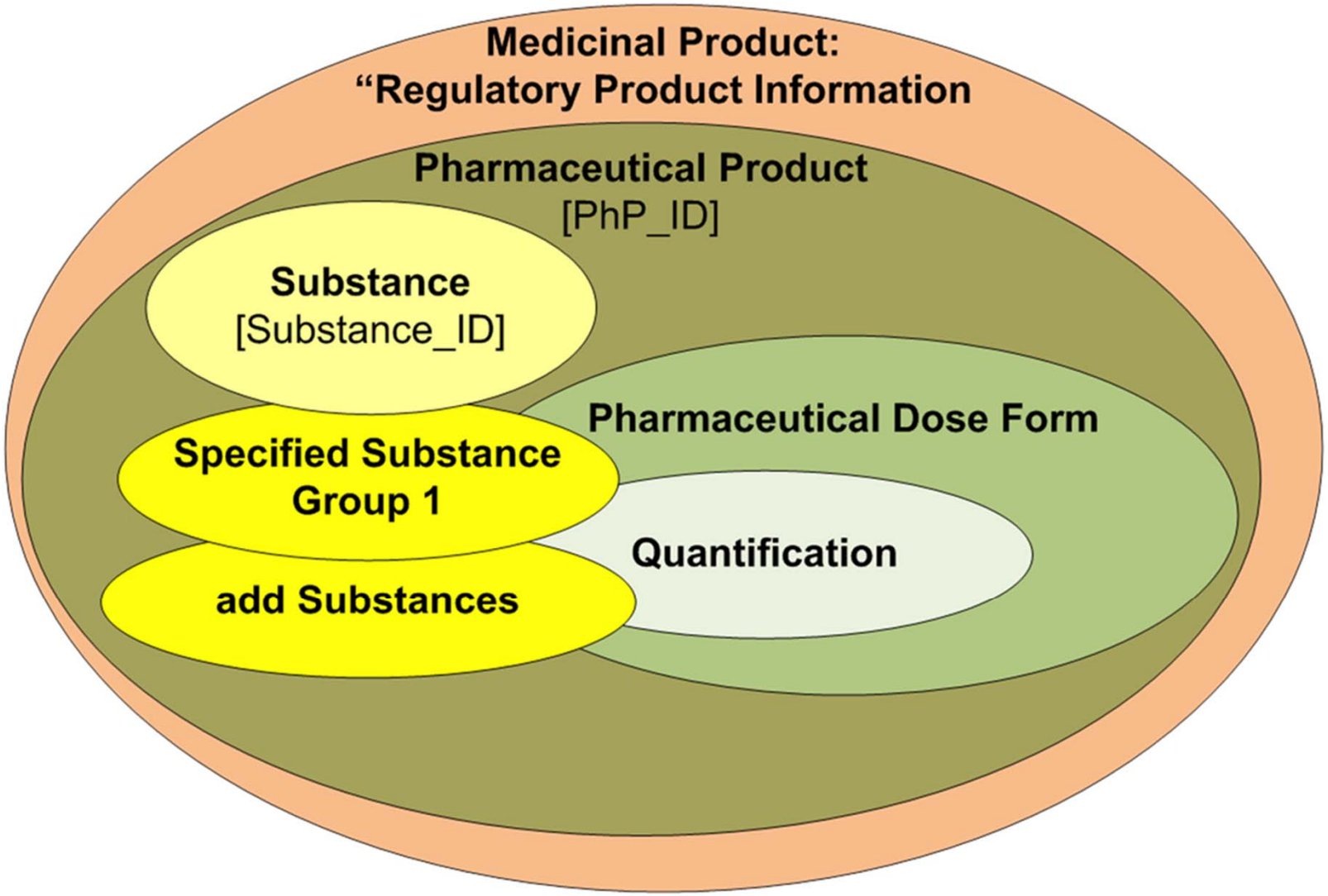
# Substances and the ISO Identification of Medicinal Product (IDMP) Standards

# Substances In Regulatory Practice

- Substances form the essence or basis of every product
- Interactions between substances are responsible for nearly all pharmacological activity.
- Substances are a lynchpin on which to organize regulatory information but many regulatory agencies only identify/define them by names or codes
- Names and codes are not sufficient to fully define or relate substances to one another, clinical trials, products or adverse events.
- Regulatory agencies need to be able to define substances scientifically in an unambiguous manner
- ISO 11238 (IDMP) provides a framework for defining all substances and related regulatory information

# IDMP Model


Medicinal Product:
"Regulatory Product Information
Pharmaceutical Product
[PhP_ID]
Substance
[Substance_ID]
Pharmaceutical Dose Form
Specified Substance
Group 1
Quantification
add Substances

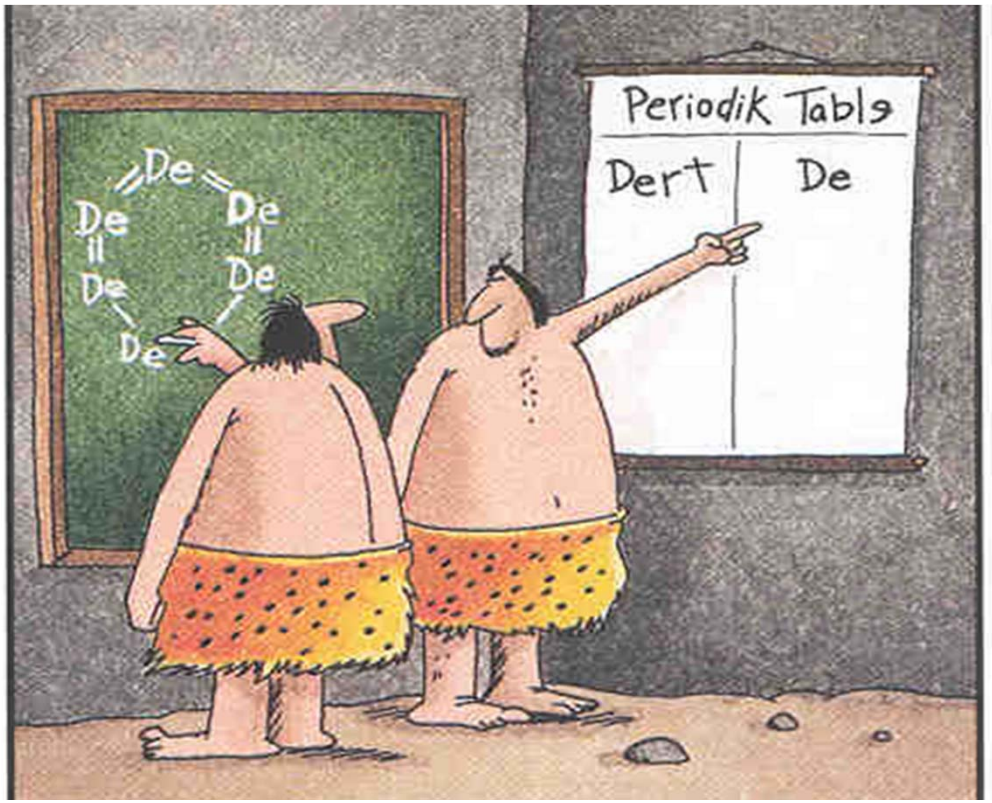
# What is a Substance

– **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**

# 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**

# What is a Substance




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

# What is a Substance: ISO 11238

- 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

# Substances (ISO IDMP)

- Five groups of elements are used to describe single substances.
  - 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
  - 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,
  - Structurally Diverse Substances
    - Taxonomic, anatomical, fractionation, physical properties, modifications

# Need for Specified Substance

- 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

- To be implemented with the GInAS Application
- An explicit grouping of elements and concepts put forward in ISO IDMP
  - Group-1 Multiple substance materials (Coatings, Colorants, Flavorants); Physical Form; Extracts
  - 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.

# Need for a Global Database

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

# GInAS Goals

- To 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;
- To develop and distribute a global identifier for every substance in medicinal products and clinical trials;
- To distribute an information system for both regulators, companies and  other interested parties to facilitate registration that is compliant with ISO 11238;
- Produce a Unique Identifier for each substance (UNII)

# GInAS Vision

- Substance should eventually be registered prior to any submission
- An Unique Identifier should be permanently associated with each registered substance
- UNIIs will be used 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)

# GInAS History

- Grew Out of a Meeting Hosted by USP and NCATs (NIH) in February 2013
- 2nd meeting hosted in the CBG in Netherlands (September 2013)
- 3rd meeting hosted at USP (June 2014)
- Uses Software Developed by NIH/NCATs
- GInAS Prototype hosted at Health Canada
- Canadian, Dutch, German, Japan, Swiss, and US regulators, EDQM and USP have involved in the development of the system and standard
- Software can be deployed locally (Each regulator/company 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 Data Integration

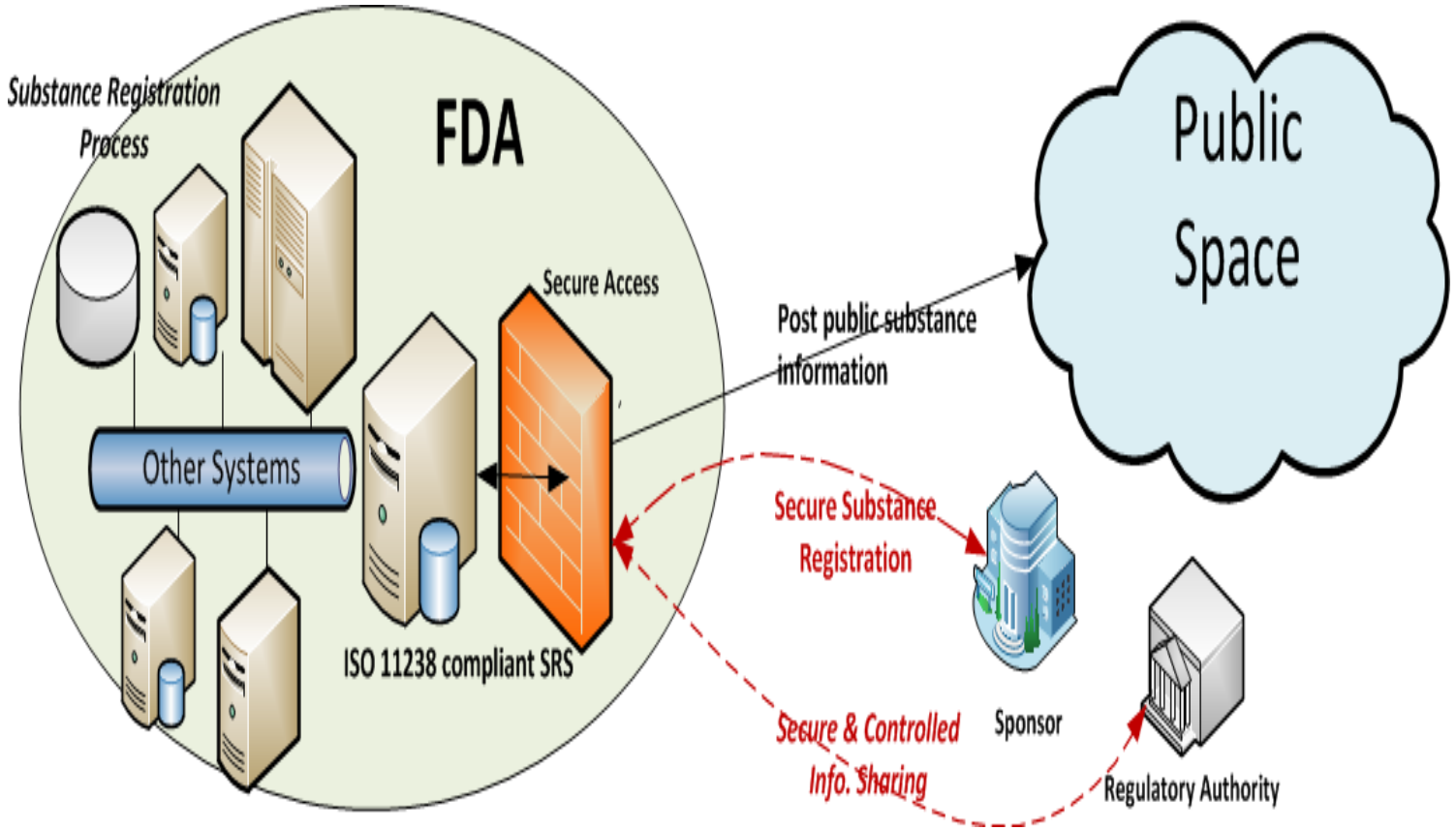
- Data That Should be Linked Substances
  - INDs, NDAs, BLAs, CFR's; Orphan Drug Applications
  - Products that Contain Each Substance
  - Pharmacological Classification
  - Active Moieties, Related Moieties and Salts
  - LADMER
    - Metabolites
    - Metabolic Enzymes, Transporters, and Effects
    - Drug target (therapeutic and other), type of interaction
    - Solubility and Permeability (BCS)
    - Protein Binding
  - Biomarkers
  - Impurities and Related Substances

# GInAS System

- Data entered through an API
- Predominantly open source
- Web-based
- Complies with the 11238 substance model
- Freely distributable
  - Regulators
  - Companies
- Database Neutral
- Works with a number of web applications server
  - Glassfish, Tomcat, Weblogic
- Java-based
- Restful Interface
- Lucene Indexing

# How Can GInAS Work

– **GINAS and FDA**



# Progress so Far

- Prototype system deployed at Health Canada
  - http://ginas.hres.ca/ginas/
  - User: tester
  - Password: ginastest
- First Version of Modules for all five types of substances, mixtures and group 1 specified substance completed.
- System is being deployed within FDA Environment
- NCATS provided a distributable system at June meeting at USP.
- Second Version of System Distributed February 2015
- Migration of some public data has already occured

# GInAS

- Health Canada Prototype
  - http://ginas.hc.ircan-rican.org/ginas/
  - User: tester
  - Password: ginastest
- Version changes often
- For Further Information Contact
  - Noel Southall  southalln@mail.nih.gov
  - Larry Callahan lawrence.callahan@fda.hhs.gov
- System presentations and functional designs
- https://tripod.nih.gov/pub/ginas
- Next meeting/workshop will be held in Summer 2015 and will feature a production-ready release

# Acknowledgements


- FDA Team
  - Yulia Borodina, Larry Callahan, Randy Levin, Mitch Miller, Archana Newatia, Frank Switzer
- Foreign Regulatory Participants
  - Thomas Balzer (BFarM)
  - Herman Diederik, Marcel Hoefnagel, Bert Kroes, Ciska Matai (MEB)
  - Takeshi Misu, Izumi Oba (PMDA)
  - Vik Srivastava (Health Canada)
  - Philipp Weyerman (Swiss Medic)
- Kew Gardens
  - ,Bob Alkins, Elizabeth Dauncey
- USP
  - Fouad Atouf, Patrick Lukaly Andrzej Wilk
- NCATS Team
  - Dammika Amugoda, Ajit Jadhav, Trung Nguyen, Tyler Peryea, Noel Southall
- IDMP Members
  - Paulo Alcini Sabine Brosch, Tim Buxton, Ilaria Del Seppia, Telonis Panagoitis (EMA)
  - Ta-Jen Chen, Vada Perkins, Mary Ann Slack (FDA)
  - Pam Cafiero, Surenda Gokhale, William Gregory, Barry Hammond, Manabu Inoue; Kostas Kidos, Andrew Marr, Wolfgang Spiegl (Industry)
  - Michel Trottier, V(Health Canada)
  - Paul Houston (EMA/CDISC)
  - Claude Coune, Chris Jarvis (EDQM)
  - Excipient Industry
  - Dave Schonecker, Katherine Ulman