

# Building a Global Framework for the Exchange of Drug Substance Information

NOEL SOUTHALL  
THE NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES  
NATIONAL INSTITUTES OF HEALTH

APRIL 23, 2015

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## U.S. Identifies Tainted Heparin in 11 Countries

By GARDINER HARRIS

Published: April 22, 2008

WASHINGTON — A contaminated blood thinner from China has been found in drug supplies in 11 countries, and federal officials said Monday they had discovered a clear link between the contaminant and severe reactions now associated with 81 deaths in the United States.

But a Chinese official disputed the assertion that the contaminant found in the drug, heparin, caused any deaths and insisted that his country's inspectors be allowed to inspect the American plant where the finished heparin vials were made. He said any future agreement to allow American inspections of Chinese firms should be reciprocal.

"We don't have a strong evidence to show that it is heparin or its contaminant that caused the problem," said the official, Ning Chen, second secretary at the Chinese Embassy.

Mr. Chen said that illnesses associated with contaminated heparin had occurred only in the United States, which he said suggested that the problem arose in this country.

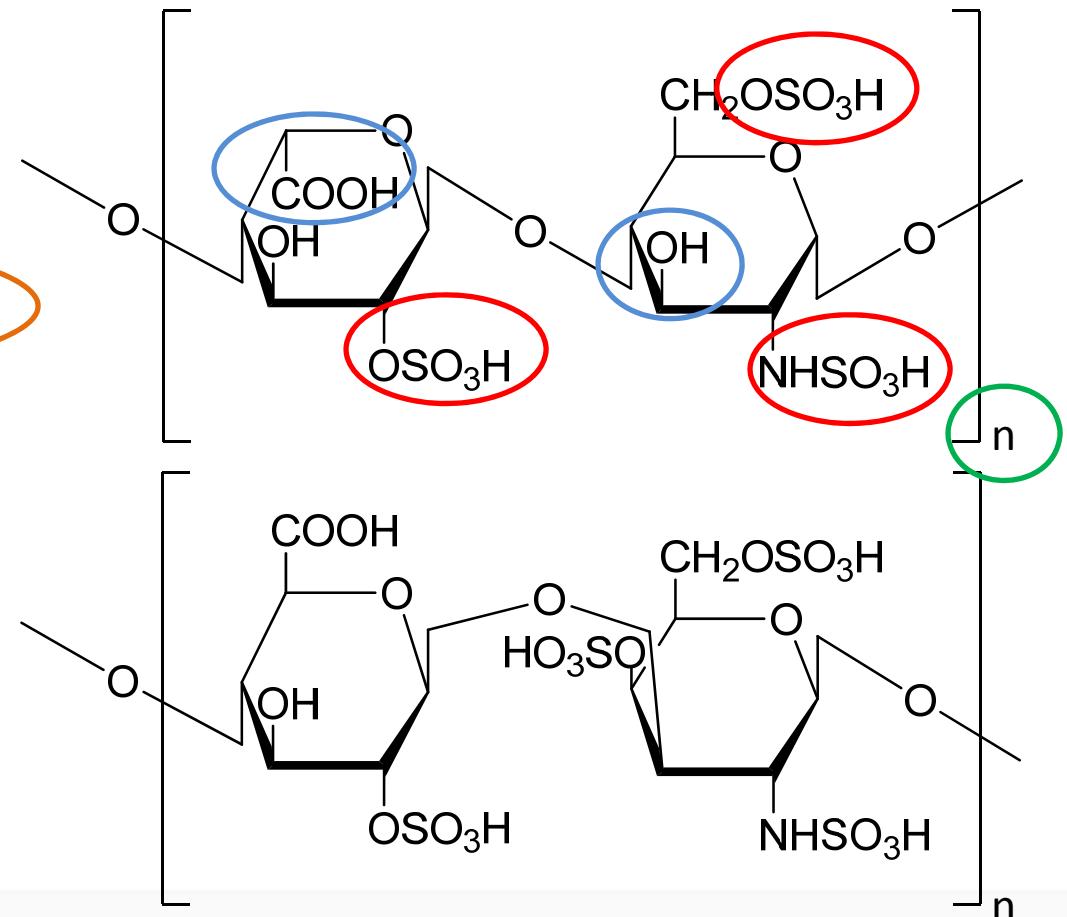
Dr. Janet Woodcock, director of the [Food and Drug Administration](#)'s drug center, said that German regulators uncovered a cluster of illnesses among [dialysis](#) patients who took contaminated heparin. She said Chinese officials had conceded that heparin produced in their country contained a contaminant, though they say it was not connected to the illnesses.



# Heparin Structure

Pharmaceutical-grade heparin is derived from mucosal tissues of slaughtered meat animals such as porcine (pig) intestines or bovine (cattle) lungs.

Heparins vary in their **species of origin** and by the **number, identity of sugar cores**, their dispersity, and **degree of sulfation**.



## Drug Facts

### Active ingredient (in each tablet)

Omeprazole 20 mg.

### Purpose

Acid reducer

**Use**

- treats frequent heartburn (occurs 2 or more days a week)
- not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect

### Warnings

**Allergy alert:** Do not use if you are allergic to omeprazole

**Do not use** if you have trouble or pain swallowing food, vomiting with blood, or bloody or black stools. These may be signs of a serious condition. See your doctor.

### Ask a doctor before use if you have

- had heartburn over 3 months. This may be a sign of a more serious condition.

**Other information** If you have questions about this medicine, ask your doctor or pharmacist.

## Drug Facts

### HPUS active ingredients

Equal volumes of each ingredient in 10X, 30X and LM1 potencies.

Aethusa cynapium, Calcarea carb, Cucurbita pepo, semen, Gambogia, Histaminum hydrochloricum, Hydrastis, Lycopodium, Nat carb, Nitricum ac, Nux vom, Ovi gallinae pellicula, Phos, Pulsatilla, Sulphur.

### Uses for temporary relief of symptoms:

- headache ■ irritability ■ stomach cramps and indigestion ■ nausea ■ gas, heartburn, and bloating ■ constipation ■ diarrhea

## Drug Facts (continued)

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away. (1-800-222-1222)

### Directions

- for adults 18 years of age and older

- this product is for 14 days

- it may take 1 to 4 days for full relief of symptoms

### 14-Day Course

- swallow 1 tablet in the morning

- take every 12 hours

- do not take more than 1 tablet at a time

- do not use for longer than 14 days without consulting your doctor

- swallow whole, not crushed

Repeated 14-day courses

■ may repeat course if symptoms return

■ do not take more than 2 courses in 4 months

■ children under 18 years of age: children may take 1 tablet daily

■ Repeated 14-day courses

■ may repeat course if symptoms return

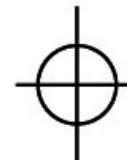
■ do not take more than 2 courses in 4 months

■ children under 18 years of age: children may take 1 tablet daily

### Information

Read the directions and warnings before use. Keep the carton. It contains important information. Store at 20-25°C (68-77°F) and protect from moisture.

**Active ingredients** camaba wax, ferric oxide red, ferric oxide yellow, hypromellose, hypromellose acetate succinate, lactose monohydrate, monoethanolamine, propylene glycol, sodium lauryl sulfate, sodium starch glycolate, sodium stearate, sodium stearyl arate, talc, titanium dioxide, triethyl citrate



Only if safety seal is intact.



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# Substance identification in regulatory practice

- Repeated substance requests inefficient
- Educate stakeholders on defining elements
- Assignment of unique identifiers
- Identifiers coordinate regulatory activity

# Prospect for a global substance database

- Enable global pharmacovigilance
- Global marketplace for ingredients requires a global system to monitor the supply chains
- Establish a consortium of regulators
- Distribute to both regulators and companies
- **Common System and Common Content results in a Better System and Better Content**

INTERNATIONAL  
STANDARD

ISO  
11238

First edition  
2012-11-01

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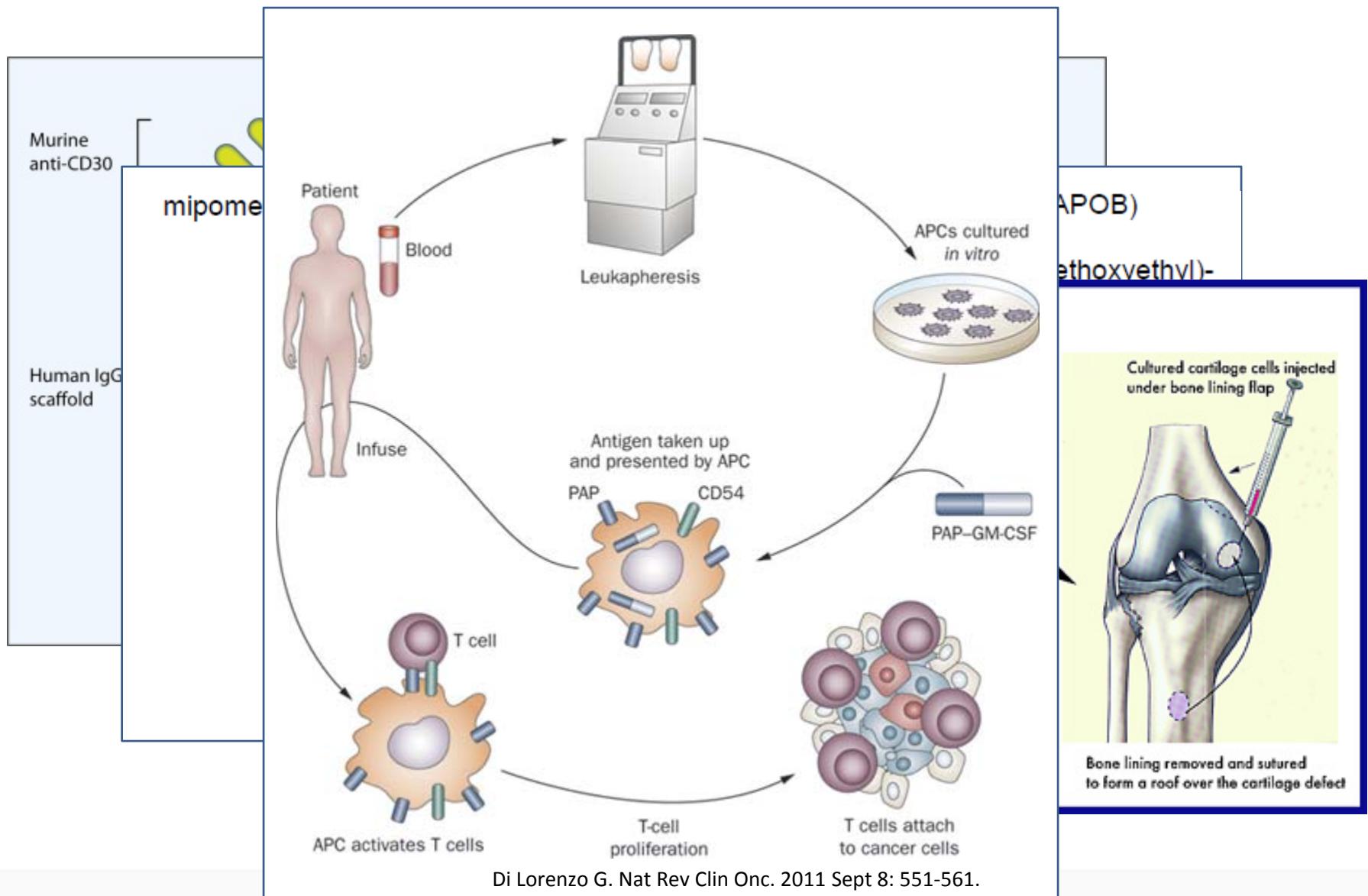
**Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated information on substances**

*Informatique de santé — Identification des médicaments — Éléments de données et structures pour l'identification unique et l'échange d'informations réglementées concernant les substances*



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National Center for Advancing  
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9800 Medical Center Drive, MSC 3370  
Bethesda, MD 20892-3370  
PH (301) 217-5757  
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### Development of a Freely Distributable Data System for the Registration of Substances and Related Information Based on ISO 11238

Monday, February 4 – Thursday, February 7 2013

USP 12601 Twinbrook Parkway, Rockville MD 20852

<http://www.usp.org/support-home/general-information/directions-usp-headquarters>

#### Meeting Agenda

Monday, February 4th 9:00am-5:00pm

- 9-9:20 Welcome and Introduction – Larry Callahan [FDA]
- 9:20-9:50 NCATS overview - Noel Southall [NIH/NCATS]
- 9:50-10:40 Overview of the IDMP – Larry Callahan [FDA]
- 10:40-11:00 Break
- 11:00-11:30 Content of the Current FDA Substance Registration System – Frank Switzer [FDA]
- 11:30-12:00 Functional Design for a Dutch Implementation of ISO 11238 – Herman Diederik and Ciska Matai [Netherlands MEB]
- 12:00-1:00 Lunch
- 1:00-1:45 Current German Regulatory Substance Information – Thomas Balzer [BfArM]



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- SMEs passionate about the project
- Scope was large
  - Pieces of a solution available
  - Expert opinion needed
- Open development was possibility
  - Many open source components available
  - Commercial pieces
- No firm commitments of resources



# Why we are working with NCATS

- Standard is Complex
  - No COTS Software Available
  - Developing compliant usable software will require a great deal of continuous input from substance SMEs
- In-depth expertise; Mutual interest
  - Developers also have core business knowledge
  - Chemistry, Biotechnology
  - FDA has developed content that can serve NCATS mission
- NCATS can provide software and content to enhance the FDA system
  - Local and within HHS. No formal contracting or extensive requirement gathering needed, no contract mods, little bureaucracy
  - Continuous agile development; continuous development of content
  - Potentially more cost-effective
- Software developed can be freely distributed
  - No barrier to implementation



# NCATS goals for FDA collaboration

- ‘Battle-test’ in-house software platform for use in regulator production setting
- Publish public regulatory data
  - ‘gold standard’ for the definitions of drug substances



Chemicals



Proteins



Nucleic Acids



Polymers



Structurally  
Diverse



The **G**lobal **I**ngredient **A**rchival **S**ystem provides a common identifier for all of the substances used in medicinal products, utilizing a consistent definition of substances globally, including active substances under clinical investigation, consistent with the ISO 11238 standard.



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<http://tripod.nih.gov/ginas>

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# Working Collaboratively



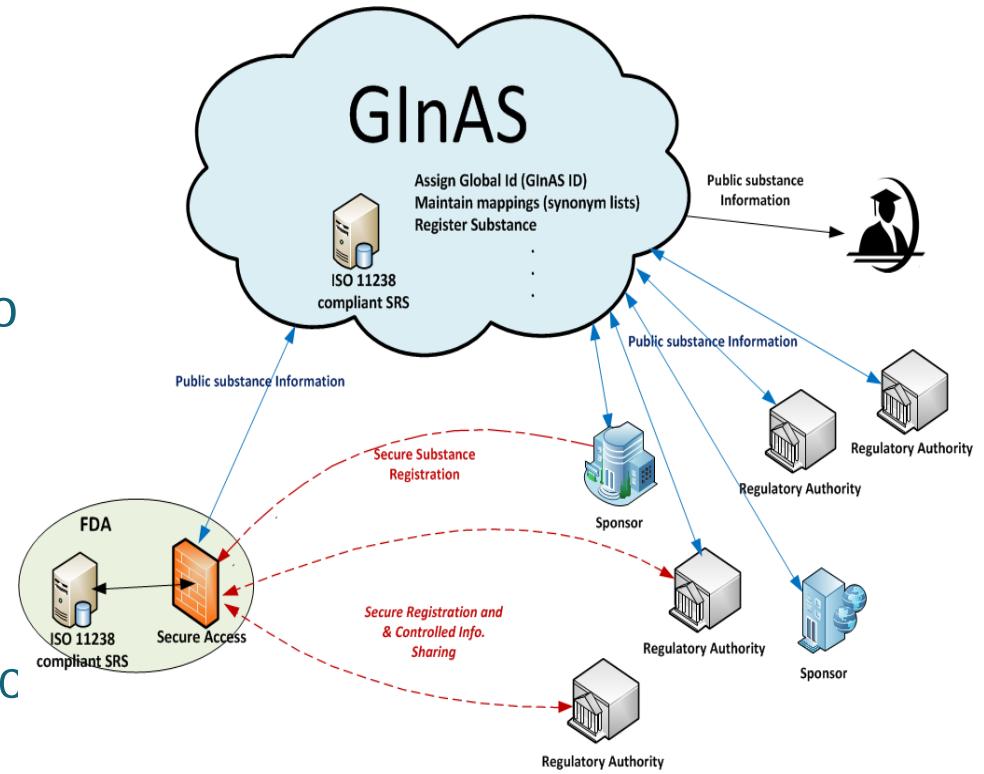
# ginas Software Implementation Goals

- Self-contained and modular
  - Run entirely on a desktop or access remotely
  - Freely distributable, predominantly Open Source
- Well-defined data access application programming interface (API)
  - GInAS or third-party clients / internal business processes
- Fine-gained security model
  - Access control for every piece of information
  - Audit trail of all data fields
- Configurable “business rules”, e.g. standardizing structures
- All data is referenced; primary sources should be retained (e.g., PDF's, MS spectra, images)
- System will be distributed with a large set of public domain data and updated periodically



# Stakeholders

- All GInAS participants comply with ISO 11238 for Substance Identification
- Each Regulatory Authority can maintain its own Substance Registration (minimum impact to its regulatory process)
- Regulatory Authorities can establish agreements with each other for substance registration & maintenance if they choose
- GInAS provides a source of public data to stakeholders



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# Development Strategy

- Core software developers with intimate domain knowledge and experience with regulatory process
- Iterative development cycle
  - Functional requirements through in-depth case studies with users/experts  
[http://tripod.nih.gov/pub/iso11238/case\\_studies/](http://tripod.nih.gov/pub/iso11238/case_studies/)
  - Discussion and feedback from case studies drive design and development
  - Evaluate implemented features with users through usability studies
  - ISO 11238 core standard; detailed system description/requirements necessitate a working implementation
- Scientific competency not process or programming prowess

Home

Search

Register ▾

Download

Report a Bug

Aspirin



Show All

25

Substances

25

Specified Substances

0

Substance Types (1)

CHEMICAL

25

Moieties (22)

ASPIRIN

16

[Al]

3

[Ca]

3

LYSINE, DL-

2

LYSINE

2

[CH<sub>4</sub>N<sub>2</sub>O]

2

(+ 17 more)

2

Query

UNII: R16C05Y76E

ASPIRIN

UNII: E33TS05V6B

ASPIRIN ALUMINUM

UNII: E62HT5S2E9

ASPIRIN SODIUM

UNII: WOD7W0DGZS

ASPIRIN CALCIUM

UNII: 2JJ274J145

RACEMIC  
ASPIRIN DL-LYSINE

UNII: 5DR11472UJ

ASPIRIN COPPER

UNII: XAN4V337CI

ABSOLUTE  
ASPIRIN LYSINE

UNII: 4995924SMK

ASPIRIN MAGNESIUM

### Substance

## Specified Substance

## Concept

## Product

Mixture

## Chemical

Protein

Nucleic Acid

Polymer

#### Structurally Diverse

er name or smiles (e.g. Ibuprofen)

Search

## Chemical Structure



## Nucleic Acid Sequence



### Amino Acid Sequence



Home

Search

Re

Names

Stru

Legend: This name

ASPIRIN

## Fetch Structure by Name



A Tyler Peryea

Log Out

### Suggestions by name:

#### Source

any

2

NCI

1

PubChem

1

#### Name

any

2

ASPIRIN

2

#### Structure

any

2

NLRCSR5JQVWT

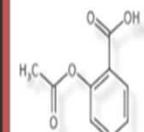
2

Next



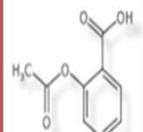
Add Name

NCI



ASPIRIN

PubChem



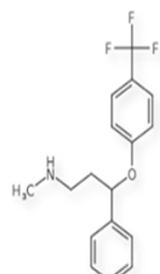
ASPIRIN

Choose

Choose

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[Previous](#)[Cancel](#)[Export](#)[Import](#)[Next](#)**Substance**

HCl

Chemical Substance

There are 2 moieties in this structure:

**UNREGISTERED**

HCl

Moiety 1  
x1**UNREGISTERED**Moiety 2  
x1**Stoichiometry**[Fixed](#)[Variable](#)**Chemical Details**

Defined Stereocenters : 0

Total Stereocenters : 1

E / Z Centers : 0

Charge : 0

**Structure References**

USP

asdasd

2014-09-24T

[Add New Reference](#) **Molecular Formula :**

C17H19ClF3NO.CH.C17H1

**Molecular Weight :**

345.787

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## Impact

- Drug Safety
- Drug Shortages
- Counterfeiting
- Review Process

**“This is an error prone  
and time demanding  
process ... but with ginas,  
clean error-free records  
can be easily generated.”**

-Dammika Amugoda-Kankanange (FDA)

**We can make it faster, cheaper and easier to review new drugs,  
identify safety concerns, and cooperate with the worldwide  
health community.**



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<http://tripod.nih.gov/ginias/>

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# Additional points

## 1. ginas project

Discussion forum for technical specification

G-SRS (Global-Substance Registration System) software

Structure/governance

Substance registration process

## 2. Goals for the meeting and the future

Update and align efforts currently underway by implementation guide participants, FDA, EMA, industry, software developers, and other important stakeholders



# Acknowledgements

## U.S. Food and Drug Administration

Yulia Borodina	Archana Newatia
Larry Callahan	Vada Perkins
Ta-Jen Chen	Mary-Ann Slack
Ramez Ghazzaoui	Frank Switzer
Elaine Johansen	Alex Welsch

## U.S. Pharmacopeial Convention

Fouad Atouf	Andrej Wilk
Tina Morris	

## Federal Institute for Drugs and Medical Devices (Germany)

Thomas Balzer

## SwissMedic

Philipp Weyermann

## European Directorate Quality of Medicines

Christopher Jarvis

## NIH/NCATS

Chris Austin	Tyler Peryea
Ajit Jadhav	Tim Sheils
Dac-Trung Nguyen	Tongan Zhao

## Medicines Evaluation Board (Netherlands)

Herman Diederik	Burt Kroes
Marcel Hoefnagel	Ciska Matai
Joris Kampmeijer	

## Health Canada

Vikesh Srivastava

## Royal Botanic Gardens, Kew (UK)

Bob Allkin	Elizabeth Dauncey
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## Dow Corning

Katherine Ulman

## European Medicines Agency

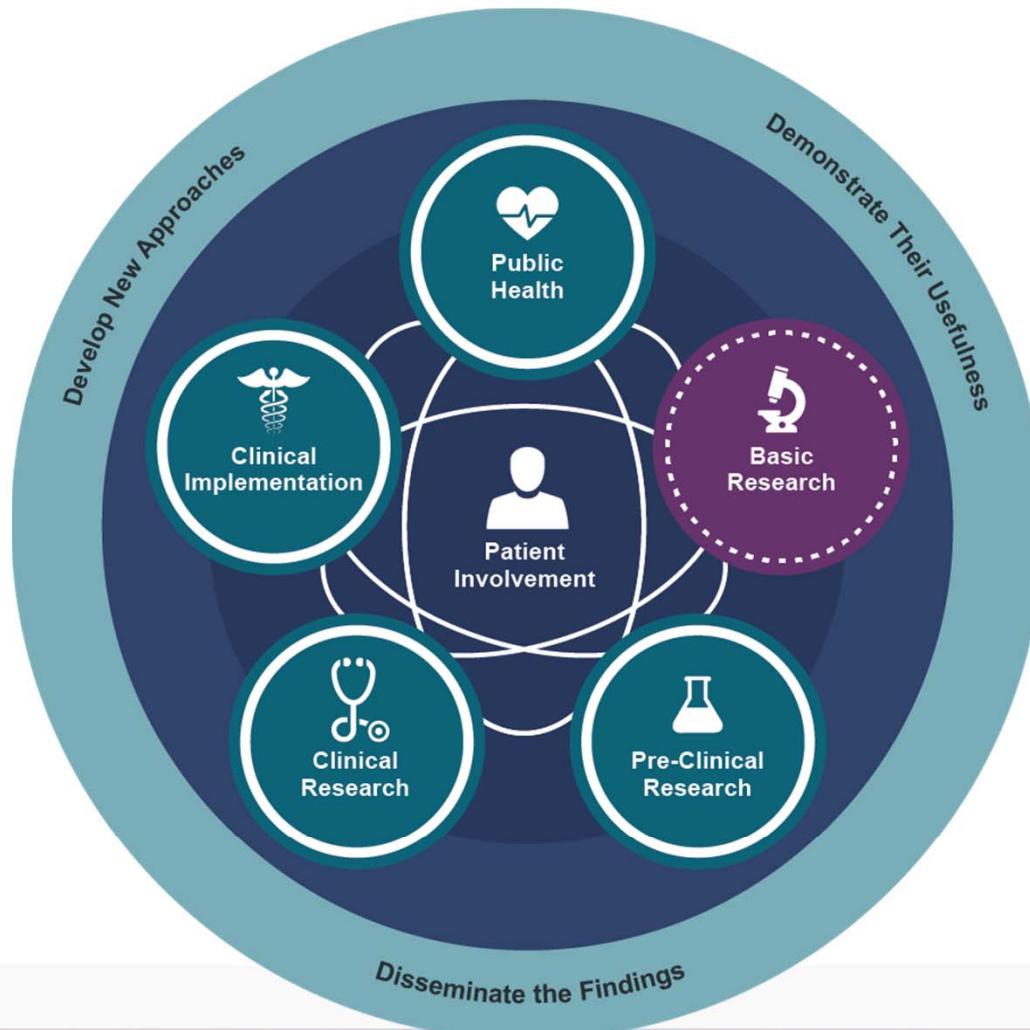
Paolo Alcini	Telonis Pangiotis
Sabine Brosch	Ilaria Del Seppia

## Uppsala Monitoring Centre / WHO

Malin Jakobsson



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**Thursday, April 23**

**2:00 FEATURED PRESENTATION: OPENFDA:  
FDA'S MOST INNOVATIVE CLOUD-BASED BIG  
DATA AND ANALYTICS PLATFORM**

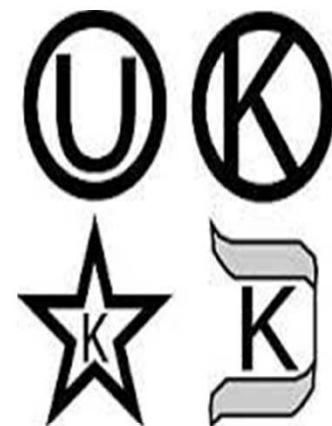
*Roselie A. Bright, Sc.D., MS, PMP, Program Manager, Office of Information Management and Technology, Office of Informatics Technology and Innovation, Office of Operations, Office of the Commissioner, U.S. Food And Drug Administration (FDA)*

OpenFDA was the first innovation created by Taha Kass-Hout, M.D., MS, upon joining FDA as the first Chief Health Information Officer in March 2013. OpenFDA was launched on June 2, 2014, allowing software developers, researchers and the public to tap into adverse events for drugs and medical devices; recalls, for drugs, devices and foods; and labeling for products on the market.



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Dairy



Wheat



Fish or  
Seafood



Nuts or Nut  
Products



Egg or Egg  
Products



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## Drug Facts

### Active ingredient (in each tablet)

Omeprazole 20 mg.

### Purpose

Acid reducer

**Use**

- treats frequent heartburn (occurs 2 or more days a week)
- not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect

### Warnings

**Allergy alert:** Do not use if you are allergic to omeprazole

**Do not use** if you have trouble or pain swallowing food, vomiting with blood, or bloody or black stools. These may be signs of a serious condition. See your doctor.

### Ask a doctor before use if you have

- had heartburn over 3 months. This may be a sign of a more serious condition.

**Other information** If you have questions about this medicine, ask your doctor or pharmacist.

## Drug Facts

### HPUS active ingredients

Equal volumes of each ingredient in 10X, 30X and LM1 potencies.

Aethusa cynapium, Calcarea carb, Cucurbita pepo, semen, Gambogia, Histaminum hydrochloricum, Hydrastis, Lycopodium, Nat carb, Nitricum ac, Nux vom, Ovi gallinae pellicula, Phos, Pulsatilla, Sulphur.

### Uses for temporary relief of symptoms:

- headache ■ irritability ■ stomach cramps and indigestion ■ nausea ■ gas, heartburn, and bloating ■ constipation ■ diarrhea

## Drug Facts (continued)

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away. (1-800-222-1222)

### Directions

- for adults 18 years of age and older

- this product is for 14 days

- it may take 1

- relief of sympto

### 14-Day Course

- swallow 1 tab

- the morning

- take every 4

- do not take

- do not use

- your doctor

- swallow wh

### Repeated 14-

- may re

- not take

- every 4 mo

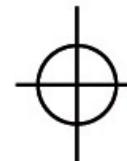
- even under

- children may

### Information

Read the directions and warnings before use. Open the carton. It contains important information. Store at 20-25°C (68-77°F) and protect from moisture.

**Active ingredients** carnauba wax, ferric oxide red, ferric oxide yellow, hypromellose, hypromellose acetate succinate, lactose monohydrate, monoethanolamine, propylene glycol, sodium lauryl sulfate, sodium starch glycolate, sodium stearate, sodium stearyl arate, talc, titanium dioxide, triethyl citrate



Only if safety seal is intact.



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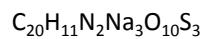
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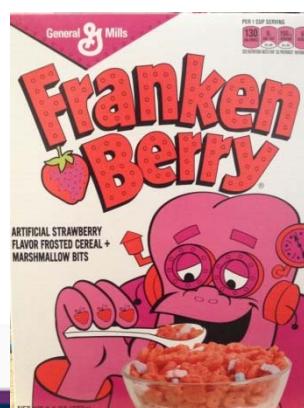
Amaranth (dye)



Amaranth (Plant)



Azorubin S



FD&C Red No. 2



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\*FDA banned FD&C Red No. 2 in 1976

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- Newest IC of the National Institutes of Health
  - To catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of interventions that tangibly improve human health across a wide range of human diseases and conditions.
- Highly collaborative across NIH, other government agencies, and with the private sector.
- *Develop, demonstrate, and disseminate* software for generating, managing, and mining data





Lilly



Johnson & Johnson



Genentech



Bristol-Myers Squibb



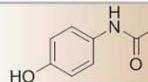
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# A Comprehensive Resource of Clinically Approved Drugs Enabling Repurposing and Chemical Genomics

Ruili Huang,\* Noel Southall,\* Yuhong Wang, Adam Yasgar, Paul Shinn,  
Ajit Jadhav, Dac-Trung Nguyen, Christopher P. Austin†

[www.ScienceTranslationalMedicine.org](http://www.ScienceTranslationalMedicine.org) 27 April 2011 Vol 3 Issue 80 80ps16

	Term	FDA	Worldwide	
Tylenol 8 Hour, Dayquil Sinus NyQuil Cough, Infants' Tylenol	Drug Product	>140,000		Product with defined package size, dose, formulation of API(s)
Tylenol, Acetaminophen, Panadol, Datril, Paracetamol	Drug	>19,000	>25,000	Brand or generic name of approved product that defines API(s)
103-90-2	API	4,695	7,980	Physical substance intended to be used in manufacture of drug product
	Molecular Entity	2,794	4,374	Chemical moiety excluding salts, esters, etc. responsible for pharmacological activity
	HTS Suitable	1,822	2,752	Chemical entity of defined structure amenable to high-throughput screening



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## HEALTH MEDICINE

# Could An Allergy Drug Treat Hepatitis C?

Alexandra Sifferlin  
@acsifferlin

April 8, 2015

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A drug that's been around for decades may help find a new solution for an expensive chronic disease

An over-the-counter drug commonly used to treat allergies may one day also contribute to the treatment of hepatitis C, according to new research in mice published in the journal *Science Translational Medicine*.





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1. Heparin / PV disaster
2. Names not sufficient
3. Ginas - share scientific definitions
4. Where we've come from
5. FDA's investment
6. Why NCATS
7. Current governance
8. Thanks to UMC
9. Everyone's duty to contribute
10. Goals for the meeting and the future