U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

FDA DRUG TOPICS

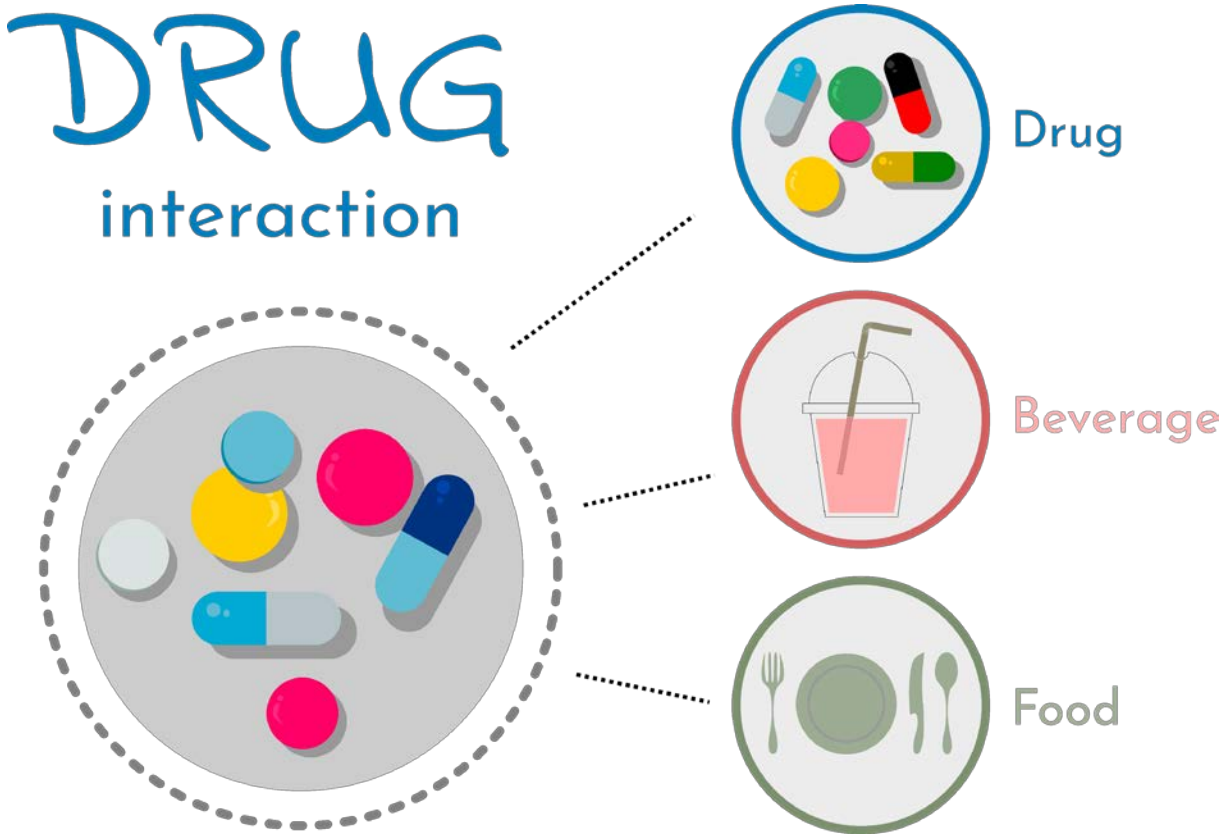
Labeling Made Simple: The How, What, and Where of Drug Interactions in Prescribing Information

Joseph A. Grillo, Pharm.D.
Associate Director of Labeling and Health Communication
Office of Clinical Pharmacology (OCP)
Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Learning Objectives

After completion of this activity, the participant will be able to:

- Identify key regulations that impact drug interaction content in prescribing information (PI)
- Locate drug interaction content in the PI
- Discuss the content structure of the DRUG INTERACTIONS section in PI
- Identify alternative methods of communicating complex drug interaction content



Impact of Drug Interactions

- Unanticipated, unrecognized, or mismanaged DDIs are major contributors to preventable morbidity and mortality
  - Estimated to represent 3–5% of preventable in-hospital adverse reactions
- Important contributor to emergency department visits and hospital admissions
  - 26% of total hospital admissions directly due to adverse drug reactions involved a DDI in one study

Grillo, J. et al. Clin. Pharmacol. Ther. 105, 1292– 1295 (2019); Leape, L.L. et al. JAMA 274, 35– 43 (1995); Raschetti, R. et al. Eur. J. Clin. Pharmacol. 54, 959– 963 (1999); McDonnell, P.J., et al. Ann. Pharmacother. 36, 1331– 1336 (2002)

Is There a Problem?

Chicago Tribune

The drug combinations

To test a pharmacy, reporters presented prescriptions for two medications that experts say are clearly risky if taken together. Five drug pairs were used:

Clarithromycin *an antibiotic* + **Ergotamine** *treats migraines*

Potentially fatal. Can cause gangrene or stroke by constricting blood vessels and decreasing flow of oxygen to the extremities and the brain.

Simvastatin *lowers cholesterol* + **Clarithromycin** *an antibiotic*

Potentially fatal. Can cause a severe breakdown in muscle tissue and lead to kidney failure.

Colchicine *treats gout* + **Verapamil** *treats high blood pressure*

Potentially fatal. Can cause breakdown of muscle tissue, loss of red and white blood cells and multiple organ failure.

Tizanidine *a muscle relaxant* + **Ciprofloxacin** *an antibiotic*

Can have a heavy sedative effect and lower blood pressure, leading to loss of consciousness.

Norgestimate/ethinyl estradiol *an oral contraceptive sold under various names* + **Griseofulvin** *an anti-fungal*

Can lead to unplanned pregnancy. A secondary effect is that griseofulvin may lead to birth defects.

Note: Griseofulvin is commonly available as a liquid.

Source: Daniel Malone, University of Arizona; John Horn, University of Washington

Pharmacies miss half of dangerous drug combinations

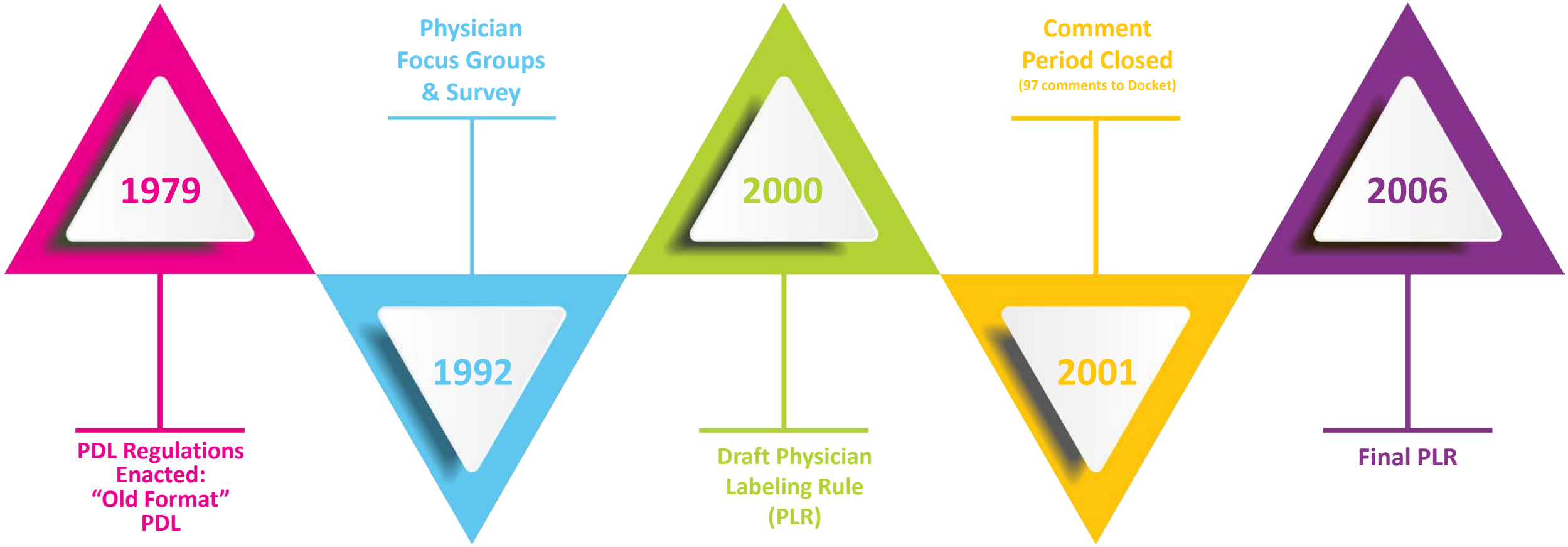
By **Sam Roe, Ray Long and Karisa King**
Chicago Tribune

DECEMBER 15, 2016, 8:44 AM

- **Tribune tested 255 pharmacies to see how often stores would dispense dangerous drug pairs without warning patients.**
- **52% percent of the pharmacies sold the medications without mentioning the potential interaction.**

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.

Evolution of the FDA Physician Labeling Rule (PLR)



PDL = Prescription Drug Labeling =Prescribing Information (PI)

PLR Content and Format

Old Format

PRODUCT TITLE

DESCRIPTION

CLINICAL PHARMACOLOGY

CLINICAL STUDIES

INDICATIONS AND USAGE

CONTRAINDICATIONS

WARNINGS

PRECAUTIONS

ADVERSE REACTIONS

DRUG ABUSE AND DEPENDENCE

OVERDOSAGE

DOSAGE AND ADMINISTRATION

HOW SUPPLIED

ANIMAL PHARMACOLOGY / ANIMAL TOXICOLOGY

REFERENCES

PLR Format

DDI Related Information

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.

Objectives of the FDA DDI Program

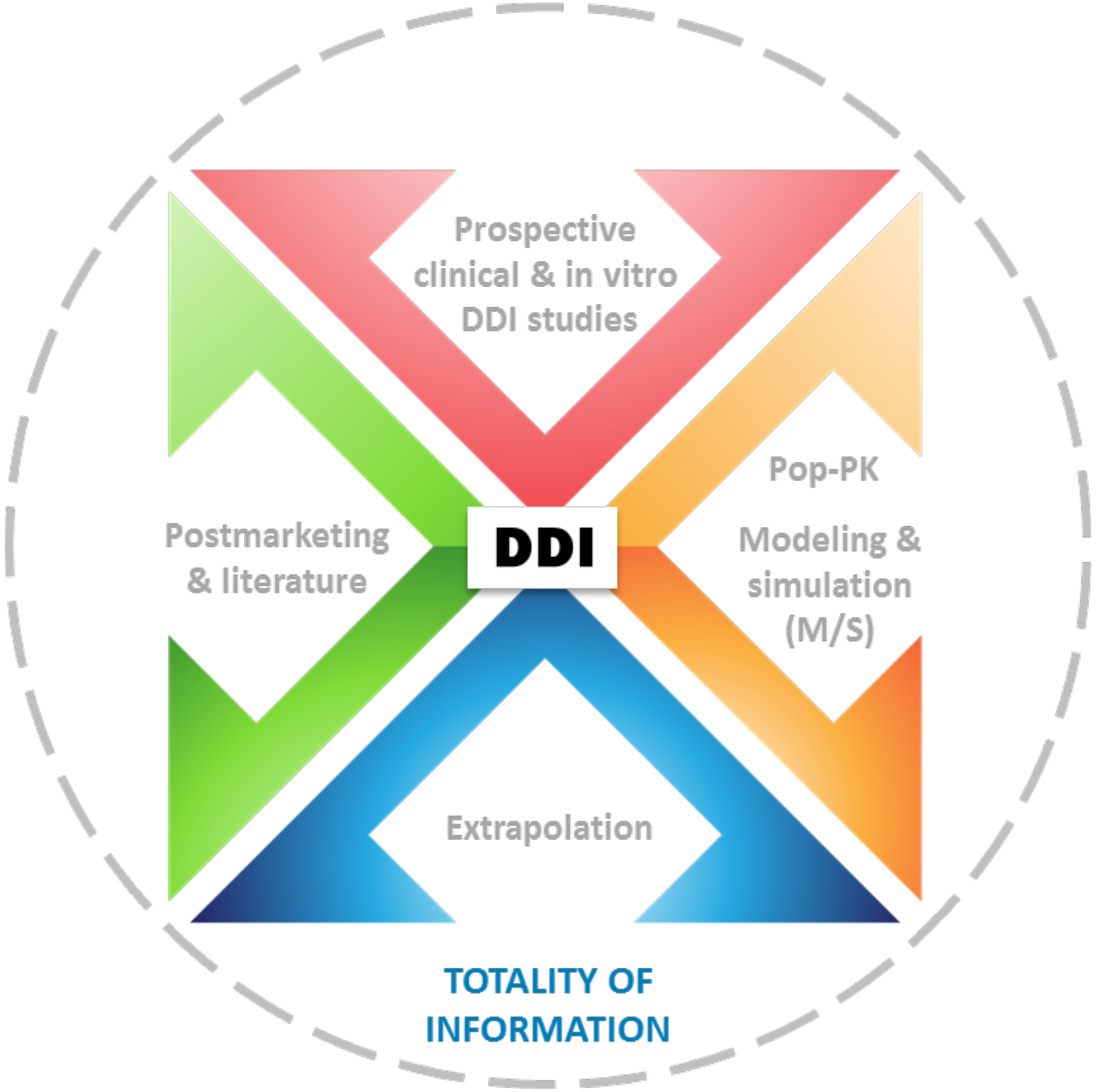
- Determine the potential for clinically significant DDIs
  - Do other drugs alter the pharmacokinetics (PK) of the investigational drug?
  - Does the investigational drug alter the PK of other drugs?
  - What is the magnitude of changes in PK parameters?
  - What is the clinical significance of the observed or expected DDIs?
- Determine appropriate management strategies for clinically significant DDIs

Clinical Significance of a DDI

- The goal of a PK DDI study is to inform management and prevention strategies by determining whether there is a clinically significant change in exposure to the substrate drug in the presence of a perpetrator drug
- An interaction is clinically significant if concomitant use of the drugs leads to safety, efficacy, or tolerability concerns greater than those present when the drugs are administered alone.

Guidance for Industry: Clinical Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions

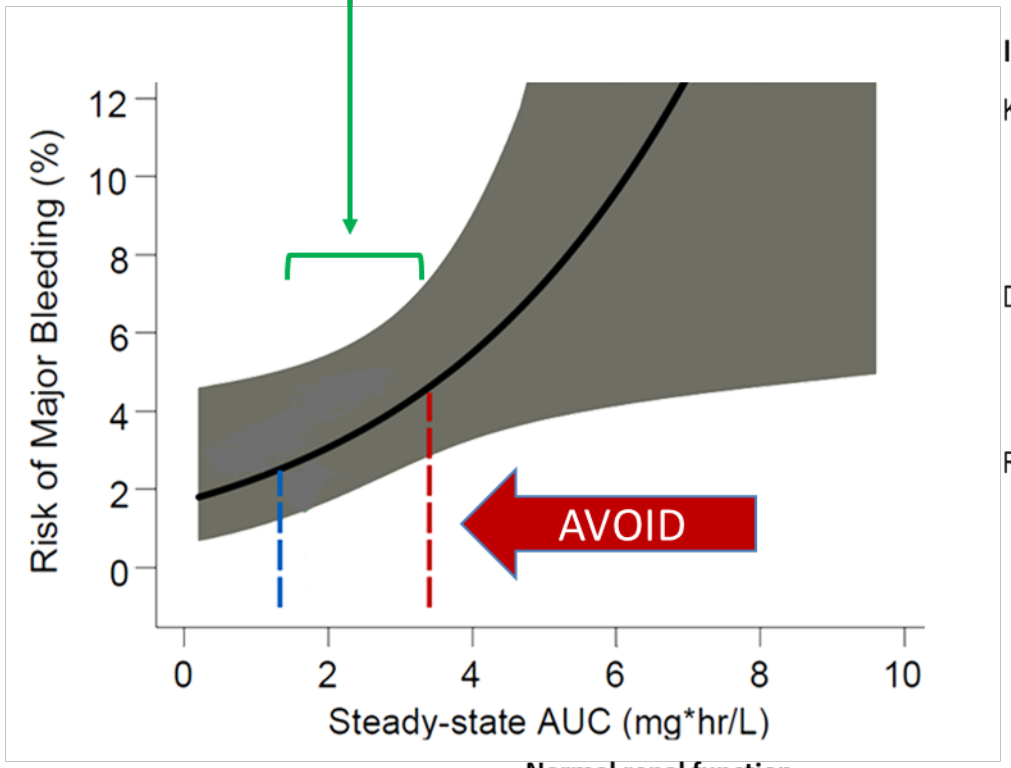
Sources of DDI-Related Information

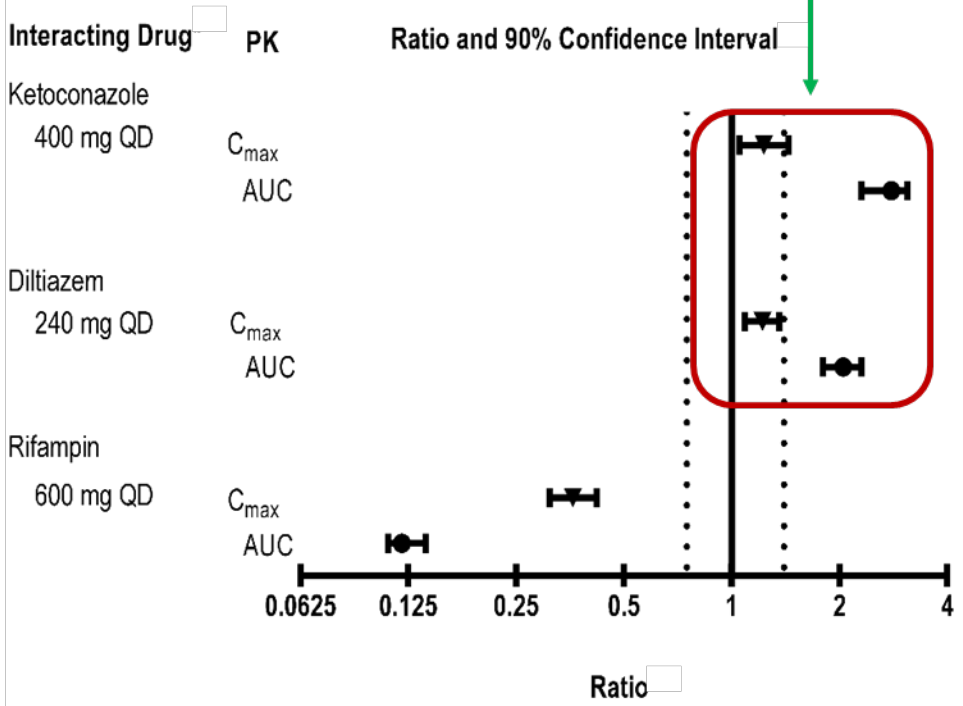


Clinical Impact Drives DDI Management

CLINICALLY RELEVANT BOUNDARY ESTABLISHED BY E-R

PROVIDES CLINICAL CONTEXT FOR INTERPRETING EXPOSURE CHANGE IN CLINICAL DDI STUDY

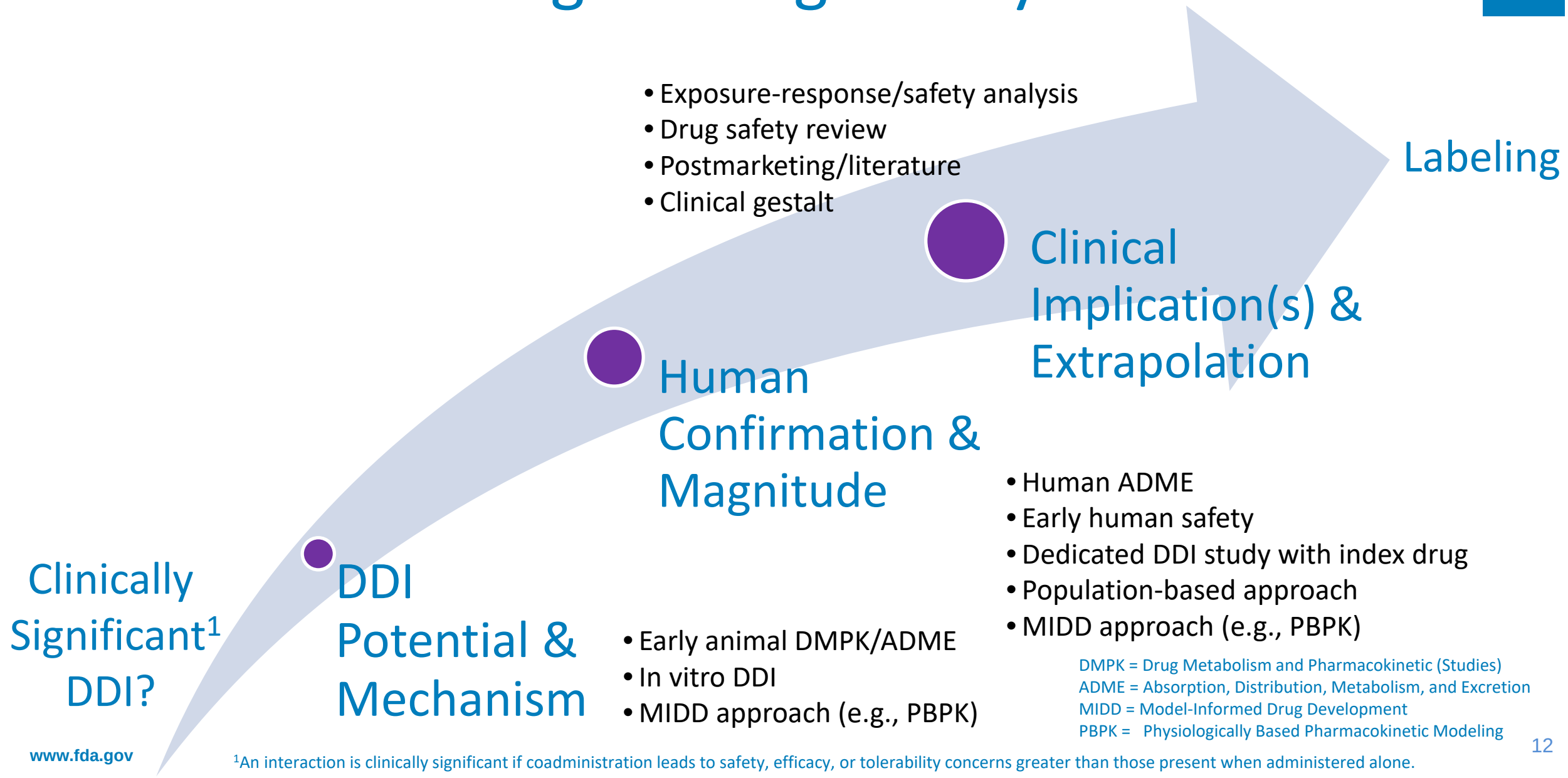




Dashed vertical lines illustrate PK changes used to inform dosing recommendations

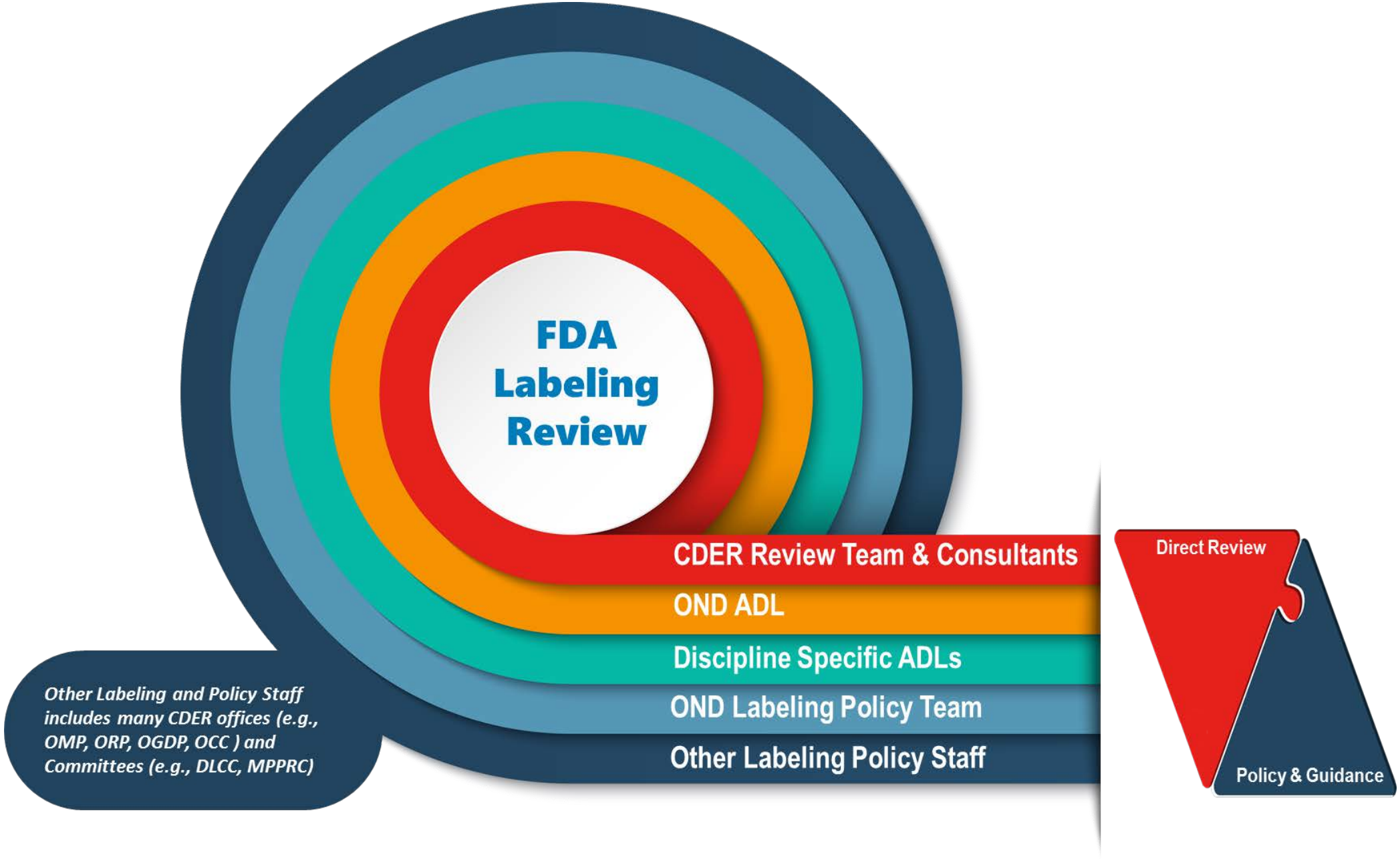
Adapted from https://wayback.archive-it.org/7993/20170405212742/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM143665.pdf

Informing the Regulatory Decision



DMPK = Drug Metabolism and Pharmacokinetic (Studies)
ADME = Absorption, Distribution, Metabolism, and Excretion
MIDD = Model-Informed Drug Development
PBPK = Physiologically Based Pharmacokinetic Modeling

[1]An interaction is clinically significant if coadministration leads to safety, efficacy, or tolerability concerns greater than those present when administered alone.



OND= Office of New Drugs; ADL= Associate Director of Labeling; OMP= Office of Medical Policy; ORP= Office of Regulations and Policy; OGDP= Office of Generic Drug Policy; OCC= Office of the Chief Counsel; DLCC= CDER Drug Labeling Coordinating Committee; MPPRC= Medical Policy and Program Review Council

Application Holder Major Responsibilities For PI Development

- 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)

DRUG INTERACTIONS Section

- Must contain a description of clinically significant interactions, either observed or predicted, with other prescription or over-the-counter drugs, classes of drugs, or foods (e.g., dietary supplements, grapefruit juice)
- Must contain specific practical instructions for preventing or managing them
- The mechanism(s) of the interaction, if known, must be briefly described
- This section must also contain practical guidance on known interference of the drug with laboratory tests

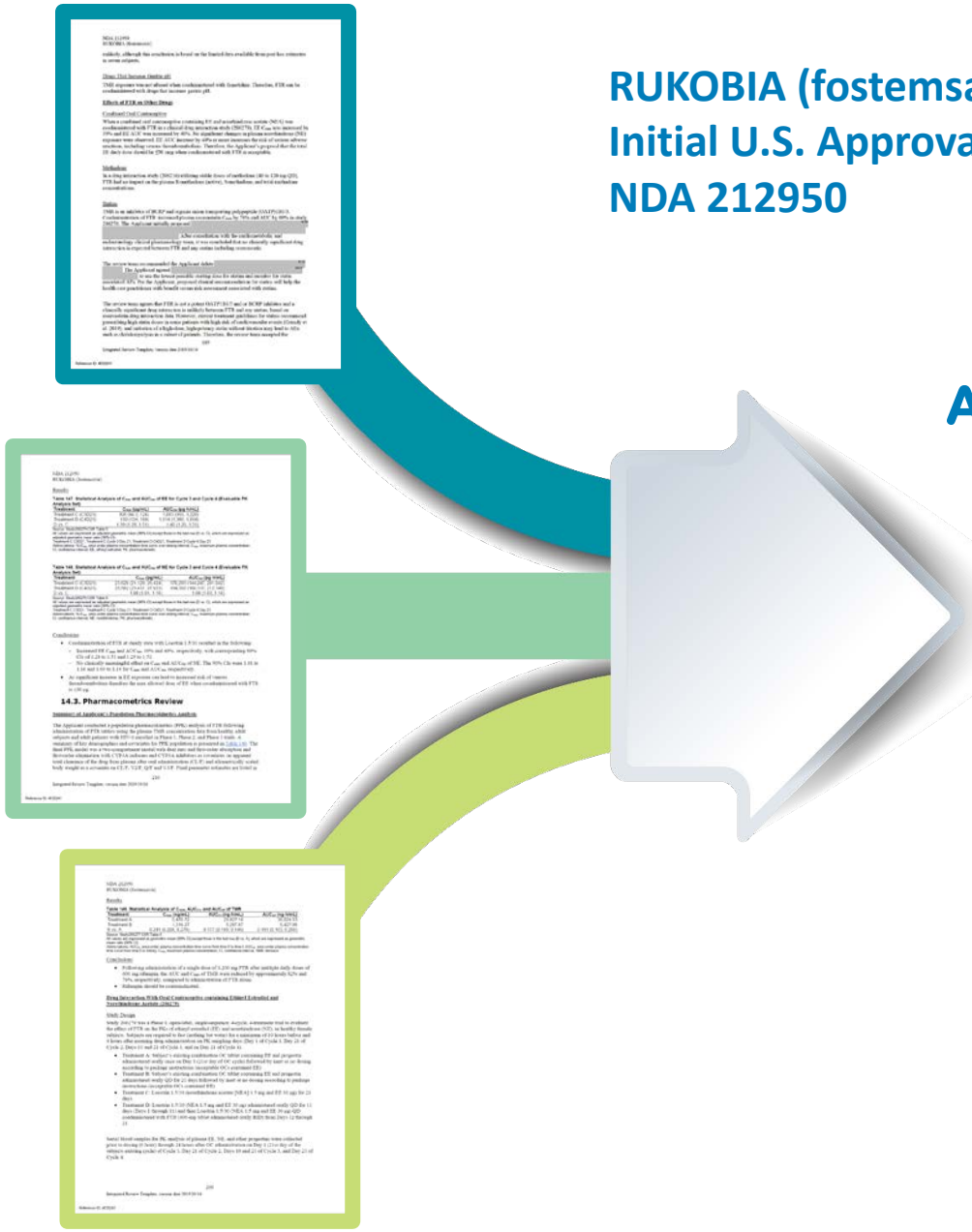
Challenges for DDI Information in the Prescribing Information

- Information regarding drug metabolic pathways and transporter systems are rapidly evolving
- Labeling is not updated in real-time
  - May not capture the drug interaction potential of newly approved drugs in the PI of an older drug that is also involved
- Healthcare providers may differ in their mechanistic understanding of underlying metabolic pathways and transporter systems involved
  - Also prefer different approaches to receiving the information
- Inconsistency between FDA-approved labeling and tertiary drug information sources and online clinical decision tools

Questions for PI development

- Is the information essential for the safe and effective prescribing of the drug?
  - Does it provide clinically important context for essential information in a cross-referenced section?
  - Can nonessential contextual information be omitted?
- Can this be understood by a healthcare provider who is not a clinical pharmacologist?
  - Can this information be described in a simpler way?
- Is the intended interpretation/ action clinically intuitive from the information proposed?
  - Is additional information to explain the impact on safe and effective prescribing needed?

OCP Integrated Review



RUKOBIA (fostemsavir) extended-release tablets, for oral use
Initial U.S. Approval: 2020
NDA 212950

Approved Prescribing Information (PI)

7 DRUG INTERACTIONS

7.1 Potential for RUKOBIA to Affect Other Drugs

…When RUKOBIA was coadministered with oral contraceptives, temsavir increased concentrations of ethinyl estradiol …

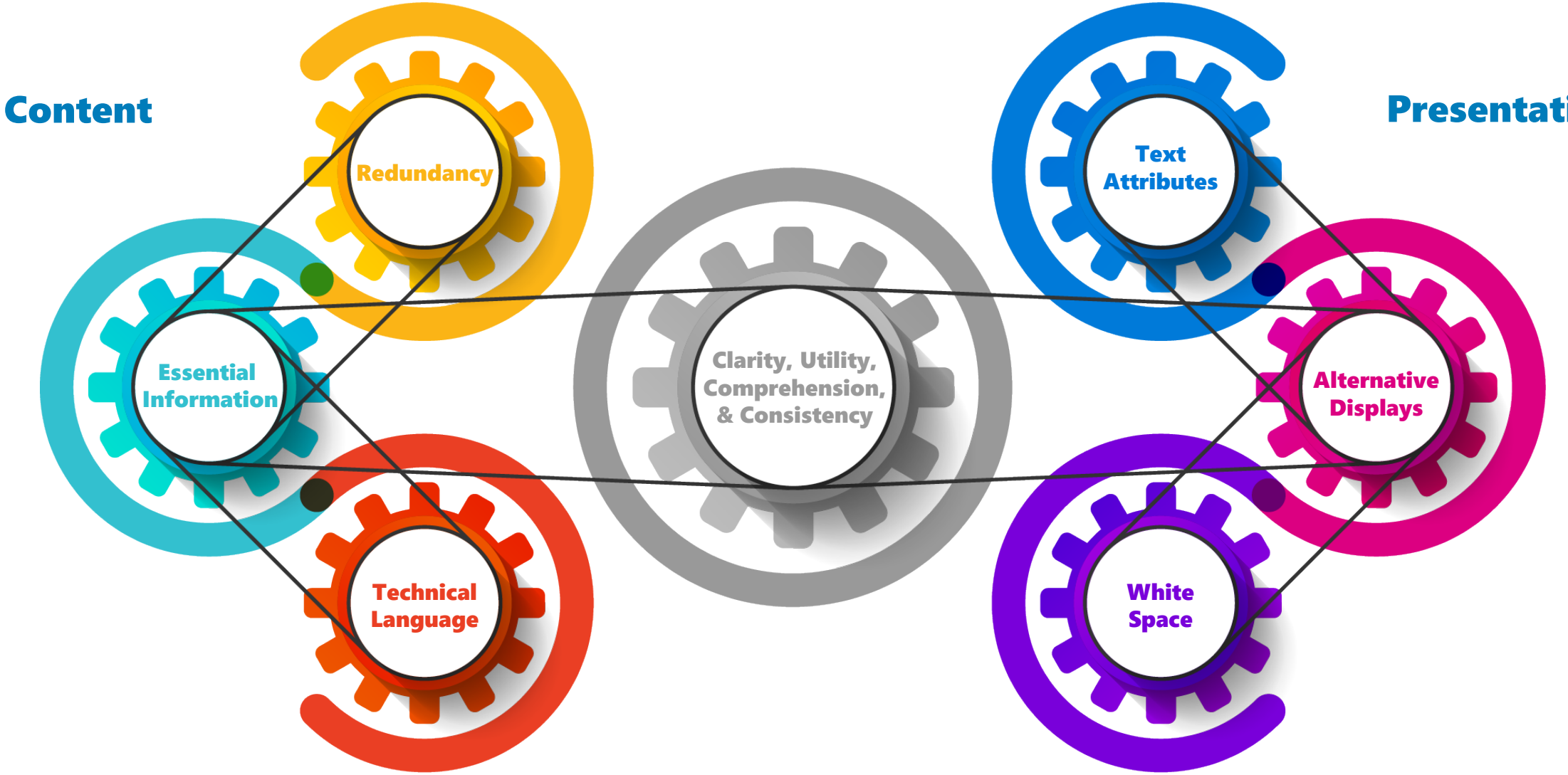
The full OCP review (redacted) and approved PI: www.bit.ly/3daOKfh


Carrier
10:32 AM
DRUGS@FDA
SEARCH
Search By Drug Name, Active Ingredient, or Application Number
LAST 7 DAYS' APPROVALS
FDA WEB PAGES
FDA HELP & SUPPORT
DRUGS@FDA

HCP Perception of PI

What's Wrong?	Ideal Presentation
• Confusing structure • Too much information • Wrong information • No conveyance of risk • No real guidance	• 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

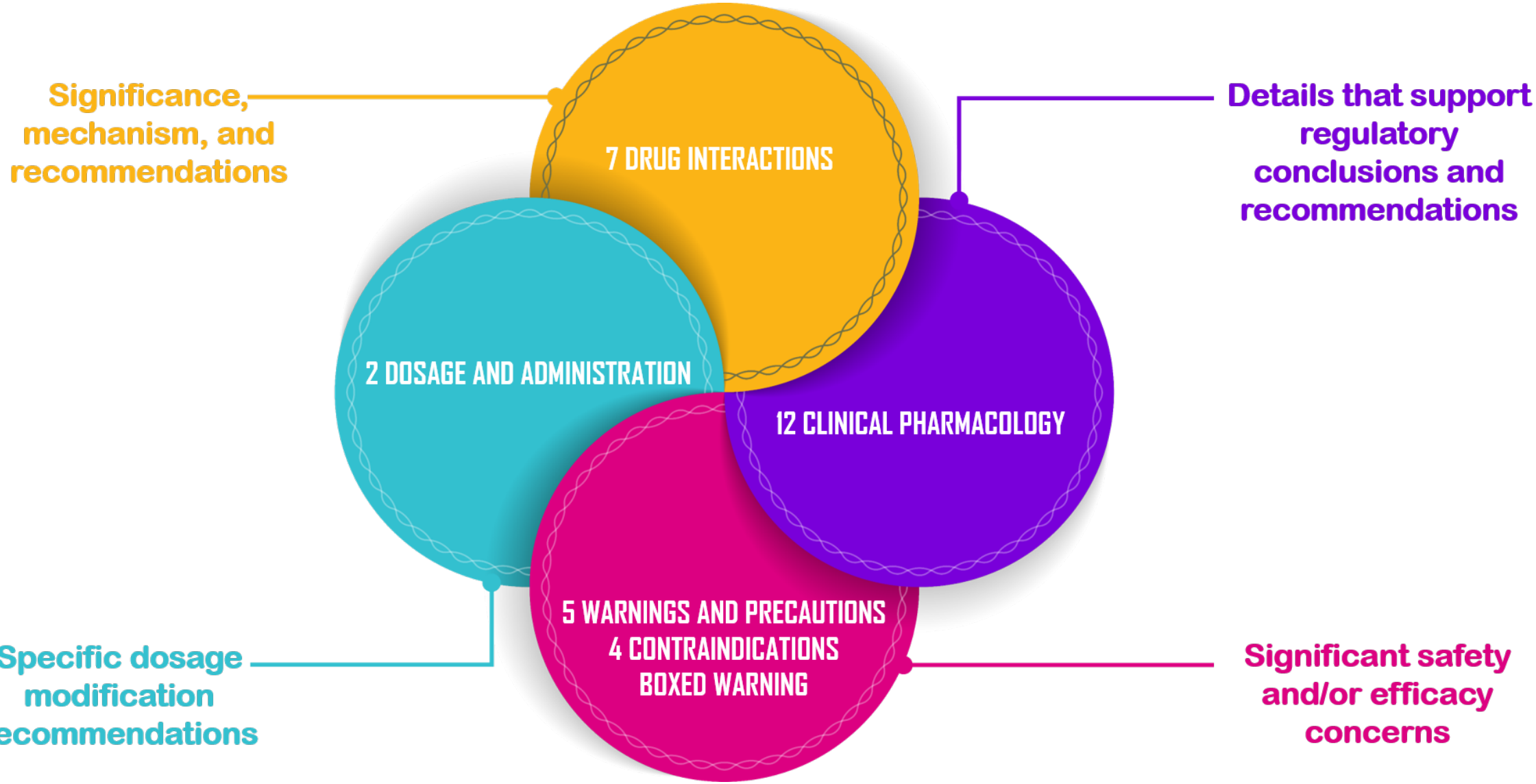
Strategies to Enhance Clinical Pharmacology Labeling Development



Clarity, Readability, and Utility

- Use active voice
- Provide sufficient detail to inform prescribing decisions
  - Actions should be clear and specific
  - Clinically significant information should be clearly identified
  - Avoid redundancy between labeling sections
  - Brevity encouraged
- Avoid vague recommendations such as “monitor closely” or “use with caution” that are not clinically “value added”
- Use white space, text attributes (bolding, bulleted lists, etc.)
- Use tables and figures where appropriate to enhance readability, clarity, and utility of complex or dense content

Cross Referencing Reduces Redundancy



DRUG INTERACTIONS Section as Text

No Enhancements Used

7 DRUG INTERACTIONS

Drugoxide undergoes metabolism by CYP3A. Use with a strong CYP3A inhibitor will increase drugoxide exposure (i.e., C_{max} and AUC) resulting in an increased syncope risk. Reduce the dosage of Drug X when coadministered with strong CYP3A inhibitors (e.g., Clarithromycin, cobicistat, conivaptan, elvitegravir and ritonavir, grapefruit juice, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, and voriconazole.) *[see Dosage and Administration (2.x), Warnings and Precautions (5.x) and Clinical Pharmacology (12.3)]*.

DRUG INTERACTIONS Section as Text

Enhancements Used

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on Drug X

Strong CYP3A Inhibitors

Reduce the dosage of Drug X when coadministered with strong CYP3A inhibitors *[see Dosage and Administration (2.x)]*.

Drugoxide undergoes metabolism by CYP3A. Use with a strong CYP3A inhibitor will increase drugoxide exposure (i.e., C_{max} and AUC) resulting in an increased syncope risk *[see Warnings and Precautions (5.x) and Clinical Pharmacology (12.3)]*.

The following are some examples of strong CYP3A Inhibitors: Clarithromycin, cobicistat, conivaptan, elvitegravir and ritonavir, grapefruit juice, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, and voriconazole.

DRUG INTERACTIONS Section Alternative Displays

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on DRUG X

Table X. Drug Interactions with DRUG X that Affect Drugoxide

Strong CYP3A Inhibitors[a]	
Clinical Impact	Concomitant use with a strong CYP3A inhibitor increases drugoxide AUC *[see Clinical Pharmacology (12.3)]* which may increase the risk of DRUG X toxicities.
Prevention or Management	Reduce DRUG X dosage when used concomitantly with a strong CYP3A inhibitor *[see Dosage and Administration (2.x)]*.
Examples[b]	Clarithromycin, cobicistat, conivaptan, diltiazem, elvitegravir and ritonavir, grapefruit juice,[c] idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, voriconazole
Strong CYP3A Inducers[d]	
Clinical Impact	Concomitant use with a strong CYP3A inducer decreases drugoxide AUC *[see Clinical Pharmacology (12.3)]* which may reduce DRUG X efficacy.
Prevention or Management	Avoid concomitant use with a strong CYP3A inducer.
Examples[b]	Carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort[e]

[a] Strong inhibitors increase the AUC of sensitive index substrates of a given metabolic pathway ≥ 5-fold.
[b] These examples are a guide and not considered a comprehensive list of all possible drugs that may fit this category. The healthcare provider should consult appropriate references for comprehensive information.
[c] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).
[d] Strong inducers decrease the AUC of sensitive index substrates of a given metabolic pathway by ≥5-fold.
[e] The induction potency of St. John's wort may vary widely based on preparation.

DRUG INTERACTIONS Section Alternative Displays

7 DRUG INTERACTIONS

7.1 Established and Potentially Significant Drug Interactions

Table X provides a listing of potential clinically significant drug Interactions between Drug X and Other Drugs

Table X: Potential Clinically Significant Drug Interactions between Drug X and Other Drugs[a,b]

Concomitant Drug Class: Drug Name	Effect on Concentration[c]	Clinical Comment
Acid Reducing Agents:	↓ Drugoxide	Drugoxide solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of drugoxide.
Antacids (e.g., Drug A and Drug B)		Recommend separating antacid and Drug X administration by at least four hours
H2-receptor antagonists (e.g., Drug C)[d]		May administer H2-receptor antagonists (up to x mg of Drug C twice daily or equivalent dosages of other H2 blockers) simultaneously with or within 12 hours of Drug X.
Proton-pump inhibitors (e.g., Drug D)[d]		May administer PPIs (up to x mg of Drug D once daily or equivalent dosages of other PPIs) simultaneously with Drug X under fasting conditions.
Antiarrhythmics: Drug F	↑ Drug F	Recommend therapeutic concentration monitoring of Drug F when coadministered with Drug X
Anticonvulsants: Drug G, Drug H, Drug I, Drug J	↓ Drugoxide	May lead to reduced therapeutic effect of drugoxide. Coadministration is not recommended.
Antimycobacterials: Drug K	↓ Drugoxide	May lead to reduced therapeutic effect of drugoxide. Coadministration is not recommended.
HMG-CoA Reductase Inhibitors: Drug L	↑ Drug L	Increased risk of myopathy, including rhabdomyolysis. Coadministration of Drug X with Drug L is not recommended.

a. This table is not all inclusive; b. These data are based on drug interaction studies or predicted based upon similar characteristics to the drugs evaluated in these studies; c. ↓ = decrease, ↑ = increase; d. *[see Dosage and Administration (2.x)]*

DDI Examples in Prescribing Information

- A listing of representative examples of drugs that affect or are affected by metabolic pathways, and transporter systems implicated in DDI is often provided in the DRUG INTERACTIONS Section
- Not required by regulation, but may not be intuitive to most healthcare providers

Option	Pros	Cons
Include the category only	• Significantly reduces length and complexity of PI • May encourage providers to seek outside information	• Health care providers may not be aware of or have access to tertiary resources • Concerns about consistency and accuracy of tertiary sources
Include category + few examples	• Reduced length and complexity of PI • Common practice	• Inconsistent examples across PI • No objective criteria for selecting examples • Concomitant use pattern may change from examples chosen at approval • Not comprehensive but providers could assume the examples are the only one's of concern
Include category + longer list of examples	• Applied consistently across PI	• Volume of examples adds to length and complexity of PI • Routine evaluation and updating of the list required • Healthcare providers may incorrectly assume the list is comprehensive

Are Examples Useful?

Drug Interactions: CLINICAL PHARMACOLOGY Section

Preferred Example:

12.3 Pharmacokinetics

Drug Interaction Studies

Strong CYP3A Inhibitors: Coadministration with a strong CYP3A inhibitor (ketoconazole) increased drugoxide C_{max} by 1.3-fold and AUC by 2-fold *[see Dosage and Administration (2.x) and Drug Interactions (7.x)]*.

Non-Preferred Example:

12.3 Pharmacokinetics

Drug Interaction Studies

Coadministration of ~~a single 40 mg dose of~~ drugoxide with the strong CYP3A inhibitor ketoconazole (~~200 mg twice daily for 14 days~~) increased the C_{max} and AUC of drugoxide by 1.3 and 2-fold, ~~respectively~~, compared to when drugoxide was given alone ~~in 14 healthy volunteers~~. T_{max} was unchanged. ~~A reduced starting dosage is recommended~~ *[see Dosage and Administration (2.x) and Drug Interactions (7.x)]*.

Alternative Displays: CLINICAL PHARMACOLOGY Section

Table

Table X. Clinically Significant Interactions Affecting Drugoxide

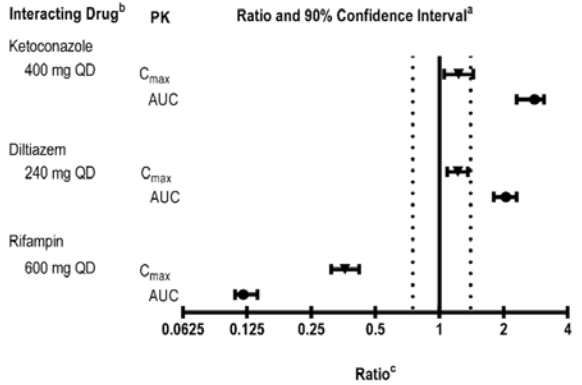
Concomitant Drug (Dosage)	Drugoxide Dosage	Ratio (90% CI) of Exposure Measures of Drugoxide Combination/No Combination [minimum to maximum][a]	
		C_{max}	AUC
Ketoconazole (400 mg once daily)	60 mg single dose	1.2 (1.1, 1.4) [0.9 to 1.9]	2.8 (2.3, 3.1) [1.9 to 4.2]
Diltiazem (240 mg once daily)		1.2 (1.1, 1.4) [0.5 to 2.9]	2.1 (1.8, 2.3) [0.9 to 3.8]
Rifampin (600 mg once daily)		0.36 (0.31, 0.42) [0.26 to 0.55]	0.12 (0.11, 0.14) [0.08 to 0.16]

[a] *[see Dosage and Administration (2.x) and Drug Interactions (7)]*

No clinically significant changes in exposure were observed for drugoxide when coadministered with Drug A, Drug B, or Drug C.

Figure

Table X. Clinically Significant Interactions Affecting Drugoxide

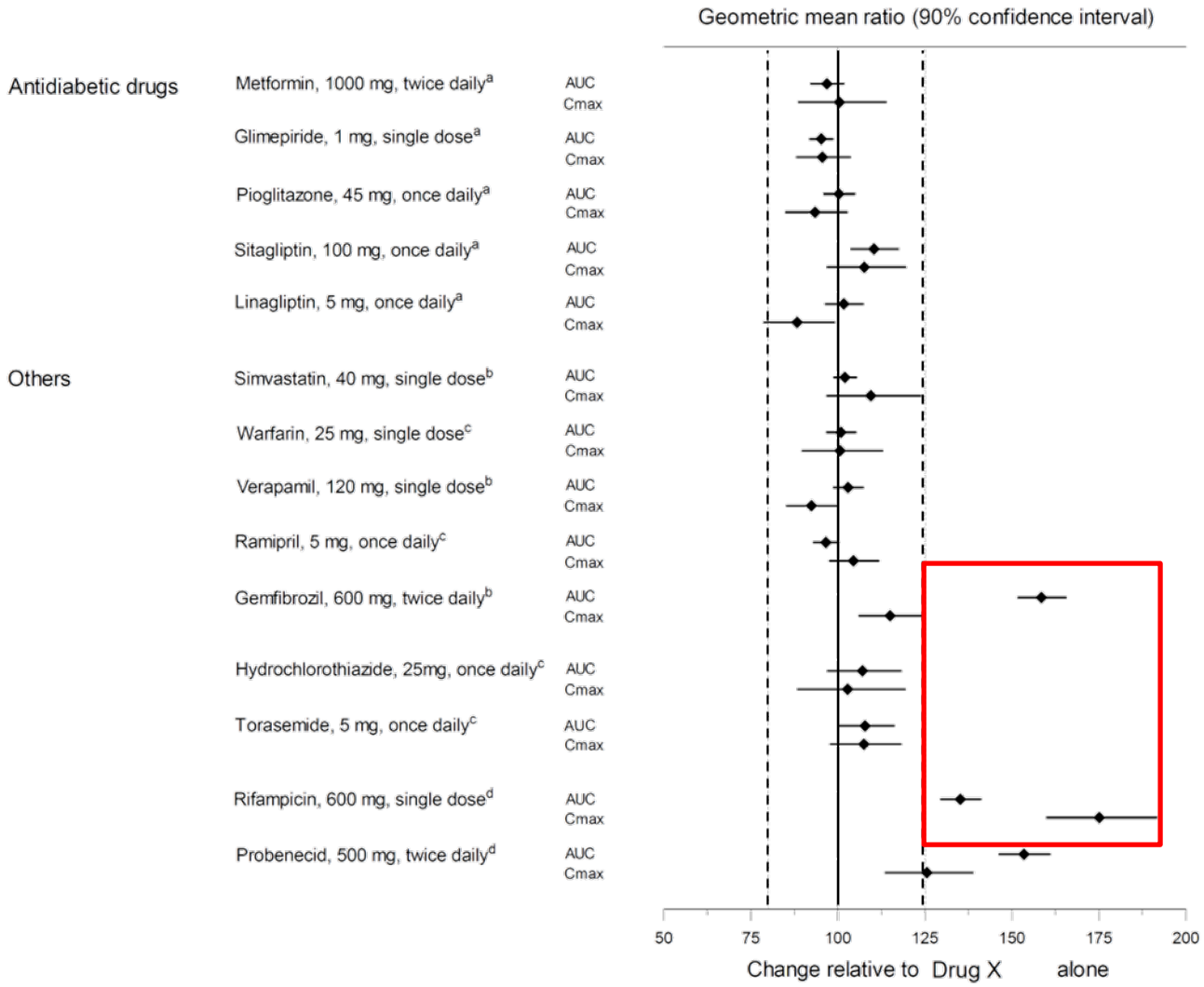


[a] Dashed vertical lines illustrate pharmacokinetic changes that were used to inform dosing recommendations *[see Dosage and Administration (2.x) and Drug Interactions (7)]*.
[b] Drug X administered as a 60 mg single dose.
[c] Log base 2 scale

No clinically significant changes in exposure were observed for drugoxide when coadministered with Drug A, Drug B, or Drug C.

Are 90% CI essential for safe effective prescribing?

“Significant” DDI Exposure Changes in Figures



- **Statistically different but not clinically significant**
- **Will not be in the DRUG INTERACTIONS section**

[a] Drug X ,100 mg, once daily; [b] Drug X, 50 mg, single dose; [c] Drug X ,50 mg, once daily; [d] Drug X 25 mg, single dose

In Vitro DDI Information

- Establish the absence of a DDI effect
- Characterize protein binding, DDI potential, metabolic and transporter pathways in the absence of clinical information
- In vitro information may be included in addition to in vivo if essential to understanding the clinical results
- Generally in *Pharmacokinetics* subsection of CLINICAL PHARMACOLOGY section
  - Rarely in DRUG INTERACTIONS section unless clinically important

Is In Vitro DDI Information Useful?

Modeling & Simulation-Based DDI Information

TIBSOVO® (ivosidenib tablets), for oral use
Initial U.S. Approval: 2018
NDA 211192

DDI Scenario	IVO Ratio[1] w/wo concurrent use	
	$AUC_{0\text{-}INF}$	C_{max}
Observed		
Itraconazole + IVO (SD)	2.69 (2.45, 2.95)	1.0 (.93, 1.13)
Predicted		
Itraconazole + IVO (SD)	2.14	1.04
Itraconazole + IVO (SS)	1.44 [3.81[2]]	1.29 [2.52[2]]
Fluconazole + IVO (SD)	1.02	1.73
Fluconazole + IVO (SS)	1.90	1.52

1=Geometric mean (90% confidence interval); 2= assuming strong CYP3A4 inhibitor but not a substrate of CYP3A
w/wo= with or without; SD= single dose; SS = multiple dosing to steady state

Approved Prescribing Information (PI)

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Drug Interaction Studies

Clinical Studies and Model-Based Approaches

Effect of Strong or Moderate CYP3A4 Inhibitors on Ivosidenib:
…~~Based on physiologically-based pharmacokinetic modeling,~~ co-administration of 500 mg ivosidenib with the moderate CYP3A4 inhibitor fluconazole (dosed to steady-state) is predicted to increase ivosidenib single-dose AUC to 173% of control with no change in Cmax. In regards to multiple-dosing, co-administration with ivosidenib and fluconazole is predicted to increase ivosidenib steady-state Cmax to 152% of control and AUC to 190% of control

The full OCP review (redacted) and approved PI: www.bit.ly/3d7QqGA

Alternative Displays: DOSAGE & ADMINISTRATION Section

2 DOSAGE AND ADMINISTRATION

2.3 Dose Modification for Use with a Moderate CYP3A4 Inhibitor

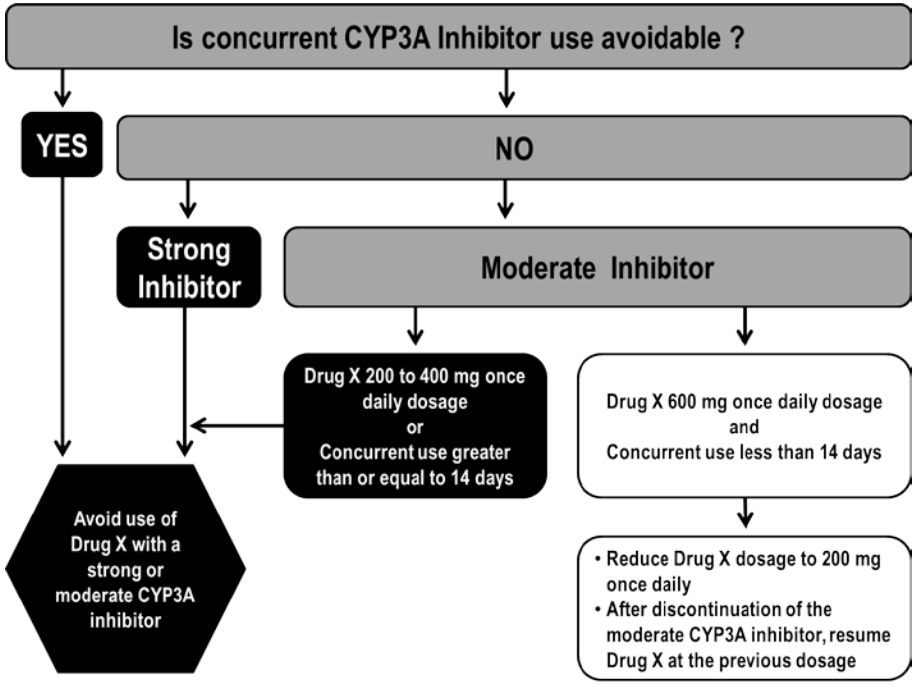
Avoid coadministration of Drug X with moderate CYP3A inhibitors.

If concurrent short term (14 days or less) use of moderate CYP3A inhibitors including certain antibiotics (e.g., erythromycin, ciprofloxacin) is unavoidable for patients who are taking a Drug X 600 mg daily dosage:

- Reduce Drug X dose to 200 mg.
- After discontinuation of a moderate CYP3A inhibitor, resume Drug X at the previous dose *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*.

2 DOSAGE AND ADMINISTRATION

2.3 Dose Modification for Use with a Strong or Moderate CYP3A4 Inhibitor



Complex Dosage Mitigation Strategies

Table X: Recommended Dosage Adjustments in Patients Taking Strong CYP2D6 Inhibitors, CYP3A Inhibitors, and/or CYP3A Inducers[a] and/or in Patients who are CYP2D6 Poor Metabolizers.

Current Dosage (mg)	Dosing Frequency (hours)	Perpetrators				Modified Dosage	Modified Frequency (hours)
		2D6 Poor Metabolizer	Concurrent/ strong				
			CYP2D6 INH	CYP3A INH	CYP3A IND		
200 mg	6	Yes	No	Yes	No	Avoid Use	NA
			No	No	Yes	400 mg	6
		No	Yes	No	No	200 mg	6
			No	Yes	No	200 mg	6
			Yes	Yes	No	Avoid Use	NA
			No	No	Yes	400 mg	6
400 mg	6	No	Yes	No	No	200 mg	6
			No	Yes	No	200 mg	6
			Yes	Yes	No	Avoid Use	NA
			No	No	Yes	600 mg	6
600 mg	6	No	Yes	No	No	400 mg	6
			No	Yes	Yes	400 mg	6
			Yes	Yes	No	Avoid Use	NA
			No	No	Yes	600 mg	6
	12	Yes	No	Yes	No	Avoid Use	NA
			No	No	Yes	400 mg	6
		No	Yes	No	No	600 mg	12
			No	Yes	Yes	600 mg	12
			Yes	Yes	No	Avoid Use	NA
			No	No	Yes	400 mg	6

INH= inhibitor; IND= inducer; NA= not applicable; a= CYP3A inducers taken for greater than 2 weeks


Our goal isn't just to have the best drug interaction information in the package insert. Our goal is to have actionable information available for prescribers, however they get that information, to make sure that drugs are prescribed properly for our patients and that they don't suffer from preventable drug interactions.
Dr. Janet Woodcock
Center Director, CDER
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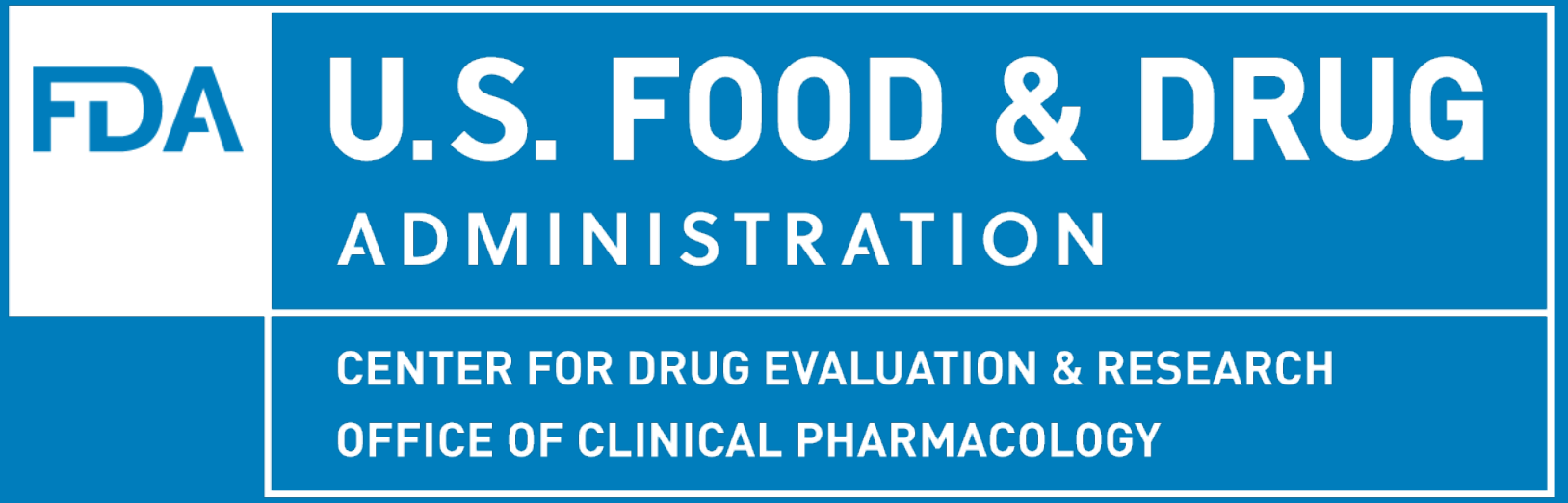
How Are We Doing?

- YOU can help OCP achieve its goal of translating its regulatory reviews into understandable and actionable labeling language.

- Provide feedback on the quality, clarity, and utility of clinical pharmacology-related information in the professional and consumer drug labeling you are using.

Email: ocp@fda.hhs.gov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