FDA Databases 101 for Clinical Pharmacologists

Anuradha Ramamoorthy, Ph.D.

Reviewer, Genomics and Targeted Therapy Group
Office of Clinical Pharmacology
OTS/CDER/OMPT/FDA

Science at Sunrise March 17, 2017

Disclaimer: This speech reflects the views of the speaker and should not be construed to represent FDA's policies

Agenda

- FDA Databases
  - FAERS
  - FDA Pharmacogenomic Biomarkers Table
  - precisionFDA Portal

Agenda

- **FDA Databases**
  - FAERS
  - FDA Pharmacogenomic Biomarkers Table
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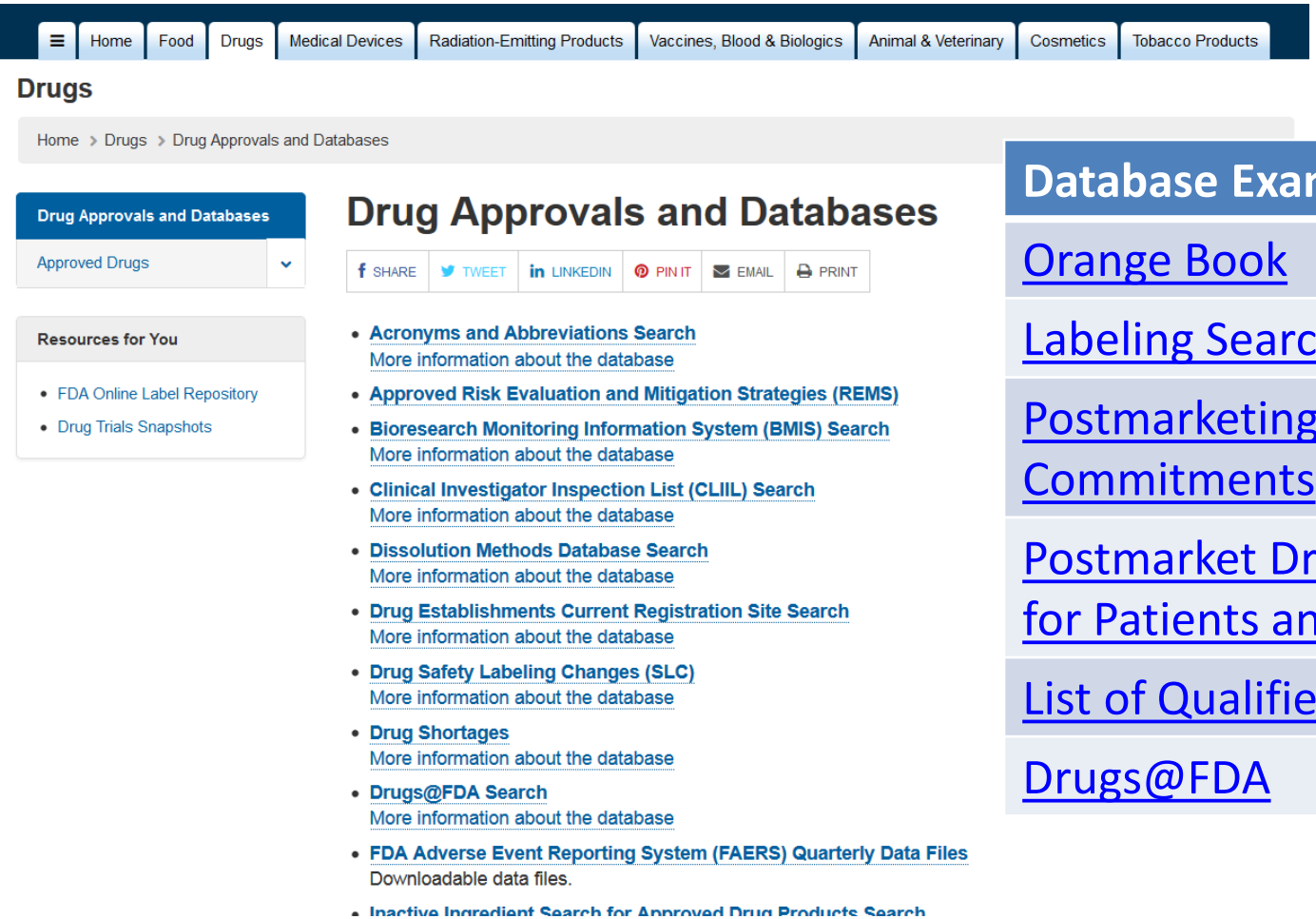
FDA Databases

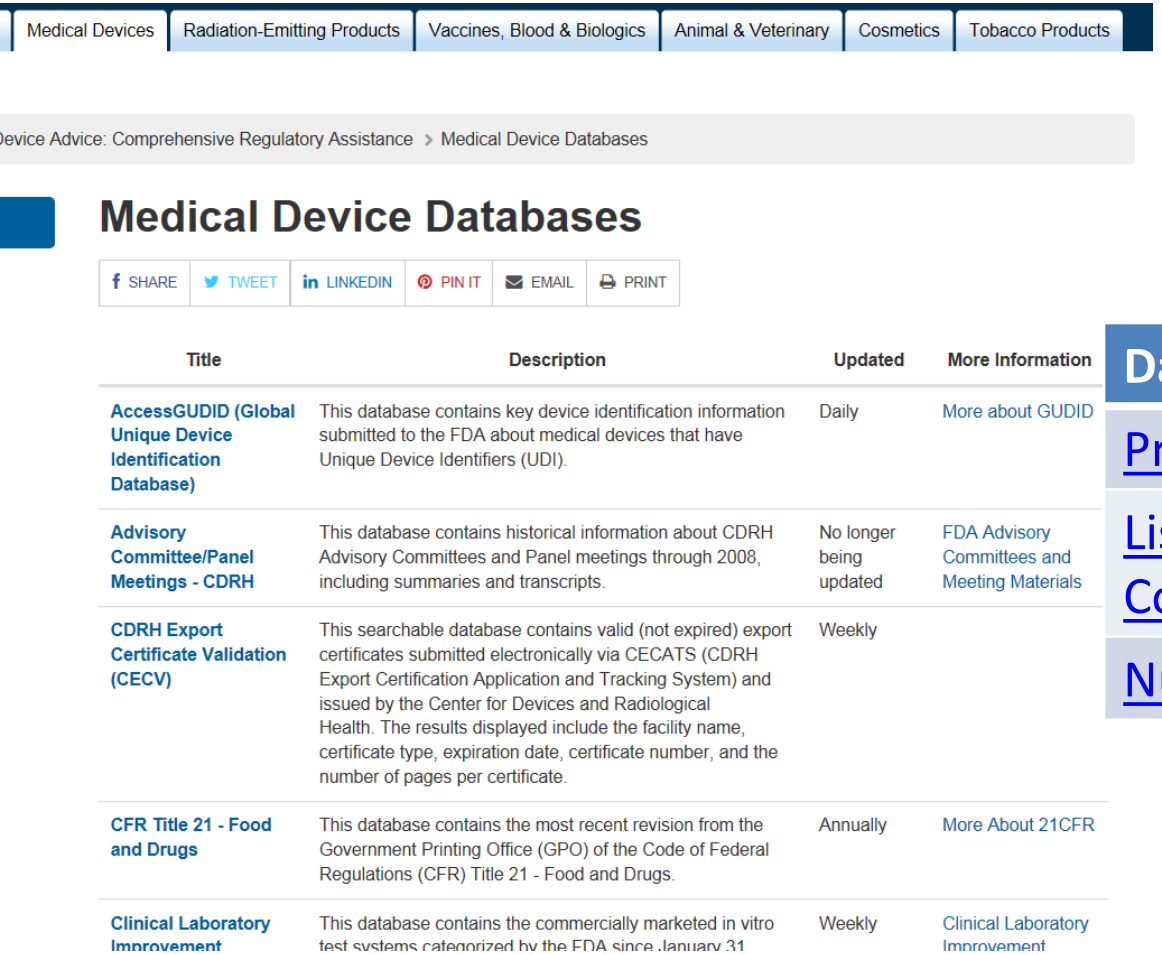
Drug Approvals and Databases



Database Examples
Orange Book
Labeling Search
Postmarketing Requirements and Commitments
Postmarket Drug Safety Information for Patients and Providers
List of Qualified Biomarkers
Drugs@FDA

FDA Databases

Medical Device Databases



Title	Description	Updated	More Information
AccessGUDID (Global Unique Device Identification Database)	This database contains key device identification information submitted to the FDA about medical devices that have Unique Device Identifiers (UDI).	Daily	More about GUDID
Advisory Committee/Panel Meetings - CDRH	This database contains historical information about CDRH Advisory Committees and Panel meetings through 2008, including summaries and transcripts.	No longer being updated	FDA Advisory Committees and Meeting Materials
CDRH Export Certificate Validation (CECV)	This searchable database contains valid (not expired) export certificates submitted electronically via CECATS (CDRH Export Certification Application and Tracking System) and issued by the Center for Devices and Radiological Health. The results displayed include the facility name, certificate type, expiration date, certificate number, and the number of pages per certificate.	Weekly	
CFR Title 21 - Food and Drugs	This database contains the most recent revision from the Government Printing Office (GPO) of the Code of Federal Regulations (CFR) Title 21 - Food and Drugs.	Annually	More About 21CFR
Clinical Laboratory Improvement	This database contains the commercially marketed in vitro test systems categorized by the FDA since January 31	Weekly	Clinical Laboratory Improvement

Database Examples

- Premarket Approval (PMA)
- List of Cleared or Approved Companion Diagnostic Devices
- Nucleic Acid Based Tests

Agenda

FDA Databases

FAERS

FDA Pharmacogenomic Biomarkers Table

precisionFDA Portal

FDA Adverse Event Reporting System

openFDA

Home openFDA Learn

openFDA › data › faers

Dataset that supplies data to openFDA

FDA Adverse Event Reporting System

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA.

About FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation (ICH E2B). Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Learn more

General information

Learn more about FDA Adverse Event Reporting System

Provider

FDA

License

Public Domain and CC0

Updates

Frequency **Quarterly**

Lag in data updates **3 months**

Time period

FDA Adverse Event Reporting System

FDA Adverse Event Reporting System (FAERS): Latest Quarterly Data Files

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The files listed on this page contain raw data extracted from the AERS database for the indicated time ranges and are not cumulative.

Users of these files need to be familiar with creation of relational databases using applications such as ORACLE®, Microsoft Office Access, MySQL® and IBM DB2 or the use of ASCII files with SAS® analytic tools.

A simple search of FAERS data cannot be performed with these files by persons who are not familiar with creation of relational databases. However, you can get a summary FAERS report for a product by sending a Freedom of Information Act (FOIA) request to FDA. You can also request individual case reports by submitting a FOIA request listing case report numbers.

- General Instructions on How to Make a FOIA Request
- Instructions for Requesting Individual Case Reports

The quarterly data files, which are available in ASCII or SGML formats, include:

- demographic and administrative information and the initial report image ID number (if available);
- drug information from the case reports;
- reaction information from the reports;
- patient outcome information from the reports;
- information on the source of the reports;
- a "README" file containing a description of the files.

For assistance, please email the FDA/CDER Office of Surveillance and Epidemiology, Division of Medication Errors and Technical Support: **cderosetracking@fda.hhs.gov**.

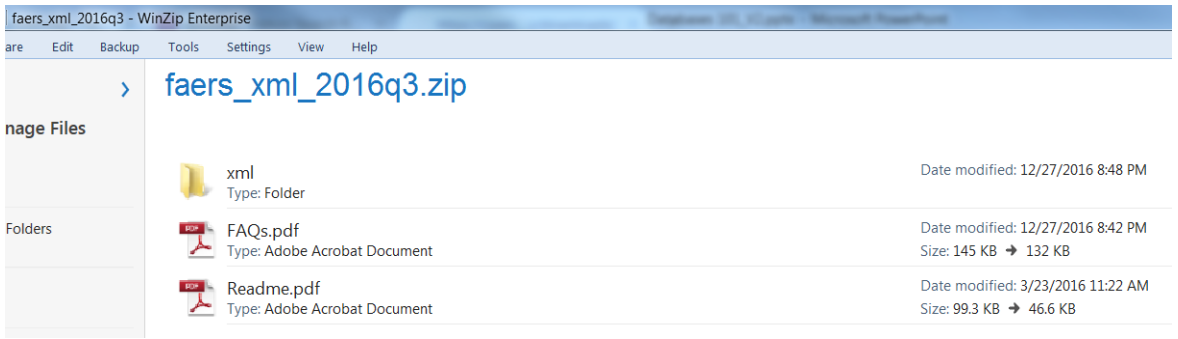
Older Quarterly Legacy AERS Data Files Page

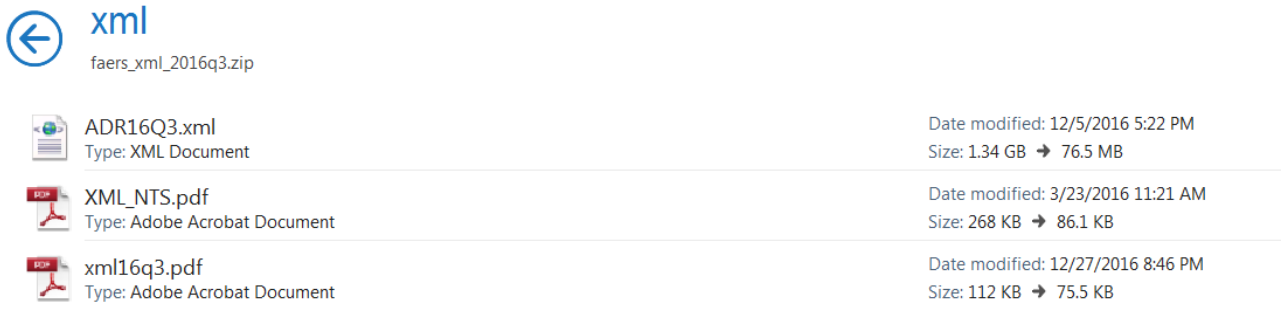
FDA Adverse Event Reporting System

FAERS Data Files

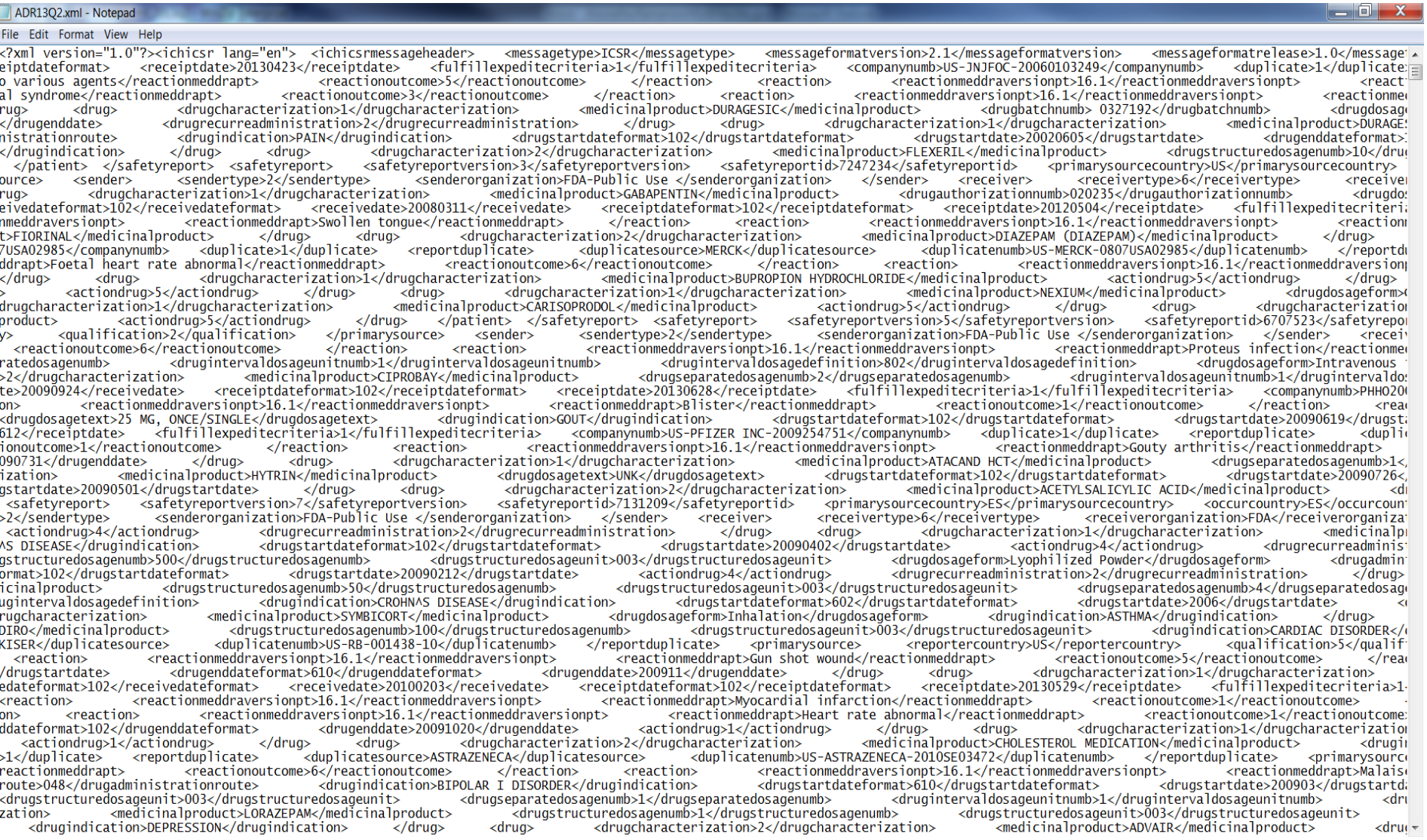
Click on a Link Below to Begin Downloading

- FAERS ASCII 2016q3 (ZIP - 40.6MB)
  July - September 2016
- FAERS XML 2016q3 (ZIP - 76.9MB)
  July - September 2016
- FAERS ASCII 2016q2 (ZIP - 42.3MB)
  April - June 2016
- FAERS XML 2016q2 (ZIP - 68.9MB)
  April - June 2016
- FAERS ASCII 2016q1 (ZIP - 43.7MB)
  January - March 2016
- FAERS XML 2016q1 (ZIP - 71.5MB)
  January - March 2016
- FAERS ASCII 2015q4 (ZIP - 39.7MB)
  October - December 2015
- FAERS XML 2015q4 (ZIP - 65.8MB)
  October - December 2015
- FAERS ASCII 2015q3 (ZIP - 44.7MB)
  July - September 2015
- FAERS XML 2015q3 . (ZIP - 73.3MB)
  July - September 2015
- FAERS ASCII 2015q2.zip (ZIP - 36.4MB)
  April - June 2015





FDA Adverse Event Reporting System



How is FAERS Used?
Literature Examples From PubMed

FAERS data have certain limitations (refer to FAERS webpage for details)

Publication dates
5 years
10 years
Custom range...

Species
Humans
Other Animals

Clear all

Show additional filters

1. Can Disproportionality Analysis of Post-marketing Case Reports be Used for Comparison of Drug Safety Profiles?
   Michel C, Scosyrev E, Petrin M, Schmouder R.
   Clin Drug Investig. 2017 Feb 21. doi: 10.1007/s40261-017-0503-6. [Epub ahead of print]
   PMID: 28224371
   Similar articles

2. An exploratory factor analysis of the spontaneous reporting of severe cutaneous adverse reactions.
   Hauben M, Hung E, Hsieh WY.
   Ther Adv Drug Saf. 2017 Jan;8(1):4-16. doi: 10.1177/2042098616670799.
   PMID: 28203363 **Free PMC Article**
   Similar articles

3. Dipeptidyl Peptidase-4 Inhibitor-Associated Risk of Bleeding.
   Rahman MM, Scalese MJ, Hansen RA.
   Ann Pharmacother. 2017 Feb 1:1060028017692816. doi: 10.1177/1060028017692816. [Epub ahead of print]
   PMID: 28166651
   Similar articles

4. Validation of New Signal Detection Methods for Web Query Log Data Compared to Signal Detection Algorithms Used With **FAERS**.
   Colilla S, Tov EY, Zhang L, Kurzinger ML, Tcherny-Lessenot S, Penfornis C, Jen S, Gonzalez DS, Caubel P, Welsh S, Juhaeri J.
   Drug Saf. 2017 Feb 2. doi: 10.1007/s40264-017-0507-4. [Epub ahead of print]
   PMID: 28155198
   Similar articles

5. Angiotensin receptor blockers and the risk of cancer: data mining of a spontaneous reporting database and a claims database.
   Fujimoto M, Kanou M, Hosomi K, Takada M.
   Int J Clin Pharmacol Ther. 2017 Jan 12. doi: 10.5414/CP202842. [Epub ahead of print]
   PMID: 28079518
   Similar articles

6. Adverse event detection using the FDA post-marketing drug safety surveillance system: Cardiotoxicity associated with loperamide abuse and misuse.
   Swank KA, Wu E, Kortepeter C, McAninch J, Levin RL.
   J Am Pharm Assoc (2003). 2017 Jan 7. pii: S1544-3191(16)30894-9. doi: 10.1016/j.japh.2016.11.011. [Epub ahead of print]

Agenda

FDA Databases

FAERS

FDA Pharmacogenomic Biomarkers Table

precisionFDA Portal

Table of Pharmacogenomic Biomarkers in Drug Labeling

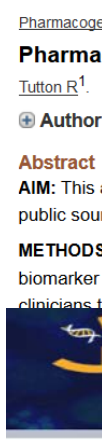
- **What is it?**

  A comprehensive regulatory scientific database that contains pharmacogenomic (PGx) information derived from CDER approved drug products from 1906 to present

- **Where can you find it?**

  Link: http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

Table of Pharmacogenomic Biomarkers in Drug Labeling – Why is it Important?



PharmGKB
Pharmacogenomics. Knowledge. Implementation.

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Drug Labels

PharmGKB annotates drug labels containing pharmacogenetic information approved by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), Pharmaceuticals and Medical Devices Agency, Japan (PMDA) and Health Canada (Santé Canada) (HCSC). PharmGKB annotations provide a brief summary of the PGx in the label, an excerpt from the label and a downloadable highlighted label PDF file. A list of genes and phenotypes found within the label is mapped to label section headers and listed at the end of each annotation. PharmGKB also attempts to interpret the level of action implied in each label with the "PGx Level" tag.

See the legend for more information about drug label sources, which labels are selected for annotation and PGx Levels.

We welcome any information regarding drug labels containing PGx information approved by the FDA, EMA, PMDA, HCSC or other Medicine Agencies around the world - please contact feedback.

view legend

B Only FDA Biomarker drugs
Only labels with dosing info

Search:

Drug		FDA	EMA	PMDA	HCSC
abacavir	B	Genetic testing required	Genetic testing required	Informative PGx	Genetic testing required
abiraterone		Informative PGx			
acetaminophen					Actionable PGx
afatinib	B	Genetic testing required	Genetic testing required		Genetic testing required
afutuzumab	B	Informative PGx			Informative PGx
alectinib	B	Genetic testing required			
alirocumab	B	Actionable PGx			
aliskiren			Informative PGx		Informative PGx
allopurinol				Actionable PGx	
amitriptyline	B	Actionable PGx			

Live Demo

Table of Pharmacogenomic Biomarkers in Drug Labeling

Link to back up slides

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FDA Databases

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FDA Pharmacogenomic Biomarkers Table

precisionFDA Portal

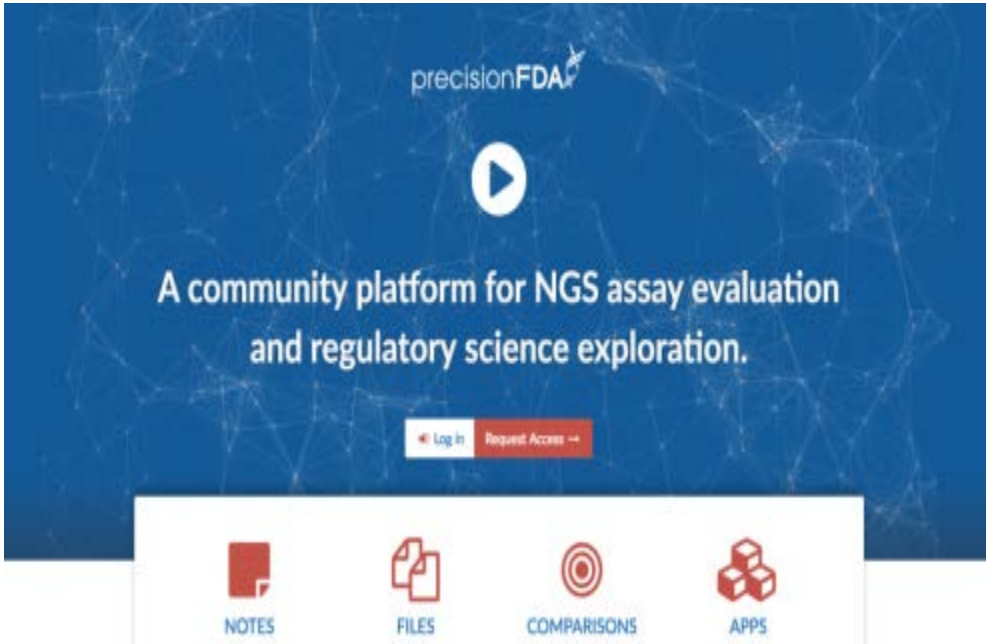
precisionFDA

precisionFDA

FDA created precisionFDA, a community research and development portal to allows for testing, piloting, and validating existing and new bioinformatics approaches to NGS processing.

Courtesy: Elaine Johanson

What is precisionFDA?



PrecisionFDA is an externally focused cloud based portal that engages a community of over 2,500 users across the world. It allows researchers to experiment, share data and tools, and collaborate to help define standards for evaluating analytical pipelines.

Courtesy: Elaine Johanson

precisionFDA and the Community

precisionFDA provides…

- Resources for computation and storage for advancement of regulatory science
- Community challenges
- A library of reference material, tools, etc. including community contributions such as:
  - GA4GH VCF comparison tool
  - BWA-MEM mapper
  - GATK 3.5 licensed to precisionFDA
  - VarSim simulator
  - RTG Core 3.7 + RTG Tools 3.6
  - NA12878 NIST, Garvan, and Platinum Genome sequences
- Ability to “dockerize” applications for ease of use, transportability and consistency in performance across platforms

Members include…

- NGS-based test providers
- Standards-making bodies
- Pharmaceutical & biotechnology companies
- Healthcare providers
- Academic medical centers
- Research consortia
- Government agencies

Courtesy: Elaine Johanson

How to Join the precisionFDA Community?

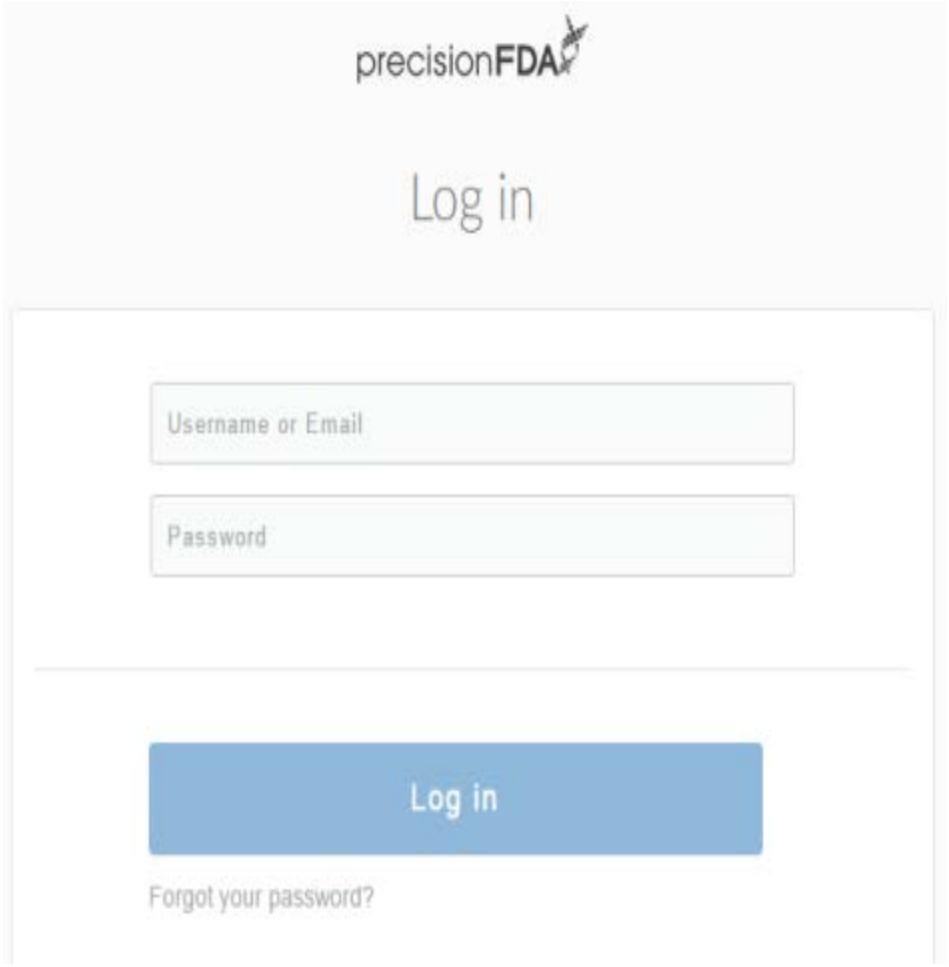
Step 1: Go to https://precision.fda.gov

Step 2: Request access and receive browse capability and instructions on how to obtain approval to be a full contributor and member of the precisionFDA community

Step 3: Request contributor access

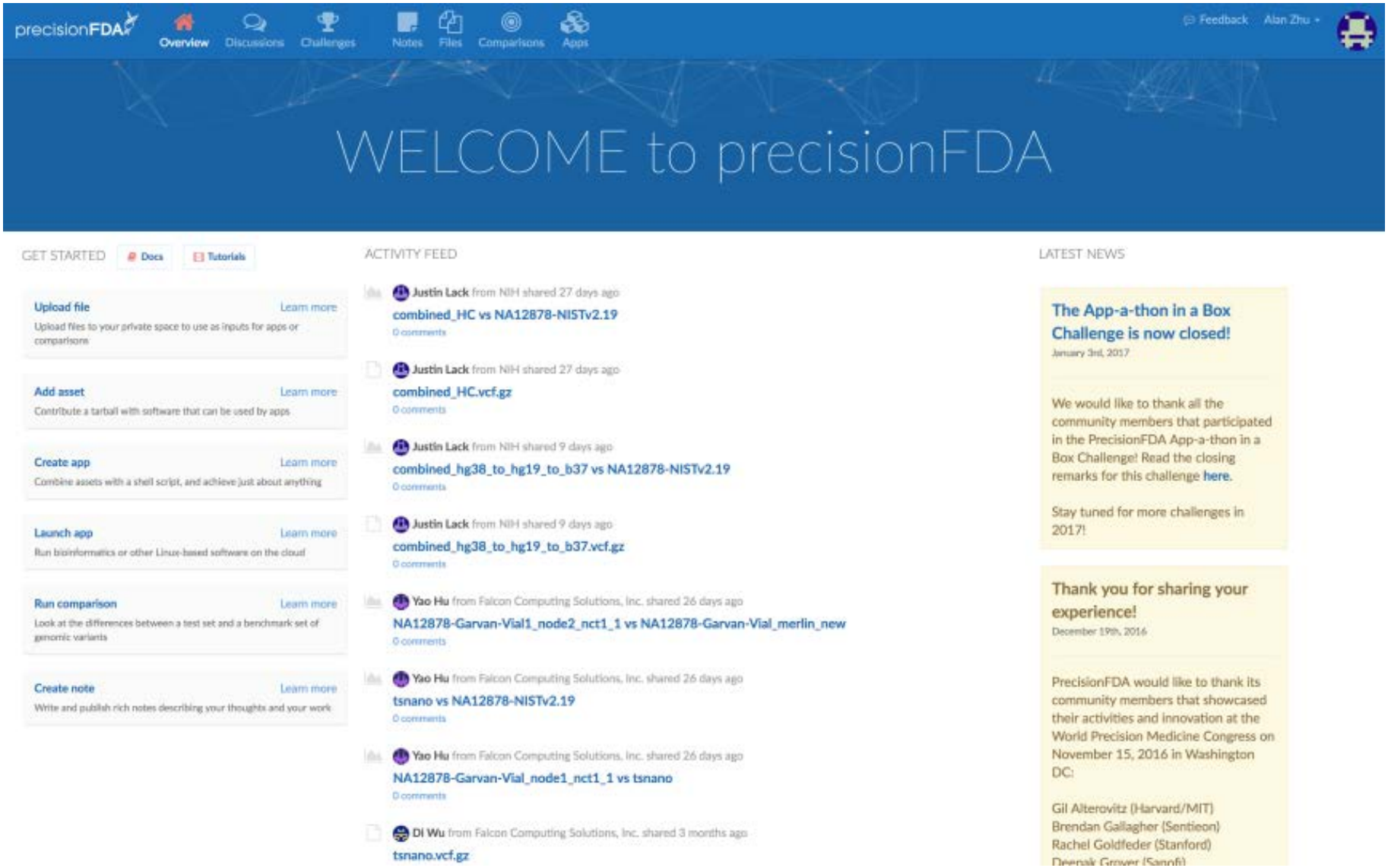
Step 4: Set up two factor authentication

Step 5: Start working with experts from around the world to help move regulatory science forward



Courtesy: Elaine Johanson

precisionFDA



Courtesy: Elaine Johanson

precisionFDA

PrecisionFDA Challenges

Participate in our challenges to engage with and contribute to the community

App-a-thon in a Box

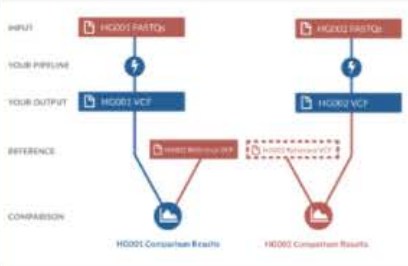
28 responses · 79 followers

- Challenge started 31 Aug 2016 12:00 UTC
- Submissions closed 31 Dec 2016 23:59 UTC
- Results announced 04 Jan 2017 22:10 UTC

Truth Challenge

25 responses · 58 followers

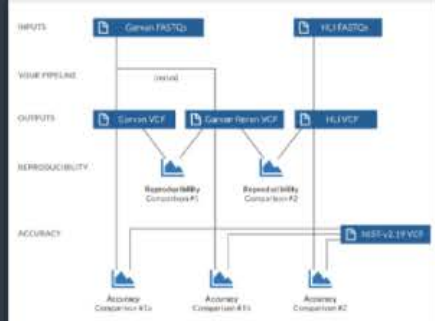
- Challenge started 27 Apr 2016 03:59 UTC
- Submissions closed 27 May 2016 03:59 UTC
- Results announced 29 Jun 2016 13:30 UTC



Consistency Challenge

17 responses · 54 followers

- Challenge started 26 Feb 2016 03:59 UTC
- Submissions closed 26 Apr 2016 03:59 UTC
- Results announced 26 May 2016 00:50 UTC



Courtesy: Elaine Johanson

precisionFDA

- Coming Soon…
  - Ask questions of our Expert of the Month – Early Spring 2017
  - Perform comparisons utilizing the new and improved GA4GH Comparator Tool – Spring 2017
  - Participate in a new precisionFDA Challenge – Summer 2017

- Questions? Reach out via email to the precisionFDA team: precisionFDA@fda.hhs.gov
- Tip: Checkout YouTube videos by UCSF-Stanford CERSI

Courtesy: Elaine Johanson

Summary

- FDA Databases
  - FAERS
  - FDA Pharmacogenomic Biomarkers Table
  - precisionFDA Portal

Acknowledgements

- Genomics and Targeted Therapy Group, OCP, FDA
  - **Mike Pacanowski, PharmD, MPH**
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  - Robert Schuck, PharmD, PhD
  - Anuradha Ramamoorthy, PhD
  - **Kate Drozda, PharmD**
  - Jielin Sun, PhD
  - Oluseyi Adeniyi, PharmD, PhD
- precisionFDA
  - precisionFDA Project Manager **Elaine Johanson**

Questions?

Backup

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FDA Databases

FAERS

FDA Pharmacogenomic Biomarkers Table

precisionFDA Portal

Table of Pharmacogenomic Biomarkers in Drug Labeling

A snapshot:

Drug	Therapeutic Area*	Biomarker†	Labeling Sections
Abacavir	Infectious Diseases	HLA-B*57:01	Boxed Warning, Dosage and Administration, Contraindications, Warnings and Precautions
Ado-Trastuzumab Emtansine	Oncology	ERBB2 (HER2)	Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Afatinib	Oncology	EGFR	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Alectinib	Oncology	ALK	Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Alirocumab	Endocrinology	Not specified	Indications and Usage, Adverse Reactions, Clinical Studies
Amitriptyline	Psychiatry	CYP2D6	Precautions
Anastrozole	Oncology	ESR1, PGR	Indications and Usage, Adverse Reactions, Drug Interactions, Clinical Studies
Arformoterol (1)	Pulmonary	UGT1A1	Clinical Pharmacology
Arformoterol (2)	Pulmonary	CYP2D6	Clinical Pharmacology
Aripiprazole	Psychiatry	CYP2D6	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology
Aripiprazole Lauroxil	Psychiatry	CYP2D6	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology
Arsenic Trioxide	Oncology	PML-RARA	Indications and Usage
Atezolizumab	Oncology	CD274 (PD-L1)	Adverse Reactions, Clinical Pharmacology, Clinical Studies

Table of Pharmacogenomic Biomarkers in Drug Labeling

- **What is included in the Table?**

  PGx biomarkers, including but are not limited to, germline or somatic gene variants, functional deficiencies, expression changes, and chromosomal abnormalities. Selected protein biomarkers (e.g., used for patient selection) may also be included.

  Consistent with ICH E15

- **What is the source of information?**
  - CDER approved product labeling found at Drugs@FDA website
    - Newly approved products
    - Labeling updates for previously approved products

- **How often is the Table updated?**

  Every 6 months*

Table of Pharmacogenomic Biomarkers in Drug Labeling

- **Where is PGx information found in the labeling for inclusion in the Table?**
  Commonly found in sections:
  - 1: Indications and Usage
  - 2: Dosage and Administration
  - 4: Contraindications
  - 5: Warnings and Precautions
  - 12: Clinical Pharmacology, and
  - 14: Clinical Studies

- **What are the inclusion criteria?**
  PGx biomarker content in labeling may be related to the following:
  - Drug exposure and clinical response variability
  - Risk for adverse events
  - Dosing
  - Mechanisms of drug action
  - Trial design features
  - Certain exclusion criteria apply*

Table of Pharmacogenomic Biomarkers in Drug Labeling: Example

Drug	Therapeutic Area*	Biomarker†	Labeling Sections
Blinatumomab	Oncology	BCR-ABL1 (Philadelphia chromosome)	Indications and Usage, Clinical Studies
Bosutinib	Oncology	BCR-ABL1 (Philadelphia chromosome)	Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies
Busulfan	Oncology	BCR-ABL1 (Philadelphia chromosome)	Clinical Studies
Imatinib (2)	Oncology	BCR-ABL1 (Philadelphia chromosome)	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Nilotinib (1)	Oncology	BCR-ABL1 (Philadelphia chromosome)	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies
Omacetaxine	Oncology	BCR-ABL1 (Philadelphia chromosome)	Clinical Studies
Dasatinib	Oncology	BCR-ABL1 (Philadelphia chromosome); T315I mutation	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Studies
Ponatinib	Oncology	BCR-ABL1 (Philadelphia chromosome); T315I mutation	Indications and Usage, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies

Table of Pharmacogenomic Biomarkers in Drug Labeling: Example

Drug	Therapeutic Area*	Biomarker†	Labeling Sections
Imatinib (1)	Oncology	KIT	Indications and Usage, Dosage and Administration, Clinical Studies
Imatinib (2)	Oncology	BCR-ABL1 (Philadelphia chromosome)	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Imatinib (3)	Oncology	PDGFRB	Indications and Usage, Dosage and Administration, Clinical Studies
Imatinib (4)	Oncology	FIP1L1-PDGFRA	Indications and Usage, Dosage and Administration, Clinical Studies

Table of Pharmacogenomic Biomarkers in Drug Labeling: Example

Drugs@FDA: FDA Approved Drug Products

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New Drug Application (NDA): 021588
Company: NOVARTIS
Drug Name(s):
- GLEEVEC (IMATINIB MESYLATE)

EMAIL

- Other Important Information from FDA

Products on NDA 021588

Approval Date(s) and History, Letters, Labels, Reviews for NDA 021588

Labels for NDA 021588

Therapeutic Equivalents for NDA 021588

Table of Pharmacogenomic Biomarkers in Drug Labeling: Example

Labels for NDA 021588

CSV | Excel | Print

Action Date	Submission	Submission Classification or Approval Type	Letters, Reviews, Labels, Patient Package Insert	Note
09/27/2016	SUPPL-47	Labeling	Label (PDF)	
08/25/2016	SUPPL-46	Labeling	Label (PDF)	
08/25/2016	SUPPL-45	Efficacy	Label (PDF)	
01/30/2015	SUPPL-42	Efficacy-Labeling Change With Clinical Data	Label (PDF)	
05/22/2014	SUPPL-40	Labeling-Package Insert	Label (PDF)	
10/30/2013	SUPPL-39	Labeling-Package Insert	Label (PDF)	
02/21/2013	SUPPL-38	Labeling-Package Insert	Label (PDF)	
01/25/2013	SUPPL-37	Efficacy-New Indication	Label (PDF)	
01/31/2012	SUPPL-35	Efficacy-Accelerated Approval	Label (PDF)	
04/01/2011	SUPPL-31	Labeling	Label (PDF)	

Table of Pharmacogenomic Biomarkers in Drug Labeling: Example

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GLEEVEC safely and effectively. See full prescribing information for GLEEVEC.

GLEEVEC® (imatinib mesylate) tablets, for oral use
Initial U.S. Approval: 2001

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.5, 1.6)	8/2016
Dosage and Administration (2.6, 2.7)	8/2016
Warnings and Precautions (5.10)	8/2016

----------INDICATIONS AND USAGE----------

Gleevec is a kinase inhibitor indicated for the treatment of:

- Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase (1.1)
- Patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in blast crisis (BC), accelerated phase (AP), or in chronic phase (CP) after failure of interferon-alpha therapy (1.2)
- Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) (1.3)
- Pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy (1.4)
- Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements as determined with an FDA-approved test (1.5)
- Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation as determined with an FDA-approved test or with c-Kit mutational status unknown (1.6)
- Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown (1.7)
- Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP) (1.8)
- Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST) (1.9)
- Adjuvant treatment of adult patients following resection of Kit (CD117) positive GIST (1.10)

----------DOSAGE AND ADMINISTRATION----------

- Adults with Ph+ CML CP (2.2): 400 mg/day
- Adults with Ph+ CML AP or BC (2.2): 600 mg/day
- Pediatrics with Ph+ CML CP (2.3): 340 mg/m^2/day
- Adults with Ph+ ALL (2.4): 600 mg/day
- Pediatrics with Ph+ ALL (2.5): 340 mg/m^2/day
- Adults with MDS/MPD (2.6): 400 mg/day
- Adults with ASM (2.7): 100 mg/day or 400 mg/day
- Adults with HES/CEL (2.8): 100 mg/day or 400 mg/day
- Adults with DFSP (2.9): 800 mg/day
- Adults with metastatic and/or unresectable GIST (2.10): 400 mg/day
- Adjuvant treatment of adults with GIST (2.11): 400 mg/day
- Patients with mild to moderate hepatic impairment (2.12): 400 mg/day
- Patients with severe hepatic impairment (2.12): 300 mg/day

All doses of Gleevec should be taken with a meal and a large glass of water. Doses of 400 mg or 600 mg should be administered once daily, whereas a

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Edema and severe fluid retention have occurred. Weigh patients regularly and manage unexpected rapid weight gain by drug interruption and diuretics (5.1, 6.1, 6.9)
- Cytopenias, particularly anemia, neutropenia, and thrombocytopenia, have occurred. Manage with dose reduction or dose interruption and in rare cases discontinuation of treatment. Perform complete blood counts weekly for the first month, biweekly for the second month, and periodically thereafter (5.2)
- Severe congestive heart failure and left ventricular dysfunction have been reported, particularly in patients with comorbidities and risk factors. Monitor and treat patients with cardiac disease or risk factors for cardiac failure (5.3)
- Severe hepatotoxicity including fatalities may occur. Assess liver function before initiation of treatment and monthly thereafter or as clinically indicated. Monitor liver function when combined with chemotherapy known to be associated with liver dysfunction (5.4)
- Grade 3/4 hemorrhage has been reported in clinical studies in patients with newly diagnosed CML and with GIST. GI tumor sites may be the source of GI bleeds in GIST (5.5)
- Gastrointestinal perforations, some fatal, have been reported (5.6)
- Cardiogenic shock/left ventricular dysfunction has been associated with the initiation of Gleevec in patients with conditions associated with high eosinophil levels (e.g., HES, MDS/MPD and ASM) (5.7)
- Bullous dermatologic reactions (e.g., erythema multiforme and Stevens-Johnson syndrome) have been reported with the use of Gleevec (5.8)
- Hypothyroidism has been reported in thyroidectomy patients undergoing levothyroxine replacement. Closely monitor TSH levels in such patients (5.9)
- Fetal harm can occur when administered to a pregnant woman. Apprise women of the potential harm to the fetus, and to avoid pregnancy when taking Gleevec (5.10, 8.1)
- Growth retardation occurring in children and pre-adolescents receiving Gleevec has been reported. Close monitoring of growth in children under Gleevec treatment is recommended (5.11, 6.11)
- Tumor lysis syndrome. Close monitoring is recommended (5.12)
- Reports of motor vehicle accidents have been received in patients receiving Gleevec. Caution patients about driving a car or operating machinery (5. 13)

----------ADVERSE REACTIONS----------

The most frequently reported adverse reactions (greater than or equal to 30%) were edema, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue and abdominal pain (6.1, 6.9)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- CYP3A4 inducers may decrease Gleevec C_{max} and AUC (2.12, 7.1, 12.3)
- CYP3A4 inhibitors may increase Gleevec C_{max} and AUC (7.2, 12.3)
- Gleevec is an inhibitor of CYP3A4 and CYP2D6 which may increase the C_{max} and AUC of other drugs (7.3, 7.4, 12.3)
- Patients who require anticoagulation should receive low-molecular weight or standard heparin and not warfarin (7.3)

See 17 for PATIENT COUNSELING INFORMATION

Table of Pharmacogenomic Biomarkers in Drug Labeling: Example

----------INDICATIONS AND USAGE----------

Gleevec is a kinase inhibitor indicated for the treatment of:

- Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase (1.1)
- Patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in blast crisis (BC), accelerated phase (AP), or in chronic phase (CP) after failure of interferon-alpha therapy (1.2)
- Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) (1.3)
- Pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy (1.4)
- Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements as determined with an FDA-approved test (1.5)
- Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation as determined with an FDA-approved test or with c-Kit mutational status unknown (1.6)
- Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown (1.7)
- Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP) (1.8)
- Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST) (1.9)
- Adjuvant treatment of adult patients following resection of Kit (CD117) positive GIST (1.10)

Table of Pharmacogenomic Biomarkers in Drug Labeling: Example

----------DOSAGE AND ADMINISTRATION----------

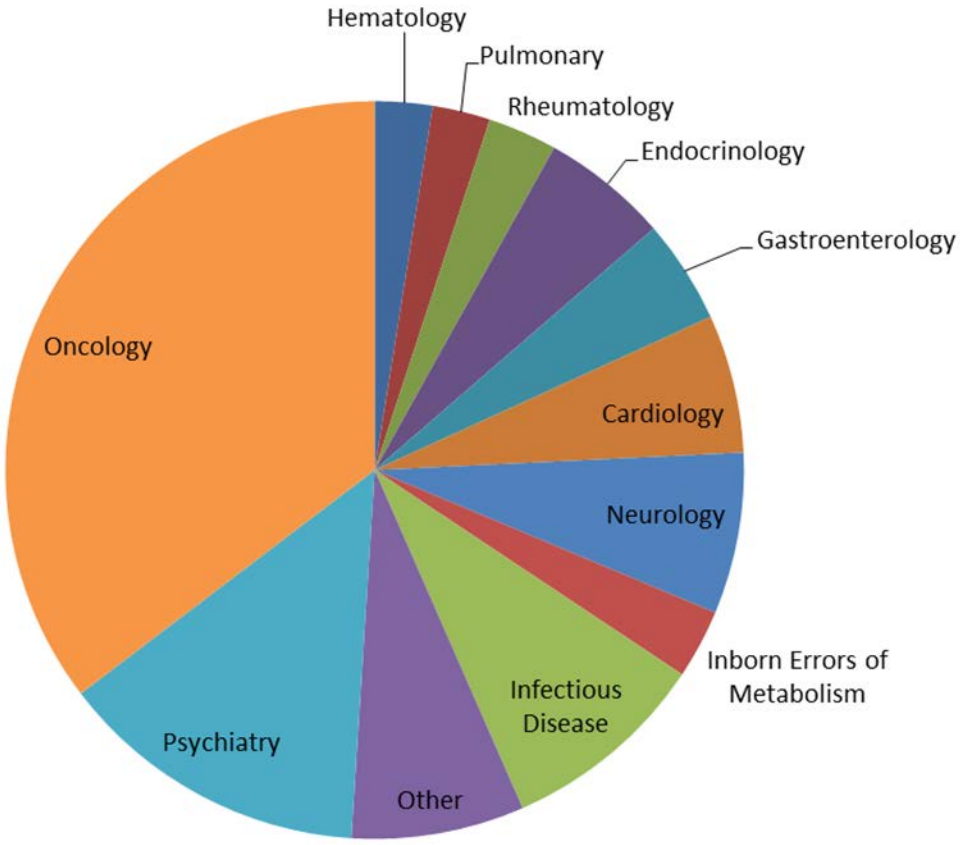
• Adults with Ph+ CML CP (2.2):	400 mg/day
• Adults with Ph+ CML AP or BC (2.2):	600 mg/day
• Pediatrics with Ph+ CML CP (2.3):	340 mg/m^2/day
• Adults with Ph+ ALL (2.4):	600 mg/day
• Pediatrics with Ph+ ALL (2.5):	340 mg/m^2/day
• Adults with MDS/MPD (2.6):	400 mg/day
• Adults with ASM (2.7):	100 mg/day or 400 mg/day
• Adults with HES/CEL (2.8):	100 mg/day or 400 mg/day
• Adults with DFSP (2.9):	800 mg/day
• Adults with metastatic and/or unresectable GIST (2.10):	400 mg/day
• Adjuvant treatment of adults with GIST (2.11):	400 mg/day
• Patients with mild to moderate hepatic impairment (2.12):	400 mg/day
• Patients with severe hepatic impairment (2.12):	300 mg/day

Table of Pharmacogenomic Biomarkers in Drug Labeling: Example

Drug	Therapeutic Area*	Biomarker†	Referenced Subgroup‡	Labeling Sections
Blinatumomab	Oncology	BCR-ABL1	Philadelphia chromosome negative	Indications and Usage, Clinical Studies
Busulfan	Oncology	BCR-ABL1	Philadelphia chromosome negative	Clinical Studies
Bosutinib	Oncology	BCR-ABL1	Philadelphia chromosome positive	Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies
Imatinib (2)	Oncology	BCR-ABL1	Philadelphia chromosome positive	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Nilotinib (1)	Oncology	BCR-ABL1	Philadelphia chromosome positive	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Omacetaxine	Oncology	BCR-ABL1	Philadelphia chromosome positive	Clinical Pharmacology, Clinical Studies
Dasatinib	Oncology	BCR-ABL1	Philadelphia chromosome positive, T315I mutation positive	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Ponatinib	Oncology	BCR-ABL1	Philadelphia chromosome	Indications and Usage,

Link to precisionFDA

Biomarkers and Genetic Factors in Product Labeling



198 gene-drug pairs

163 drugs, 54 biomarkers*

43% metabolism/transport

34% target/pathway

23% immunologic/other safety

92 actionable**

Otherwise, descriptive of study design feature or presence/absence of gene-drug interaction

* Includes some products with multiple drugs and families of biomarkers resulting in a phenotype (e.g. urea cycle disorders)

** Management recommendations excluding "use with caution"

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