Overview of Global Substance Registration System (GSRS) and Identification of Medicinal Products (IDMP)

Outline of Talk

- Organizing Information
- IDMP Standard
- What is a substance
- GInAS/GSRS
- Status of Development
- Adverse Event Data

Organizing Information

- FDA has the most important/valuable repository of human biological and product data but limited integration.
  - Submission process
    - Paper
    - PDF's
  - Organizational
    - Different Centers
    - Different Contractors
    - Business Process
- The amount of information is increasing
  - Rapid Screening Methods
  - Enzyme and Receptor Profiling
    - Cyp , Transporter and Receptor
  - Genomics
  - Epigenomics
 - Electronic Health Records
  - Many CMC changes

Organizing Information

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- Identification of Medicinal Products (IDMP)
  - ISO project; 5 standards
- Approach of the IDMP to organizing information
  - Goal is to get data organized prior to submission
  - Fielded data is better than non-fielded Data
  - Controlled vocabulary is better that non-controlled vocabulary
  - Codes are better than names in electronic systems particularly relevant to substances
  - Substance terminology on definitions (truth) not hierarchy
  - All substances in medicinal products should be be defined and assigned a unique ID

Goals of IDMP Project

- Develop a common data structure and terminology for the description of medicinal products
  - Facilitate data exchange
    - Pharmacovigilance
    - Quality of pharmaceutics/detect/prevent counterfeiting
    - Predict/prevent drug-drug food-drug interactions
    - Incorporation of diverse data into databases
    - Prevent drug shortages
    - Promote Drug Development
  - Consistent review
  - Enter once use many (substances, organizations)
  - Assist in mining of EHRs (Effectiveness. Safety, Better Dosing)

Global Health Benefits of IDMP
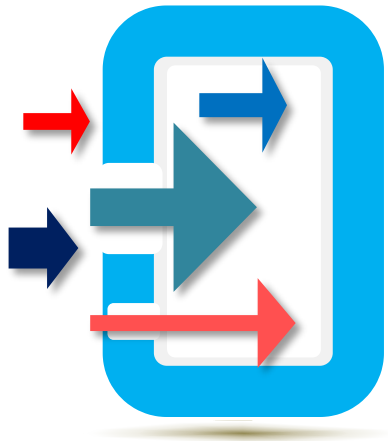
- **Improve Pharmacovigilance**
  - Globally detect safety signals from medicinal products referenced in adverse events

- **Support Mitigation of Drug Shortages**
  - Allows the identification of pharmaceutically equivalent products across regions

- **Promote Greater Understanding and Sharing**
  - Supports the exchange of post-market medicinal product information between companies and regulators
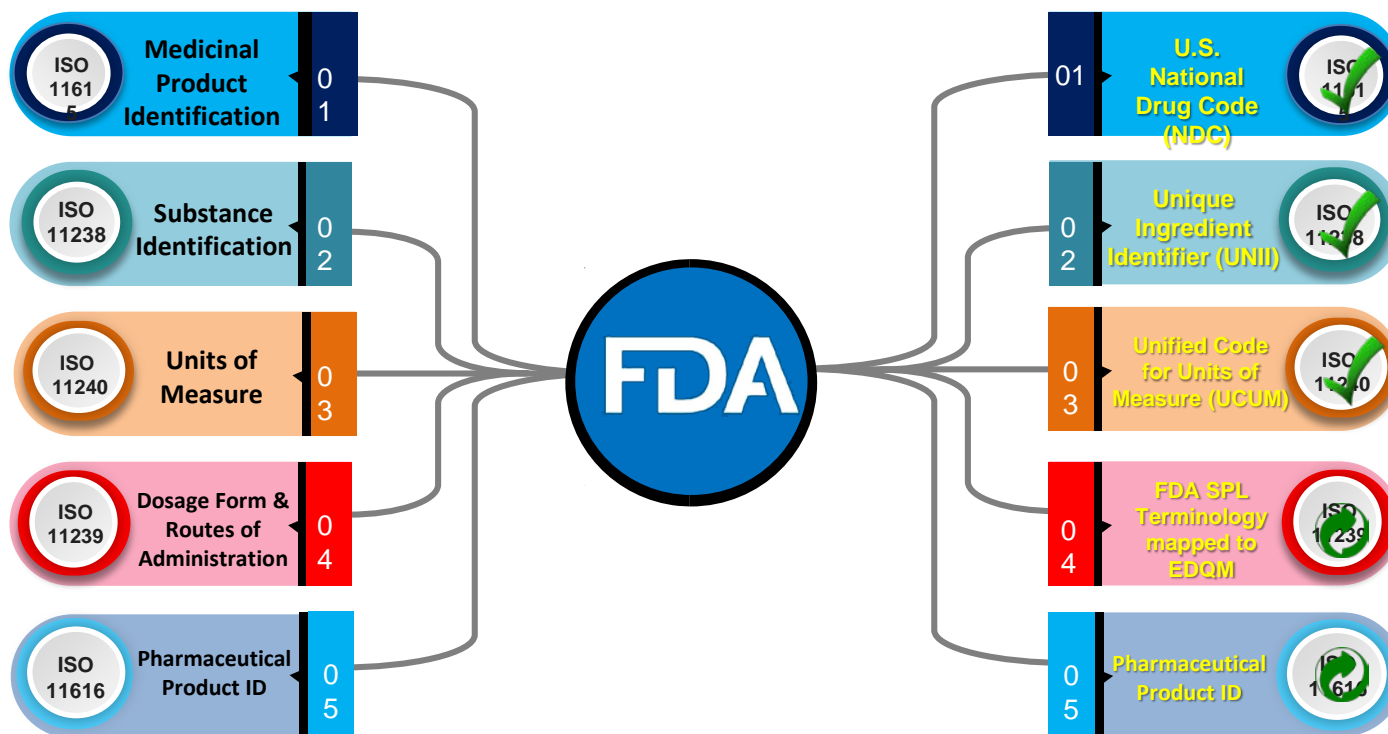
IDMP Overview
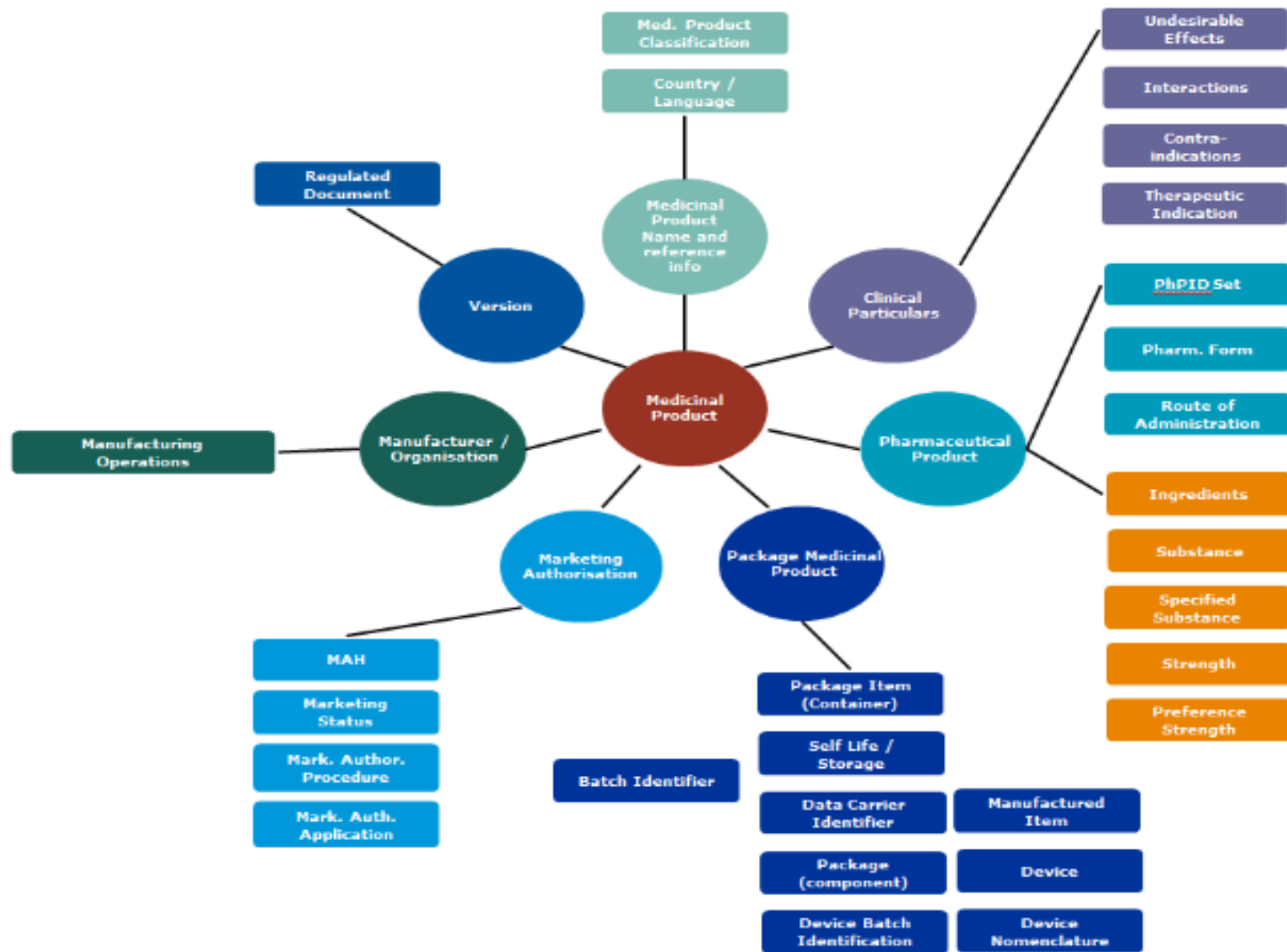
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FDA's Approach to ISO IDMP Standards
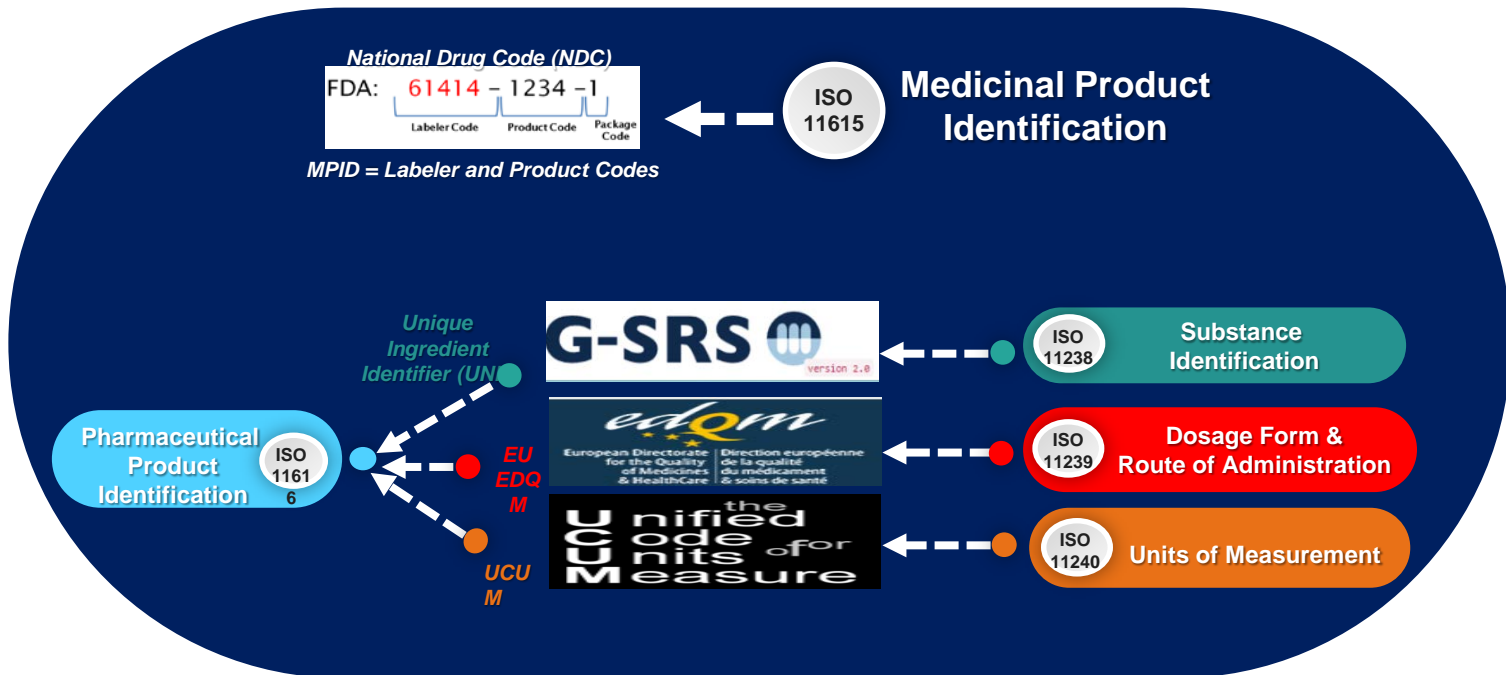
FDA's Approach to ISO IDMP Standards

What is a Substance: ISO 11238

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- 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 me 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 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

Why Register Substances

Need to tie substances to regulatory submissions

- Enhance review and drug development
  - Active substance and inactive substances under review

  - Biomarkers can be defined and tracked

  - Use substances and related substance information to structure submissions
    - Quality
    - Manufacturing
    - In-vitro data
    - Clinical Information
      - » Clinical trial registration
      - » ICSR
  - Starting materials

  - Processing materials

  - Impurities

Need to tie substances to other substances

- Relationships between substances
  - Active Moiety
  - Salt/Solvate-> Parent relationships
  - Metabolites
  - Impurities
  - Drug target
  - Metabolic Enzymes (substrate, inhibitor, inducer)
  - Transporters (substrate, inhibitor, inducer)
  - Off target enzymes and receptors

Why Register Substances?

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Need to tie substances to products

- Quality perspective
    - Change in substance can lead to a change in product
    - Find all products that could contain a "bad" ingredient (heparin, diethylene glycol)
    - Consistent specifications
- Safety perspective
    - Track adverse events based on substances
    - Tie substances to targets and pathways
- Drug Utilization
    - Predict and prevent shortages
    - Global marketplace need a global systems

Need to tie substances to manufacturer

- Quality
    - Who makes it
    - Where they make it
    - How they make it
    - Coordinate Inspections and testing

Tie Substances to other Information

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- Quality
  - Characterization
  - Specifications
  - Stability
- Physical Properties
  - Molecular weight
  - Solubility
  - pKa or pKb
  - Partition coefficients
  - Polymorph (crystal, amorphous)
- Toxicology and Animal Pharmacology
  - Genotoxicity
  - Cellular Cytoxicity
  - Summary Animal Toxicology
- Acute , Subchronic and Chronic
  - NOAEL, tissue distribution
  - Environmental Fate
  - Lab on a Chip results

- Clinical Pharmacology (LADMER)
  - Dissolution Data
  - Pharmacokinetics (Cmax, Tmax, Half-life, Vd, etc.)
  - Metabolism
  - Excretion
  - Pharmacodynamics
- Health and Disease
  - Indications (treatment, prevention, causative)
  - Adverse Events
  - Drug-Drug Interactions
  - Drug-Food Interactions
  - Health Outcomes
  - - omics

How it's used at FDA

- FDA has adapted GSRS to integrate with existing internal databases and systems.
  - Adverse events
  - Products
  - Applications (INDs, NDAs)
  - Clinical Trials
- Industry uses the data from GSRS to find the UNII codes for their substances, which are submitted to the FDA.
  - In the future, they will be able to create a JSON message defining their substance to the FDA

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
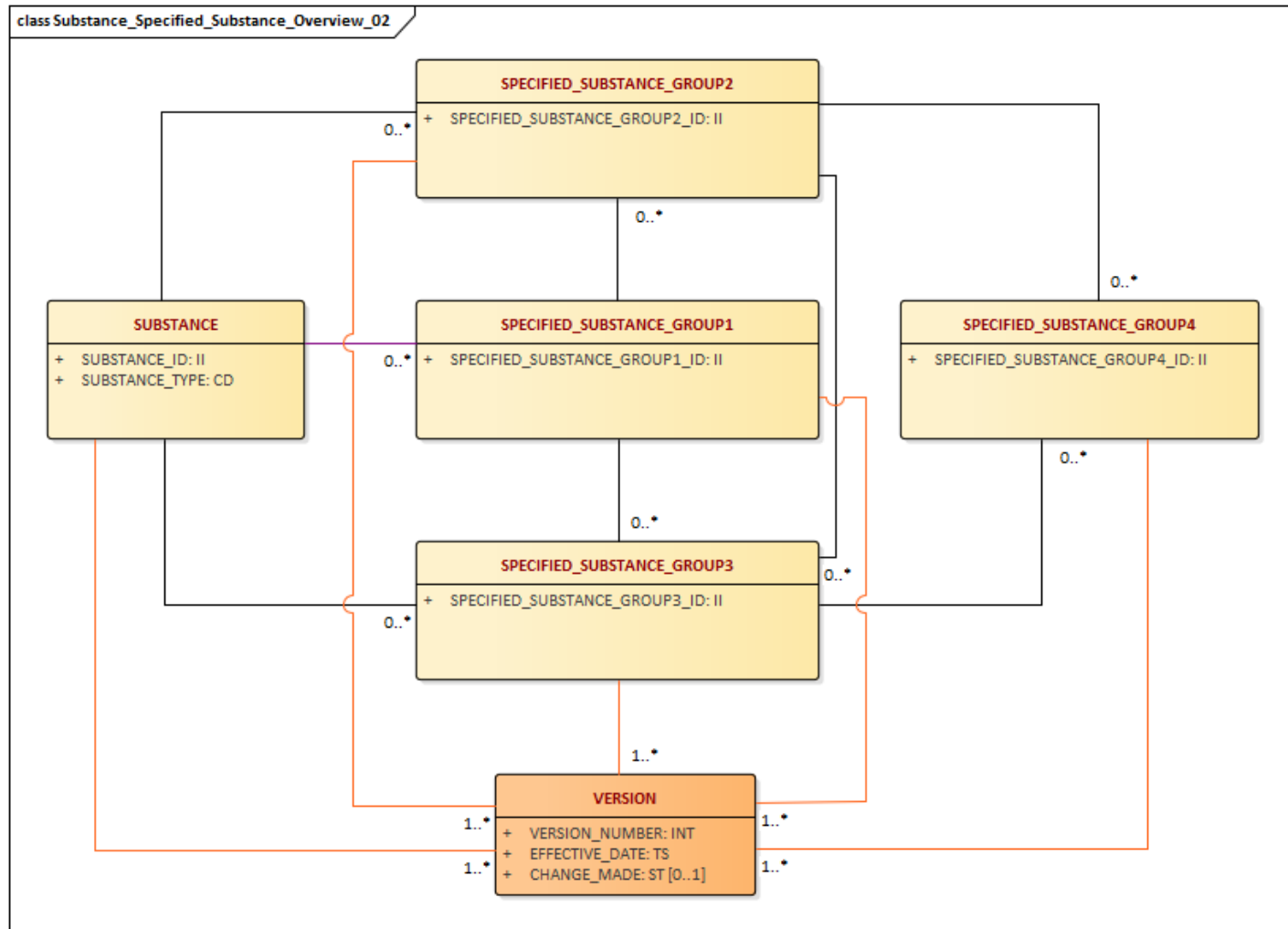
What is the GSRS?

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

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

Registers and defines
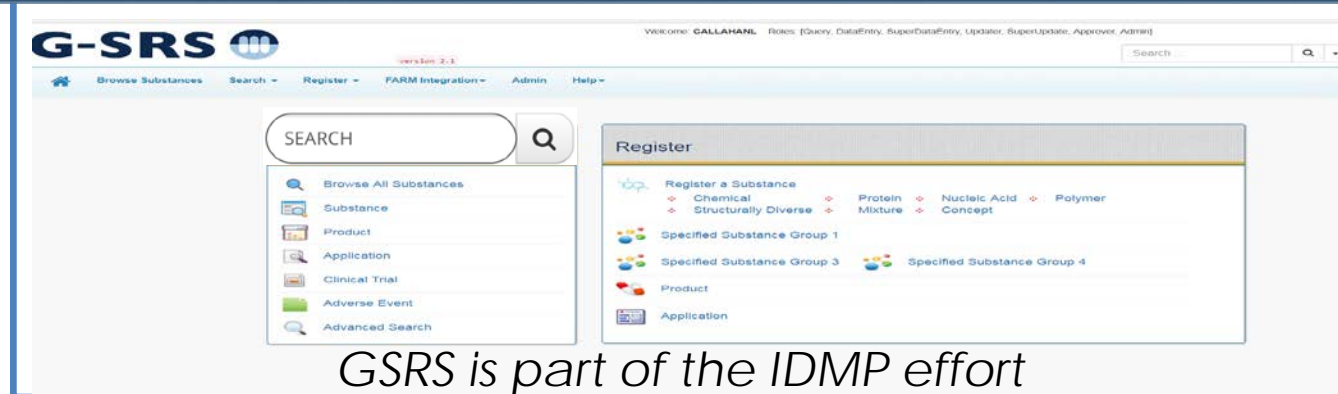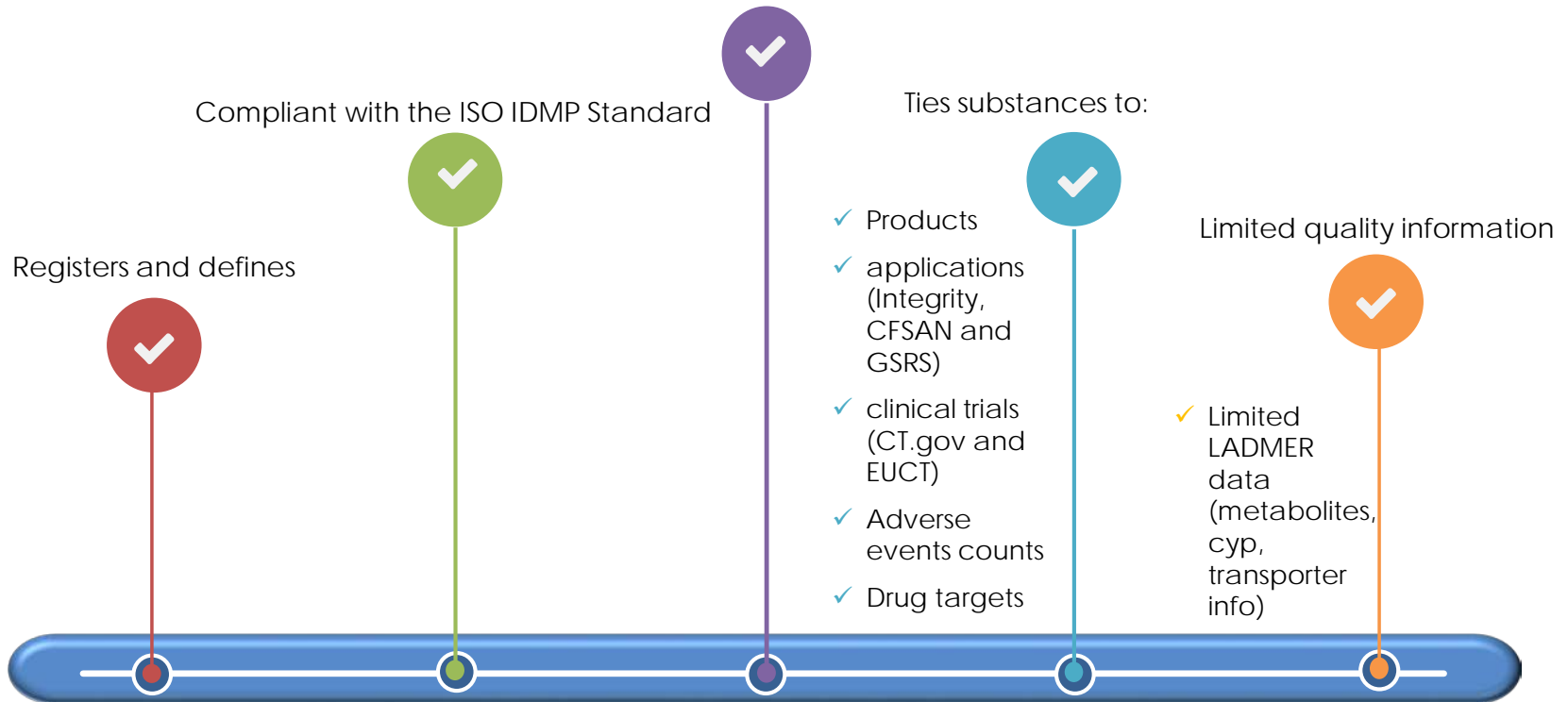
GSRS is part of the IDMP effort

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Global Substance Registration System

GSRS

- Global marketplace for ingredients requires a global system to monitor the global supply chain

- A Global Repository of Regulatory Information and Data on Ingredients (Shortages, substandard and counterfeit ingredients, coordinate inspections)

- Standard is complex, difficult and expensive to implement

- Data abstraction and curation is very expensive

- Global database means better data, less redundancy, more data, less mapping

GSRS is a Software Application
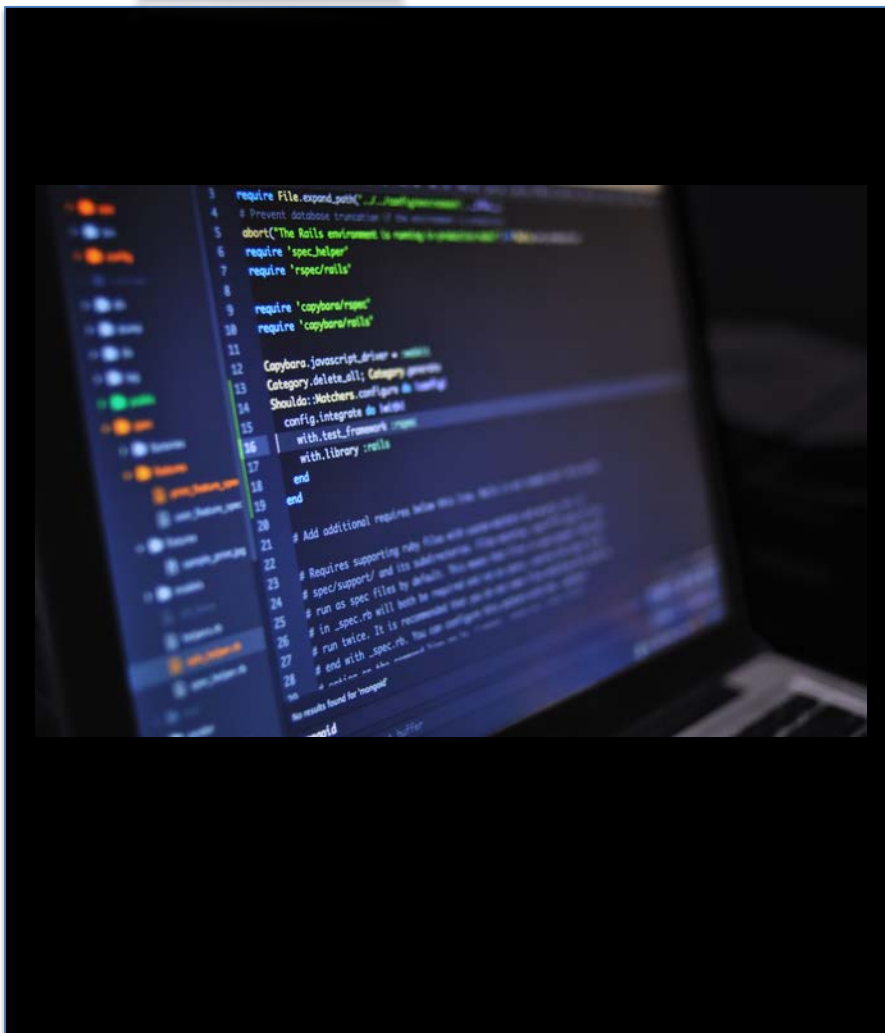
❑ Freely distributable (NCATS version, substance only)

❑ Predominantly open source

❑ Data accessed and entered through an API

❑ Backend Java, Oracle

❑ Works with Oracle, PostgreSQL, MySQL has built-in H2 database

❑ Has native JSON message can be adapted to HL7-FHIR

❑ UI development Angular 1.0, Scala, Play framework

❑ Extensive use of Lucene Indexes

❑ Implemented Substance, Specified Substance Group 1, 2, 3 and part of Specified Substance Group 4

❑ Excel tools for batch updating and queries

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GSRS Software

GSRS

- Works in all modern browsers: IE, Chrome, and Firefox
- System will be distributed with a large set of curated public domain data and updated periodically
  - Over 100,000 substances
  - Over 800,000 names, 800,000 codes (CAS numbers, WHO-ATC, etc)
  - 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

Where we are going?

key milestones

Date	Milestone
Oct 2018	Create robust communications procedures
Dec 2018	Communication Procedures
Jun 2019	Develop distributable Version of FDA software / NCATS to distribute
Oct 2019	Deploy portal for direct substance registration for industry and other regulators
Nov 2019	Modify internal process for substance communication / Modify w/Integrity & FAERS product Dictionary
Jan 2020 – Nov 2020	Begin entering SSG1 data
Oct 2020	Software updates to current version of SOLR
Nov 2020	UI development angular 6
Jan 2021	Develop and deploy R applications for substance based analysis

ZIDOVUDINE

4B9XT59T7S

> Overview

Product, Application, > Clinical Trial, Adverse Event

> Structure

> Names [38]

> Classification [19]

> Identifiers [20]

▼ Product, Application, Clinical Trial, Adverse Event

Product	Application	**Clinical Trial**	Adverse PT	Adverse DME

Clinical Trial US	Clinical Trial EU

Clinical Trial US

📊 Clinical Trial US Export to Excel

Show 10 ▾ entries

Previous **1** 2 3 4 5 … 62 Next

Showing 1 to 10 of 611 entries

Details	NCT Number	Title	Sponsor	Conditions	Outcome Measures
View Details	2004-000390-59-GB	Safety and Efficacy of SCH-417690 in HIV-infected Treatment-Naive Subjects	Schering Plough Research Institute		
View Details	2004-000441-38-IE	Large, Simple Trial Comparing Two Strategies for Management of Anti-Retroviral Therapy (The SMART Study)	National Institute of Allergy and Infectious Diseases, National Institutes of Health		
View Details	2004-000441-38-IT	A Large, Simple Trial Comparing Two Strategies for Management of Anti-Retroviral Therapy	COMMUNITY PROGRAMS FOR CLINICAL RESEARCH ON AIDS		

G-SRS

version 2.3.1 RC1

Welcome: **CALLAHANL**   Roles: [Query, DataEntry, SuperDataEntry, Updater, SuperUpdate, Approver, Admin]

Search ...   Q ▼   Advanced Search

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Browse Substances   Search ▼   Register ▼   FARM Integration ▼   **Admin**   Help ▼   & CALLAHANL

Clinical Trial Europe Details

Eudract Number: 2004-000390-59-GB
Title: Safety and Efficacy of SCH-417690 in HIV-infected Treatment-Naive Subjects
Sponsor Name: Schering Plough Research Institute

| Clinical Trial Europe | **Product (3)** | Medical (1) | Meddra (1) |

Products in Clinical Trial

#	Product Name	Trade Name	Substances	IMP Route of Administration	Pharmaceutical Form	IMP Section	IMP Role
1	N/A		• VICRIVIROC MALEATE	Oral use	Tablet	1	Test
2	Sustiva	Sustiva	• EFAVIRENZ	Oral use	Capsule, hard	2	Comparator
3	Combivir	Combivir	• ZIDOVUDINE • LAMIVUDINE	Oral use	Film-coated tablet	3	Comparator

Comparing Adverse Events in G-SRS

- FDA product dictionary allows coding of all suspect products to be coded to and active moiety

- Counts of adverse events with a given PT term are mapped from product to active moiety

- Linking GSRS to FAERS system will allow structure based analysis

- Use PRR as a metric of association

What is PRR?

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PRR = Proportional Reporting Ratio
is The degree of disproportionate reporting of an AE for a product of
interest compared to this same event for all other products

	Event Y	All other events	
Product X	a	b	a + b
All other products	c	d	c + d
	a + c	b + d	Total

PRR = [a/(a+b)] / [c/(c+d)] → If PRR >> 1 then Event Y is "disproportionately reported for Product X
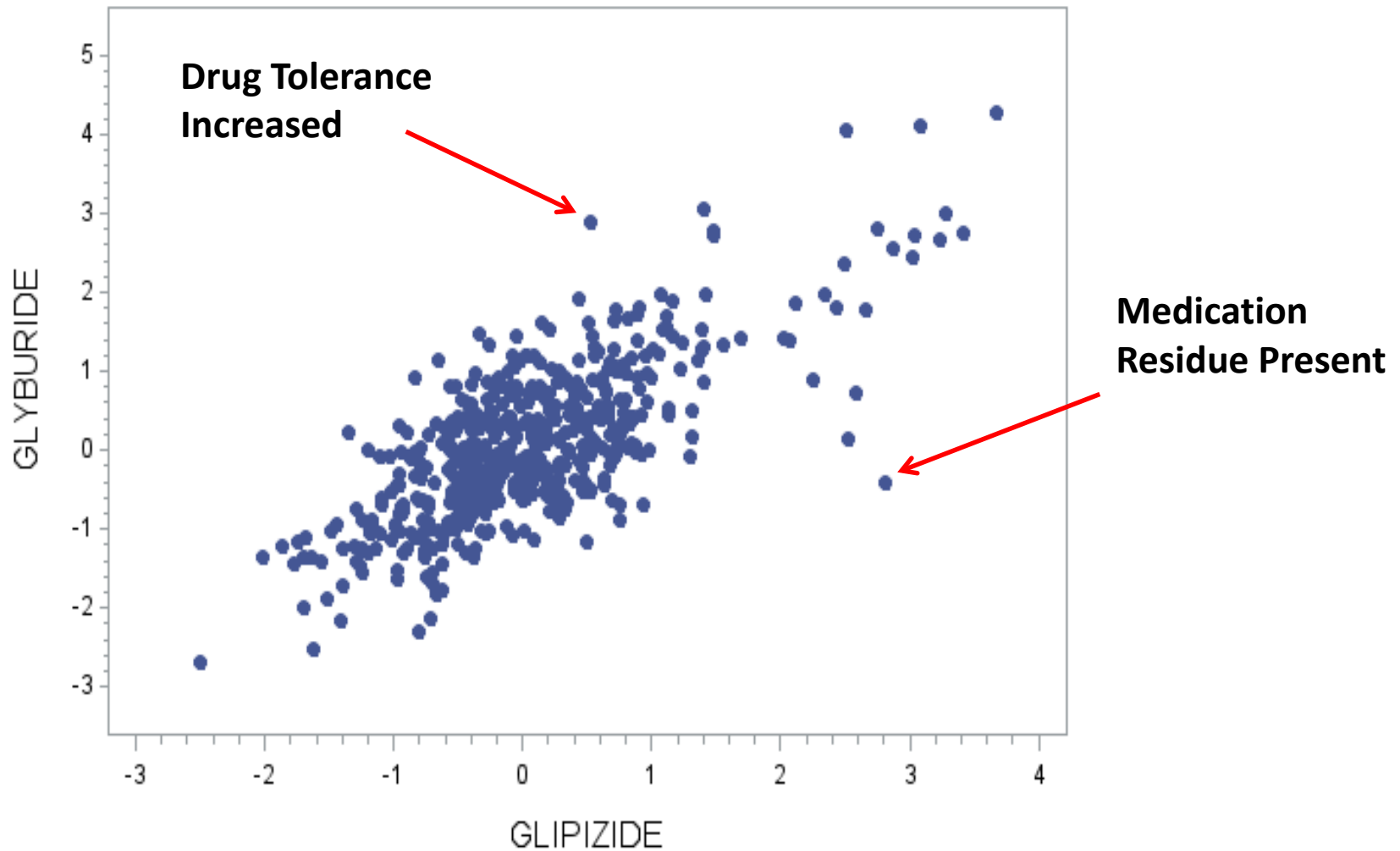
Issues with PRR:
1. It does not adjust for small counts
2. Every report represents a suspicion of an AE related to a product

Lactic Acidosis vs. Hemolytic Anemia Outliers
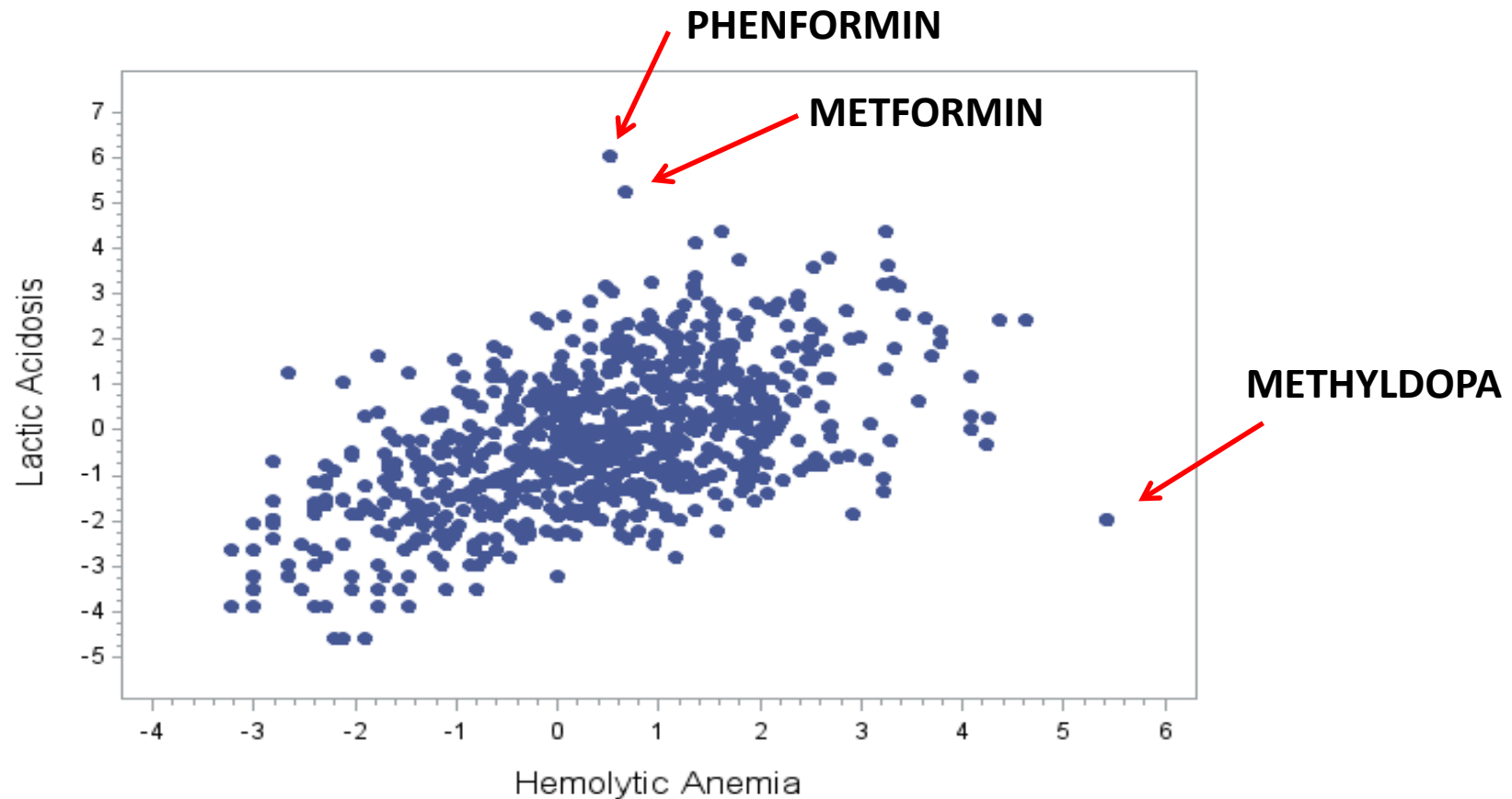
GLYBURIDE vs. GLIPIZIDE Outliers

PT-Terms of the Top 5% PRR -- Sulfonylurea Drugs

GLICLAZIDE (N=2827)

	GLICLAZIDE	PT COUNT
1	HYPOGLYCAEMIA	548
2	LACTIC ACIDOSIS	152
3	METABOLIC ACIDOSIS	119
4	DIABETES MELLITUS INADEQUATE CONTROL	117
5	HYPERKALAEMIA	95
6	HYPOGLYCAEMIC COMA	63
7	PANCREATIC CARCINOMA	41
8	PEMPHIGOID	38
9	HYPERLACTACIDAEMIA	33
10	ACIDOSIS	31
11	DIABETIC METABOLIC DECOMPENSATION	31
12	BRADYPHRENIA	23
13	HEPATITIS CHOLESTATIC	16
14	GASTROINTESTINAL MOTILITY DISORDER	15
15	VOMITING PROJECTILE	15
16	CARDIOACTIVE DRUG LEVEL INCREASED	14
17	DISTRIBUTIVE SHOCK	14
18	HAEMOGLOBIN INCREASED	14
19	HAND DEFORMITY	14
20	JOINT NOISE	14
21	SCOLIOSIS	14
22	BRONCHIECTASIS	13
23	POISONING DELIBERATE	13
24	PULSE ABNORMAL	13
25	HEPATITIS FULMINANT	12
26	LICHEN PLANUS	12
27	NORMOCHROMIC NORMOCYTIC ANAEMIA	12
28	IDIOPATHIC PULMONARY FIBROSIS	11
29	URINARY TRACT DISCOMFORT	10
30	BRADYKINESIA	8
31	DIABETIC HYPEROSMOLAR COMA	8
32	SLEEP TERROR	8
33	FOETAL DISORDER	7
34	JEALOUS DELUSION	7
35	RIGHT VENTRICULAR DYSFUNCTION	7
36	ACUTE LUNG INJURY	6
37	IMPULSE-CONTROL DISORDER	6
38	INHIBITORY DRUG INTERACTION	6
39	ANAEMIA VITAMIN B12 DEFICIENCY	5
40	BODY MASS INDEX DECREASED	5
41	CALCIPHYLAXIS	5
42	DIABETIC KETOSIS	5
43	DIABETIC ULCER	5
44	HALO VISION	5
45	HYPOGLYCAEMIA NEONATAL	5
46	ORBITAL OEDEMA	5
47	SLOW RESPONSE TO STIMULI	5

GLYBURIDE (N=11205)

	GLYBURIDE	PT COUNT
1	HYPOGLYCAEMIA	2671
2	LACTIC ACIDOSIS	244
3	DIABETES MELLITUS INADEQUATE CONTROL	168
4	HYPOGLYCAEMIC COMA	114
5	DRUG TOLERANCE INCREASED	70
6	HYPOGLYCAEMIC UNCONSCIOUSNESS	29
7	SHOCK HYPOGLYCAEMIC	25
8	HYPOGLYCAEMIC ENCEPHALOPATHY	18
9	MUCOSAL EROSION	17
10	CONGENITAL MUSCULOSKELETAL ANOMALY	13
11	OTITIS EXTERNA	13
12	QUADRIPARESIS	13
13	MACROSOMIA	12
14	METABOLIC ALKALOSIS	12
15	SCROTAL OEDEMA	12
16	NEPHROCALCINOSIS	11
17	GRANULOMATOUS LIVER DISEASE	9
18	PULMONARY HYPOPLASIA	9
19	DRUG CLEARANCE DECREASED	8
20	SPINE MALFORMATION	8
21	MICROALBUMINURIA	7
22	BLOOD GLUCOSE	6
23	BLOOD ZINC DECREASED	6
24	TYMPANIC MEMBRANE DISORDER	6
25	HYPERINSULINAEMIA	5
26	INSULIN C-PEPTIDE INCREASED	5
27	PLATELET COUNT NORMAL	5
28	RIB HYPOPLASIA	5
29	TRANSVERSE PRESENTATION	5

GLIPIZIDE (N=9980)

	GLIPIZIDE	PT COUNT
1	HYPOGLYCAEMIA	1358
2	HYPERGLYCAEMIA	705
3	BLOOD GLUCOSE DECREASED	452
4	DIABETES MELLITUS INADEQUATE CONTROL	287
5	GLYCOSYLATED HAEMOGLOBIN INCREASED	195
6	BLOOD GLUCOSE FLUCTUATION	144
7	MEDICATION RESIDUE PRESENT	110
8	HYPOGLYCAEMIC COMA	38
9	GLUCOSE TOLERANCE DECREASED	13
10	ACCIDENTAL POISONING	8
11	BLOOD GLUCOSE	7
12	MEDICAL DEVICE SITE INFECTION	6
13	MICROALBUMINURIA	6
14	STOOL ANALYSIS ABNORMAL	6

CHLORPROPAMIDE (N=1904)

	CHLORPROPAMIDE	PT COUNT
1	HYPOGLYCAEMIA	222
2	INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION	31
3	JAUNDICE CHOLESTATIC	31
4	CORONARY ARTERY BYPASS	21
5	CATARACT OPERATION	11
6	LEG AMPUTATION	10
7	TOE AMPUTATION	9
8	VENOUS OCCLUSION	9
9	DIABETIC COMPLICATION	8
10	DIABETIC COMA	7
11	ANGIOPLASTY	6

TOLAZAMIDE (N=1223)

	TOLAZAMIDE	PT COUNT
1	HYPERGLYCAEMIA	137
2	HYPOGLYCAEMIA	116
3	AMBLYOPIA	70
4	JAUNDICE CHOLESTATIC	15
5	INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION	14
6	GANGRENE	11
7	KETOACIDOSIS	11
8	PATHOLOGICAL FRACTURE	10
9	GASTROINTESTINAL CARCINOMA	8

Working Collaboratively

GInAS Meeting

- To get the software and data from NCATS
  - https://tripod.nih.gov/ginas
- Fifth Meeting November 16, 2018
- At USP 12601 Twinbrook Parkway
  - Rockville Maryland 20852
- Free and Open to Public
- To Get on the GInAS Notification List
  - Contact Danny Katzel at
  - Daniel.Katzel@nih.gov

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