

FDALabel Database: Enabling Insights from Drug Labeling to Advancement of Drug Safety and Regulatory Sciences

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Disclaimer

The views expressed in this presentation are those of the speaker and not necessarily those of the Food and Drug Administration (FDA).

What is in a Drug Labeling?

- The official description of a drug product approved by the FDA
- Includes what the drug is used for, who should use it, side effects, instructions for use, and safety information
- It has ~20 pages with >80 sections (e.g., [ONIVYDE](#))

ONIVYDE (Irinotecan liposome injection) used in combination with other drugs, for patients with metastatic **pancreatic cancer** previously treated with gemcitabine-based therapy

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: SEVERE NEUTROPENIA AND SEVERE DIARRHEA

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Important Use Information
- 2.2 Recommended Dose
- 2.3 Dose Modifications for Adverse Reactions
- 2.4 Preparation and Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Severe Neutropenia
- 5.2 Severe Diarrhea
- 5.3 Interstitial Lung Disease
- 5.4 Severe Hypersensitivity Reaction
- 5.5 Embryo-Fetal Toxicity

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience

7 DRUG INTERACTIONS

- 7.1 Strong CYP3A4 Inducers
- 7.2 Strong CYP3A4 or UGT1A1 Inhibitors

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

What is FDA Approved Drug Labeling?

- Prepared by manufacturers and approved by FDA
 - Data from preclinical and clinical trials and updated with the post-market case reports (FAERS)
 - Drug labeling represents the consensus and combined experience of regulators, drug manufacturers, and scientific experts
- Defined by Code of Federal Regulations ([CFR](#)) Title21 (**CFR201.57**)
 - In 1979, a Final Rule “Old” labeling format (see 21 CFR 201.80)
 - In 2006, the Physician Labeling Rule (PLR) (see 21 CFR 201.56) amended regulations regarding format and content of the Prescribing Information
 - These revisions are mandatory for new drug labeling as well as for drugs that have been on the market up to five years before the effective date of the PLR (June 30, 2006)
 - The amount of information captured in drug labeling has grown rapidly and labeling is updated daily due to new Labeling Laws and FDA Regulations

Labeling Guidance for Industry

Labeling

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Below is a sortable listing of Labeling Guidances. For more information about the Physician Labeling Rule (PLR), labeling regulations and related guidance documents, and additional labeling resources see [PLR Requirements for Prescribing Information](#).

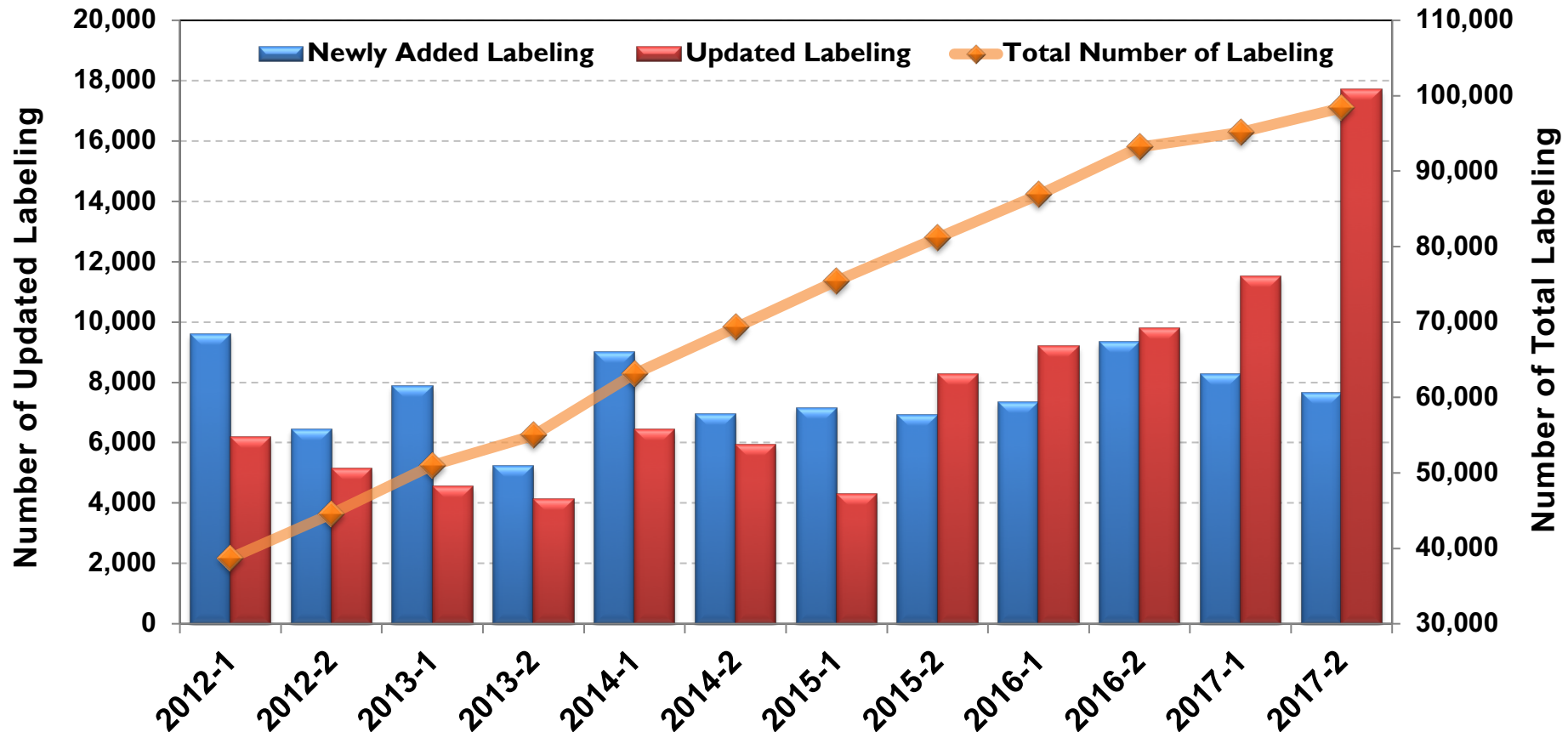
Category ↕	Title ↕	Type ↕	Date ↕
Labeling	Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (PDF - 52KB)	Final Guidance	01/18/06
Labeling	Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products—Considerations, Content and Format (PDF - 117KB)	Draft Guidance	08/13/14
Labeling	Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (PDF - 127KB)	Final Guidance	01/18/06
Labeling	Content and Format for Geriatric Labeling (PDF - 38KB)	Final Guidance	10/01/01
Labeling	Contents of a Complete Submission for the Evaluation of Proprietary Names (PDF - 146KB)	Final Guidance	04/05/16

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065010.htm>

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

Rapid Increase in the Number of FDA's Structured Product Labeling (SPL)

Labeling Additions, Updates, and Totals for 2012-2017



Average Biannual Statistical Updating

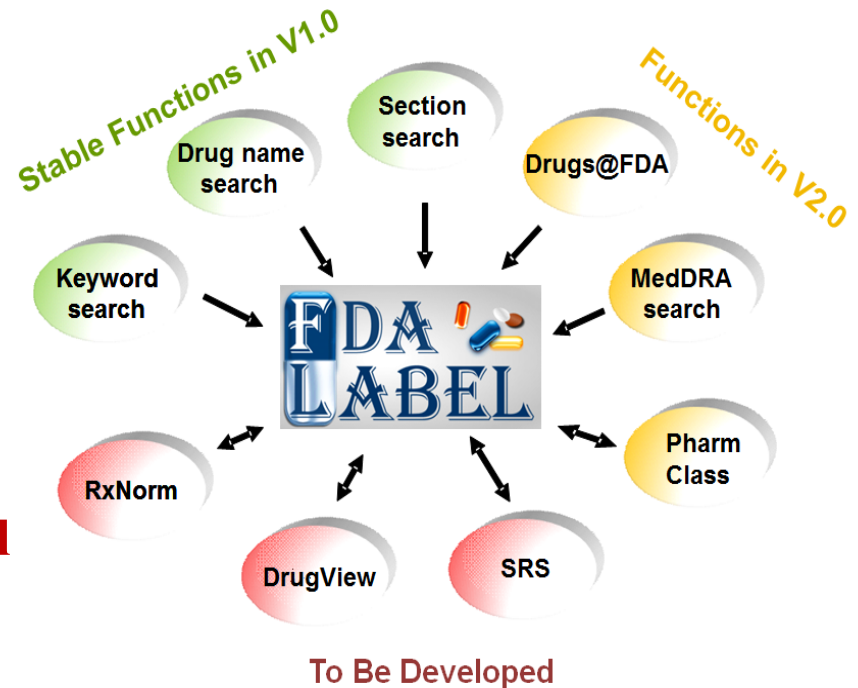
- newly added labeling = 7,647
- updated labeling = 7,762

The total number of labeling has increased by about 59,000 within past 5 years

FDA Label Database

FDA's Structured Product Labeling (SPL)

- A database for managing and querying drug labeling information
- User-friendly interface with searches against the entire text of labeling
- Data source: FDA's SPL (Structured Product Labeling) downloaded from DailyMed
 - Weekly update (currently with >100,000 labeling)
- Advanced Integrations for **Translational and Regulatory Science:**
 - Pharmacologic Class
 - MedDRA
 - Link to other FDA databases (e.g., Drugs@FDA)
 - SRS (Substance Registration System)



FDALabel User Interface (version 2)

Labeling Types

Quick pick list (choose one or more): [Animal Rx](#) [Animal OTC](#) [Human Rx](#) [Human OTC](#) [Medical Device](#) [Medical Device Rx](#) [Vaccine](#)

or Choose alternatives from the full list:

&

Product Name(s)

Generic or trade name

contains

Enter any part(s) of product name

&

Labeling Full Text Search

Enter full text query

Query syntax: use 'and' or 'or' between words if they are not required to occur contiguously

&

Labeling Section(s)

Enter query terms

within

The query may be empty to check for presence of a section

Quick pick list (choose one): [Product Title](#) [Initial U.S. Approval](#) [Boxed Warning](#) [Recent Major Changes](#) [Indications & Usage](#) [Dosage & Admin.](#) [Dosage forms & Strengths](#) [Contraindications](#) [Warnings & Precautions](#) [Adverse Reactions](#) [Drug Interactions](#) [Use in Specific Populations](#) [Revision Date](#)

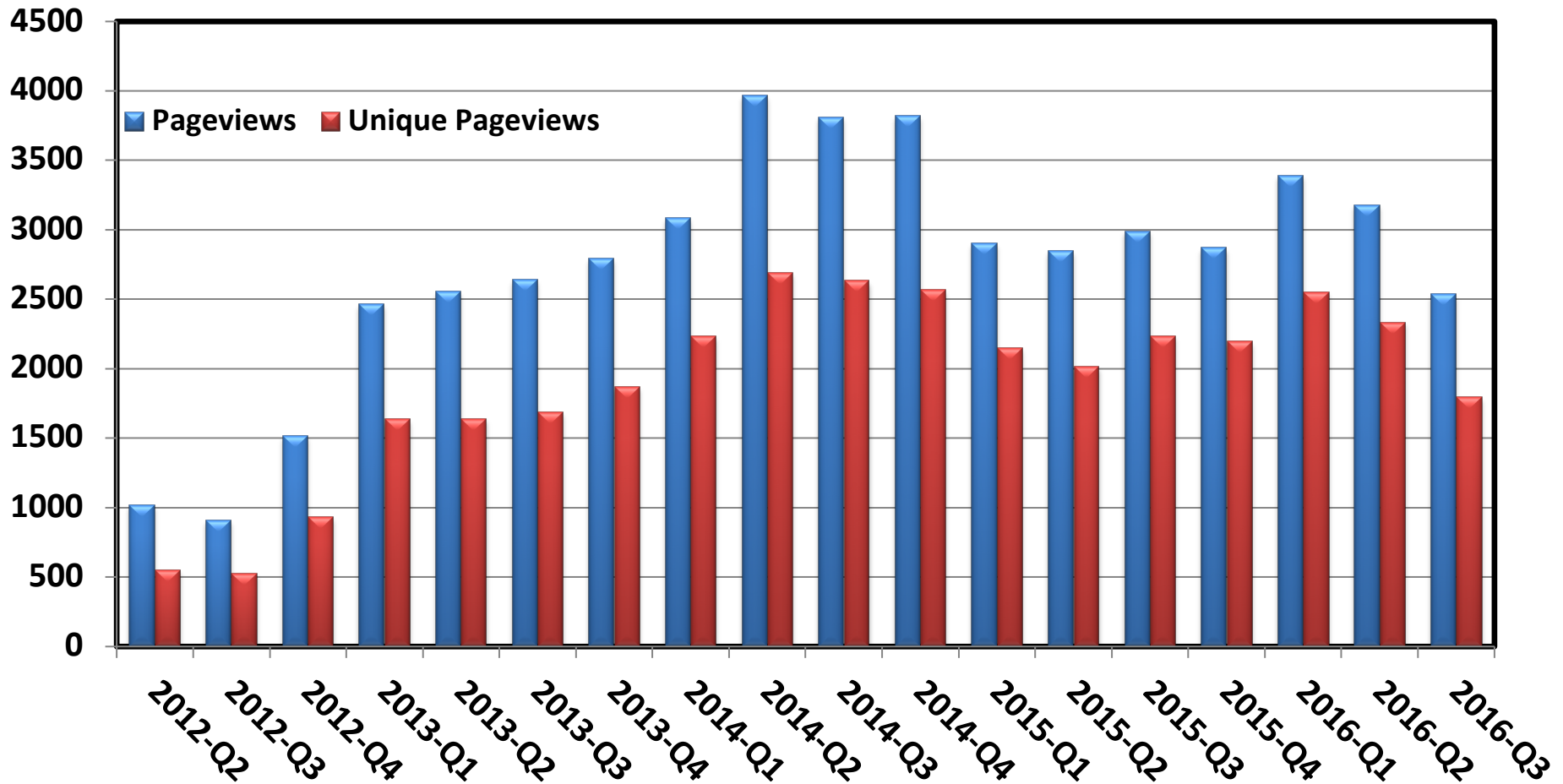
Add more criterion(s)

[Labeling Full Text Search](#) | [Product Name\(s\)](#) | [Labeling Section\(s\)](#) | [Labeling Types](#) | [Pharmacological Classes](#) | [Application Types or Marketing Categories](#) | [Market Status](#) | [MedDRA Terms](#) | [Chemical Structure](#) | [Labeling, Product, and Active Ingredient Identifiers](#)

Will be hosted on Amazon Cloud soon!!! Please check our FDALabel webpage:
<https://www.fda.gov/ScienceResearch/BioinformaticsTools/ucm289739.htm>

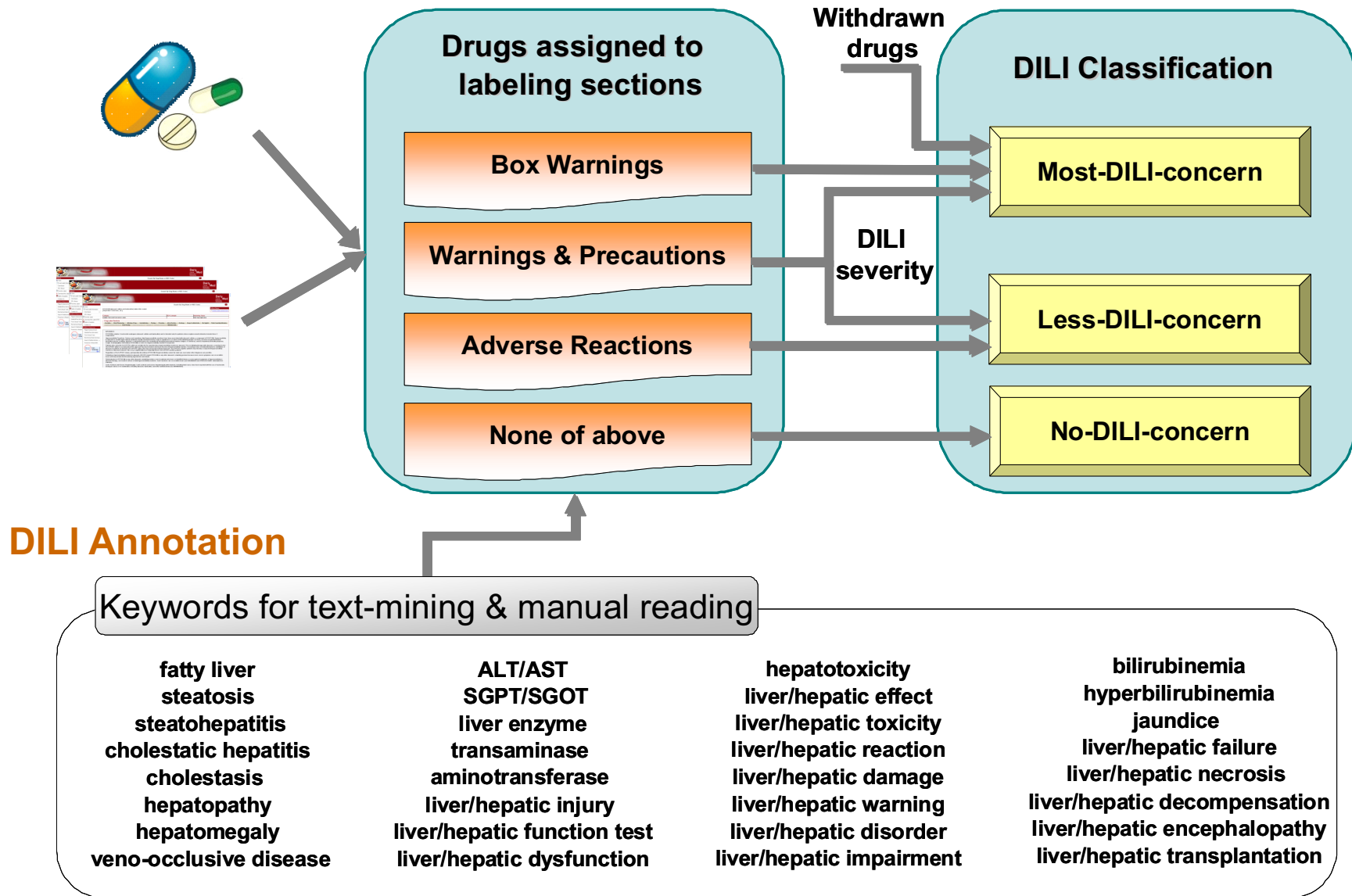
FDALabel User Statistics (Public V1.0)

From Google Analytics 2012-2016

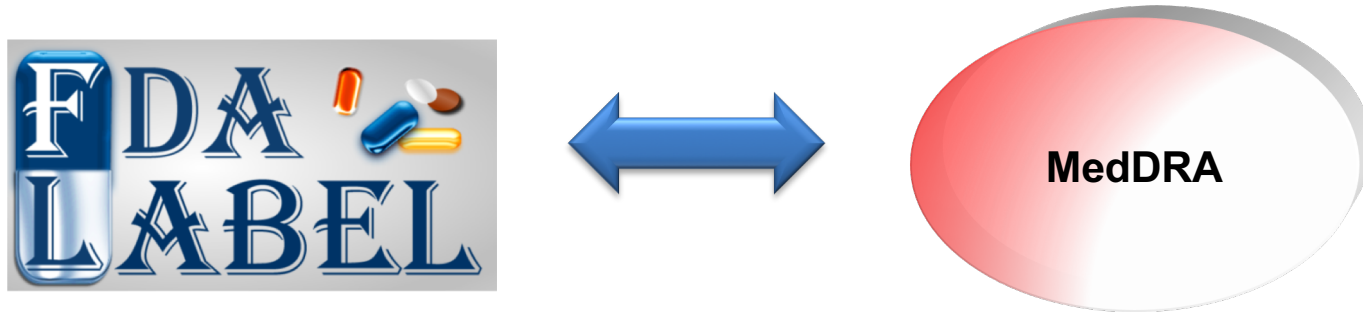


Applications of ADR Study Using FDA Approved Drug Labeling

Liver Toxicity Knowledge Base: Example of ADR Study



FDALabel Integrated with MedDRA (Medical Dictionary and Standard Terminology)

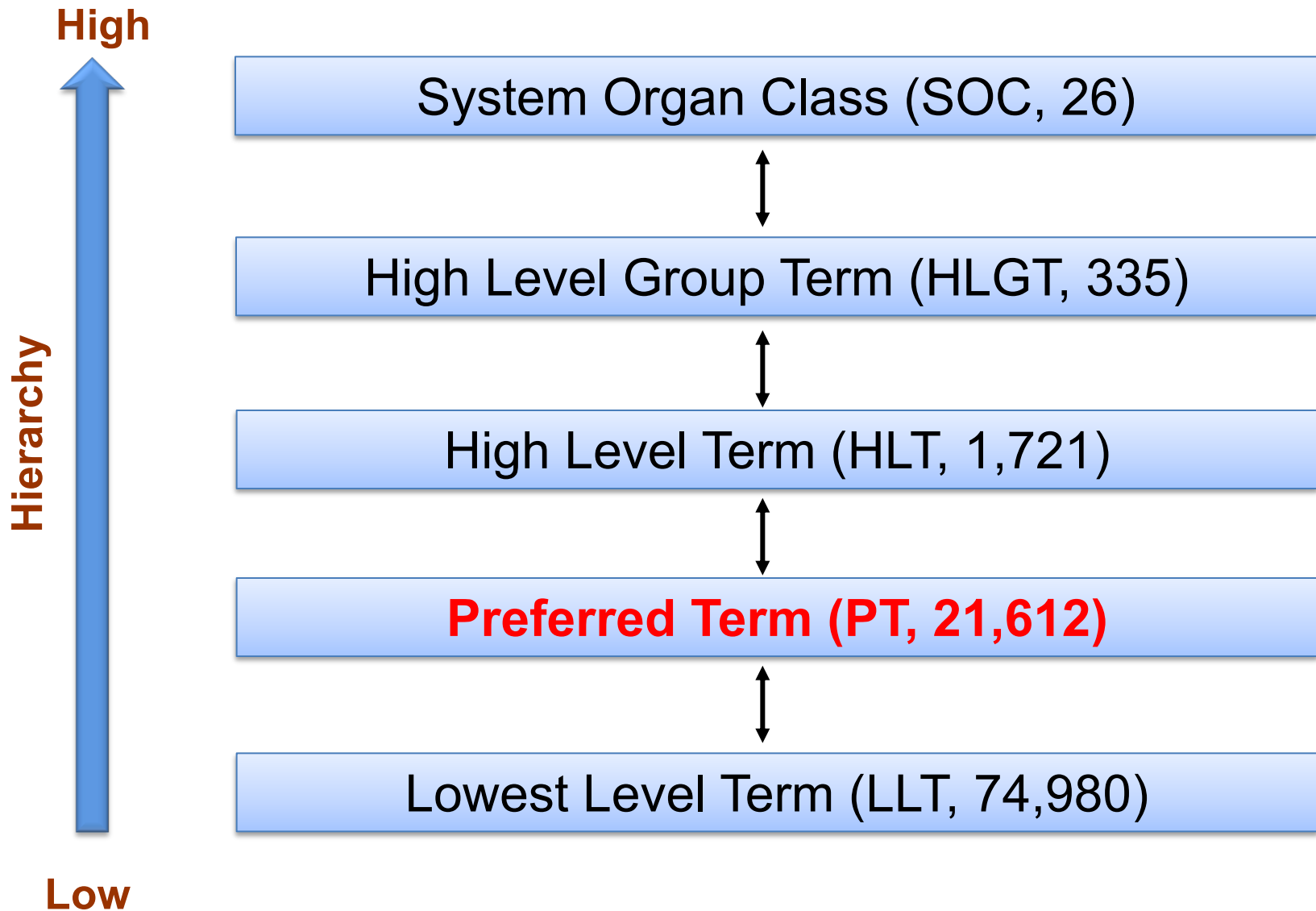


Medical Dictionary for Regulatory Activities (MedDRA):

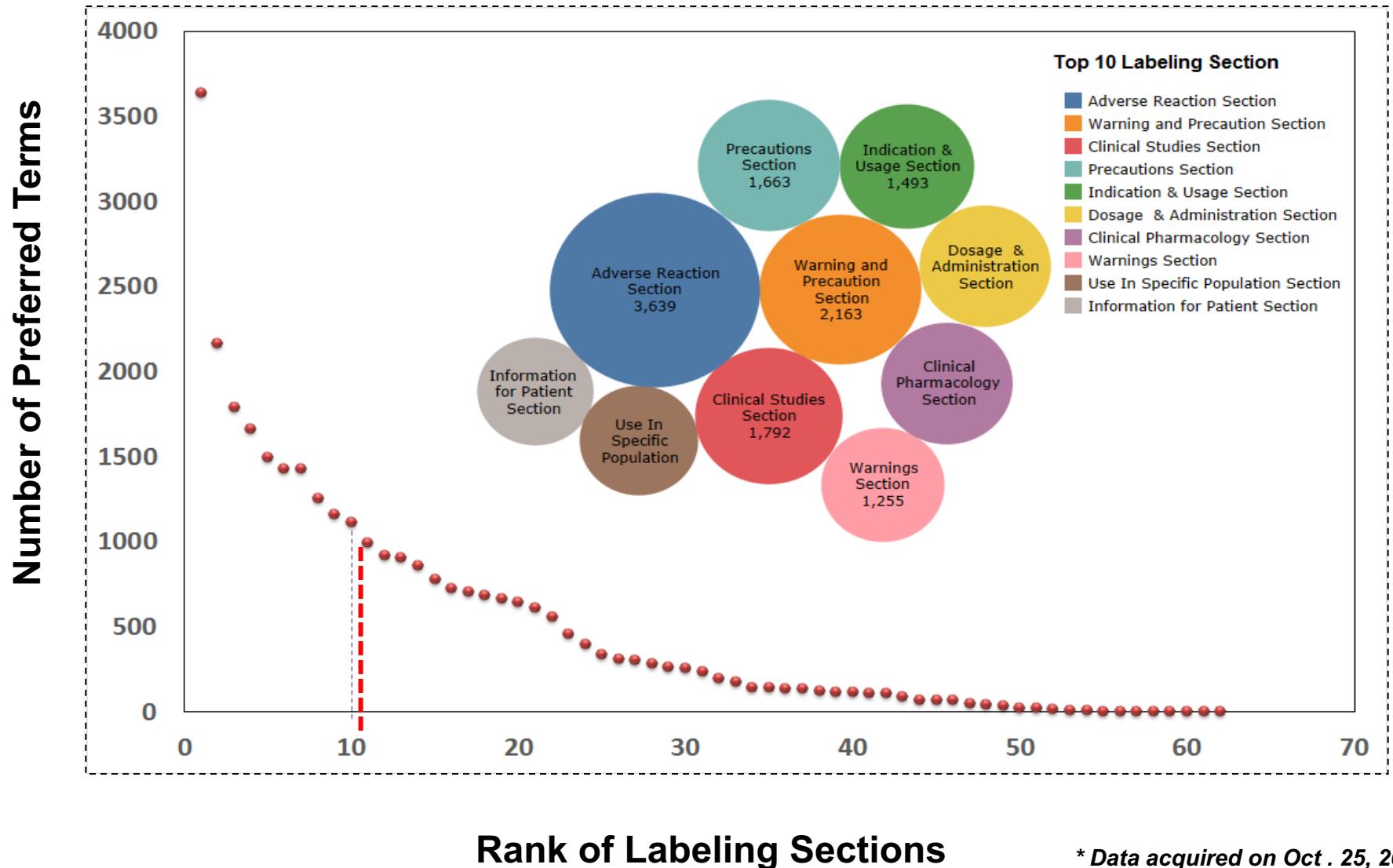
The terminology is used through the entire regulatory process, from pre-marketing to post-marketing, and for data entry, retrieval, evaluation, and presentation.

- FAERS codes adverse event using MedDRA
- MedDRA is widely used internationally, including in the [United States](#), [European Union](#), and [Japan](#).
- Originally available in English and Japanese, MedDRA is now also translated into Chinese, Czech, Dutch, French, German, Hungarian, Italian, Portuguese and Spanish.
- Its use is currently mandated in Europe and Japan for safety reporting.

MedDRA Hierarchy



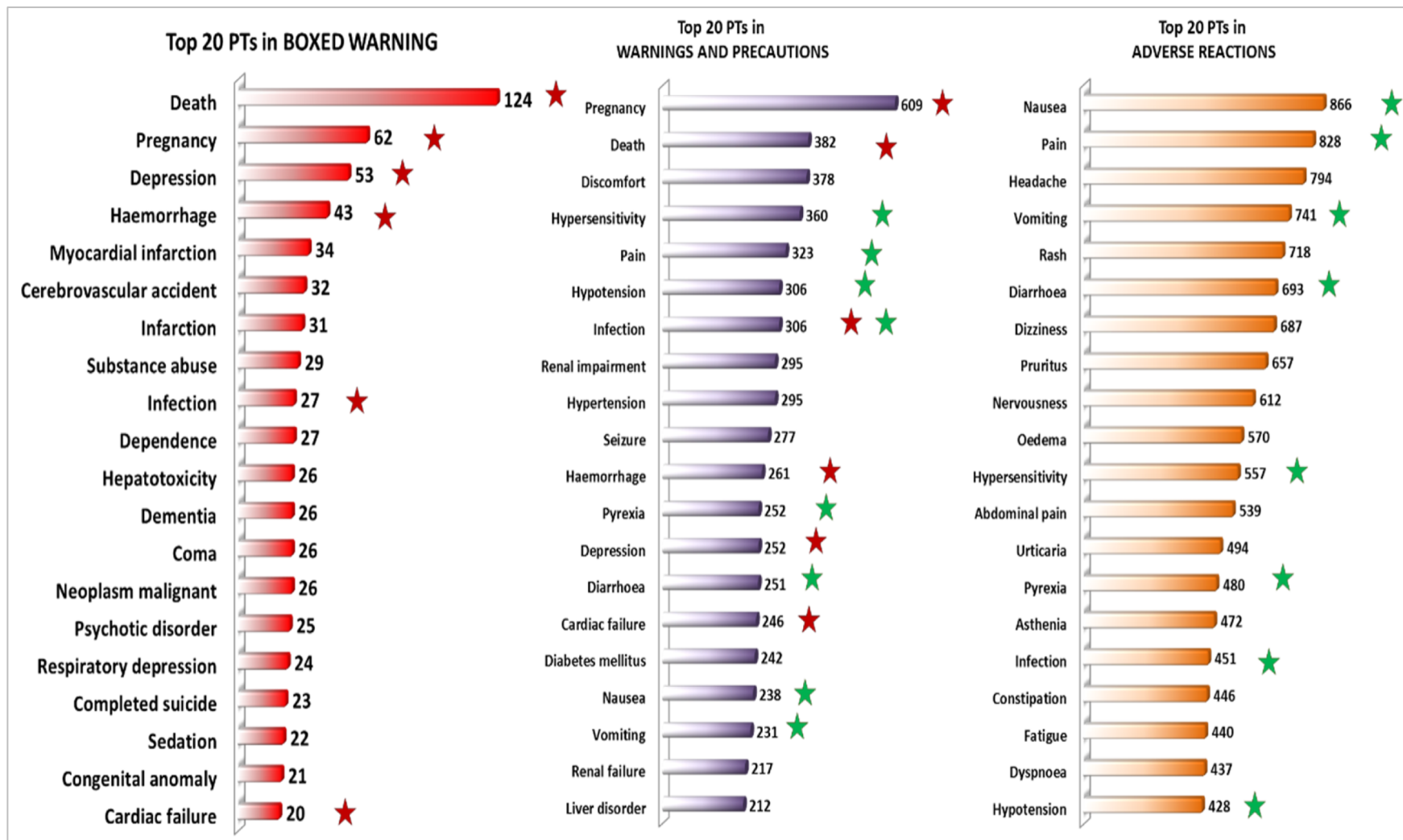
Distribution of MedDRA (PTs) in All Drug Labeling Sections



Number of Drugs and Frequency of PTs in the Top Three Adverse Event Labeling Sections

Labeling Section	Number of Drugs	Number of LLTs	Number of PTs	PT/Drug Ratio
BOXED WARNING	367	601	463	1.26
WARNINGS & PRECAUTIONS	1148	3206	2023	1.76
ADVERSE REACTIONS	1152	5300	2961	2.57
Whole Labeling Document	1164	7287	3819	--

Top 20 Most Observed PTs in BOXED WARNING, WARNING & PRECAUTIONS, and ADVERSE REACTIONS



Hierarchical Clustering Analysis (HCA) of Drug ATC and MedDRA PT/SOC Association in Boxed Warning Drugs

ATC classes

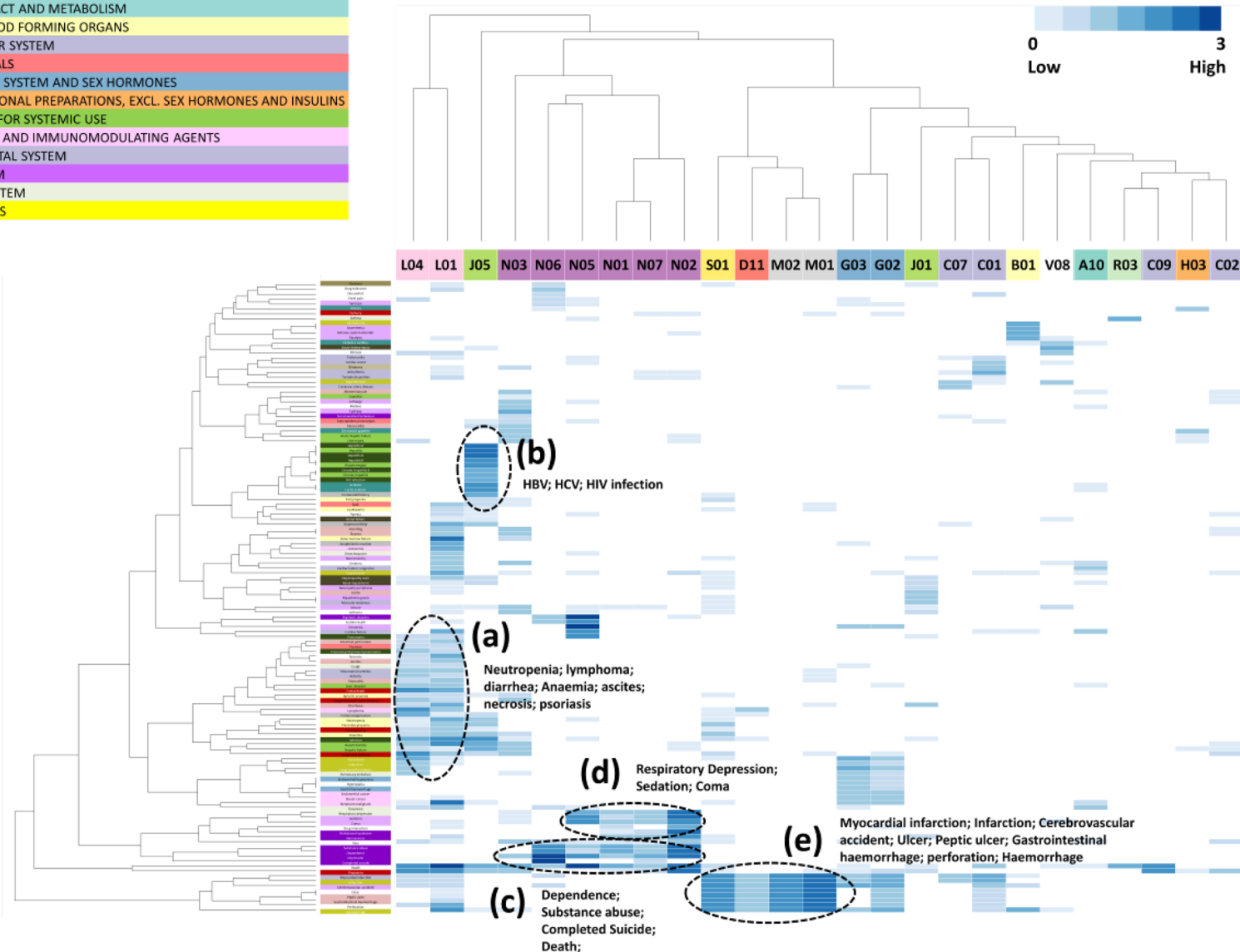
A	ALIMENTARY TRACT AND METABOLISM
B	BLOOD AND BLOOD FORMING ORGANS
C	CARDIOVASCULAR SYSTEM
D	DERMATOLOGICALS
G	GENITO URINARY SYSTEM AND SEX HORMONES
H	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS
J	ANTIINFECTIVES FOR SYSTEMIC USE
L	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS
M	MUSCULO-SKELETAL SYSTEM
N	NERVOUS SYSTEM
R	RESPIRATORY SYSTEM
S	SENSORY ORGANS
V	VARIOUS

SOC Labels

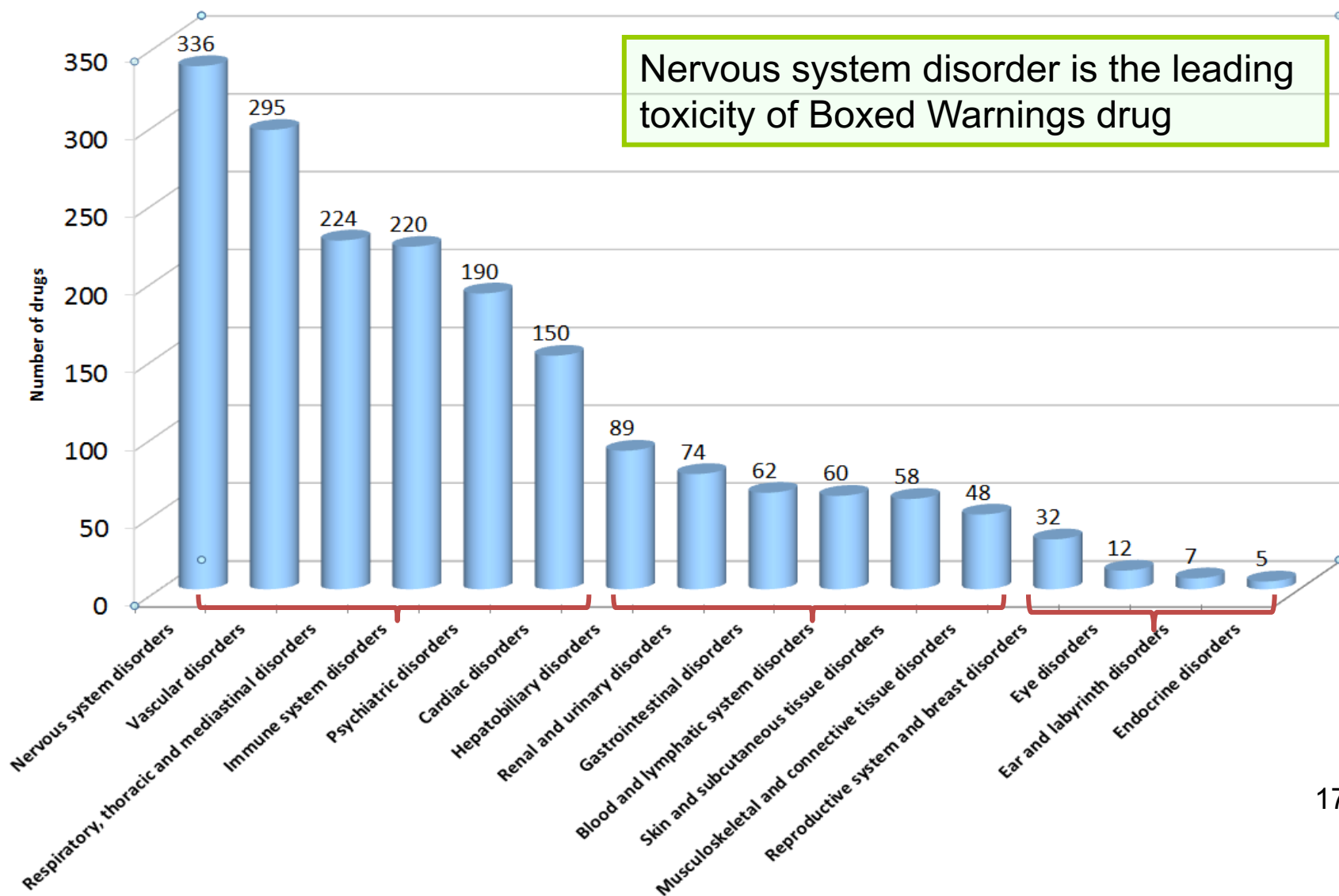
Blood
Card
Cong
Ear
Eye
Gastr
Genrl
Hepat
Immun
Infec
Metab
Musc
Neopl
Nerv
Preg
Psych
Renal
Repro
Resp
Skin
Vasc

Color Legend: Log2 (Frequency)

0 Low 3 High

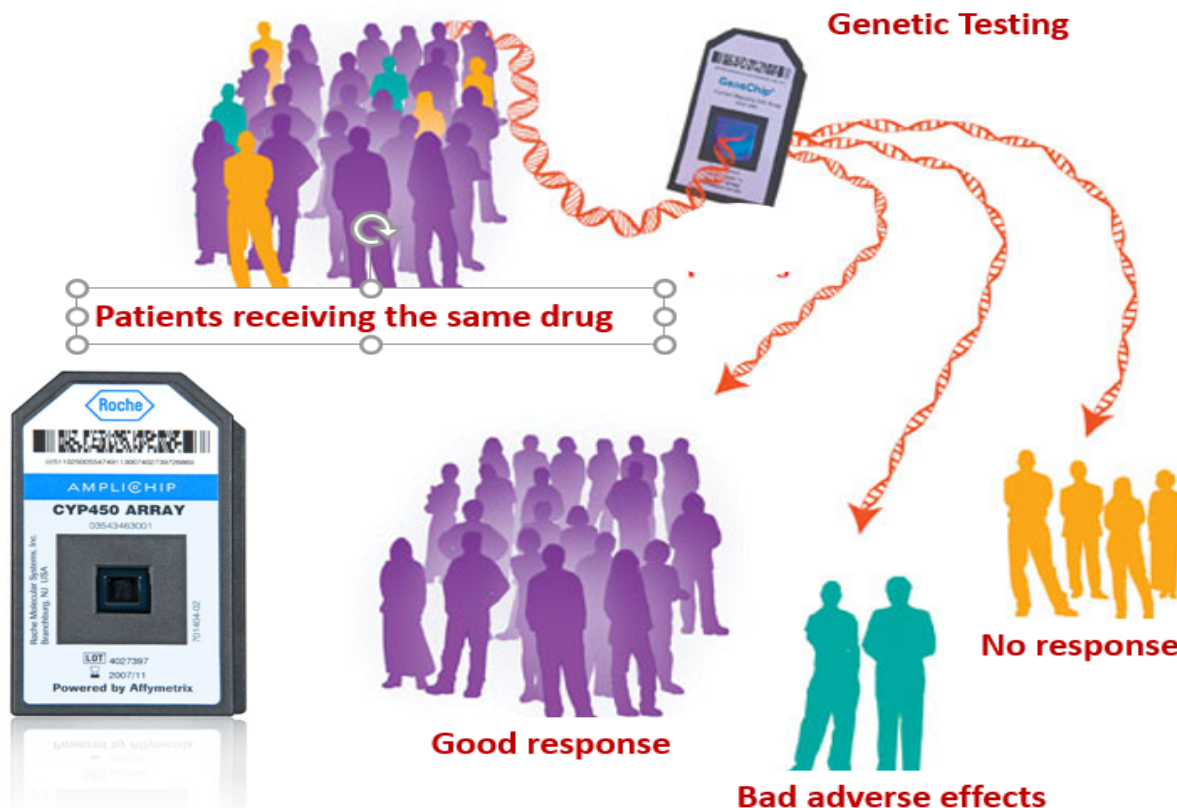


Boxed Warning Drug Toxicities in 16 Body Organs Using MedDRA SOCs



Application in Pharmacogenomics

- Pharmacogenomics (PGx) is a field of research that studies the relationship between drug response and genetic makeup of an individual/population.
- Patients Respond Differently to the Same Drug Treatment
- **Right Drug, Right Dose, Right Patient (Precision Medicine)**

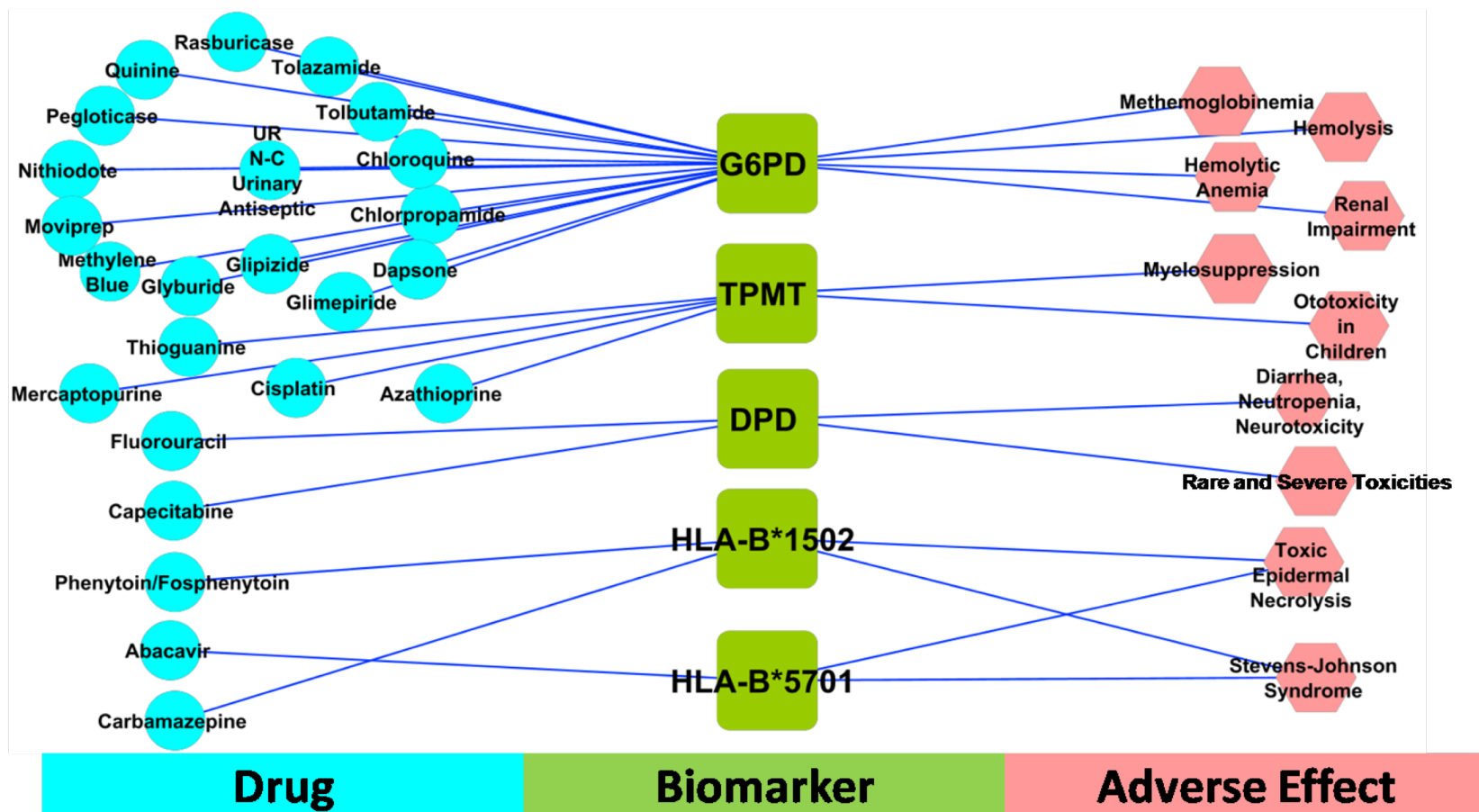


Pharmacogenomics Biomarkers in Drug Labeling

A total of 225 drugs were identified from 62 biomarkers that were investigated. The collected genomic biomarkers can be grouped into three categories:

- Involving drug metabolism variability (e.g. CYP enzymes)
- Associated with increased risk of adverse events (e.g. G6PD, TPMT, UGT1A1)
- Associated with the drug's mechanism of action (e.g. CD30, CFTR)

PGx Biomarkers for Adverse Effects



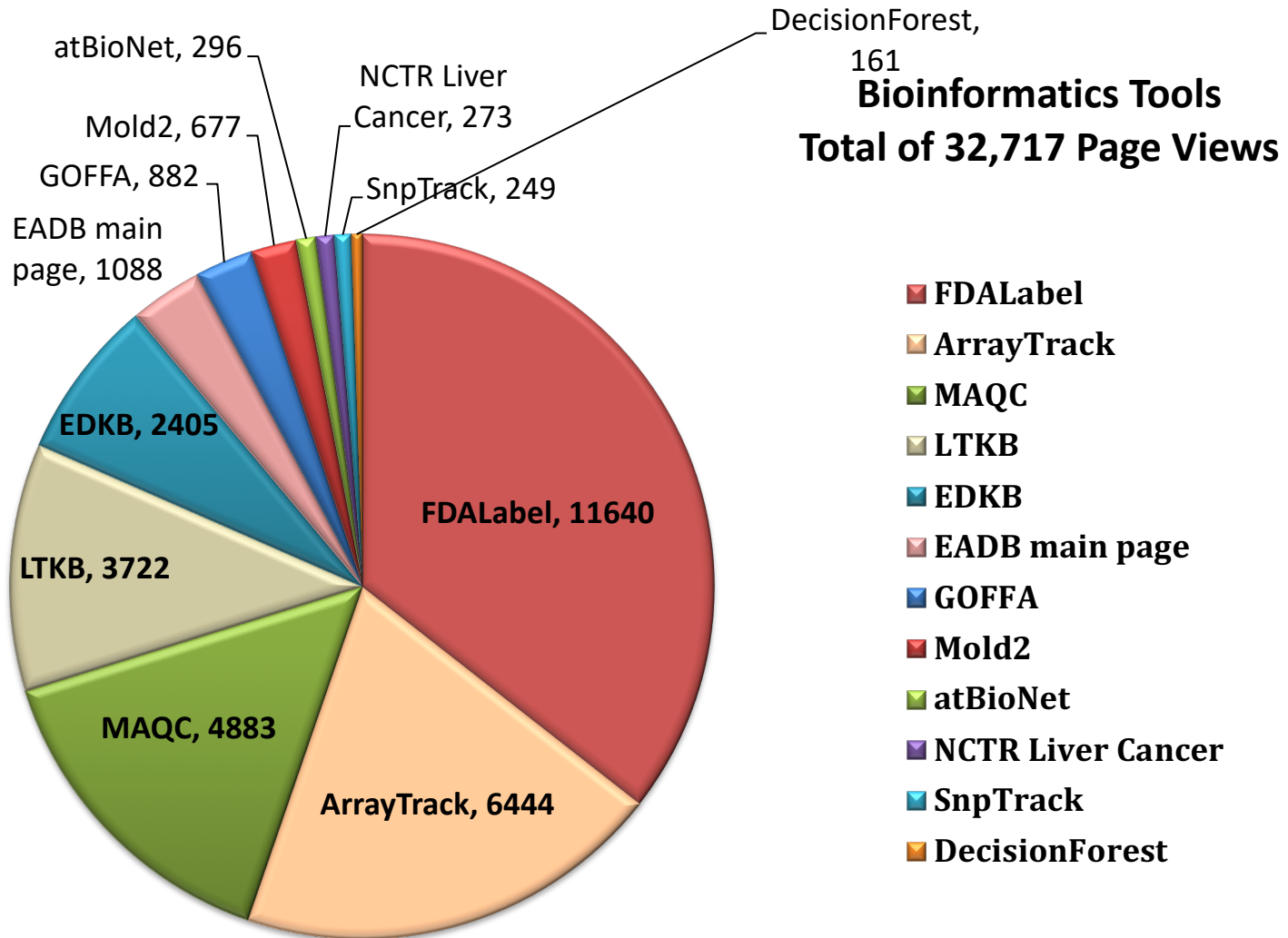
Patients who carry the HLA-B*5701 allele are at a higher risk for experiencing a hypersensitivity reaction (HR) to Abacavir®.

Summary of Drug Info @FDALabel

To pharmaceutical companies for drug development, to researchers for study of efficacy and drug safety, to FDA medical officers for drug review

- **FDALabel** is a powerful tool to retrieve ADR, PGx etc. information from FDA approved drugs.
- Information can be identified from drug labeling sections such as Indication and Usage, Boxed Warnings, Warning and Precautions, Adverse Reactions, and Patient Subpopulations.
- This research exemplifies the importance of the FDALabel database in Drug Safety and Precision Medicine.
- Facilitates transparent knowledge exchange among the public, pharmaceutical companies, and government regulatory agencies to advance translational and regulatory sciences.

Bioinformatics Tools User Statistics by Google Analytics



Access FDALabel Database

- **Home Page**

<http://www.fda.gov/ScienceResearch/BioinformaticsTools/ucm289739.htm>

- **Public Version 1.0**

<https://rm2.scinet.fda.gov/druglabel/#simsearch-0>

- **Version 2.2 (FDA internal, New)**

<http://fdalabel.fda.gov/fdalabel/ui/search>

- **User Support:**

Contact: Hong Fang at Hong.Fang@fda.hhs.gov or at NCTRBioinformaticsSupport@fda.hhs.gov

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