U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

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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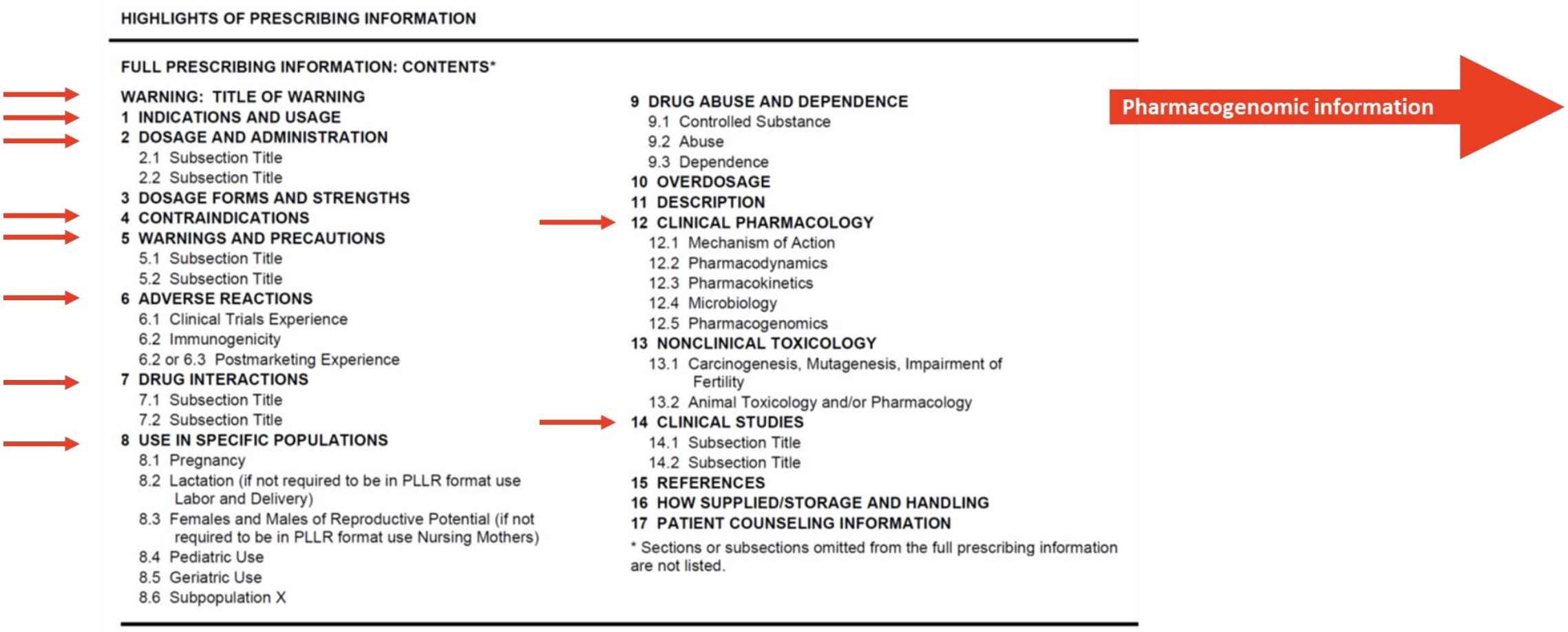
Learning Objectives

- 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.

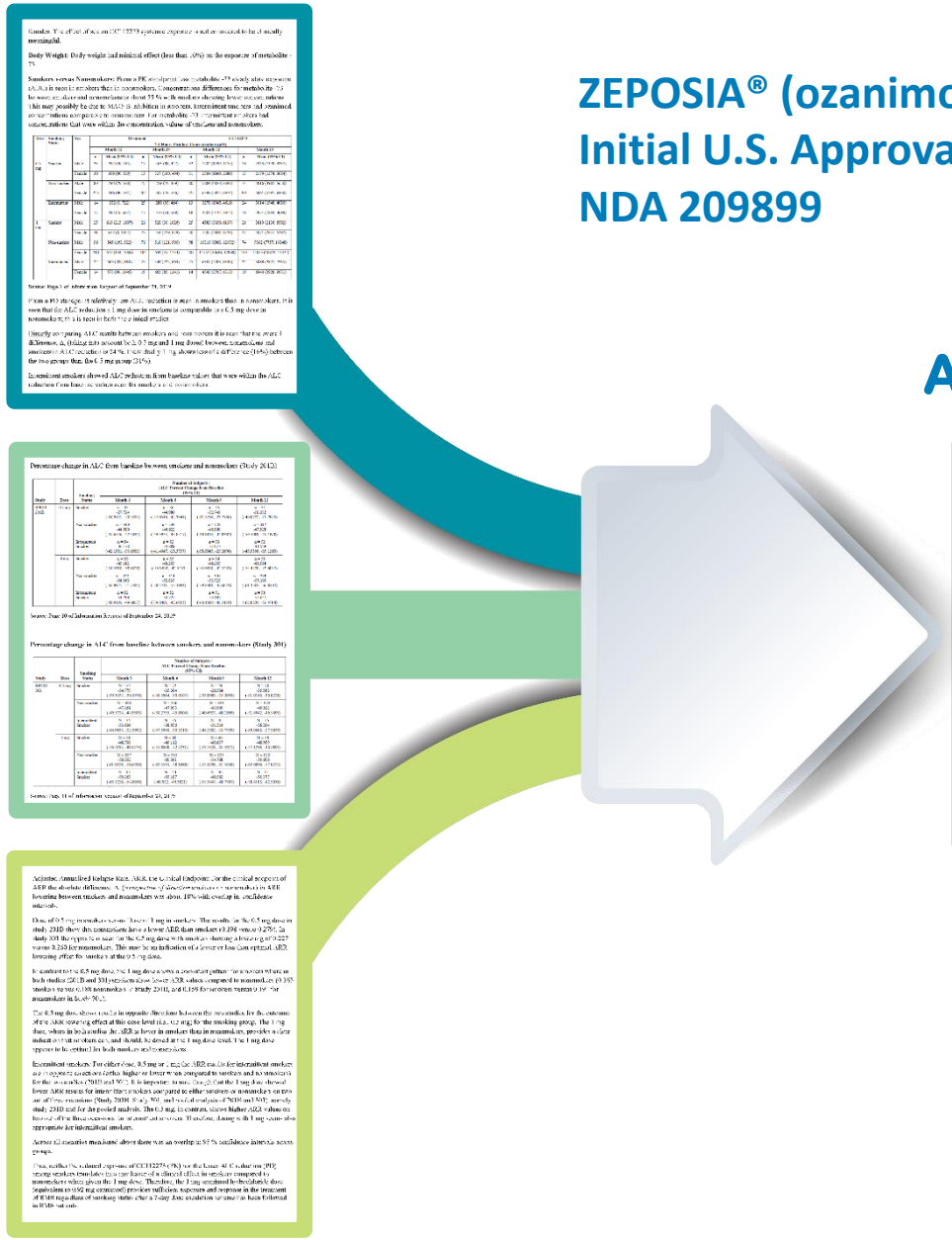
Major Application Holder Responsibilities

- 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)

OCP Integrated Review



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

The full OCP review (redacted) and approved PI: https://bit.ly/3dLnaV4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10:32 AM
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SEARCH
Search By Drug Name, Active Ingredient, or Application Number
LAST 7 DAYS' APPROVALS
FDA WEB PAGES
FDA HELP & SUPPORT
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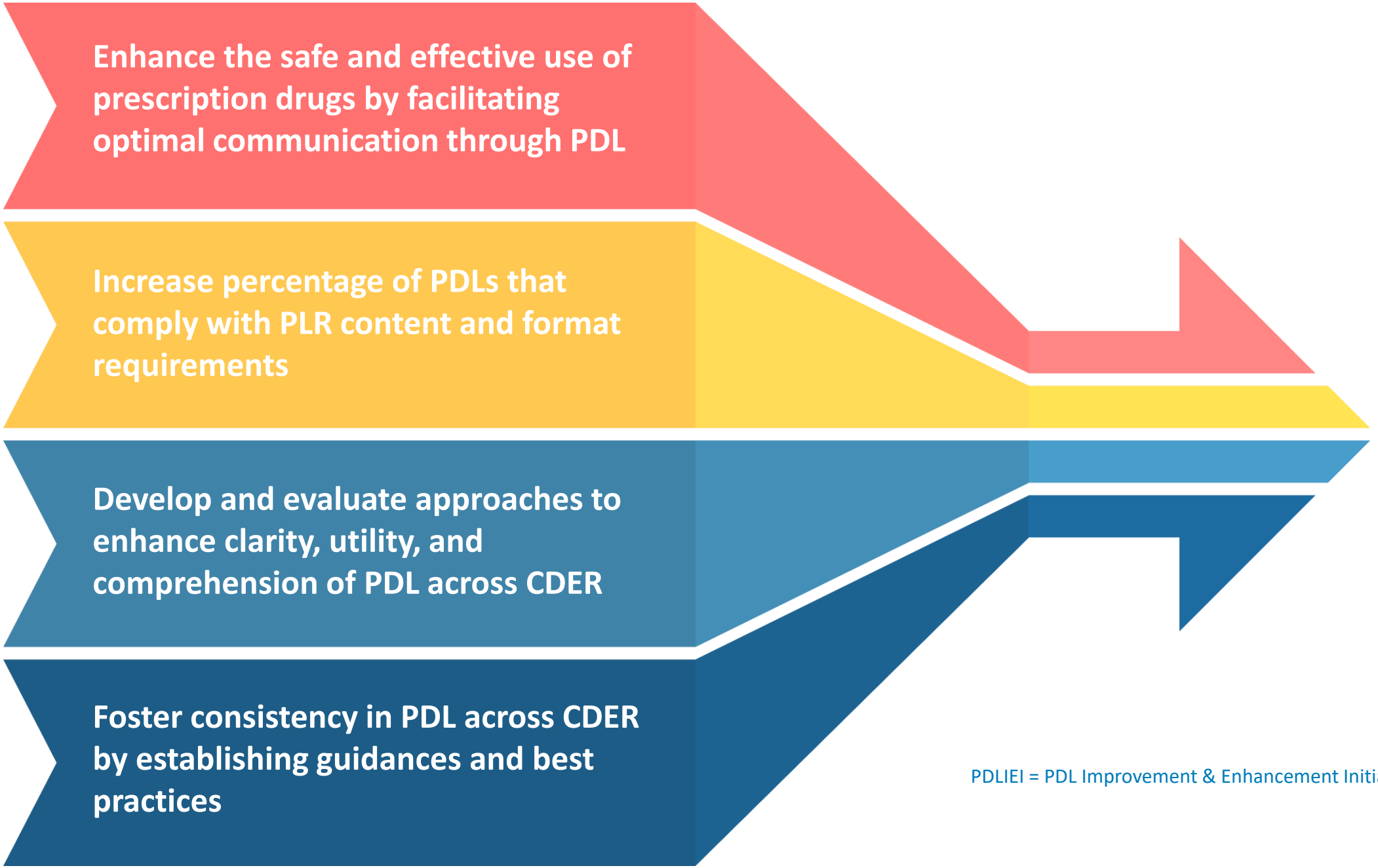
HCP Perception of Prescribing Information

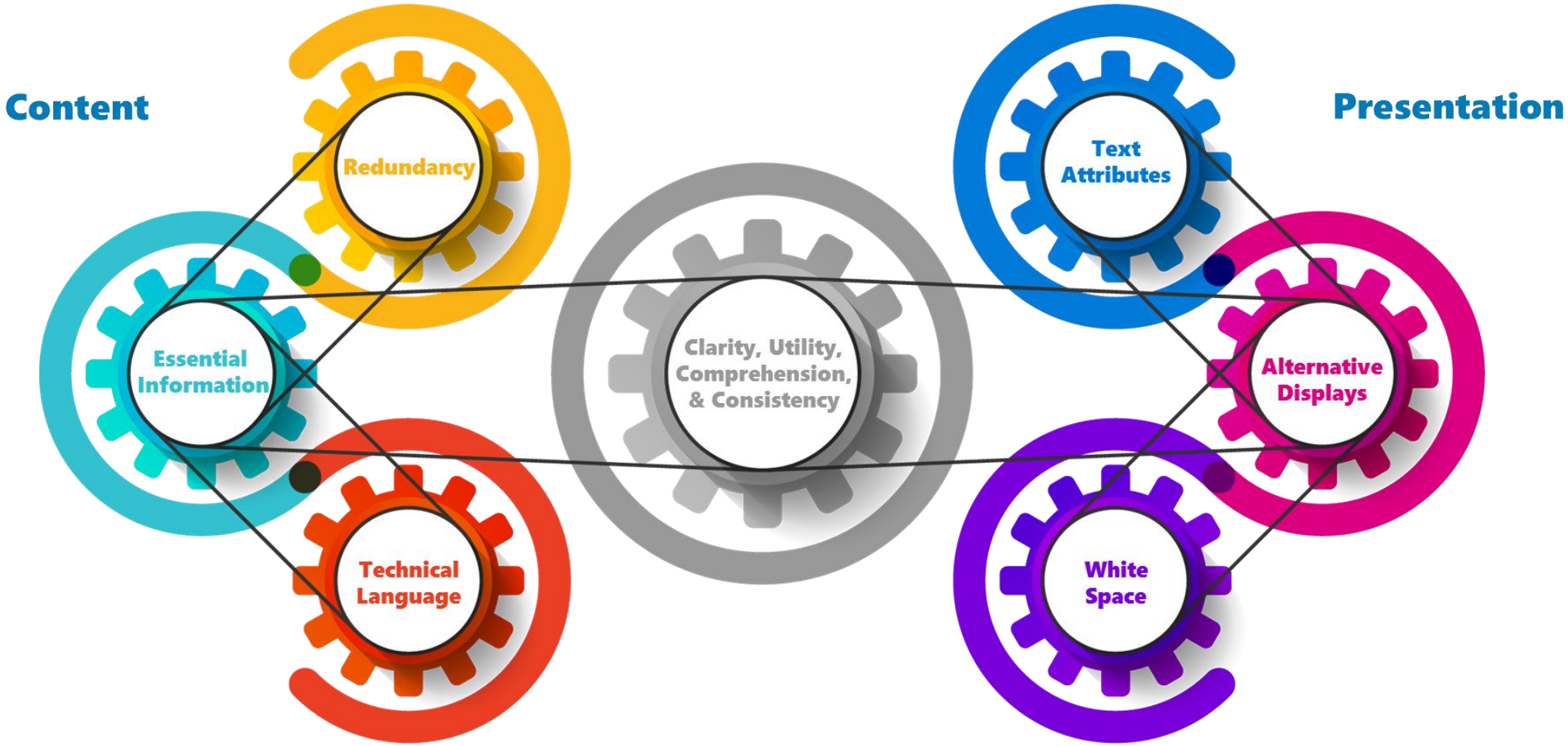
What's Wrong?	Ideal Presentation
• Confusing structure	• Easy to access and navigate
• Too much information	• Minimizes pharmacology jargon
• Wrong information	• Clinically intuitive structure
• No conveyance of risk	• Imparts sense of severity or risk
• No real guidance	• Provides risk management instructions
	• Omits unnecessary information
	• Up to date



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

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

Where Should PGx Information be Included?

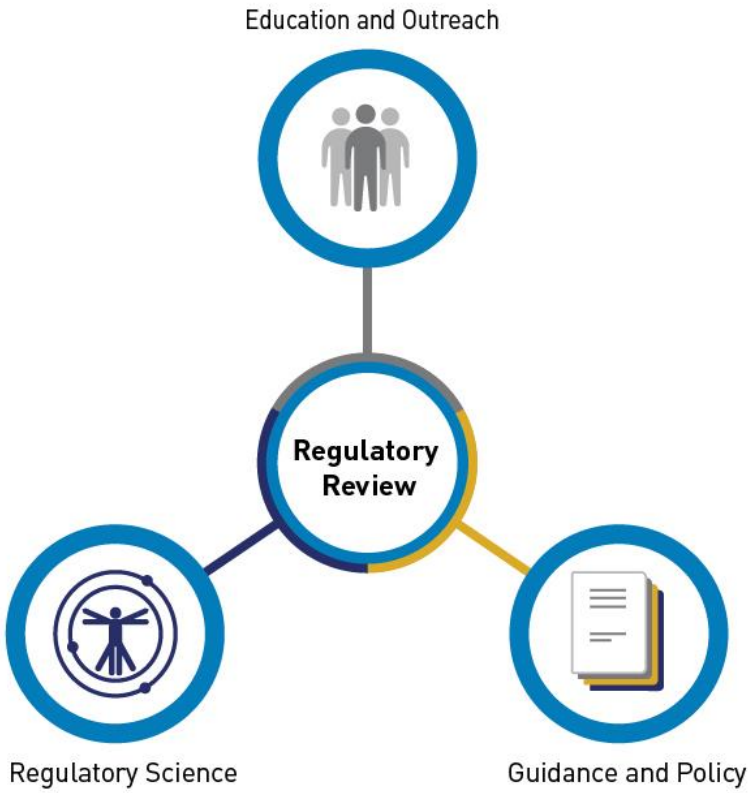
Section of Label	Types of Information
INDICATIONS AND USAGE	PGx information for proper patient selection (e.g., PGx testing)
DOSAGE AND ADMINISTRATION	Dosing recommendations for patient subgroups based on genetic makeup
BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and/or ADVERSE REACTIONS	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

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

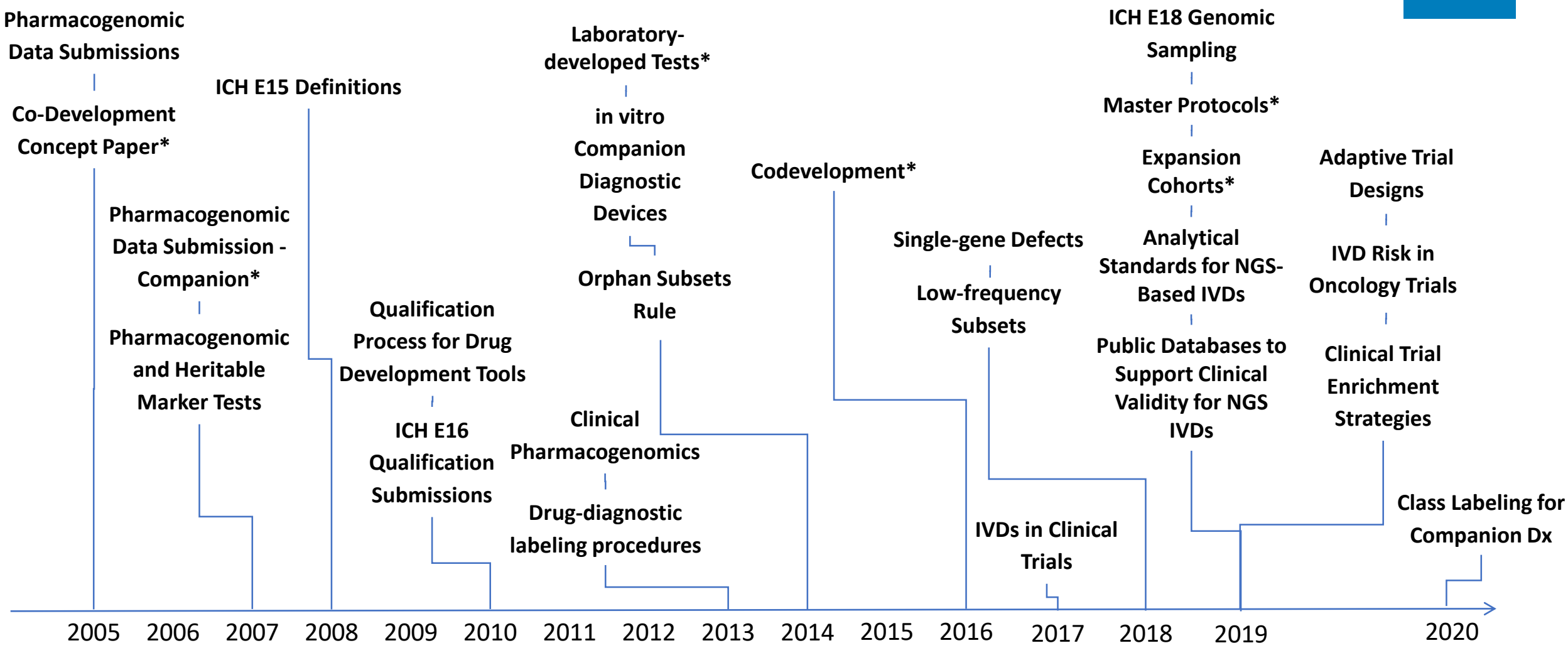
Gene-Drug Interactions in FDA Labeling

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

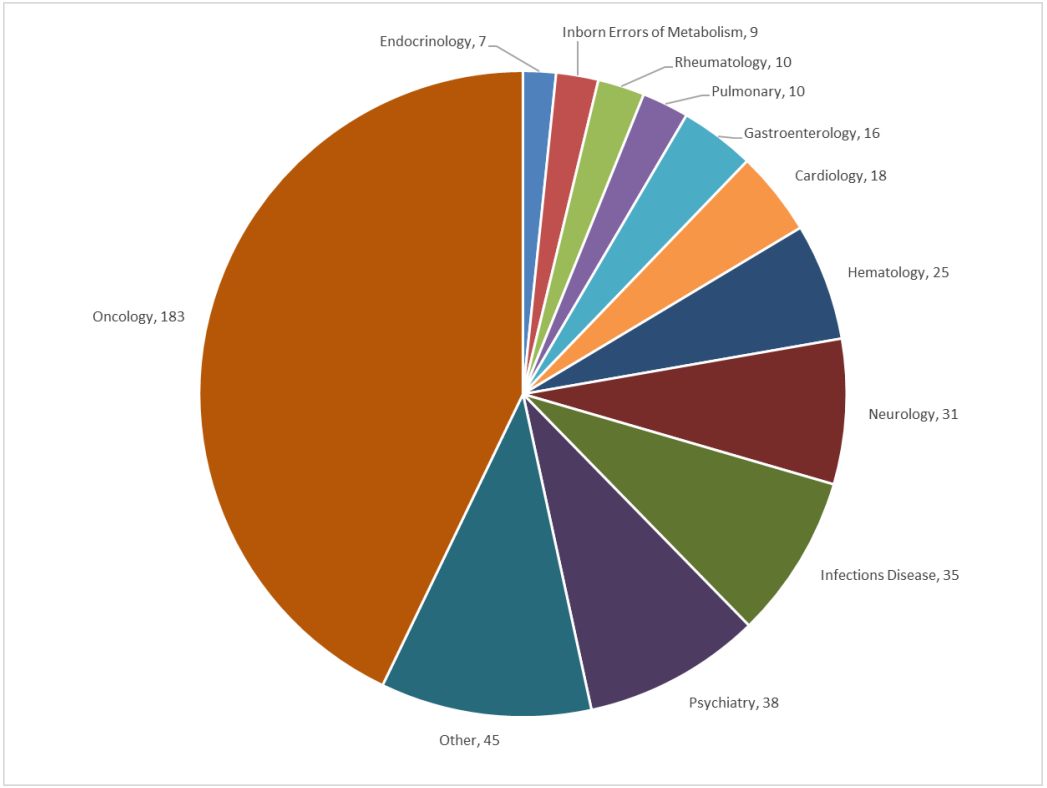


Last Updated July 2020

*** Draft**

21st Century Cures ★

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**

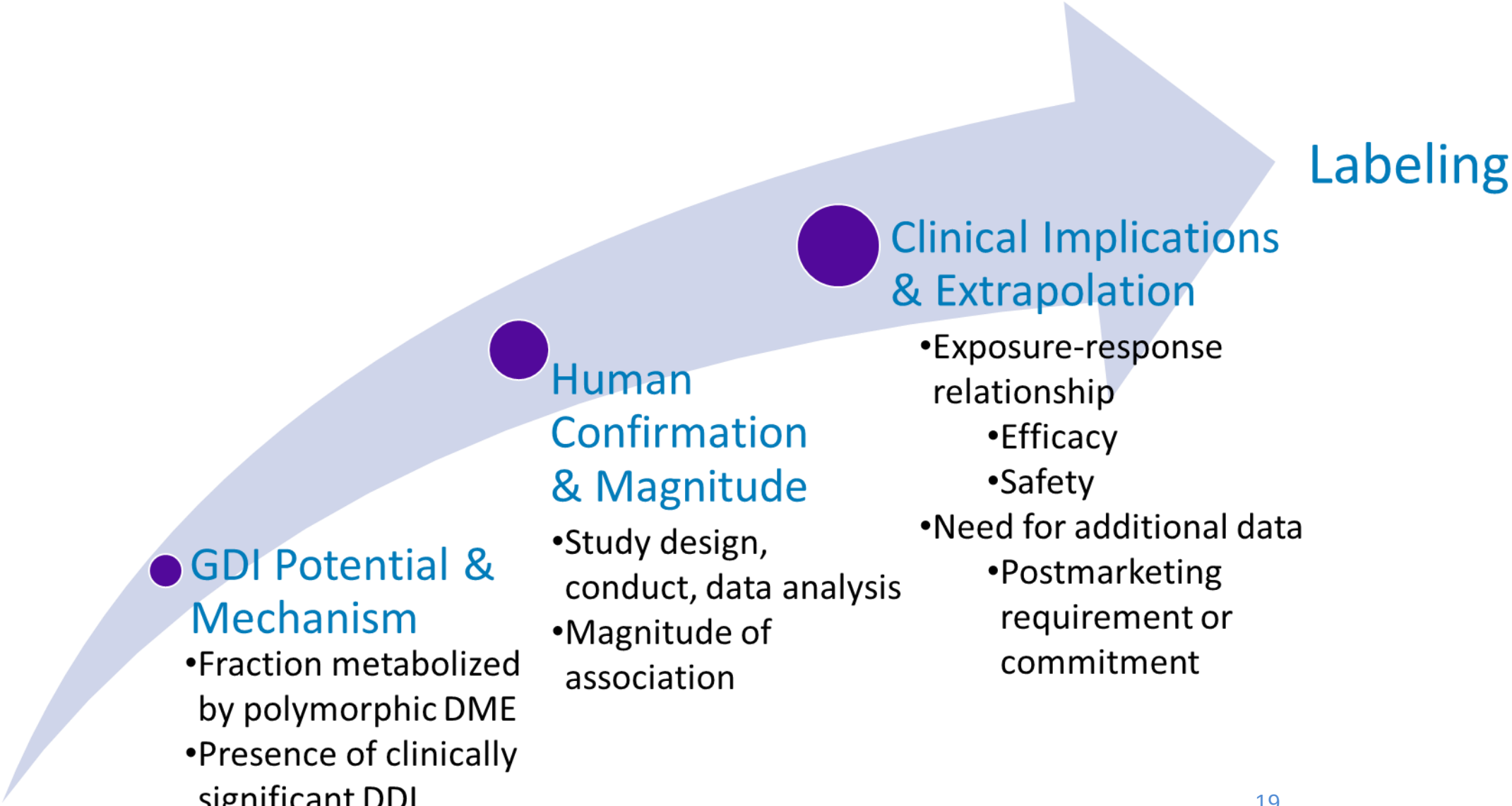
Otherwise, descriptive of study design feature or presence/absence of gene-drug interaction

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

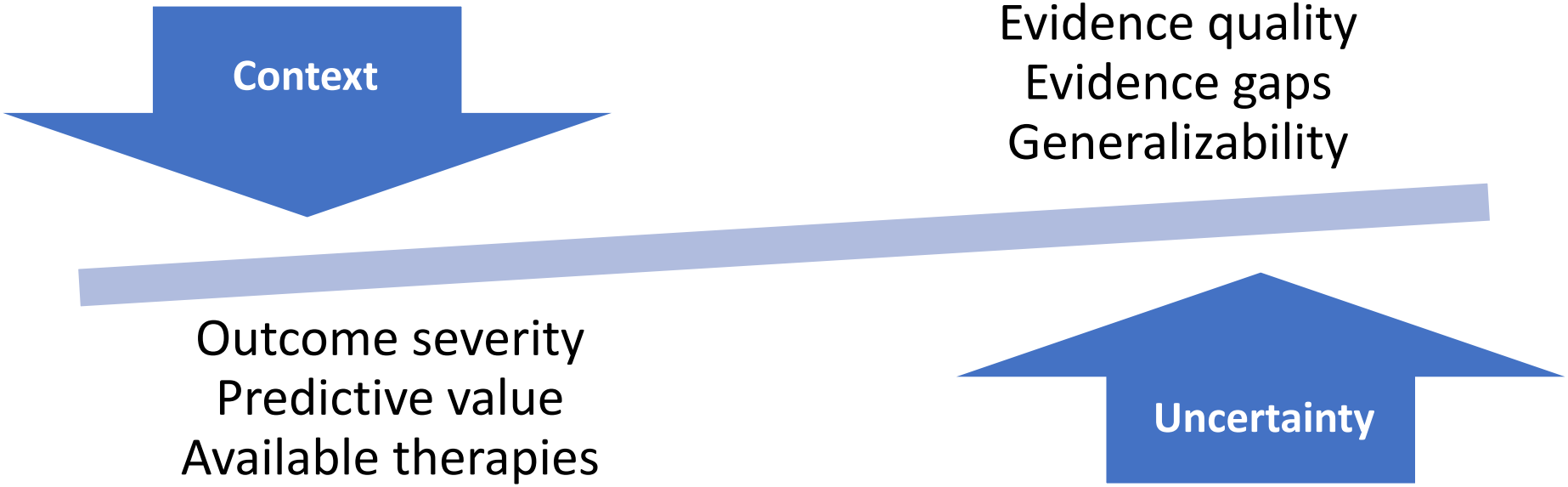
**** Management recommendations excluding "Use with Caution"**

June 2020

Informing the Regulatory Decision



Factors Guiding the Strength of Recommendations



Testing approaches

Silent / clinical judgement

Test at a certain threshold

Test a targeted, at-risk subset

Test everyone

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

Erdafitinib	FGFR	Efficacy	Indicated population
Siponimod	CYP2C9	Bradyarrhythmia & AV conduction	Adjust dose, Contraindication
Amifampridine	NAT2	Seizures	Start at low end of dose range if known
Tafamidis	TTR	PD effect, study description	Treat as usual
Avatrombopag	CYP2C9	PK effect	Treat as usual

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

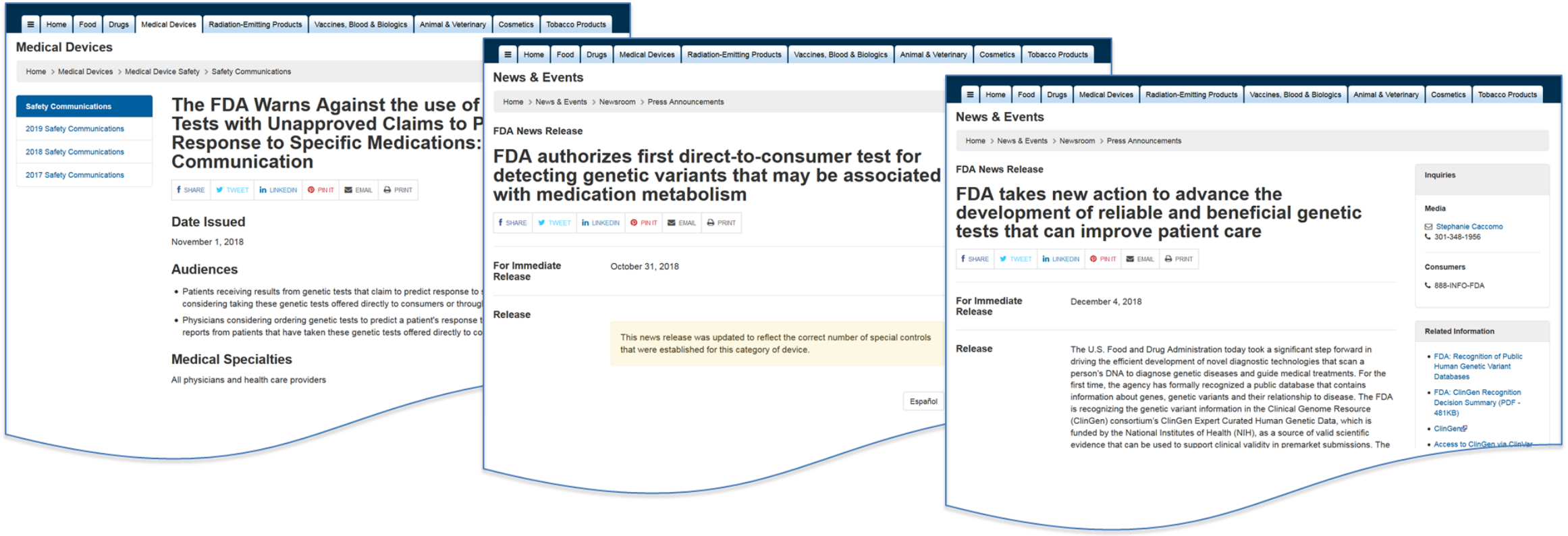
- Regulations require that labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.
  - 21 c.F.R. § 201.56 (2010)

- 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

Valproic Acid	POLG	Liver failure	Contraindicated
Pimozide	CYP2D6	Sudden death	Dose cap/slow titration
Citalopram	CYP2C19	QT prolongation	Dose cap
Carbamazepine	HLA-B*1502, HLA-A*3101	Severe skin reactions	Warnings
Meloxicam	CYP2C9	Substantially higher exposure	Monitor for AEs

Pharmacogenetic Testing



- 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

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.

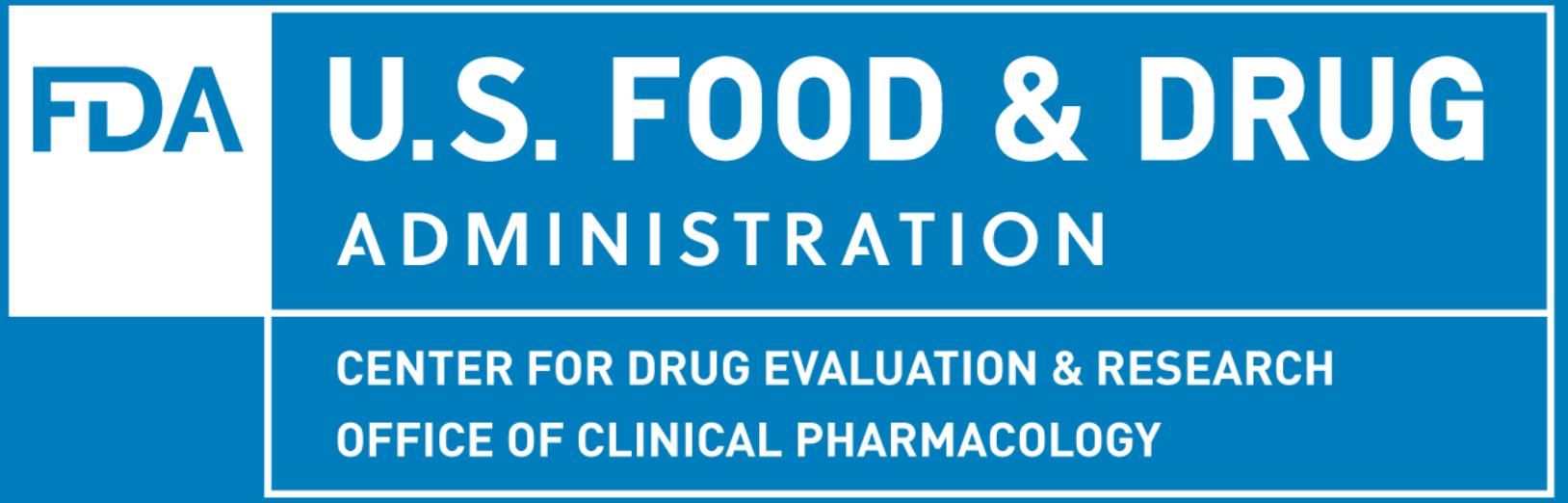
FDA Table of Pharmacogenetic Associations February 2020

- 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

Schuck RN, Grillo JA. AAPS J. 2016;18(3):573-7.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