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

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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

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

* OID for GS1 GTIN
Medicinal Product overarching model
IDMP roadmap

![Diagram showing the IDMP roadmap with steps and revisions](image-url)
IDMP roadmap

19844
- Publis h i.1
- NP i.2
- DTS i.2
- NP i.3
- Publish
- Revision

2015
- SFO
- BE
- AMS
- Lillehammer

2016

2017
- DTS
- DIS
- Publish

rev. 11238
IDMP impact on Clinical Processes

Source: Dr. L. Grandia, Amsterdam, 2016
IDMP impact on Clinical Processes

ISO new projects

ISO 17251

ISO 27953

ISO DTS 19293

ISO-17523

ISO-19256

Source: Dr. L. Grandia, Amsterdam, 2016
Main IDMP identifiers

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

Example: Paracetamol/Acetaminophen

- PhPID_SUB_L1 ➔ paracetamol
- PhPID_SUB_L2 ➔ paracetamol, 500 mg
- PhPID_SUB_L3 ➔ paracetamol, tablet
- PhPID_SUB_L4 ➔ paracetamol, 500 mg, tablet

- PhPID_SUB_L1 ➔ paracetamol
- PhPID_SUB_L2 ➔ paracetamol, 500 mg
- PhPID_SUB_L3 ➔ paracetamol, caplet
- PhPID_SUB_L4 ➔ paracetamol, 500 mg, caplet

- PhPID_SUB_L1 ➔ paracetamol
- PhPID_SUB_L2 ➔ paracetamol, 500 mg
- PhPID_SUB_L3 ➔ paracetamol, capsule
- PhPID_SUB_L4 ➔ paracetamol, 500 mg, capsule
Substance ID as food for PhPID generation

- PhPID_SUB_L1 \rightarrow \text{paracetamol}
- PhPID_SUB_L2 \rightarrow \text{paracetamol, 500 mg}
- PhPID_SUB_L3 \rightarrow \text{paracetamol, tablet}
- PhPID_SUB_L4 \rightarrow \text{paracetamol, 500 mg, tablet}
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
Substances/Specified Substances -
the most challenging aspect of the IDMP
**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)
**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

- 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).
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

(*) Monodisperse substances are substances that can be described as a single molecular entity
Five groups of elements are used to describe single substances (cont.)

- **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**
    - 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

Source: ISO/TS 19844

<table>
<thead>
<tr>
<th>Substances</th>
<th>Single Substance</th>
<th>Multi Substance Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substance</td>
<td>Monodisperse</td>
<td>Polydisperse</td>
</tr>
<tr>
<td>Protein Substance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemical Substance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nucleic acids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixture Substance</td>
<td>Polydisperse</td>
<td></td>
</tr>
<tr>
<td>Mixture Substance (Limited Set of Molecular Entities)</td>
<td>Polydisperse</td>
<td></td>
</tr>
<tr>
<td>Polymer Substance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structurally Diverse Substance (Numerous Unknown Molecular Entities)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

2. 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.
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

[Diagram of Substance model with classes and associations]

Version 24
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
Specified Substance Group 3
Allergy & Intolerance Drug Sub-project

Purpose

Describe the need for interoperability to support the wide range of services and systems required to support allergy and intolerance management, including clinical decision support, treatment plans, and patient education.

Goal

- Identify and prioritize key functional requirements for allergy and intolerance systems.
- Develop a set of use cases that demonstrate the value of interoperability in clinical settings.
- Develop a roadmap for implementing interoperability in allergy and intolerance systems.

Open Questions

1. How can systems efficiently and effectively manage patient allergies and intolerances across different settings?
2. What are the best practices for integrating allergy and intolerance information into electronic health records?
3. How can systems support the safe and effective management of allergy and intolerance reactions?

Specific Questions

- What are the key challenges and barriers to interoperability in allergy and intolerance systems?
- How can systems support real-time communication between providers and patients?
- What are the best practices for managing allergy and intolerance data across different systems and devices?
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
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 stoichiometric 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

<table>
<thead>
<tr>
<th>Related Record</th>
<th>Type</th>
<th>Details</th>
<th>References</th>
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<td>ACTIVE MOIETY</td>
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<td>(1)</td>
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<td>CODEINE SULFATE</td>
<td>CODEINE ANHYDROUS</td>
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<table>
<thead>
<tr>
<th>Related Record</th>
<th>Type</th>
<th>Details</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>U0M0Y2ZYT</td>
<td>PARENT -&gt; SALT/SOLVATE</td>
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<td>(1)</td>
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<tr>
<td>CODEINE SULFATE</td>
<td>CODEINE ANHYDROUS</td>
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</tr>
</tbody>
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Products that Contain Codeine Sulfate
### Product Details

**Product NDC:** 0054-0243  
**Application Number:** NDA022492  
**Product Name:** Codeine sulfate  
**Product Name Type:** HUMAN PRESCRIPTION DRUG  
**Non Proprietary Name:** CODEINE SULFATE  
**Proprietary Name Suffix:**  
**Labeler Name:** West-Ward Pharmaceuticals Corp.  
**Dosage Form Name:** TABLET  
**Marketing Category Name:** NDA  
**Start Marketing Date:** 20050716  
**Route Name:** ORAL  
**End Marketing Date:**  
**Color:** WHITE  
**Flavor:**  
**Shape:** ROUND  
**Imprint Text:** 15:54.613  
**Size (mm):** 6  
**Number of Fragments:** 2

### Active Ingredients (1)

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<tr>
<th>Name</th>
<th>Active Molecule Name</th>
<th>Structure</th>
<th>Unit</th>
<th>Strength Number (Unit)</th>
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<td>CODEINE ANHYDROUS</td>
<td><img src="image" alt="Chemical Structure" /></td>
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<td>0.015 (g)</td>
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## Active Ingredients (1)

<table>
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## Inactive Ingredients (30)

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<tr>
<td>STARCH 1551</td>
<td>0B232NY35U</td>
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<tr>
<td>CELLULOSE, MICROCRYSTALLINE 301</td>
<td>0P1R32D61U</td>
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<tr>
<td>CELLULOSE MICROCRYSTALLINE, AQUEOUS</td>
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<td></td>
</tr>
<tr>
<td>SILICON DIOXIDE</td>
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<tr>
<td>STARCH, PREGLATINIZED CORN</td>
<td>0B232NY35U</td>
<td></td>
</tr>
<tr>
<td>STARCH, CORN 21</td>
<td>0B232NY35U</td>
<td></td>
</tr>
<tr>
<td>GLUCO-G 20</td>
<td>ET.JZ6XBU4</td>
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### Codeine Codes and Classification

#### Merck Index

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<td>5000</td>
<td>PART 1308 — SCHEDULES OF CONTROLLED SUBSTANCES Sec. 1308.12 Schedule II. Substances, vegetable origin or chemical synthesis</td>
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- Cellular or Molecular Interactions [MoA]
- Receptor Interactions [MoA]
- G-Protein-linked Receptor Interactions [MoA]
- Opioid Receptor Interactions [MoA]
- Opioid Agonists [MoA]
- Full Opioid Agonists [MoA]
Codeine Relationships
Codeine Relationships

2.2.3.
TRICHLOROETHANOL

76176629K
METABOLITE
ACTIVE -> PRODRUG

Comments:
MINOR METABOLITE
INTERACTION TYPE:
MINOR

MORPHINE

2H937Y47
METABOLITE
ACTIVE -> PRODRUG

Comments:
MAJOR METABOLITE MAY BE RESPONSIBLE FOR ANALGESIC EFFECT
INTERACTION TYPE:
MAJOR

CODEINE-6-GLCURONIDE

2H937T401
METABOLITE
INACTIVE -> PRESENT

Comments:
Metabolic Enzyme - cytochrome P-450 3A4

COMMENTS:

(2)
Adverse Events to Active Moiety

<table>
<thead>
<tr>
<th>PT Term</th>
<th>Prim SOC</th>
<th>Case Count</th>
<th>PT Count</th>
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<td>DRUG HYPERSENSITIVITY</td>
<td>IMMUNE SYSTEM DISORDERS</td>
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<td>2941</td>
<td>30.064</td>
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<td>TOXICITY TO VARIOUS AGENTS</td>
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<td>16484</td>
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</table>
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. Methyl salicylate

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.
Specific Questions

1. Morphine derivatives. Morphine and related. List as Morphine and let drug check worry about x-reactivity?
2. Beta Lactamase Inhibitors.
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
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.
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

- 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.
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

Substance mapping exercises (led by Herman Diederik)
Thank you for your attention

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Convenor ISO/TC 215 WG6, GS1