

Pharmacogenomic Information in Drug Labeling

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Conflict of Interest Disclosure

Dr.s Grillo and Schuck have no relevant financial relationships with a commercial interest pertaining to the content of this presentation

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Learning Objectives

- Describe the type and location of pharmacogenomics information in FDA-approved drug labels
- Explain the regulatory process for integrating pharmacogenomics information into FDA-approved drug labels, both during and after the drug approval process

The prescribing information is a summary of the essential information for safe and effective use of a drug. It is the primary tool for FDA to communicate drug information to health care providers.

Physician Labeling Rule (PLR) Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

Pharmacogenomic information

Major Application Holder Responsibilities

- The Prescribing Information is written for the healthcare practitioner (HCP) and must:
 - Contain a summary of essential scientific information needed for safe and effective use of the human prescription drug or biological product.
 - Be informative and accurate and neither promotional in tone nor false or misleading
 - Be updated when new information becomes available that causes labeling to become inaccurate, false, or misleading
 - Application holders should review PI at least annually for outdated information.

21 CFR 201.56(a)

Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements (February 2013)

ZEPOSIA® (ozanimod) capsules, for oral use

Initial U.S. Approval: 2020

NDA 209899

Approved Prescribing Information (PI)

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Smokers

Population PK analyses showed that CC112273 steady-state exposure (AUC) was approximately 50% lower in smokers than in nonsmokers. The clinical impact of smoking on ozanimod treatment for patients with RMS is not known.

RMS =relapsing forms of multiple sclerosis
CC112273 = A major circulating active metabolite

Conclusion: The effect of dose on CC112273 exposure response is not as sensitive to body weight as previously reported. Only weight and clinical effect (less than 10%) in the exposure of metabolite-1.

Study Weight: Only weight and clinical effect (less than 10%) in the exposure of metabolite-1.

Conclusion: The effect of dose on CC112273 exposure response is not as sensitive to body weight as previously reported. Only weight and clinical effect (less than 10%) in the exposure of metabolite-1.

Study Weight: Only weight and clinical effect (less than 10%) in the exposure of metabolite-1.

Percentage change in AUC from baseline between smokers and nonsmokers (Study 2012)

Study	Time	Smokers	Nonsmokers	Smokers	Nonsmokers
Study 2012	Day 1	100	100	100	100
Study 2012	Day 2	100	100	100	100
Study 2012	Day 3	100	100	100	100
Study 2012	Day 4	100	100	100	100
Study 2012	Day 5	100	100	100	100
Study 2012	Day 6	100	100	100	100
Study 2012	Day 7	100	100	100	100
Study 2012	Day 8	100	100	100	100
Study 2012	Day 9	100	100	100	100
Study 2012	Day 10	100	100	100	100
Study 2012	Day 11	100	100	100	100
Study 2012	Day 12	100	100	100	100
Study 2012	Day 13	100	100	100	100
Study 2012	Day 14	100	100	100	100
Study 2012	Day 15	100	100	100	100
Study 2012	Day 16	100	100	100	100
Study 2012	Day 17	100	100	100	100
Study 2012	Day 18	100	100	100	100
Study 2012	Day 19	100	100	100	100
Study 2012	Day 20	100	100	100	100
Study 2012	Day 21	100	100	100	100
Study 2012	Day 22	100	100	100	100
Study 2012	Day 23	100	100	100	100
Study 2012	Day 24	100	100	100	100
Study 2012	Day 25	100	100	100	100
Study 2012	Day 26	100	100	100	100
Study 2012	Day 27	100	100	100	100
Study 2012	Day 28	100	100	100	100
Study 2012	Day 29	100	100	100	100
Study 2012	Day 30	100	100	100	100
Study 2012	Day 31	100	100	100	100
Study 2012	Day 32	100	100	100	100
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Study 2012	Day 42	100	100	100	100
Study 2012	Day 43	100	100	100	100
Study 2012	Day 44	100	100	100	100
Study 2012	Day 45	100	100	100	100
Study 2012	Day 46	100	100	100	100
Study 2012	Day 47	100	100	100	100
Study 2012	Day 48	100	100	100	100
Study 2012	Day 49	100	100	100	100
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Study 2012	Day 51	100	100	100	100
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Study 2012	Day 67	100	100	100	100
Study 2012	Day 68	100	100	100	100
Study 2012	Day 69	100	100	100	100
Study 2012	Day 70	100	100	100	100
Study 2012	Day 71	100	100	100	100
Study 2012	Day 72	100	100	100	100
Study 2012	Day 73	100	100	100	100
Study 2012	Day 74	100	100	100	100
Study 2012	Day 75	100	100	100	100
Study 2012	Day 76	100	100	100	100
Study 2012	Day 77	100	100	100	100
Study 2012	Day 78	100	100	100	100
Study 2012	Day 79	100	100	100	100
Study 2012	Day 80	100	100	100	100
Study 2012	Day 81	100	100	100	100
Study 2012	Day 82	100	100	100	100
Study 2012	Day 83	100	100	100	100
Study 2012	Day 84	100	100	100	100
Study 2012	Day 85	100	100	100	100
Study 2012	Day 86	100	100	100	100
Study 2012	Day 87	100	100	100	100
Study 2012	Day 88	100	100	100	100
Study 2012	Day 89	100	100	100	100
Study 2012	Day 90	100	100	100	100
Study 2012	Day 91	100	100	100	100
Study 2012	Day 92	100	100	100	100
Study 2012	Day 93	100	100	100	100
Study 2012	Day 94	100	100	100	100
Study 2012	Day 95	100	100	100	100
Study 2012	Day 96	100	100	100	100
Study 2012	Day 97	100	100	100	100
Study 2012	Day 98	100	100	100	100
Study 2012	Day 99	100	100	100	100
Study 2012	Day 100	100	100	100	100

Study Weight: Only weight and clinical effect (less than 10%) in the exposure of metabolite-1.

Adverse, unexplained findings from AUC, the clinical endpoint for the clinical impact of smoking on ozanimod treatment for patients with RMS is not known.

Conclusion: The effect of dose on CC112273 exposure response is not as sensitive to body weight as previously reported. Only weight and clinical effect (less than 10%) in the exposure of metabolite-1.

Study Weight: Only weight and clinical effect (less than 10%) in the exposure of metabolite-1.



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HCP Perception of Prescribing Information

What's Wrong?

- Confusing structure
- Too much information
- Wrong information
- No conveyance of risk
- No real guidance

Ideal Presentation

- Easy to access and navigate
- Minimizes pharmacology jargon
- Clinically intuitive structure
- Imparts sense of severity or risk
- Provides risk management instructions
- Omits unnecessary information
- Up to date

Enhance the safe and effective use of prescription drugs by facilitating optimal communication through PDL

Increase percentage of PDLs that comply with PLR content and format requirements

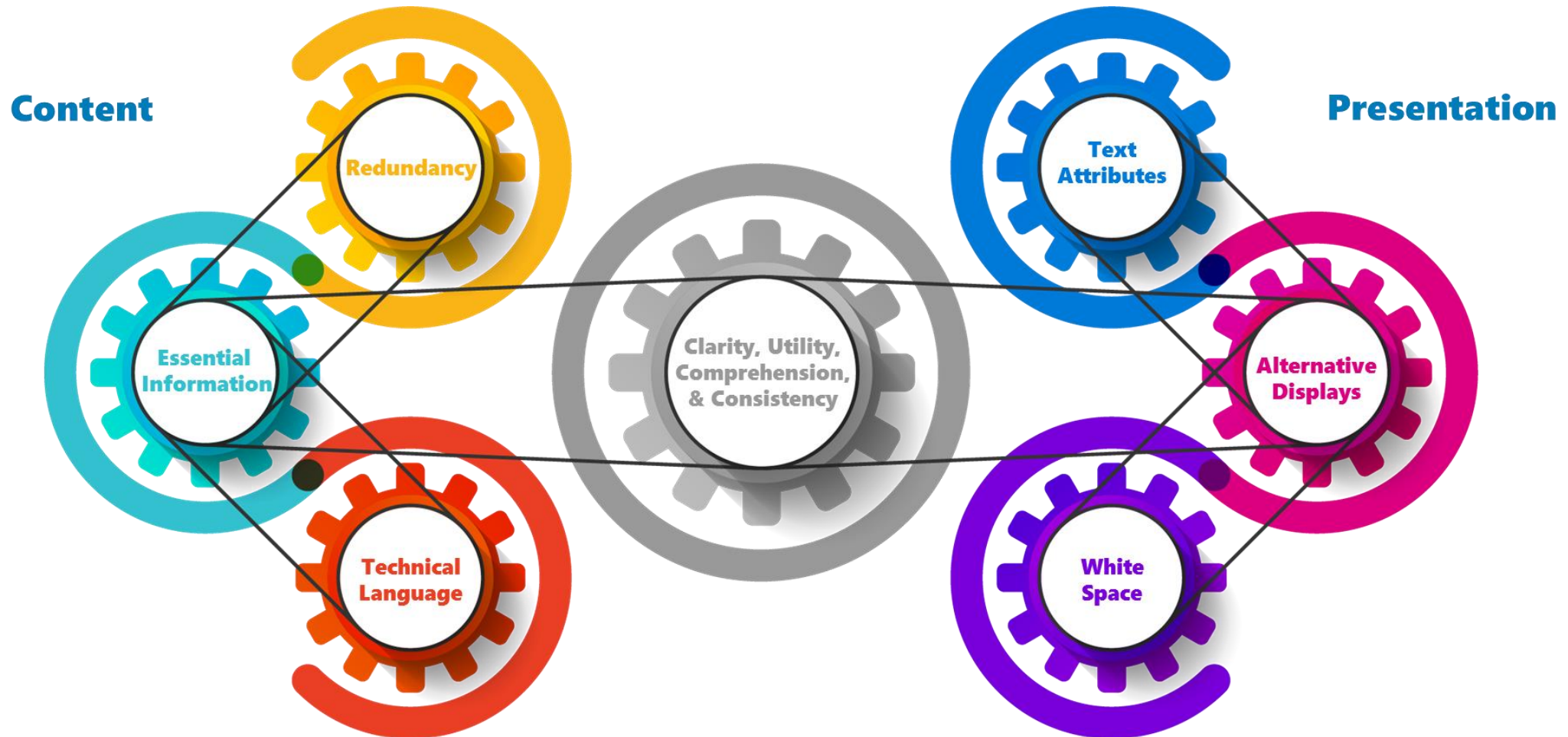
Develop and evaluate approaches to enhance clarity, utility, and comprehension of PDL across CDER

Foster consistency in PDL across CDER by establishing guidances and best practices

PDLIEI

PDLIEI = PDL Improvement & Enhancement Initiative

Strategies to Enhance Clinical Pharmacology Labeling Development



Including Pharmacogenomics (PGx) Information in Labeling



- PGx information that is considered essential is included in labeling
- Should inform prescribers about:
 - The impact (or lack of impact) of genotype on phenotype
 - Whether a genomic test is available, and, if it is recommended or necessary
- A “Pharmacogenomics” subsection (12.5) should include clinically relevant information on the effect of genetic variations affecting drug therapy

[Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling](#)
21 CFR 201.56(a)

What PGx Information Should be Included?

- Information on the frequencies of relevant alleles, genotypes, haplotypes, or other genomic markers
- Description of the functional effects of genomic variants
 - e.g., genetically based differences in enzyme activity
- Effect of genotype on important PK parameters or PD endpoints
- Description of PGx studies that provide evidence of genetically-based differences in drug benefit or risk
- Dosing & patient selection recommendations based on genotype
- A “Pharmacogenomics” subsection (12.5) should include clinically relevant information on the effect of genetic variations affecting drug therapy

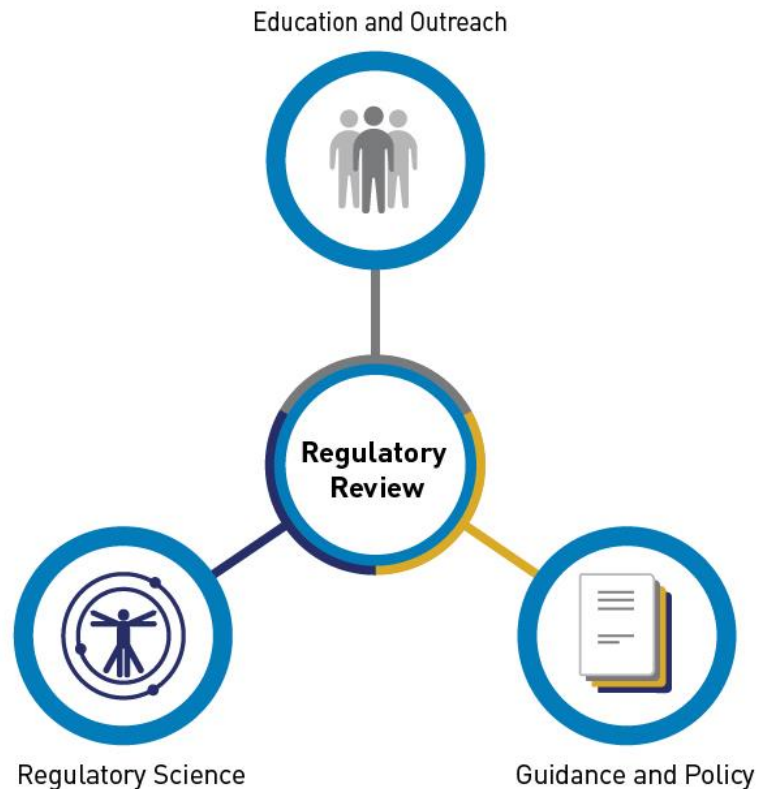
Where Should PGx Information be Included?

Section of Label	Types of Information
INDICATIONS AND USAGE	PGx information for proper patient selection (e.g., PGx testing)
DOSAGE AND ADMINISTRATION	Dosing recommendations for patient subgroups based on genetic makeup
BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and/or ADVERSE REACTIONS	PGx information affecting drug safety
WARNINGS AND PRECAUTIONS and USE IN SPECIFIC POPULATIONS	Genotype(s) known to be associated with an adverse reaction in a specific population
DRUG INTERACTIONS	Role of genetic variations in drug-drug interactions The clinical consequences of the combination of genetic polymorphisms in the context of the drug's metabolism, transport, and action
CLINICAL PHARMACOLOGY	PGx impact on PK or PD
CLINICAL STUDIES ^a	Efficacy differences related to PGx

^a If studied and the evidence is substantial; or if observed neutral findings (i.e., lack of a pharmacogenetic effect) would be pertinent clinical information

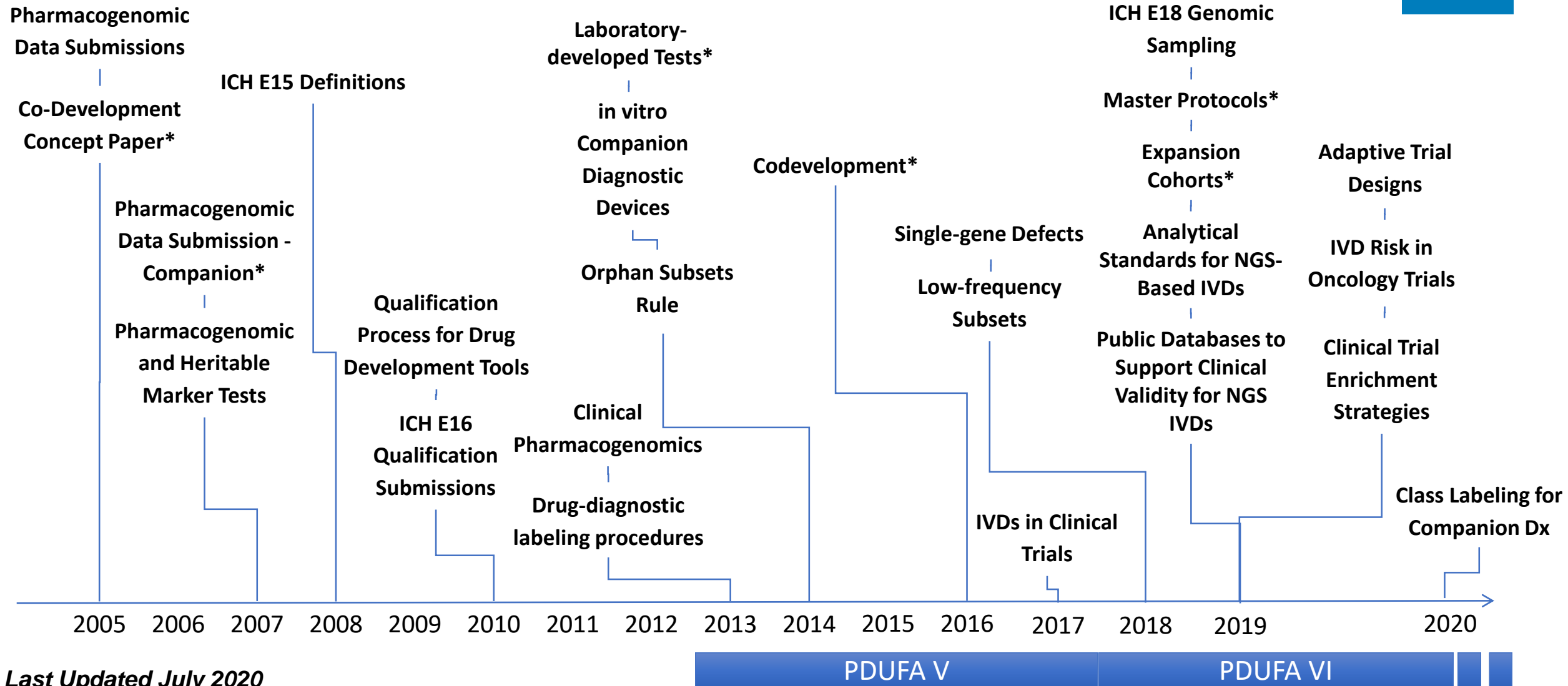
Gene-Drug Interactions in FDA Labeling

Genomics at FDA



- **Drug & Biomarker Evaluation**
 - Influence use of biomarkers to enhance benefit/risk profile of drugs
- **Guidance & Policy**
 - Develop and implement policies related to biomarker use in drug development
- **Partnerships & Outreach**
 - Engage stakeholders and cultivate expertise on emerging issues
- **Regulatory Science**
 - Conduct pragmatic research to enhance regulatory policy and practice

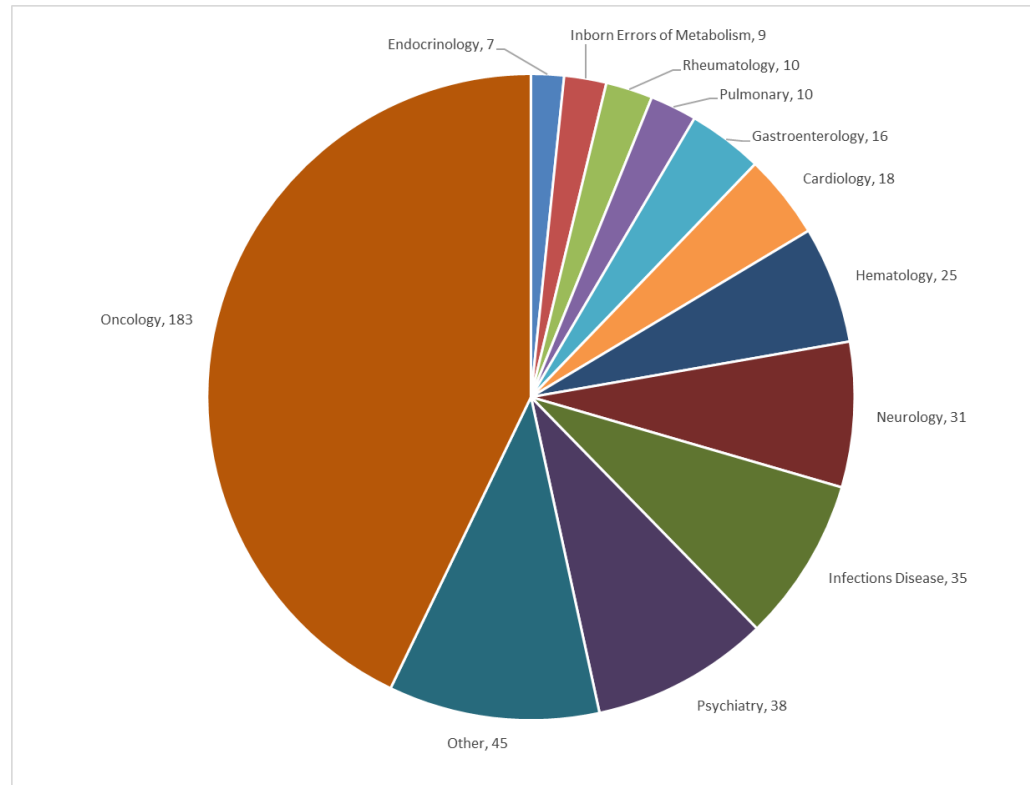
Guidance and Policy in Precision Medicine



Last Updated July 2020

* Draft

Biomarkers and Genetic Factors in Labeling



427 biomarker-drug pairs

296 drugs, 112 biomarkers*

33% metabolism/transport

41% target/pathway

26% immunologic/other safety

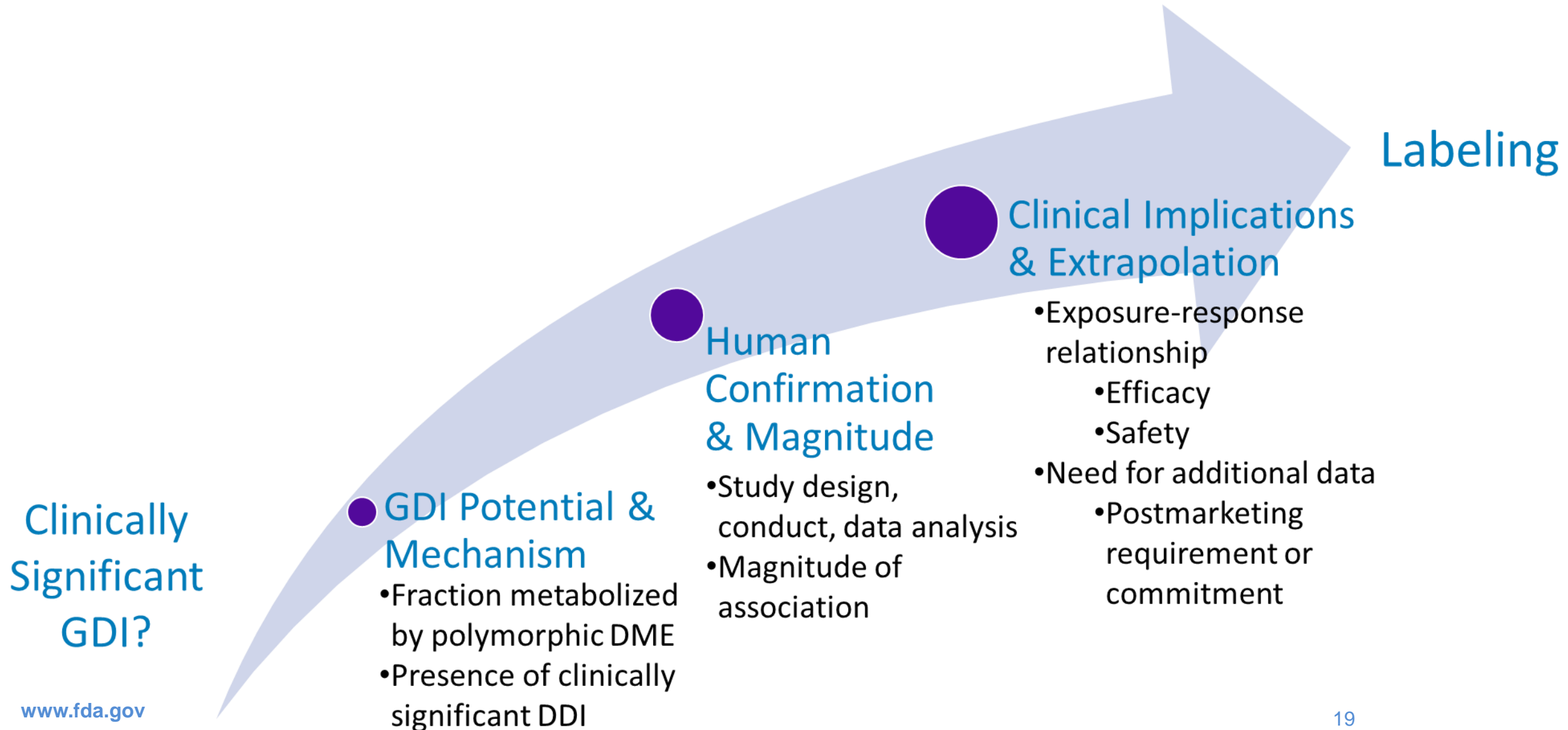
230 actionable**

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

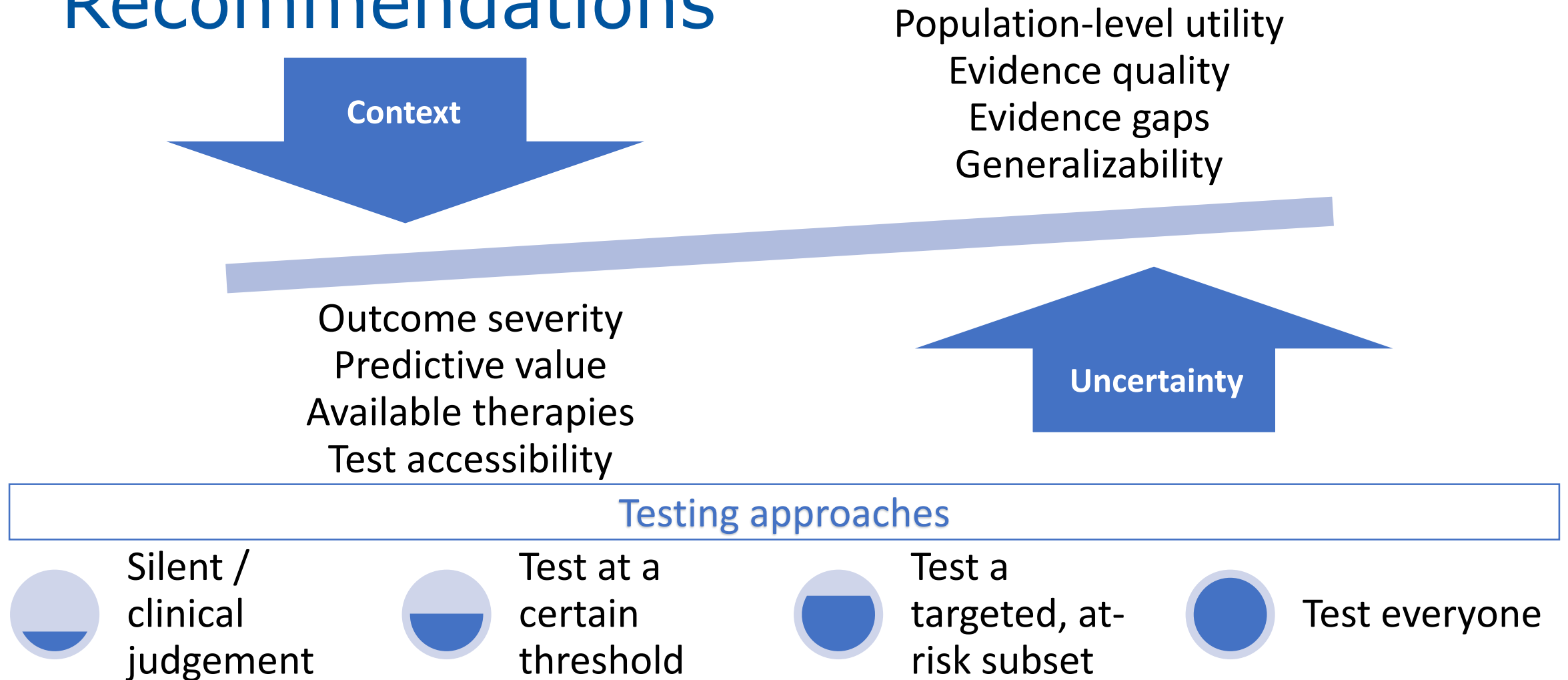
* Includes some products with multiple drugs and families of biomarkers resulting in a phenotype (e.g., urea cycle disorders)

** Management recommendations excluding "Use with Caution"

Informing the Regulatory Decision



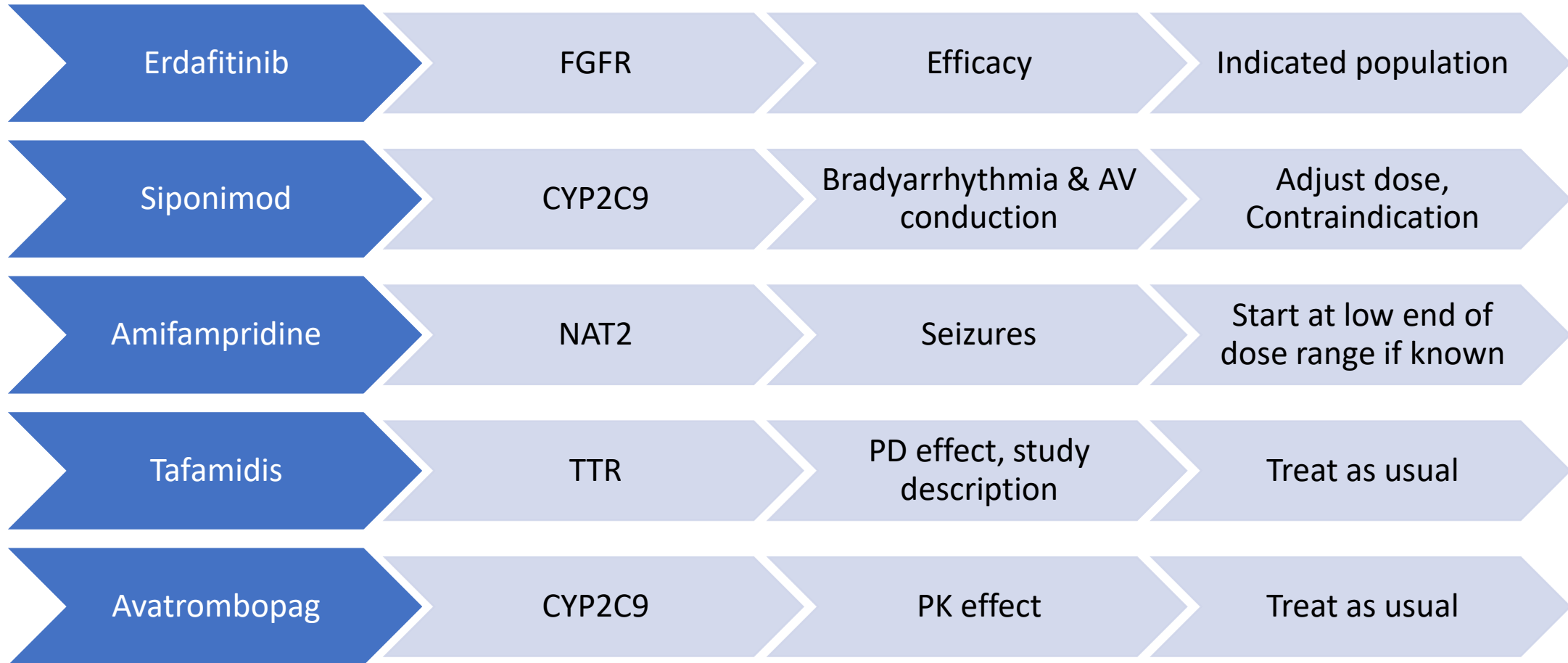
Factors Guiding the Strength of Recommendations



Premarketing

- Initial drug labeling contains information derived from studies submitted to support marketing approval
- Data are critically reviewed by FDA staff
 - Summary of the essential scientific information needed for the safe and effective use of the drug is agreed upon by the FDA and the submitting pharmaceutical company
- Regulations require that labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.
 - 21 c.F.R. § 201.56 (2010)

Select Initial Drug Labels



Siponimod Labeling Considerations

GDI Potential & Mechanism

- >75% metabolized by CYP2C9
- Dual CYP2C9/CYP3A4 inhibitor increases AUC ~2-fold

Human Confirmation & Magnitude

- PopPK and dedicated GDI studies
- CYP2C9*1/*3 and *2/*3
 - ~2-fold higher AUC
- CYP2C9*3/*3
 - ~4-fold higher AUC

Clinical Implications & Extrapolation

- Exposure-dependent bradyarrhythmia and AV conduction delays
- CYP2C9*3/*3 patients excluded from pivotal trials for safety reasons

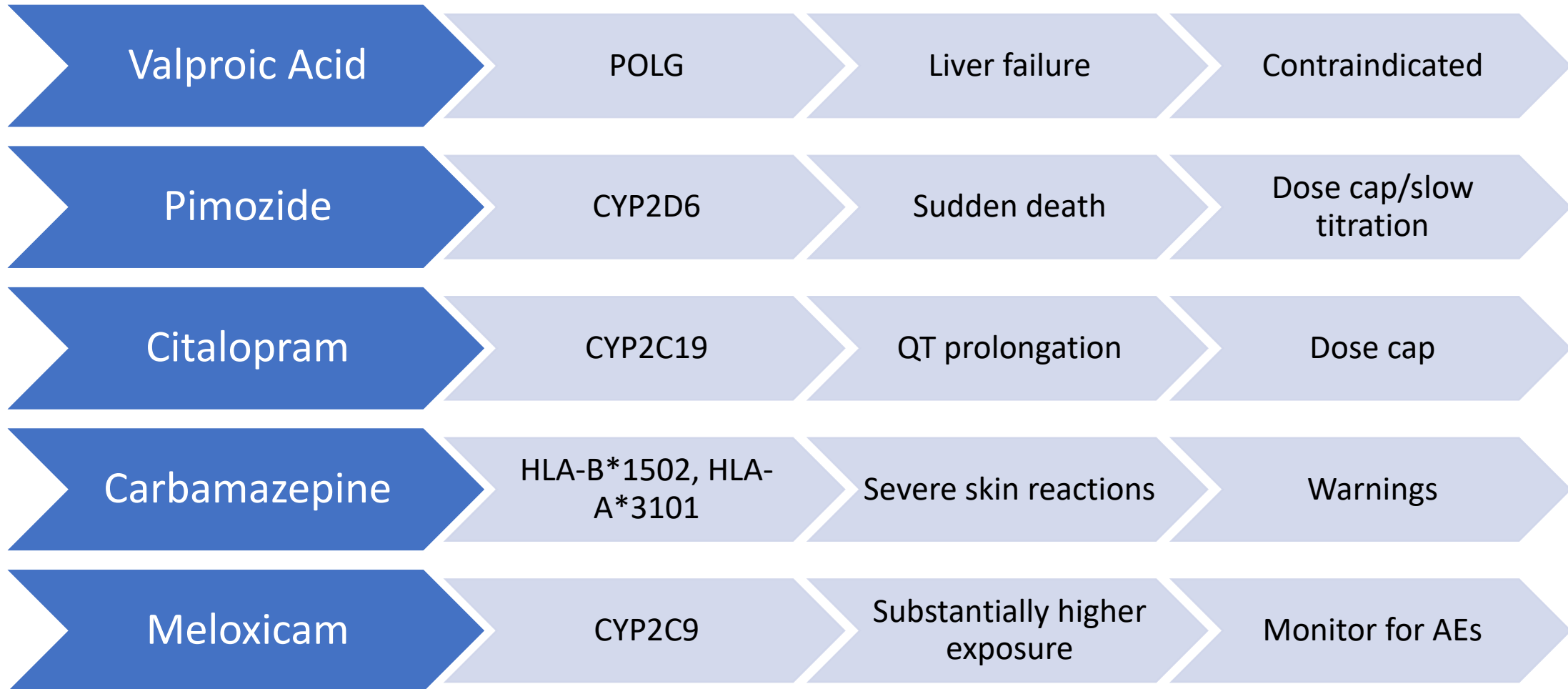
Labeling

- Genotype prior to prescribing
- Contraindication in CYP2C9*3/*3
- Dose reduction in CYP2C9*1/*3 and *2/*3
- PMC for assay

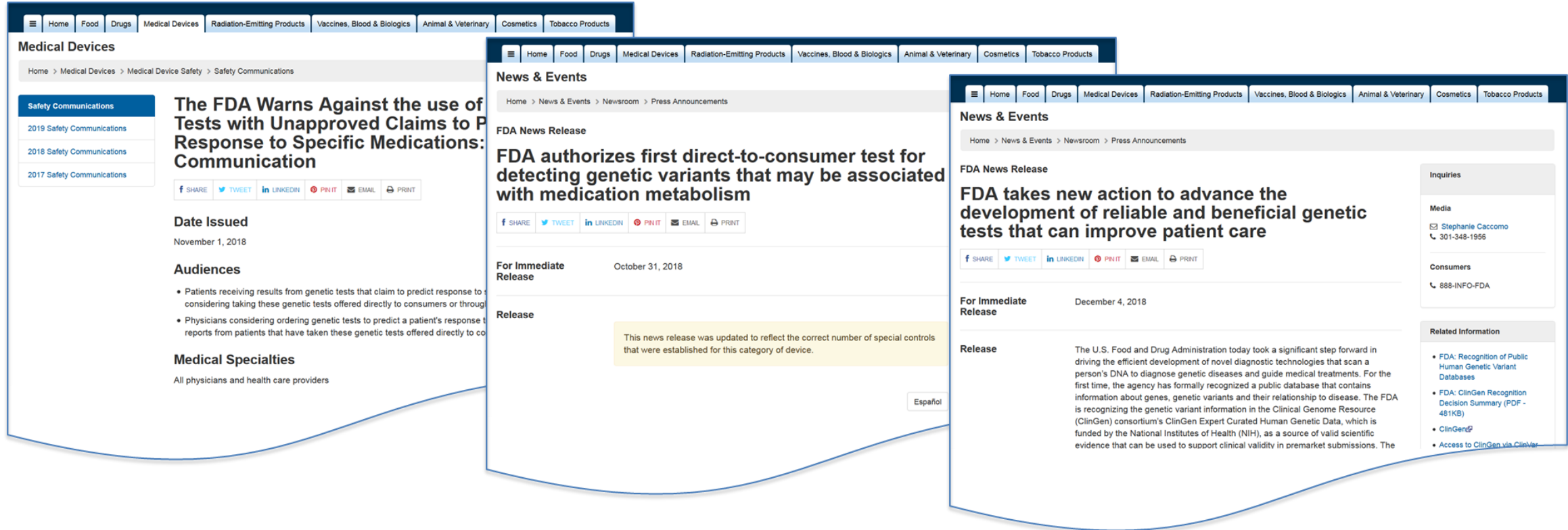
Postmarketing Labeling Updates

- Regulations require that labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.
 - 21 c.F.R. § 201.56 (2010)
- FDA or the application holder may request to change labeling based on updated safety or efficacy data.
 - Under Title IX of the Food and Drug Administration Amendments Act of 2007 (FDAAA), ***FDA may compel changes to previously approved labeling when new safety information becomes available for the drug***
 - New safety information may come from clinical trials, adverse event reports, peer-reviewed biomedical literature, and other appropriate scientific data

Selected Post-Marketing Revisions



Pharmacogenetic Testing



The image displays three overlapping screenshots of the FDA website, illustrating regulatory actions and communications regarding pharmacogenetic testing.

Left Screenshot: Medical Devices - Safety Communications

- Page Title:** Medical Devices
- Breadcrumb:** Home > Medical Devices > Medical Device Safety > Safety Communications
- Section:** Safety Communications
- Sub-sections:** 2019 Safety Communications, 2018 Safety Communications, 2017 Safety Communications
- Article Title:** The FDA Warns Against the use of Tests with Unapproved Claims to Predict Response to Specific Medications: Communication
- Date Issued:** November 1, 2018
- Audiences:**
 - Patients receiving results from genetic tests that claim to predict response to medications
 - Physicians considering ordering genetic tests to predict a patient's response to medications
- Medical Specialties:** All physicians and health care providers

Middle Screenshot: News & Events - FDA News Release

- Page Title:** News & Events
- Breadcrumb:** Home > News & Events > Newsroom > Press Announcements
- Section:** FDA News Release
- Article Title:** FDA authorizes first direct-to-consumer test for detecting genetic variants that may be associated with medication metabolism
- Date:** October 31, 2018
- For Immediate Release**
- Release:** This news release was updated to reflect the correct number of special controls that were established for this category of device.

Right Screenshot: News & Events - FDA News Release

- Page Title:** News & Events
- Breadcrumb:** Home > News & Events > Newsroom > Press Announcements
- Section:** FDA News Release
- Article Title:** FDA takes new action to advance the development of reliable and beneficial genetic tests that can improve patient care
- Date:** December 4, 2018
- For Immediate Release**
- Release:** The U.S. Food and Drug Administration today took a significant step forward in driving the efficient development of novel diagnostic technologies that scan a person's DNA to diagnose genetic diseases and guide medical treatments. For the first time, the agency has formally recognized a public database that contains information about genes, genetic variants and their relationship to disease. The FDA is recognizing the genetic variant information in the Clinical Genome Resource (ClinGen) consortium's ClinGen Expert Curated Human Genetic Data, which is funded by the National Institutes of Health (NIH), as a source of valid scientific evidence that can be used to support clinical validity in premarket submissions. The

Related Information:

- FDA: Recognition of Public Human Genetic Variant Databases
- FDA: ClinGen Recognition Decision Summary (PDF - 481KB)
- ClinGen®
- Access to ClinGen via ClinVar

- Most pharmacogenomic tests are not considered companion diagnostics (essential for safe and effective use of the drug)
 - Not co-developed and authorized with drugs
- Marketed tests identified with unsupported claims
- FDA has issued safety communication and warning letter on pharmacogenomic tests



Table of Pharmacogenetic Associations

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Pharmacogenetic associations for which the data support therapeutic management recommendations

Drug	Gene	Affected Subgroups+	Description of Gene-Drug Interaction
Abacavir	HLA-B	*57:01 allele positive	Results in higher adverse reaction risk (hypersensitivity reactions). Do not use abacavir in patients positive for HLA-B*57:01.
Amifampridine	NAT2	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Use lowest recommended starting dosage and monitor for adverse reactions. Refer to FDA labeling for specific dosing recommendations.
Amifampridine Phosphate	NAT2	poor metabolizers	Results in higher systemic concentrations. Use lowest recommended starting dosage (15 mg/day) and monitor for adverse reactions.
Amphetamine	CYP2D6	poor metabolizers	May affect systemic concentrations and adverse reaction risk. Consider lower starting dosage or use alternative agent.

FDA Table of Pharmacogenetic Associations

February 2020



- Includes pharmacogenetic associations that FDA has evaluated and believes there is sufficient scientific evidence
 - Not intended to affect current regulatory requirements or policies
- Limited to pharmacogenetic associations related to drug metabolizing enzyme/transporter gene variants or predisposition to adverse events
- Divided into three tiers:
 - Pharmacogenetic associations for which the data support therapeutic management recommendations
 - Pharmacogenetic associations for which the data indicate a potential impact on safety or response
 - Pharmacogenetic associations for which the data demonstrate a potential impact on pharmacokinetic properties only

Conclusions

- CDER is committed to enhancing the safe and effective use of prescription drugs by facilitating optimal communication through prescribing information
- Precision medicine strategies and pharmacogenomics are becoming more prevalent in research, drug development, and clinical practice
- Including appropriate pharmacogenomic information and accurately describing it in labeling is critical

FDA

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OFFICE OF CLINICAL PHARMACOLOGY**