codes directly into drug product.*
- *Maps to ATC, INN, RxNorm, WHO-DD, DEA list, yellow list etc.*
- *No license issue.*
- *UNII assigned early in the development process, ability to connect preclinical data to post marketing data. G-SRS links products, clinical trials, and adverse events from US systems; can be readily extended to products in other realms.*

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Specific Questions

1. Morphine derivatives. Morphine and related. List as Morphine and let drug check worry about x-reactivity?
2. Beta Lactamase Inhibitors.
3. Salicylates. A class? Infer topical salicylates? Include ASA? ASA (salicylates)
4. influenza virus vaccine, inactivated. Etc. CVX seems too specific, but no general terms available for components.
5. narcotic analgesics. Opioids?
6. Estrogens. Class or IN.
7. ASPIRIN BUFFERED.
8. Tetanus. tetanus toxoid vaccine, inactivated?
9. Nitrates, Organic
10. Nickel, nickel sulfate
11. POVIDONE IODINE.
12. iodinated glycerol
13. aloe vera topical
14. VACCINES
15. quinine and analogues
16. Tegaderm. Adhesive, or this product?
17. sulfa topicals

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Answer/Hint (1/2)

- *It is better to separate a classification (groups into categories based on similar properties), terminology (set of terms representing the system of concepts in a particular field) etc. since many of the specific questions may easily create confusion to a certain extent. G-SRS is based on the definition of a substance. Classification for example, is a separate exercise.*

- *IDMP captures strength, dosage form, and approved routes of administration and both active and inactive ingredient.*

- *In IDMP/G-SRS, products are defined in much more detail, mappings between substances and products required information, is freely available. Both active and inactive substances are captured. The G-SRS has distributable data and a distributable registration system that allows easy submission and use; it will also have a product registration system.*

- *Built in JSON message for detailed substance information exchange (also allows a relatively easier path to be adapted to HL7). API driven system. All FAERS data mapped to active moiety and actual ingredient.*

Answer/Hint (2/2)

- One of the many advantages of using "definitional" approach compared to a classification system approach is that additional information on inactive ingredients is conveyed to cover allergic reactions. Otherwise, neither patients or physicians would have any way to identify that an inactive ingredient like, for example, lactose, is present in a product.

- Many "allergenic-like" reactions can be due to lactose or other inactive ingredients. A classification or various terminology systems would not have any way of knowing this.

Where IDMP/G-SRS is currently

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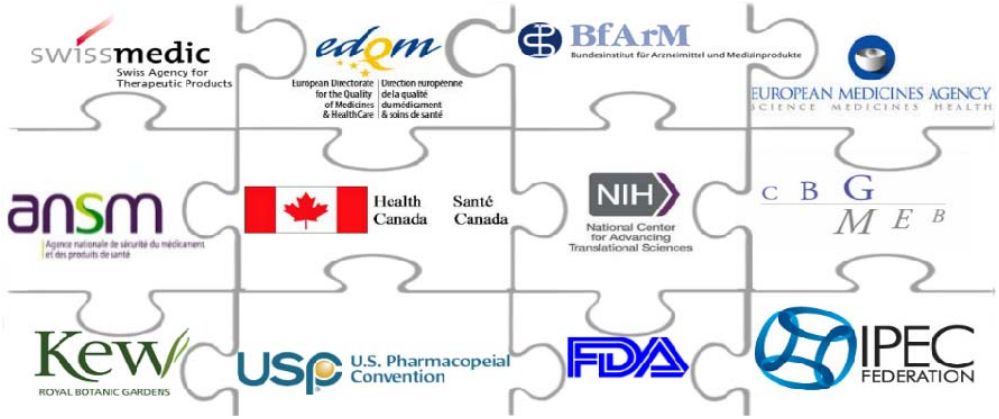
- IDMP/G-SRS System has been deployed in FDA environment
- Has implemented the Substance information level of ISO 11238 / ISO/TS 19844 and Specified Substance Group 1.
- Migration and supplementation of data
- IT tools developed for API access and Batch Updating
- Integrated product (SPL), application, clinical trial with current FDA systems
- Integrated modules for product and application information
- System will/is into production at FDA.
- EMA/EU in phased implementation (SPOR), O-R first, S-P follow http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000645.jsp&mid=WC0b01ac058078fbe2

Working Collaboratively



Next Steps

- Develop modules for Specified Substance Groups 2-4
- Start entering Specified Substance Group 1 information
- Develop better forms and presentation of data
- Expand quality (impurities) and pharmacology (targets, metabolite, cyp and transporter information)
- Deploy full instances with all public data at Open FDA and NLM
- Establish mechanism for system-system communication
- Integrate G-SRS into a clinical trial registry system (C-DISC)

Snapshots from EU/NCA Technical work

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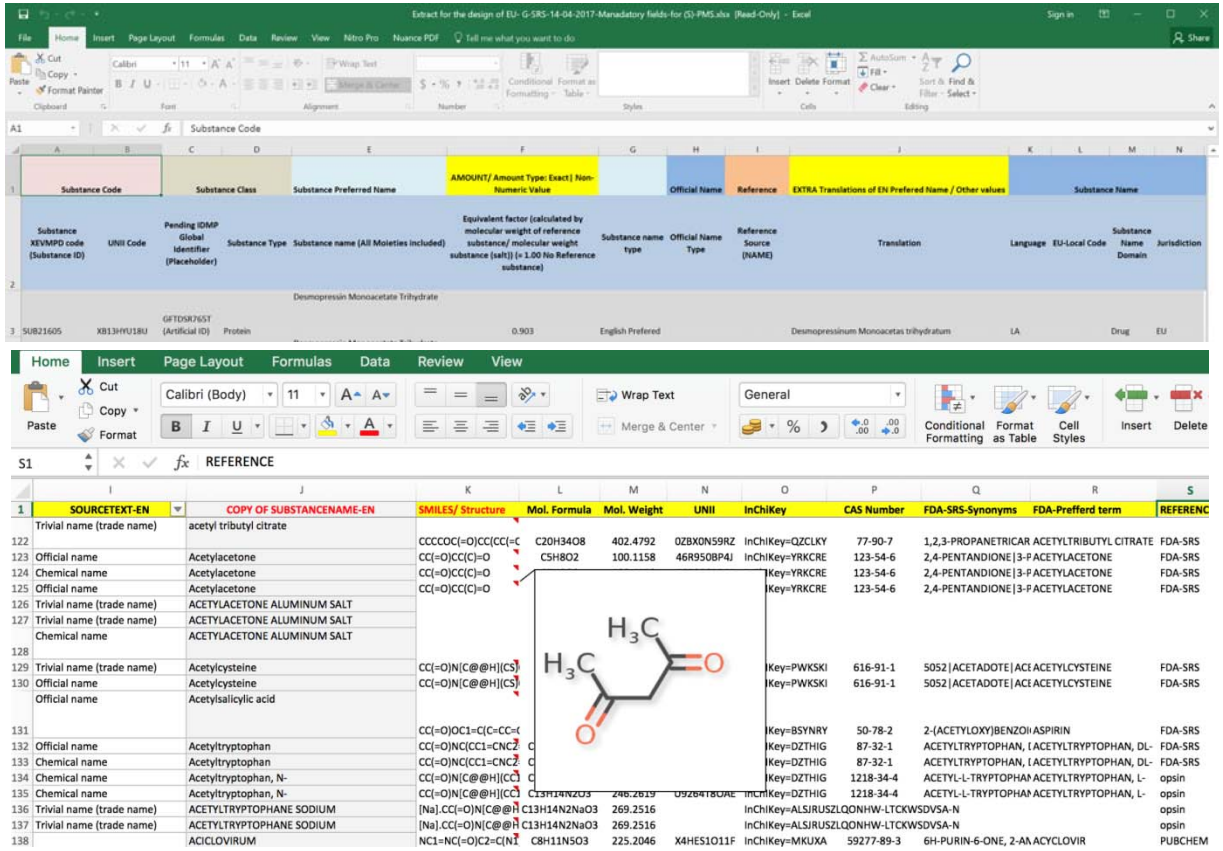
Substance mapping exercises (led by Herman Diederik)



	I	J	K	L	M	N	O	P	Q	R	S
1	SOURCETEXT-EN	COPY OF SUBSTANCENAME-EN	SMILES/ Structure	Mol. Formula	Mol. Weight	UNII	InChIKey	CAS Number	FDA-SRS-Synonyms	FDA-Prefferd term	REFERENC
	Trivial name (trade name)	acetyl tributyl citrate									
122			CCCCOC(=O)CC(CC(=C	C20H34O8	402.4792	0ZBX0N59RZ	InChIKey=QZCLKY	77-90-7	1,2,3-PROPANETRICAR	ACETYLTRIBUTYL CITRATE	FDA-SRS
123	Official name	Acetylacetone	CC(=O)CC(C)=O	C5H8O2	100.1158	46R950BP4J	InChIKey=YRKCRE	123-54-6	2,4-PENTANDIONE|3-P	ACETYLACETONE	FDA-SRS
124	Chemical name	Acetylacetone	CC(=O)CC(C)=O				InChIKey=YRKCRE	123-54-6	2,4-PENTANDIONE|3-P	ACETYLACETONE	FDA-SRS
125	Official name	Acetylacetone	CC(=O)CC(C)=O				InChIKey=YRKCRE	123-54-6	2,4-PENTANDIONE|3-P	ACETYLACETONE	FDA-SRS
126	Trivial name (trade name)	ACETYLACETONE ALUMINUM SALT									
127	Trivial name (trade name)	ACETYLACETONE ALUMINUM SALT									
	Chemical name	ACETYLACETONE ALUMINUM SALT									
128											
129	Trivial name (trade name)	Acetylcysteine	CC(=O)N[C@@H](CS)				InChIKey=PWKSKI	616-91-1	5052|ACETADOTE|ACE	ACETYLCYSTEINE	FDA-SRS
130	Official name	Acetylcysteine	CC(=O)N[C@@H](CS)				InChIKey=PWKSKI	616-91-1	5052|ACETADOTE|ACE	ACETYLCYSTEINE	FDA-SRS
	Official name	Acetylsalicylic acid									
131			CC(=O)OC1=C(C=CC=C				InChIKey=BSYNRY	50-78-2	2-(ACETYLOXY)BENZOI	ASPIRIN	FDA-SRS
132	Official name	Acetyltryptophan	CC(=O)NC(CC1=CNC2	C			InChIKey=DZTHIG	87-32-1	ACETYLTRYPTOPHAN, L	ACETYLTRYPTOPHAN, DL-	FDA-SRS
133	Chemical name	Acetyltryptophan	CC(=O)NC(CC1=CNC2	C			InChIKey=DZTHIG	87-32-1	ACETYLTRYPTOPHAN, L	ACETYLTRYPTOPHAN, DL-	FDA-SRS
134	Chemical name	Acetyltryptophan, N-	CC(=O)N[C@@H](CC	C			InChIKey=DZTHIG	1218-34-4	ACETYL-L-TRYPTOPHAN	ACETYLTRYPTOPHAN, L-	opsin
135	Chemical name	Acetyltryptophan, N-	CC(=O)N[C@@H](CC	C13H14N2O3	246.2619	09Z84T8OAE	InChIKey=DZTHIG	1218-34-4	ACETYL-L-TRYPTOPHAN	ACETYLTRYPTOPHAN, L-	opsin
136	Trivial name (trade name)	ACETYLTRYPTOPHANE SODIUM	[Na].CC(=O)N[C@@H	C13H14N2NaO3	269.2516		InChIKey=ALSJRUSZLQ	ONHW-LTCKWSDVSA-N			opsin
137	Trivial name (trade name)	ACETYLTRYPTOPHANE SODIUM	[Na].CC(=O)N[C@@H	C13H14N2NaO3	269.2516		InChIKey=ALSJRUSZLQ	ONHW-LTCKWSDVSA-N			opsin
138		ACICLOVIRUM	NC1=NC(=O)C2=C(N1	C8H11N5O3	225.2046	X4HES1O11F	InChIKey=MKUXA	59277-89-3	6H-PURIN-6-ONE, 2-AM	ACYCLOVIR	PUBCHEM

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Thank you for your attention

Panagiotis.Telonis@ema.europa.eu

Scientific Administrator, IDMP Project Manager

Christian.Hay@gs1.ch

Convenor ISO/TC 215 WG6, GS1