



GInAS: Global Ingredient Archive System

Toward an open implementation of
Substance Registration and ISO
11238



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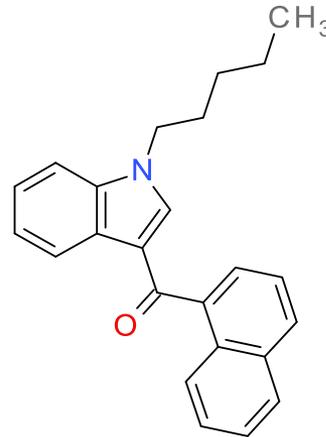
USP Fouad Atouf, Tina Morris, Andrzej Wilk

GInAS Global Drug Regulatory Landscape

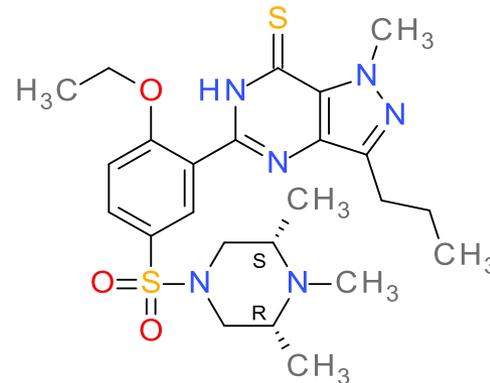
- Global Market for Ingredients
 - Very few products have all ingredients sourced from a single jurisdiction or the marketed jurisdiction
 - Heparin
 - Glycerin
 - Milk Proteins (Melamine, Botulism)
 - Catastrophic Events (Disrupt Supply Chain)
 - Global Proliferation of Inspections
 - API Manufacturers (200+ Inspections)
- Continuing Proliferation of Substandard, Counterfeit Adulterated and Mislabeled Health Products
 - Africa and Asia
 - Fake Malaria Drugs
 - US
 - Dietary Supplements that Contain Approved and Unapproved APIs (Cannabinoids, Sildenafil Analogs)

G In A S Global Drug Regulatory Landscape

JWH-018
UNII G391998J57
Spice



SULFOAILDENAFIL
UNII 33DX49E09G
Libigrow, Blue Diamond,
Mojo Nights, Casanova

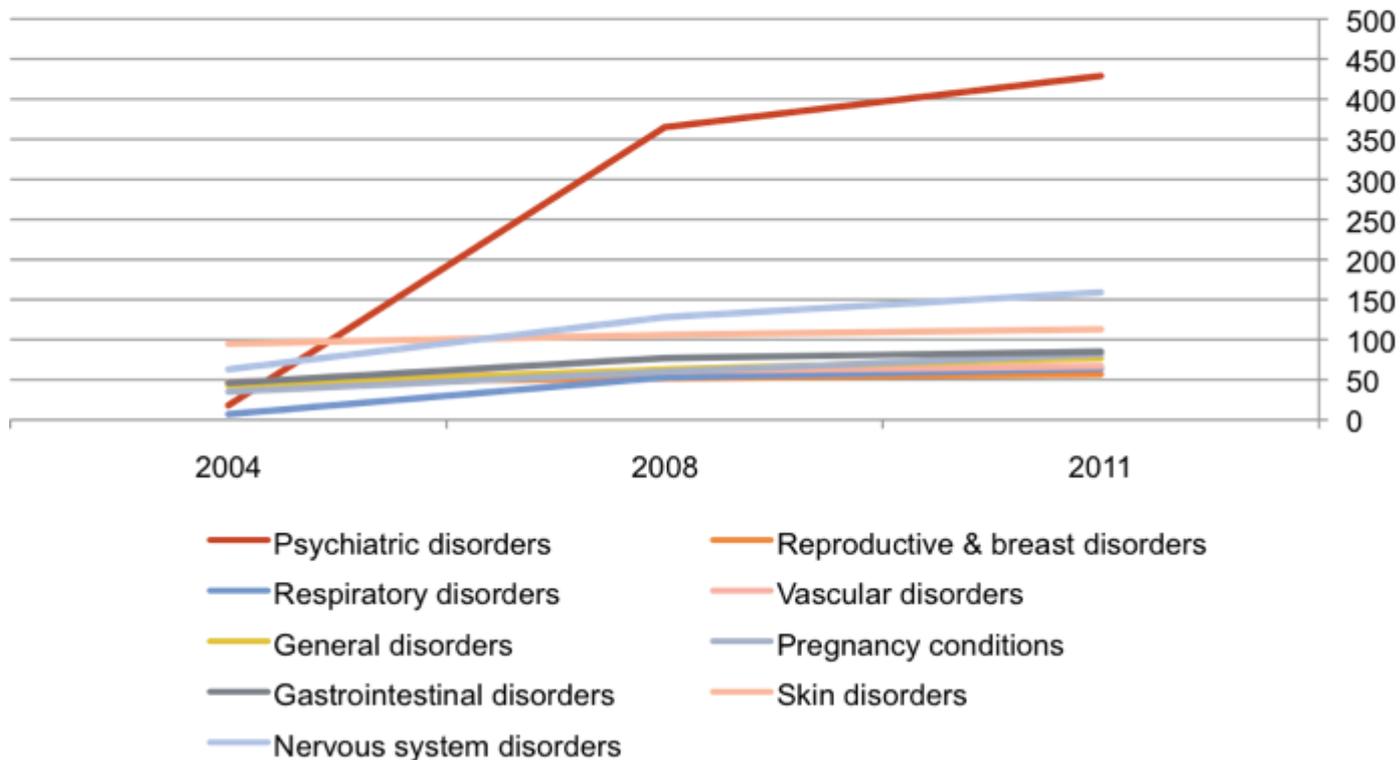


Global Drug Regulatory Landscape

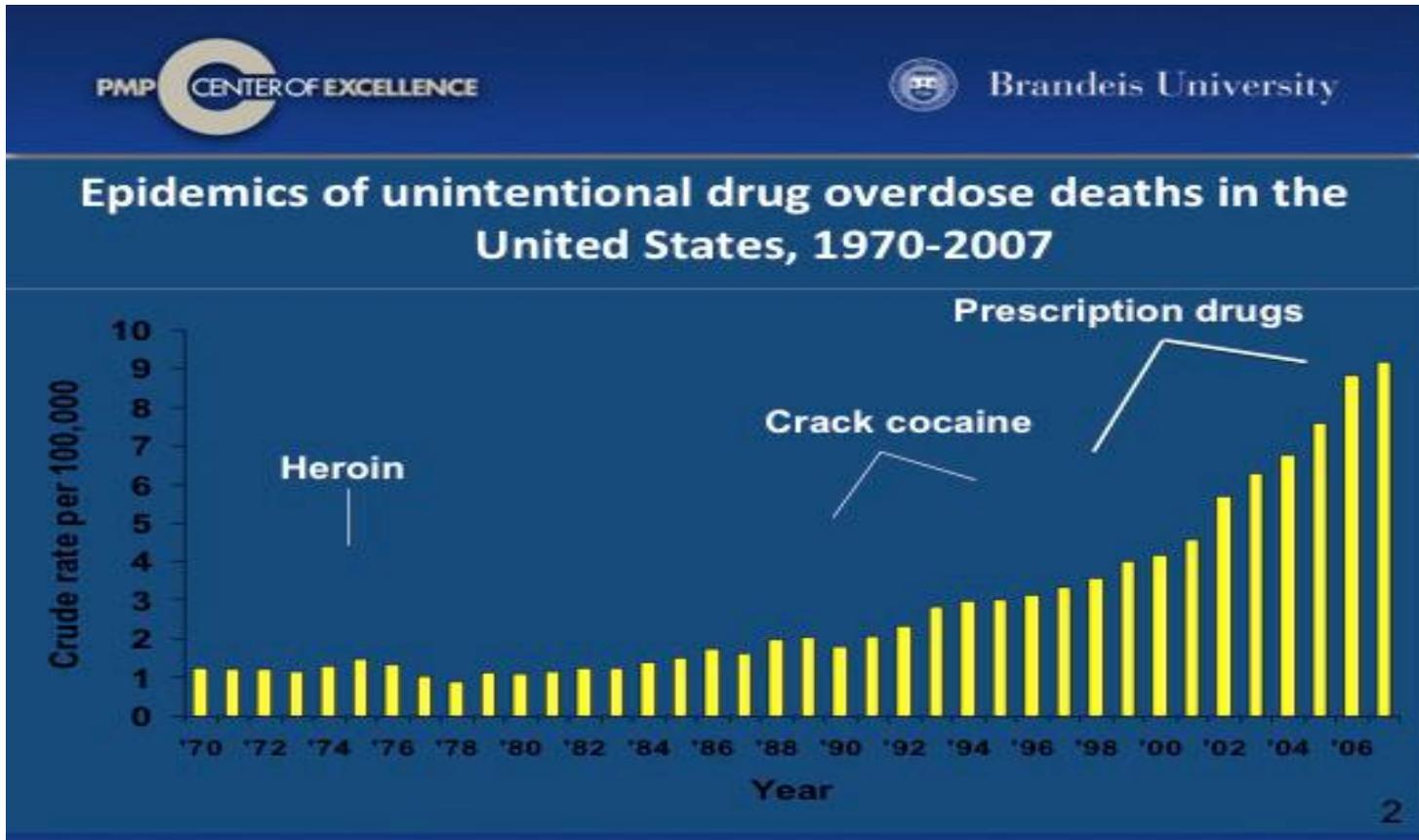
- Epidemic of Adverse Events
 - Drug Use is increasing
 - Polypharmacy (1/3 of Americans take 5 or more medications)
 - Chronic Diseases (HIV, Hepatitis C, Diabetes, Depression)
 - US over 700,000 Emergency Room Visits, 100,000 hospitalizations due to drug adverse events
<http://psnet.ahrq.gov/primer.aspx?primerID=23>
 - US over 100,000 deaths per year?
Vioxx, Oxycontin
 - Europe over 197,000 deaths due to ADRs?
 - General Belief 60-80% of Adverse Events are preventable

G In A S Global Drug Regulatory Landscape

Number of adverse drug reactions reported to the MHRA



Global Drug Regulatory Landscape



G In A S Global Drug Regulatory Landscape

- Reformulated Oxycodone Product
 - Forms hydrogel, difficult to snort; difficult to inject
 - Appears To Reduce Abuse and Misuse
 - American Pain Society Meeting 2012
- Heparin package changes (Dennis Quaid Incident)





GInAS Need

- Global marketplace for ingredients requires a global system to monitor the global supply chain
- Global database means better data, less redundancy, more data, less mapping
- ISO 11238 has recently been developed to describe substances/specified substances in medicinal products
- Complex, Expensive to implement a system based on 11238 on a individual basis may prevent adoption of standard
- Pharmacovigilence based on substances with global data
- Better coordination of regulatory activity and clinical trials (inspections, specifications, drug shortages)
- Standards can converge more rapidly



GInAS Goals

- Develop and deploy an information system that can serve as a global repository for definitional, regulatory and scientific information on substances
- Establish a consortium of regulators and other international organizations to manage and govern the repository
- Develop and distribute a global identifier for every substance in marketed medicinal products and clinical research
- Distribute an information system to both regulators, companies and other interested parties to facilitate registration into the global repository
- **Common System, Common Content** → **Better System, Better Content**



GInAS IS (Will Be)

- A freely distributable software system that will facilitate the implementation of the 11238 Standard and provide a Global Identifier
- A system capable of registering diverse substances and specified substances
 - Chemicals, Proteins, Nucleic Acids, Polymers and Structurally Diverse
- A central repository of substance definitions and identifiers
- A central repository of information related to substances
 - Physical Properties (Solubilities, Viscosity, Melting points; Isoelectric Points)
 - Specification Information (Impurities, Properties, Assay)
 - Manufacturing Information (Company; Facility; Starting, Processing, Final Materials, Critical Parameters)
 - Pharmacological/ Toxicological Information (Metabolites, LADMER data, Targets, NOAEL)
 - Regulatory Data (Classifications, Authorizations)
- Capable of maintaining public data and confidential data at the element and record level.
 - Roles, User, Depositor can control access



GInAS Will Not

- Replace regulatory procedures
- Replace legal obligations
- Be mandatory



GInAS

- Grew Out of a Meeting Hosted by USP and NCATS (NIH) in February 2013
- Will use software developed by NCATS
- Content managed by regulators
- Prototype hosted at Health Canada
- Canadian, Dutch, German, Swiss, and US regulators, EDQM and USP involved in the the development of the system
- Will contain definitional, analytical, manufacturing and biological information (target, metabolites, metabolic enzymes, and transporters)
- Software can also be deployed locally (Each regulator can have their own independent system using NCATS software and public data)
- System will be distributed by NCATS with a large set of public domain data and updated periodically

GInAS Implementation Roadmap

Staged Development

- Stage I (alpha) <http://ginas.hc.ircan-rican.org/>
 - Functional design, use cases from FDA & CBG-MEB
 - Implement core services and data models for substance categories
 - HealthCanada: Host GINAS demonstration instance for substance registration, July 2013
 - FDA: Local deployment for chemicals, proteins, structural diverse migrated from FDA public SRS, October 2013
- Stage II (beta)
 - Support for other substance types, including specified level 1, and 3 December 2013
 - Open test deployments to other organizations, April 2014
- Stage III (public release)
 - Higher levels specified substance support, June 2014
 - API supports incremental data updates; software updates bi-annually



Identification of Medicinal Products

Five Interrelated ISO Standards

11615 Health Informatics — Identification of Medicinal Products — Data elements and structures for the unique identification and exchange of regulated medicinal product information (Editor: Sabine Brosch EMA)

11616 Health informatics – Identification of Medicinal Products -Data elements and structures for the unique identification and exchange of regulated pharmaceutical product information (Editor: Vada Perkins FDA)

11238 Health Informatics — Identification of Medicinal Products — Data elements and structures to uniquely identify and describe substances (Editors: Larry Callahan and Frank Switzer FDA)

11239 Health Informatics — Identification of Medicinal Products — Data elements and structures to uniquely identify pharmaceutical dose forms, units of presentation and routes of administration (Editor: Chris Jarvis EDQM)

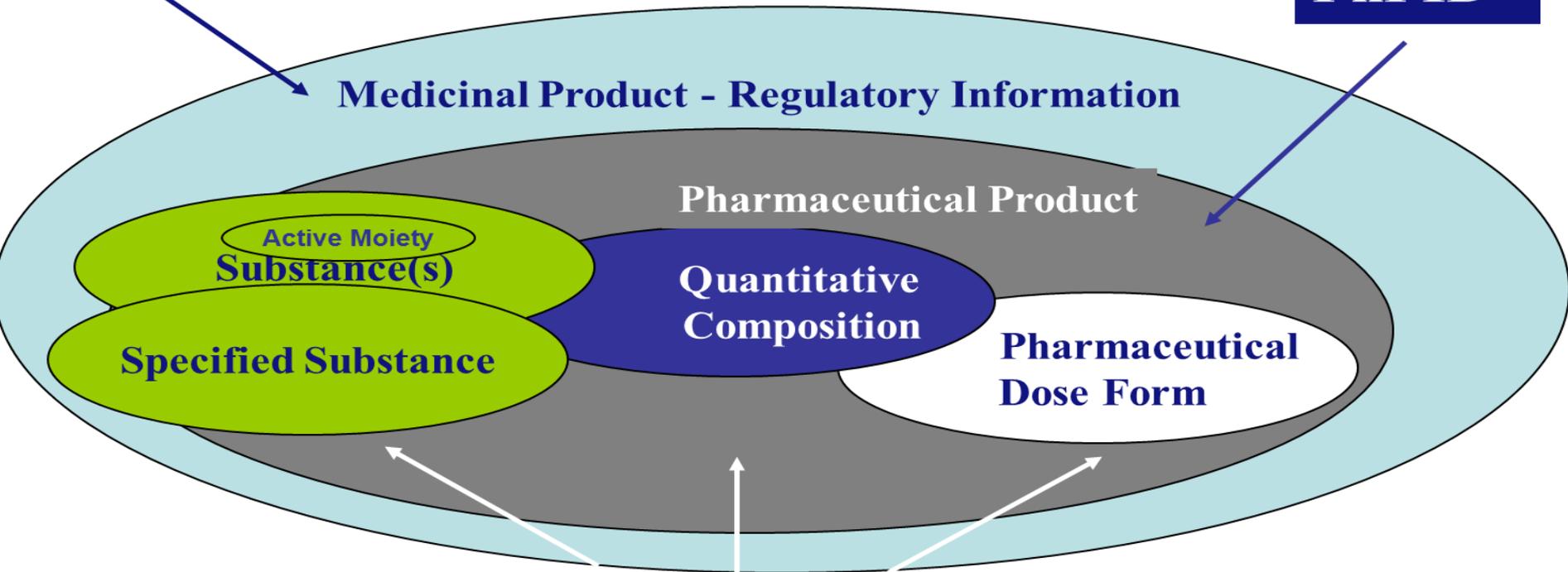
11240 Health informatics — Identification of Medicinal Products — Data elements and structures to uniquely identify Units of Measurement (Editors: Christof Gessner and Aniello Santoro EMA)



Conceptual Model

MPID

PhPID

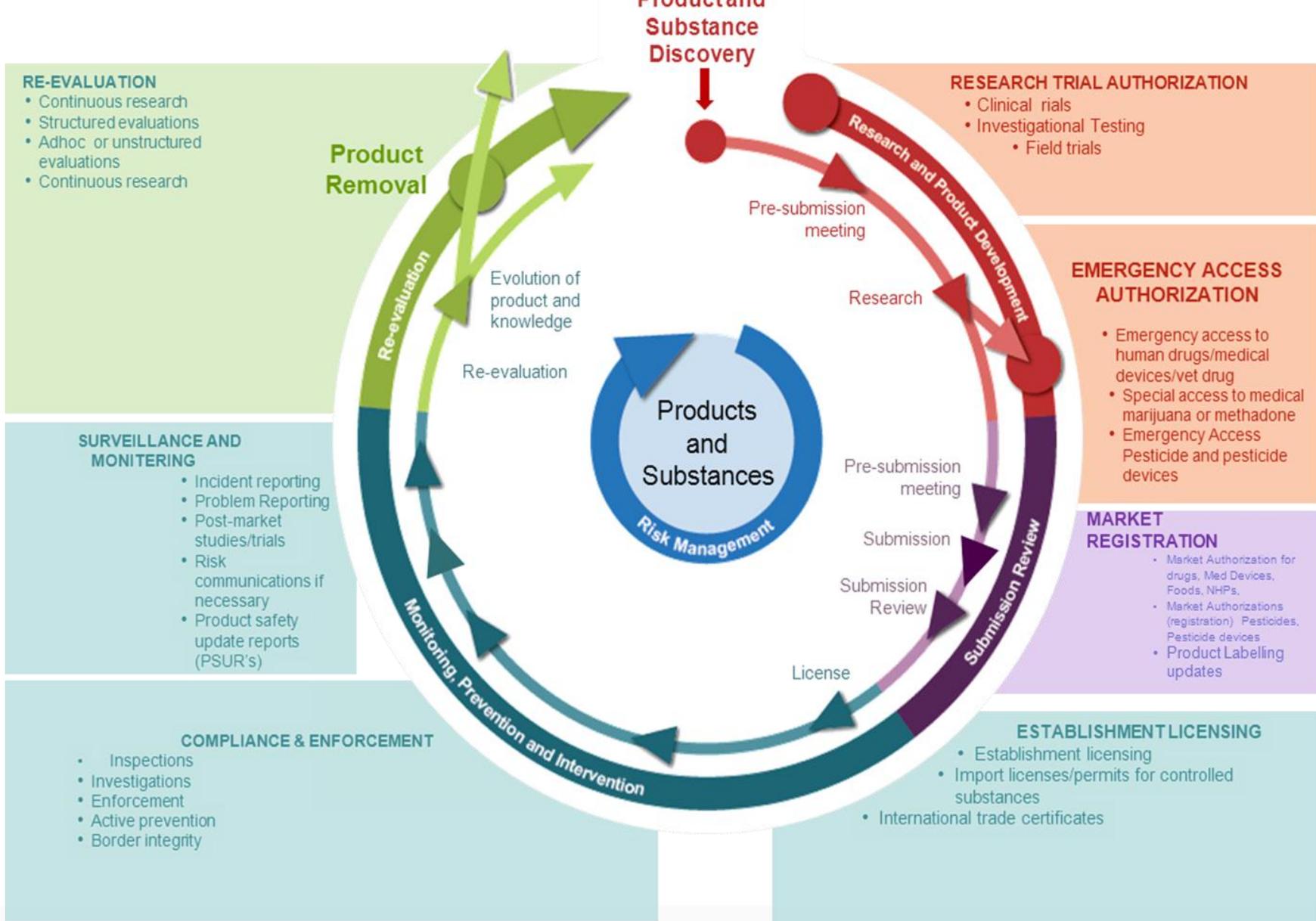


Vocabularies

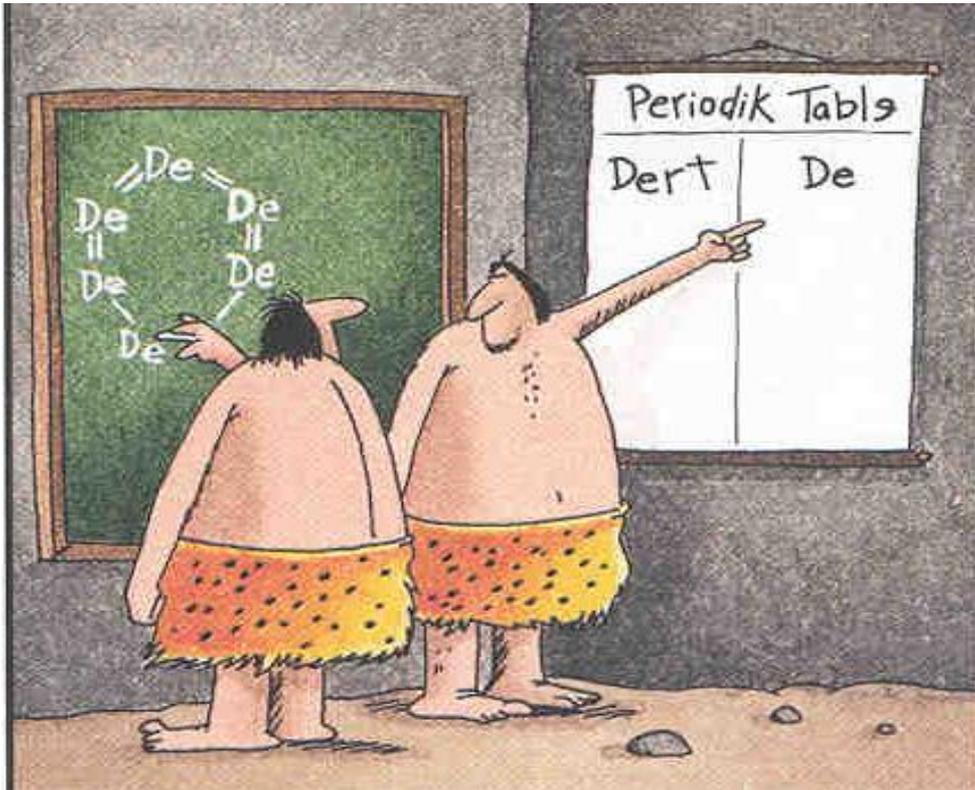


IDMP

- FOUR LEVELS OF INFORMATION
- SUBSTANCE (Global Identifier)
- SPECIFIED SUBSTANCE (Global/Regional)
- PHARMACEUTICAL PRODUCT (Global Identifier) substance, strength, dosage form
- MEDICINAL PRODUCT (Regional)
- 11238 ADDRESSES BOTH SUBSTANCES AND SPECIFIED SUBSTANCES
- Much of the Overall Model could be used for all products



What is a Substance



**Early
Chemists
describe
the first
DIRT
MOLECULE
(The Far Side by
Gary Larson)**



What is 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**



What is Substance

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 will be defined based on taxonomic, anatomical and limited fractionation information

What is Substance

- Processes that irreversibly change the molecular structure result 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 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 (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

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

- Currently used to describe substances that are related substances isolated together.
- Proportions are not captured
- Variations in amounts can be large specification would be captured the specified substance level.
- All single entities typically present in amounts greater than 1% either by weight or mole percent would 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)

GIAS Need for Specified Substance

- Organize additional information on ingredients.
- 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)
- Need to tie 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

- An explicit grouping of elements and concepts put forward in ISO IDMP
 - Group-1 Multiple substance materials, physical form, constituents 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.

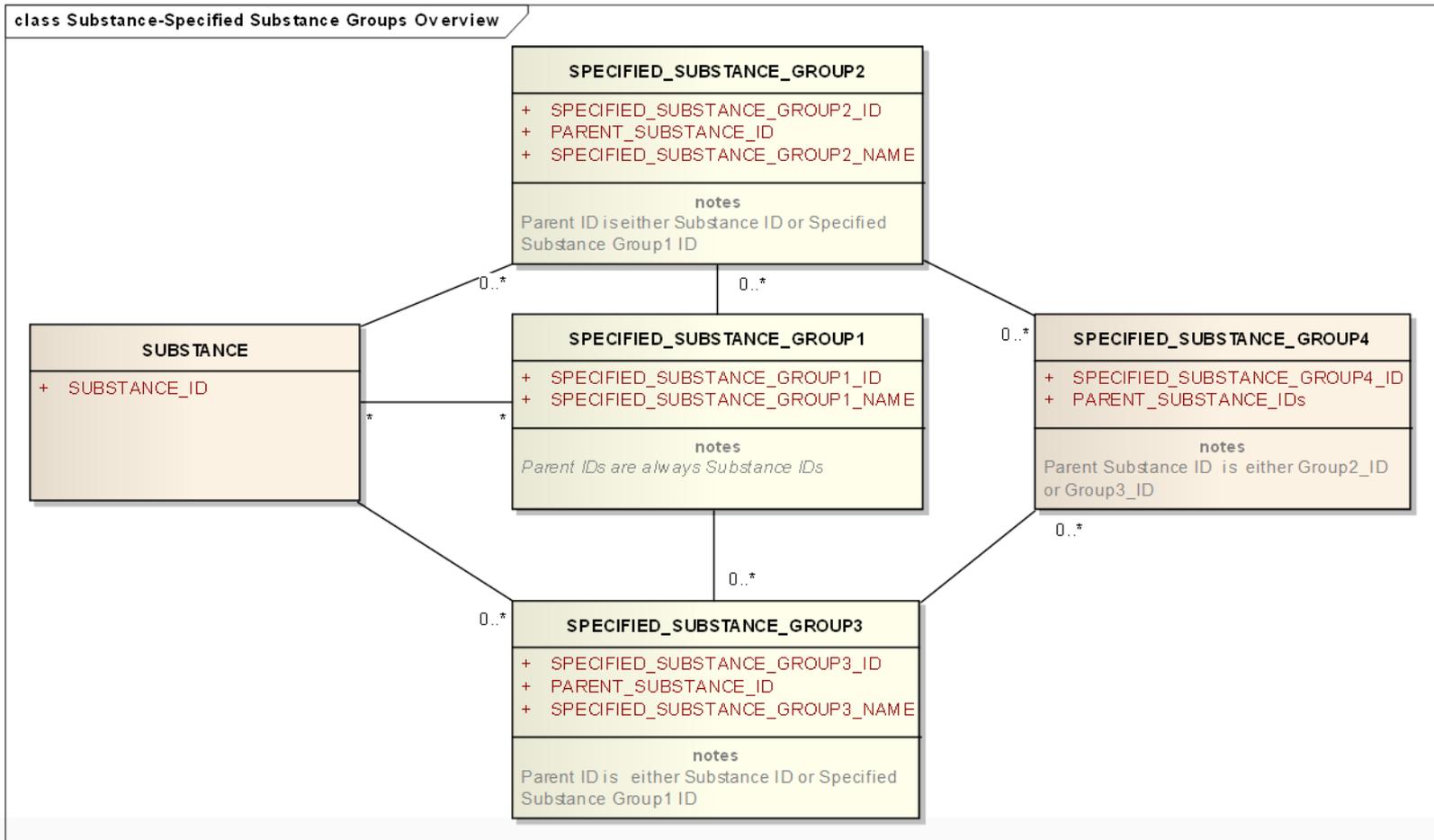


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Substance -Specified Substance





Specified Substance

- Not yet implemented at FDA
- Group 1
 - Implementable today
- Group 2
 - Could be implementable
 - Global ID for Manufacturer and Facility may be needed?
- Group 3
 - Implementable today
- Group 4
 - May need to further develop model
 - Need to develop more controlled vocabulary

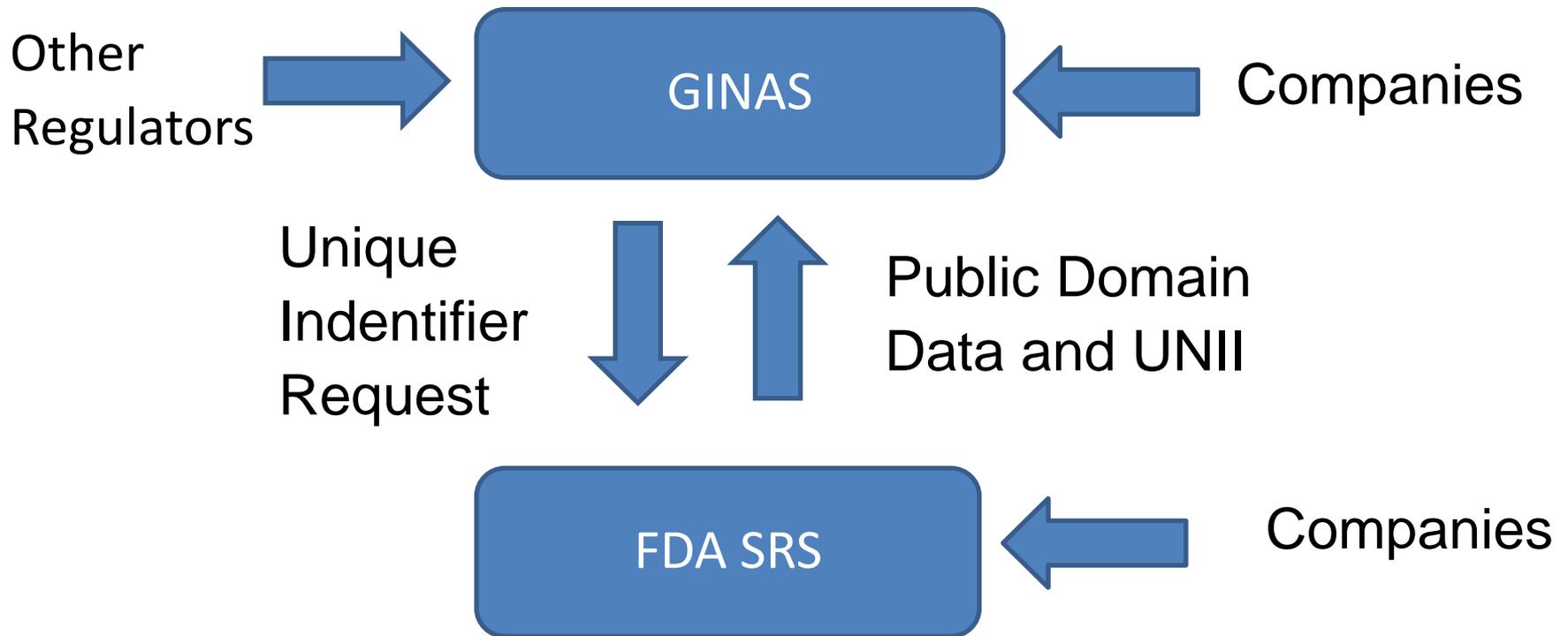


GINAS and FDA

- FDA intends to use a local deployment of GINAS to supplant the current FDA SRS
- FDA has established an MOU with NCATS and provided seed money
- FDA will provide a test bed for GINAS software and data models
- FDA will provide public data to GINAS
- FDA will provide a Unique ID to GINAS if requested



GINAS and FDA





Current SRS System

Welcome to the Substance Registration System / Ingredient Dictionary

Product and activity information available at FDA and from external reference sources for the substances present in regulated products

Substance | Product | Application | Clinical Trial

Search for Substances

Exact Match ▾ Substance Name ▾ **Search**

More Options

Structure

Structure Search Mode:

- Substructure Search
- Similarity Search %
- Exact Structure

[clear](#)

Display Suggestions

Current SRS System

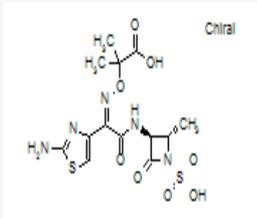
Substance Search Results for

Substance Name: AZTREONAM

Cancel

New Search

Records Found: 1

Substance ID:	UNII:	Structure:	BDNUM:	Ingredient Name:	Application Count	Product Count	Clinical Trial Count
6795	G2B4VE5GH8	 <p>Chiral</p>  	0116723AA	AZTREONAM (SRS Preferred Term)	ANDA: 2 IND: 5 NDA: 3 Total: 10 Application SRS MF: 6 Total: 6	Active: 17 InActive: 0 Total: 17	Total: 7

Records Found: 1

Cancel

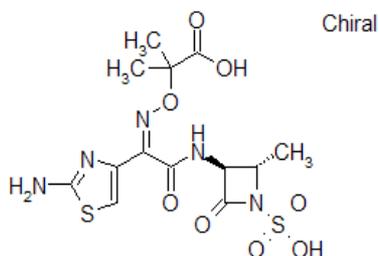
New Search

Current SRS System

Identifying Information

Substance ID: **6795**

UNII: [G2B4VE5GH8](#)



Molecular Weight: **435.44**

Inchi: [\[+Expand\]](#)

CLASS:

J01DF01

- ATC
- ANTIINFECTIVES FOR SYSTEMIC USE
- ANTIBACTERIALS FOR SYSTEMIC USE
- OTHER BETA-LACTAM ANTIBACTERIALS
- Monobactams
- aztreonam

Reference Information

[Cancel](#)

Name	Name Category	Source
AZTREONAM	Preferred Term	USP DICTIONARY
(2S-(2A,3B(Z)))-3-(((2-AMINO-4-THIAZOLYL)-((1-CARBOXY-1-METHYLETHOXY)IMINO)ACETYL)AMINO)-2-METHYL-4-OXO-AZETIDINE SULFONIC ACID	Synonym	
(Z)-2-(((2-AMINO-4-THIAZOLYL)(((2S,3S)-2-METHYL-4-OXO-1-SULFO-3-AZETIDINYL)CARBAMOYL)METHYLENE)AMINO)OXY)-2-METHYLPROPIONIC ACID	Synonym	USP DICTIONARY
AZACTAM	Trade Name	USP DICTIONARY
AZONAM	Trade Name	STN (SCIFINDER)
AZTHREONAM	Synonym	
AZTREON	Trade Name	STN (SCIFINDER)
AZTREONAM [INN]	Synonym	INN
AZTREONAM [MART.]	Synonym	MARTINDALE
AZTREONAM [MI]	Synonym	MERCK INDEX
AZTREONAM [ORANGE BOOK]	Synonym	ORANGE BOOK
AZTREONAM [USAN]	Synonym	USP DICTIONARY
AZTREONAM [USP]	Synonym	USP/NF
AZTREONAM [VANDF]	Synonym	NDF-RT
AZTREONAM [WHO-DD]	Synonym	WHO DRUG DICTIONARY
FINECS 278-839-9	Code	CHEMID

Current SRS System

NDF-R1	N0000175493	NDF-R1
SWISS MEDIC	16873	SWISS MEDIC
WHO-ATC	J01DF01	WHO-ATC
WIKIPEDIA	AZTREONAM	WIKIPEDIA

Product

Application

Clinical Trial

Relationship

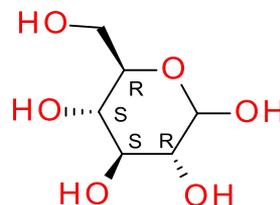
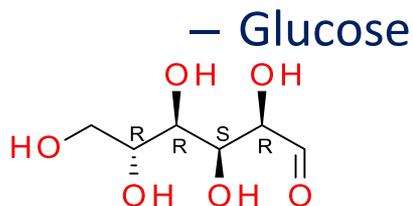
Substance Relationship Found: 11 1 - 10

Substance Name	Related Substance Name	Relationship Type	Related Structure	Related UNII	Public Domain
AZTREONAM	AZTREONAM	ACTIVE MOIETY		G2B4VE5GH8	N
AZTREONAM	AZTREONAM LYSINE	SALT/SOLVATE - PARENT		XNM7LT65NP	N
AZTREONAM	SQ-26992	IMPURITY - PARENT		Z0397SYG7R	Y
AZTREONAM	OPEN-RING DESULFATED	IMPURITY - PARENT		D2GEP437EQ	Y

11]

Current SRS System

- Not compliant with ISO 11238 even at substance level
- Deficiencies
 - Only one structure per substance



- **Description Field**

- Home Spun XML
- Currently used for Proteins, Nucleic Acids, Polymers and Structurally Diverse Substances
- Difficult to validate
- Strong Need to Field Definitional Description Data



GInAS Information Resources

- Health Canada Prototype
 - <http://ginas.hc.ircan-rican.org/>
- System presentations and functional designs
 - <https://tripod.nih.gov/pub/ginas/>
- Retrieval by name
 - <https://tripod.nih.gov/ginas/v6/OXYTOCIN/name>
- Substructure searching
 - <https://tripod.nih.gov/ginas/v6/c1ncncn1/sub>
- Tanimoto similarity searching
 - [https://tripod.nih.gov/ginas/v6/CCNC1=NC\(Cl\)=NC\(NCC\(O\)=O\)=N1/sim?cutoff=.75](https://tripod.nih.gov/ginas/v6/CCNC1=NC(Cl)=NC(NCC(O)=O)=N1/sim?cutoff=.75)
- Name resolver
 - <https://tripod.nih.gov/ginas/v6/resolver/gleevec/glivec/names>