Defining Excipients in the Substance Registration System

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Goals of Substance Registration System (SRS)

- Develop a scientifically meaningful, consistent and useful definition for all substances in products that the FDA regulates
- Develop a global substance identifier
  - Unambiguous
  - Non-semantic
  - Non-sequential
  - Free to use
- Use the unique ingredient identifier (UNII) to identify all substances in regulated products

SRS History

- Developed from the CDER Ingredient Dictionary (Links to Inactive Ingredient Guide, Orange Book).
- Initially a Collaboration between USP and FDA
- UNIIs Required for Electronic Listing and Structured Product Labels.
- Every listed ingredient must have a UNII
- Electronic Listing required by statute (2007 FDAAA Act) since December 2009.

Why SRS

- Ingredient dictionary was name based.
  - Names are ambiguous
  - Many chemical names for a given substance
  - Official names differ by jurisdiction and domain
    - i.e. Macrogol, Polyoxyl, PEG, Polyethylene Glycol, Polyethylene Oxide
- Other Codes Systems
  - Don’t have the breadth of coverage (Foods, Vaccines, Drugs, Materials in Devices)
  - Copyright, confidentiality, consistency and control
- UNII is a strong non-proprietary identifier consisting of 9 random alphanumeric characters plus a check character that is permanently associated with every defined substance ~10^{13} codes are available.

SRS Vision

- Obtaining a UNII should be an integral part of all submission business processes
- UNIIs should eventually be obtained prior to any submission
- Use identifiers to develop meaningful relationships between substances and submissions (impurities, metabolites, targets, specified substances and products).
- SPL-like process to obtain and exchange information related to substances.
- UNIIs will be used to link data both within and outside the FDA (USP, NLM, EMA, PCPC, Martindale, Merck Index, Wikipedia)
- SRS will be consistent with the ISO IDMP 11238 by 2014

SRS Integration

- Five essential levels to organize information at FDA
  - Substances
  - Products
  - Uses/biology
  - Submissions (Preapproval/Postapproval)
  - Manufacturers/Marketer/Sites
- Data should be linked to all information levels

SRS Integration

- Data That Should be Linked Substances
  - LADMER
  - Targets
  - Metabolites
  - Constituents of Complex Materials
  - Specifications
  - Physical and Biological Properties
  - Environmental Fate
  - Uses
  - Toxicological, Animal, and Clinical Studies
  - ICSRs (Safety Reports)
  - Manufacturers, Sites, and Manufacturing Data
- Both Internal and External Links

What is a Substance

- **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 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

What is a Substance

- Processes that irreversibly changes the molecular structure of material results in a new substance
  - Hydrogenated castor oil is different from castor oil
  - An irreversibly-denatured protein would be a different substance from a non-denatured protein
- Supramolecular interactions will not be captured at the substance level
- 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
    - Peg is not a substance but peg-20 is
  - Stereochemistry should be completely defined
- Materials that are defined as the same substance are not necessarily bioequivalent or pharmaceutical equivalents.

Substances

- 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
  - 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

Mixtures

- Mixtures are comprised of combinations of single substances and biological source where relevant .
- Used to describe substances that are related substances isolated together or the result of the same synthetic process.
  - Proportions are not captured
    - Variations in amounts can be great specification 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 and Aluminum lakes are not substances but consist of two substances).

Defining Substances

- Substances are defined based on a unique combination of molecular structure and descriptive elements
- UNII's are generated in a two step process
  - One chemist will enter the data another approves it.
- Names, codes and trade names are associated with every substance.
- Each substance and name must have a source
- There is a confidentiality flag for both names and the defining substance information

Sources for Names and Definitions

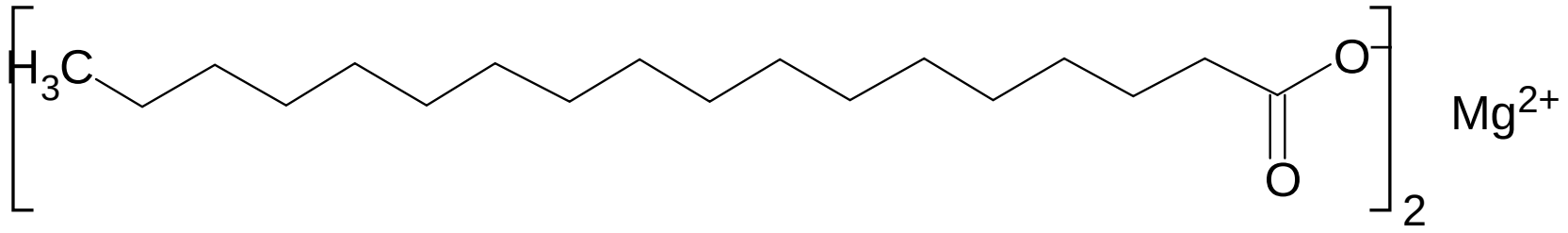
- Pharmacopeias (USP, EP, JP)
- Submissions (INDs, NDA, BLA, DMFs)
- US Adopted Name (USAN/USP Dictionary)
- International Normalized Name (INN)
- Homeopathic Pharmacopeia US (HPUS)
- Martindale
- Merck Index
- NLM (ChemID and Pubchem)
- CAS
- Pharmaceutical Excipients
- Food Chemicals Codex
- Herbs of Commerce
- Personal Care Products Council (INCI)
- Catalogue of Life (Accepted organism taxons)
- ITIS (FDA Seafood List)
- Manufacturers Information

Defining Excipients

- Excipients are defined like any other material
- Excipients are often multi-substance ingredients (colorants, flavors, fragrances)
  - Each substance should be defined
- Excipients are often the most difficult substances to define
  - No official naming body that defines most excipients
  - Insufficient information in pharmacopeias
  - Manufactures are inconsistent in the type information provided (trade secrets)
  - Many are polymers
    - Frequently contain partial information (i.e. molecular weight without the MW type),

Excipient Substance Examples

- Magnesium Stearate



(PolyDisperse) Polymers

Hypromellose Example

USP 33: Labeling—Label it to indicate its substitution type and its nominal viscosity value in milli-Pascal per second (mPa·s).

Hypromellose is the INN and BAN

CAS *9004-65-3*

(PolyDisperse) Polymers

Hypromellose Example

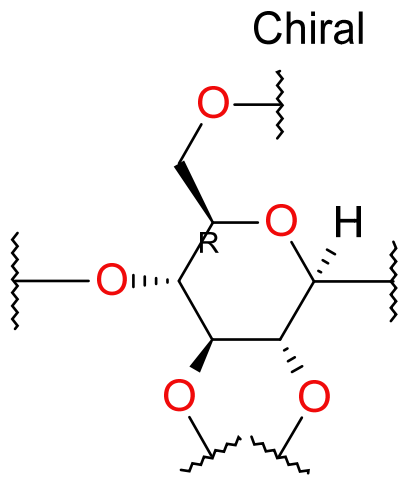
USP 33: Hypromellose is a methyl and hydroxypropyl mixed ether of cellulose. It contains, calculated on the dried basis, methoxy (–OCH3: 31.03) and hydroxypropoxy (–OC3H6OH: 75.09) groups conforming to the limits for the types of Hypromellose (hydroxypropyl methylcellulose) set forth in the accompanying table.

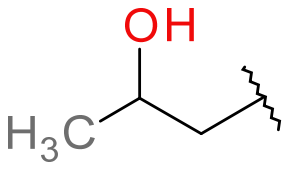
	Methoxy (percent)		Hydroxypropoxy (percent)	
Substitution Type	Min.	Max.	Min.	Max.
1828	16.5	20.0	23.0	32.0
2208	19.0	24.0	4.0	12.0
2906	27.0	30.0	4.0	7.5
2910	28.0	30.0	7.0	12.0

Hypromellose

HYPROMELLOSE 2910 (3 MPA.S)	0VUT3PMY82
HYPROMELLOSE 2910 (5 MPA.S)	R75537T0T4
HYPROMELLOSE 2910 (6 MPA.S)	0WZ8WG20P6
HYPROMELLOSE 2910 (15 MPA.S)	36SFW2JZ0W
HYPROMELLOSE 2910 (50 MPA.S)	1IVH67816N
HYPROMELLOSE 2910 (4000 MPA.S)	RN3152OP35
HYPROMELLOSE 2910 (15000 MPA.S)	288VBX44JC
HYPROMELLOSE 2906 (50 MPA.S)	612E703ZUQ
HYPROMELLOSE 2906 (4000 MPA.S)	5EYA69XGAT
HYPROMELLOSE 2208 (3 MPA.S)	9H4L916OBU
HYPROMELLOSE 2208 (100 MPA.S)	B1QE5P712K
HYPROMELLOSE 2208 (4000 MPA.S)	39J80LT57T
HYPROMELLOSE 2208 (15000 MPA.S)	Z78RG6M2N2
HYPROMELLOSE 2208 (100000 MPA.S)	VM7F0B23ZI

HYPROMELLOSE 2910 (3 MPA.S)





R1

R2

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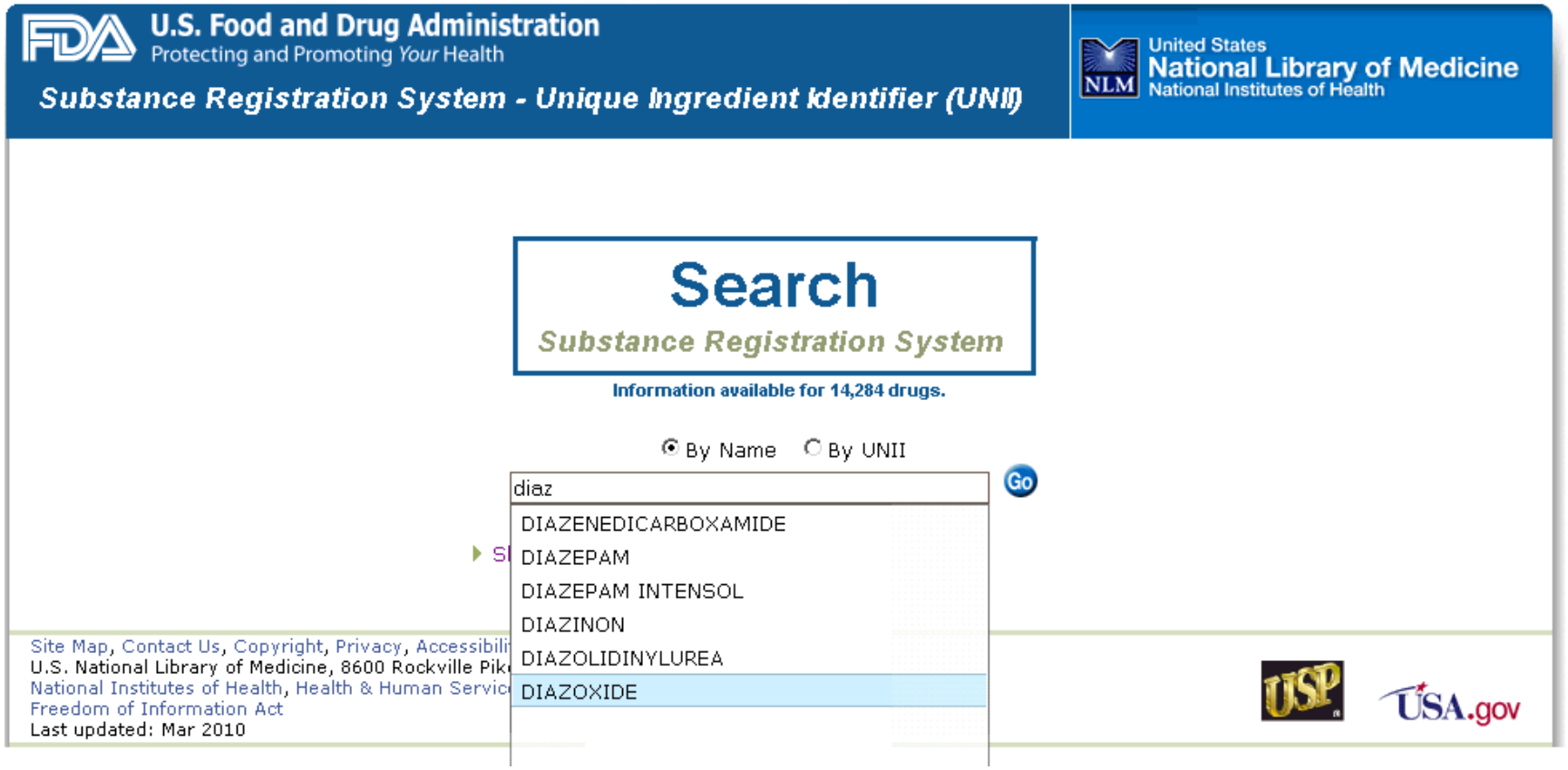
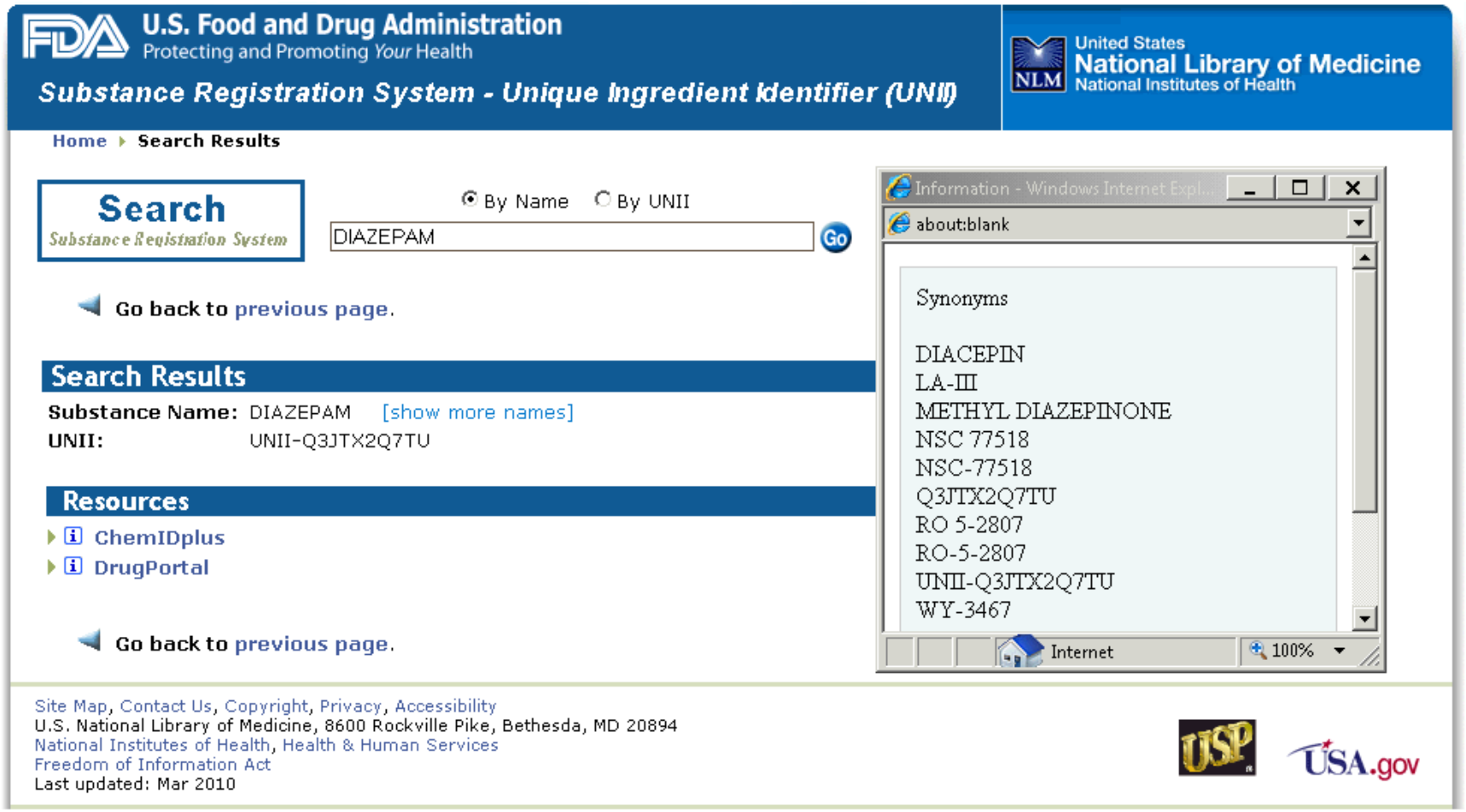
http://fdasis.nlm.nih.gov/srs/srs.jsp



Search Output



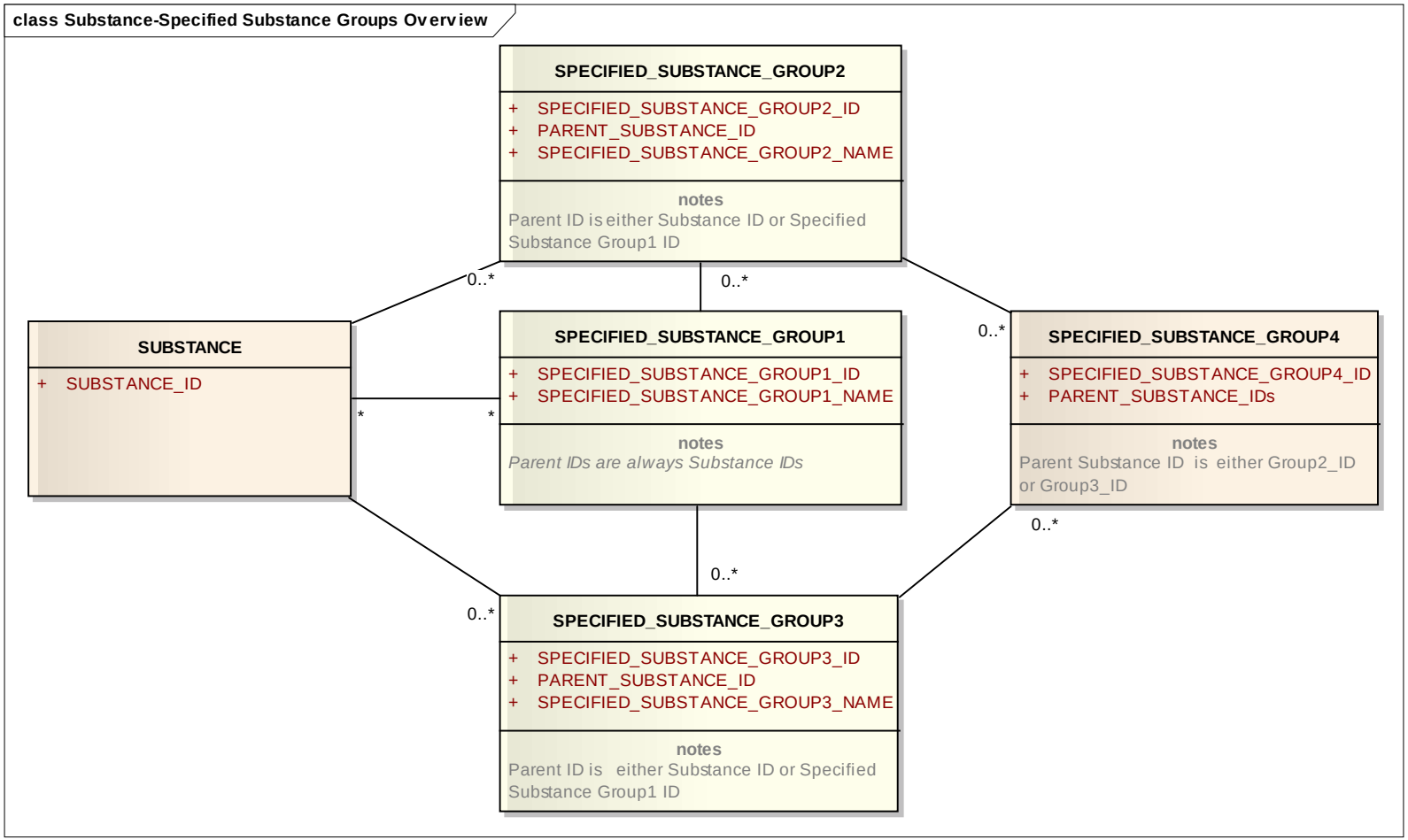
Current SRS System

- Uses MDL/Symyx/Accelrys Mol 2000 representation
- Molecular structure and a limited set of xml-tagged fields are used.
- Specified substance not yet implemented
- Reference Information and Relationships not yet implemented.
- 52000 substances, 36000 UNIIs

Specified Substance

- An explicit grouping of elements and concepts is put forward in ISO not yet implemented in SRS
  - Group-1 Multiple substance materials, physical form, constitiutents and amount, extracts allergenic and herbal.
  - Group-2 Manufacturer and minimal manufacturing information
  - Group-3 Grade of material (USP, EP, technical, standardized etc.)
  - Group-4 Detailed manufacturing information, impurities, degradents etc.

Substance -Specified Substance



Suggestions

- Collaborate with IPEC to make sure all excipients in pharmaceutical products are assigned proper UNII's.
  - IPEC could provide a market survey of excipients used throughout the world and the manufacturers of such excipients.