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

FDA DRUG TOPICS

Tips to Navigating Drug Interaction information in Prescribing Information (PI)

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

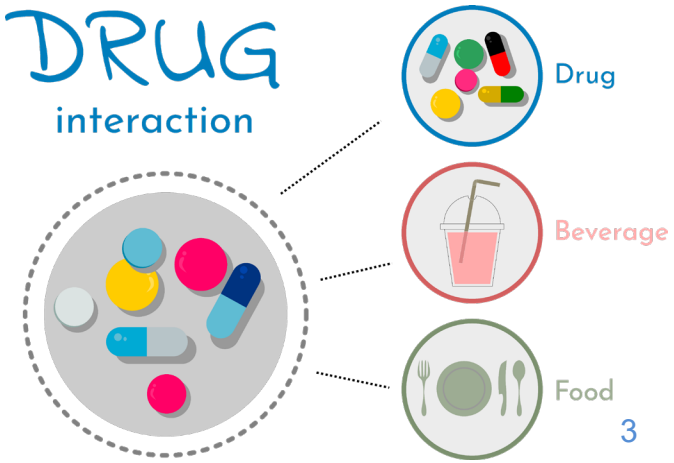
Disclaimer

- Any labeling text, tables, or figures presented today are meant to be illustrative only and are not intended to limit the use of other possible formats and approaches to convey critical information under current regulations
- The field of metabolic and transporter pharmacology is rapidly evolving, thus websites discussed herein are meant to be a guide and not considered a comprehensive list of all possible interacting drugs and substances (e.g., foods, including dietary supplements).
- The websites discussed herein contain examples of drugs with CYP enzyme-based and transporter-based interactions, but does not include drugs with other mechanisms leading to drug interactions such as:
  - Certain interactions affecting drug absorption (e.g., chelating agents, resin-based binders, interactions, and drugs that change gut pH)
  - Interactions affecting drug plasma protein binding
  - Pharmacodynamic interactions

Learning Objectives

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

- Identify three key elements that must be included in the DRUG INTERACTIONS section of the prescribing information (PI)
- Distinguish between the type of information that should be included in the DRUG INTERACTIONS and CLINICAL PHARMACOLOGY sections of the PI
- Locate examples of drugs that interact with Cytochrome P450 (CYP) enzymes and transporter systems by searching the FDA resource https://www.fda.gov/CYPandTransporterInteractingDrugs
- Describe the utility of physiologically based pharmacokinetic (PBPK) modeling for identifying potential drug interactions in drug development

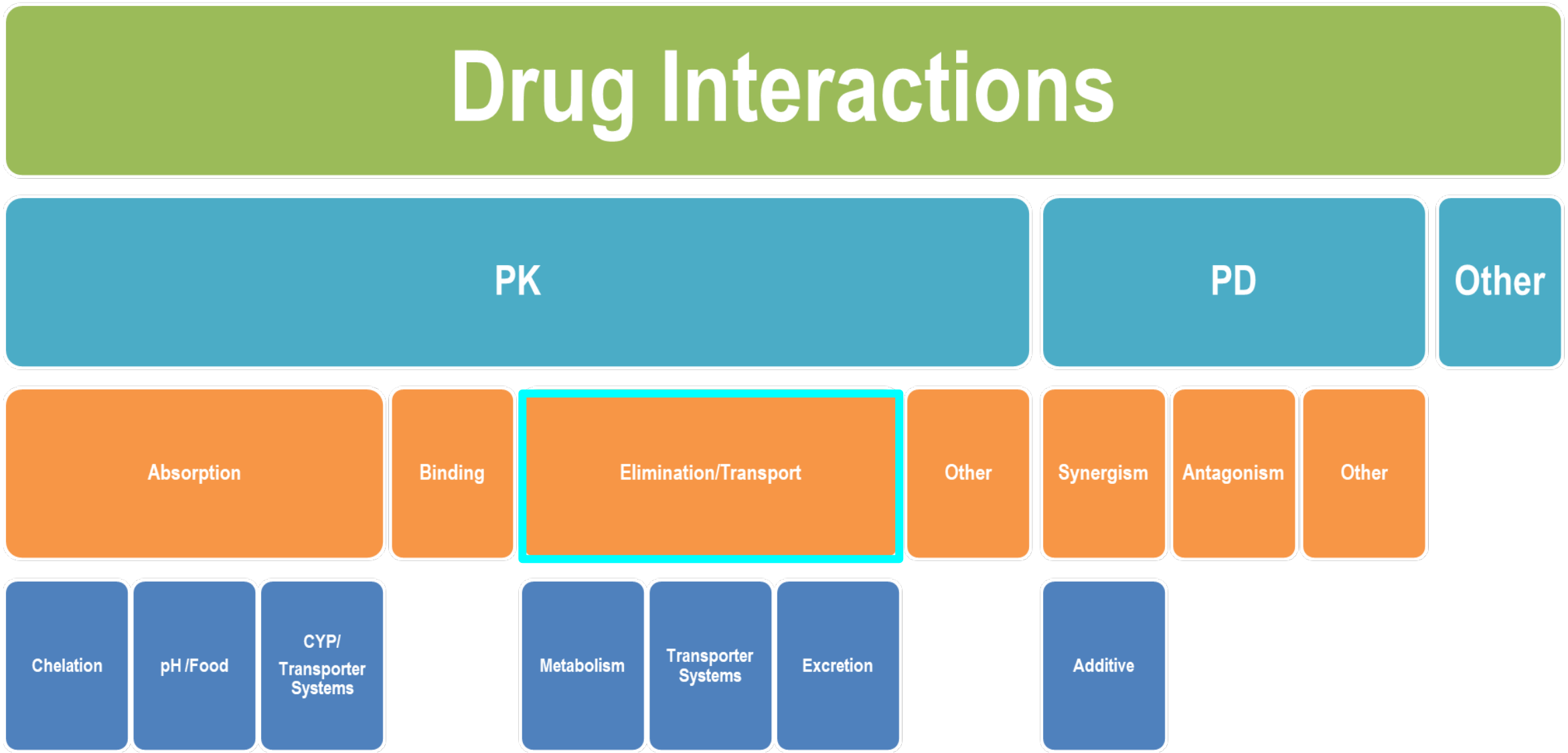


Impact of Drug Interactions (DIs)

- Unanticipated, unrecognized, or mismanaged DIs 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 DI
- Chicago Tribune investigation (2016)
  - Reporters presented pharmacies with prescriptions for drugs that are known to be harmful or even fatal if taken together
  - 52 % of the time the prescriptions were filled without warning

Grillo, J. et al. Clin. Pharmacol. Ther. 105, 1292– 1295 (2019);
https://www.chicagotribune.com/investigations/ct-drug-interactions-pharmacy-met-20161214-story.html

Common Mechanisms of DI



Objectives of the FDA DI Program

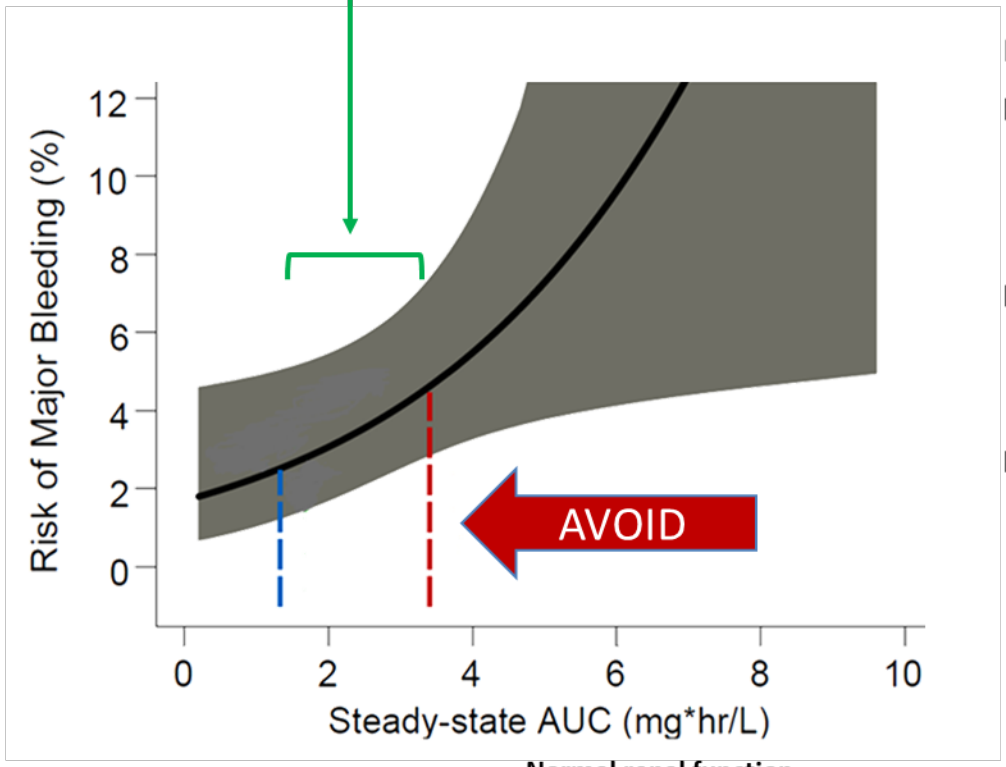
- Determine the potential for clinically significant DIs
  - Do other drugs alter the pharmacokinetics (PK) or Pharmacodynamics (PD) of the investigational drug?
  - Does the investigational drug alter the PK/PD of other drugs?
  - What is the magnitude of changes in PK/PD parameters?
  - What is the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

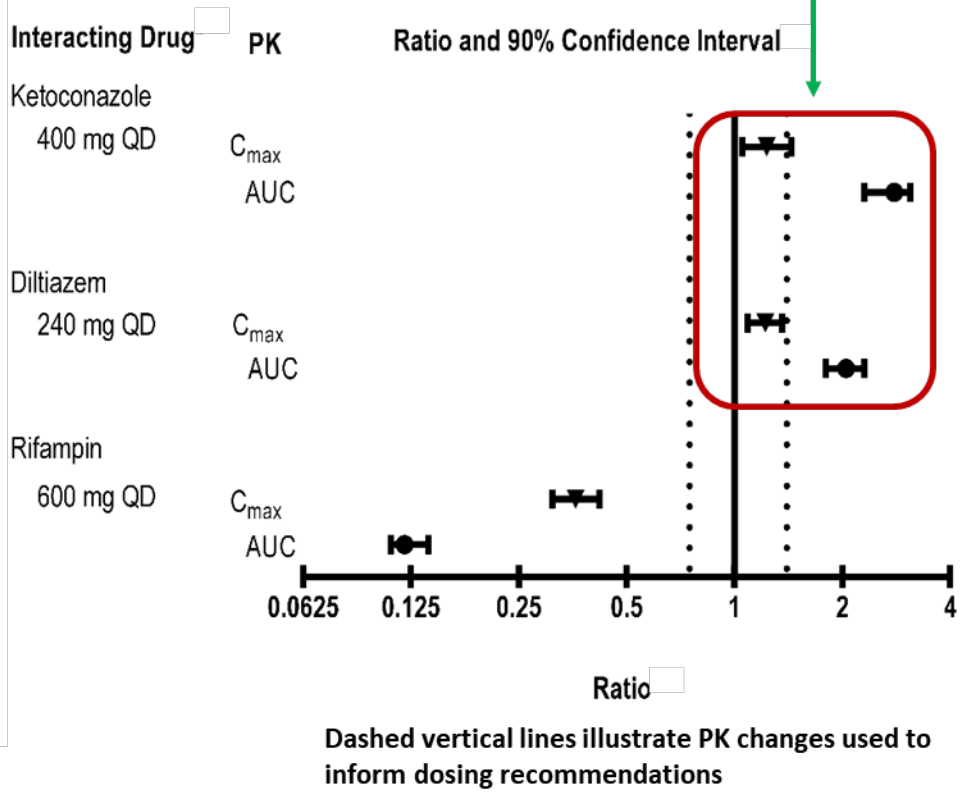
Sources of DI-Related Information For Regulatory Review

Clinical Impact Drives DI 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

US PI Content and Format

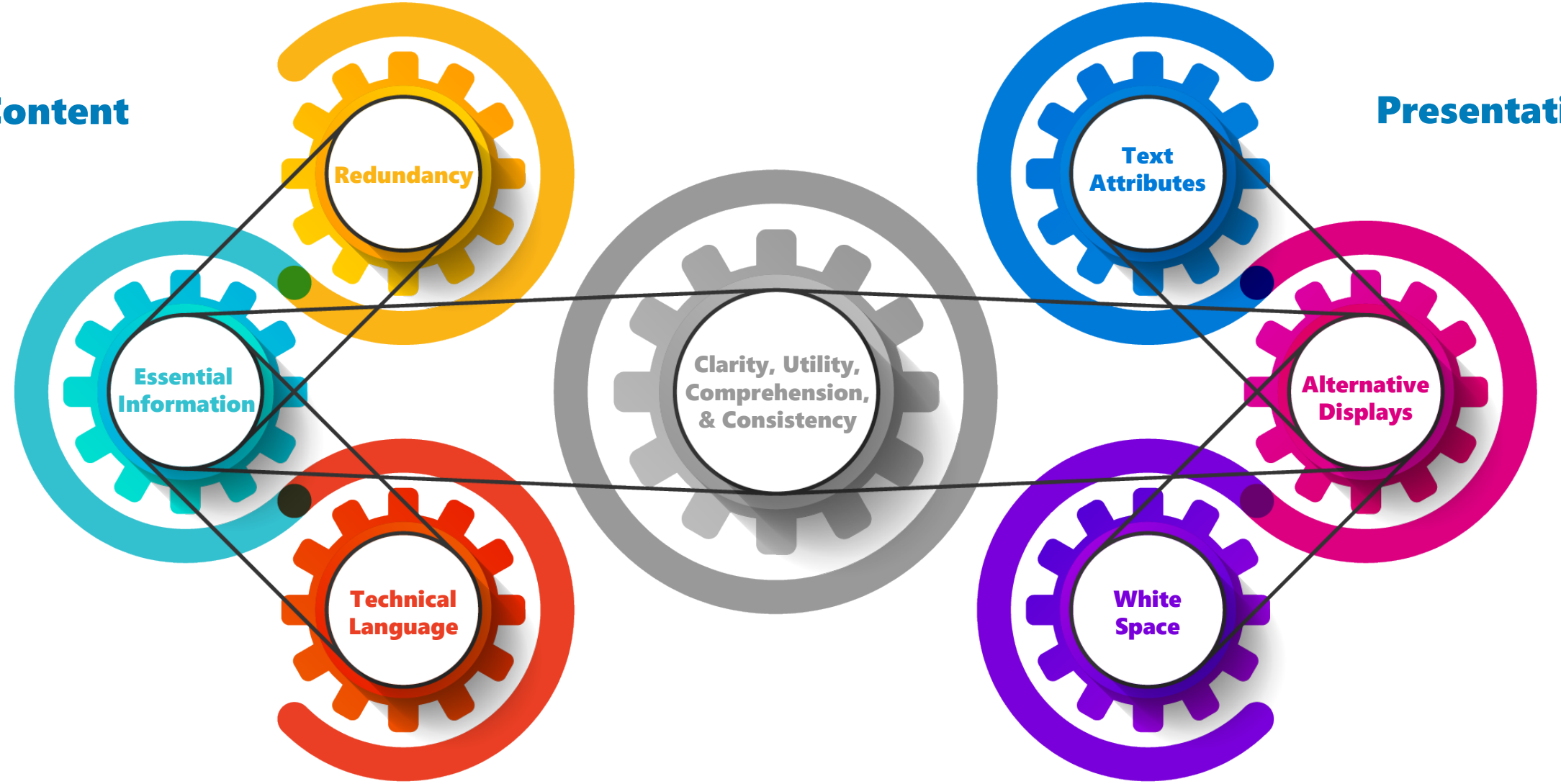
HIGHLIGHTS OF PRESCRIBING INFORMATION

DI Related Information

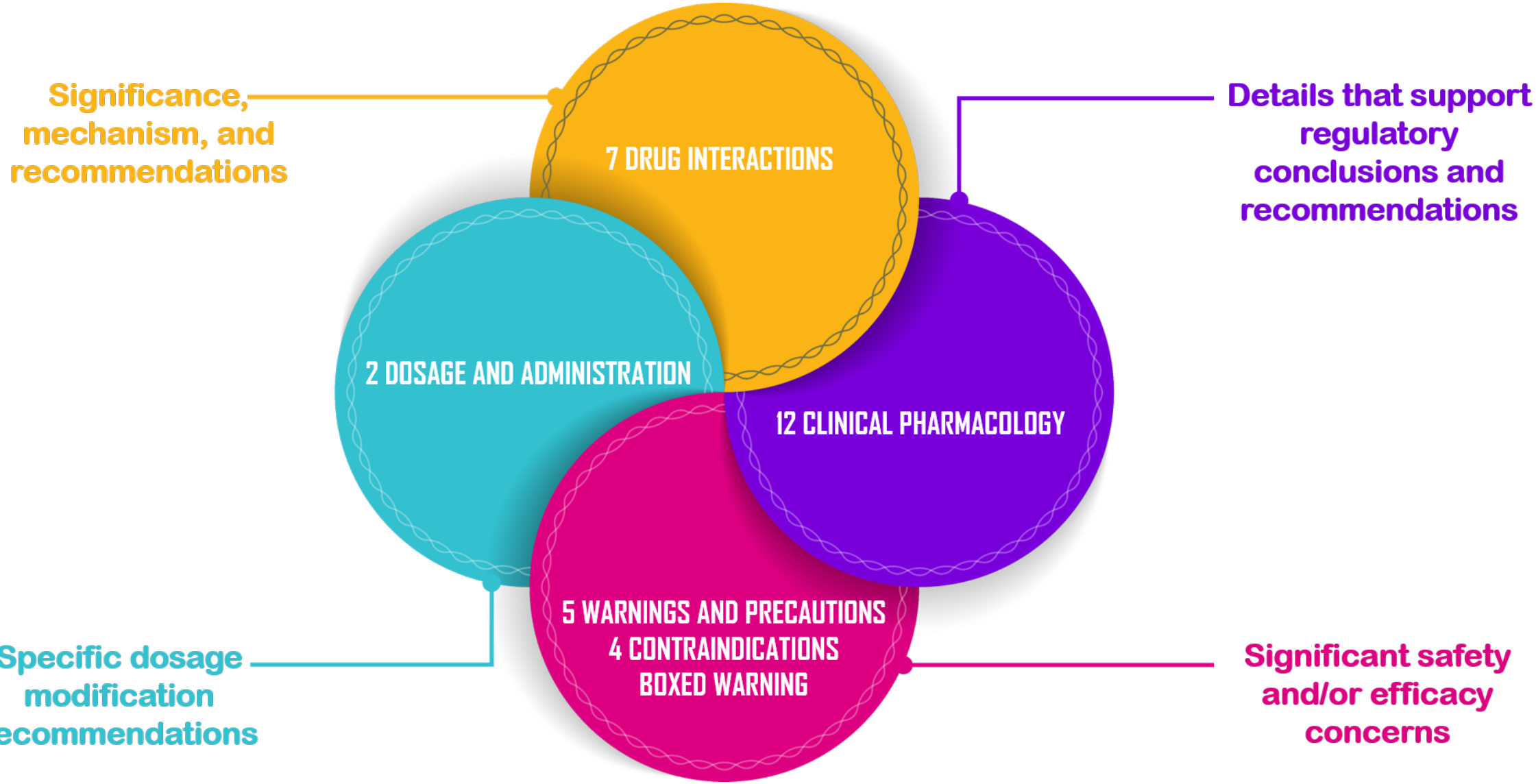
FULL PRESCRIBING INFORMATION: CONTENTS*

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

Strategies to Enhance Drug Interaction Related Labeling Development



Cross Referencing Reduces Redundancy



DRUG INTERACTIONS Section Regulations

- 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 DI Information in the PI

- 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

DRUG INTERACTIONS Section as Text

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)]*.

Drugazide is a CYP3A substrate. Use with a strong CYP3A inhibitor increases drugazide C_{max} and AUC which may increase the risk of Drug X related syncope *[see Warnings and Precautions (5.x) and Clinical Pharmacology (12.3)]*.

DRUG INTERACTIONS Section Alternative Display

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on Drug X

Table X describes drug interactions where concomitant use of another drug affects DRUG-X.

Table X. Drug Interactions with DRUG-X that Affect Drugazide

Strong CYP3A Inhibitors		
Mechanism and Clinical Effect(s)	Drugazide is a CYP3A substrate. Concomitant use with a strong CYP3A inhibitor increases drugazide C_{max} and AUC *[see Clinical Pharmacology (12.3)]*, which may increase the risk of DRUG-X adverse reactions.	
Prevention or Management	Reduce DRUG-X dosage when used concomitantly with strong CYP3A inhibitors *[see Dosage and Administration (2.x)]*.	
Strong CYP3A Inducers		
Mechanism and Clinical Effect(s)	Drugazide is a CYP3A substrate. Concomitant use with a strong CYP3A inducer decreases drugazide C_{max} and AUC *[see Clinical Pharmacology (12.3)]*, which may reduce DRUG-X efficacy.	
Prevention or Management	Avoid concomitant use with a strong CYP3A inducer.	
Gastric Acid Reducing Agents		
Mechanism and Clinical Effect(s)	Concomitant use with a proton pump inhibitor (PPI) decreases drugazide AUC *[see Clinical Pharmacology (12.3)]* which may reduce DRUG-X efficacy.	
Prevention or Management	PPI	Avoid concomitant use.
	H2-receptor antagonist	Avoid concomitant use.
	Antacid	Administer DRUG-X 2 hours before or after an antacid *[Dosage and Administration (2.x)]*.

7.1 Effects of DRUG-X on Other Drugs

CYP3A Substrates

Avoid concomitant use unless otherwise recommended in the Prescribing Information for CYP3A substrates where minimal concentration changes may lead to serious adverse reactions.

Drugazide is a CYP3A inhibitor. Drugazide increases exposure of CYP3A substrates [see Clinical Pharmacology (12.3)], which may increase the risk of adverse reactions related to these substrates.

Therapeutic Proteins

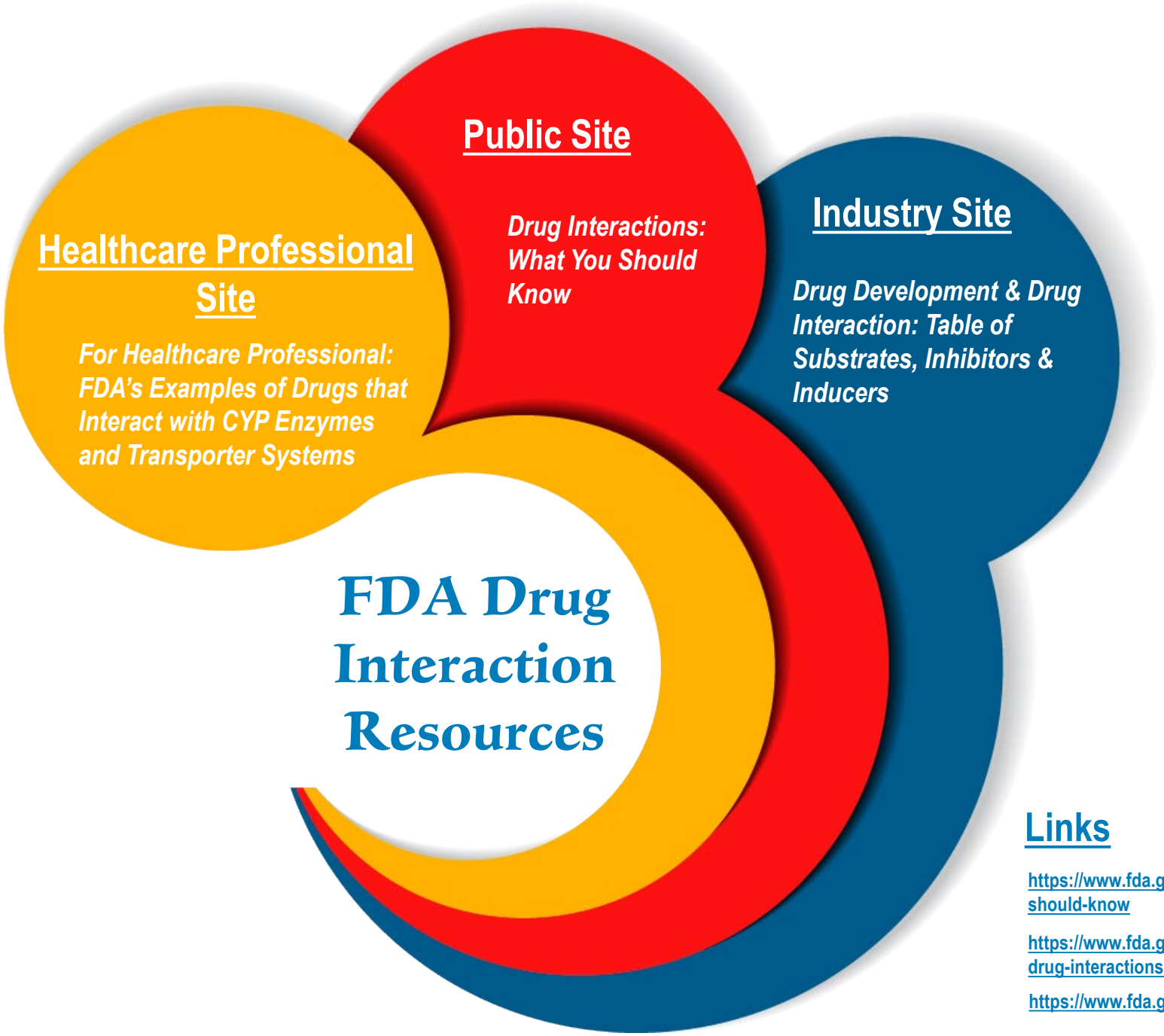
7 DRUG INTERACTIONS

7.1 Certain CYP Substrates

For CYP substrates where minimal:

- Decreases in the concentration may reduce CYP substrate effectiveness, monitor for reduced effectiveness of the CYP substrate upon DRUG-X initiation.
- Increases in the concentration may increase CYP substrate adverse reactions, monitor for increased adverse reactions of the CYP substrate after DRUG-X discontinuation.

Increased concentrations of cytokines (e.g., IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation associated with certain diseases including small cell lung cancer may suppress the formation of CYP enzymes. Therapeutic proteins, including drugazumab, that decrease the concentrations of these pro-inflammatory cytokines may increase the formation of CYP enzymes resulting in decreased CYP substrate exposure.



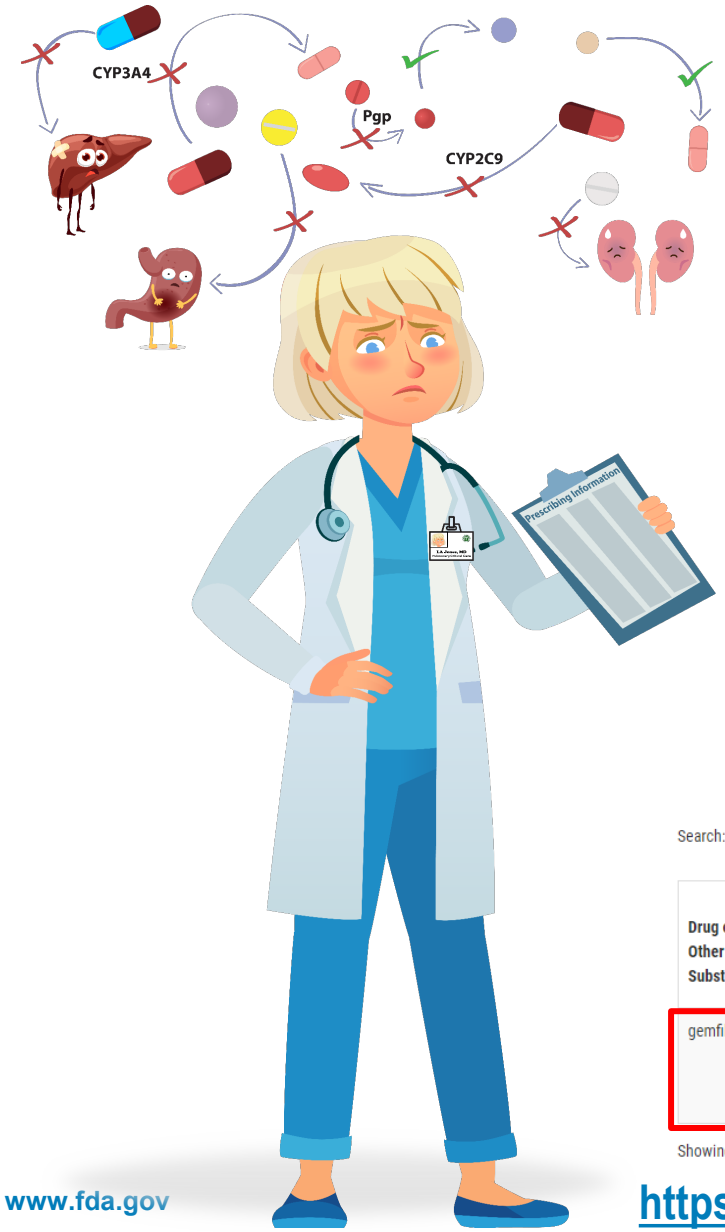
Links

https://www.fda.gov/drugs/resources-drugs/drug-interactions-what-you-should-know

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

https://www.fda.gov/CYPandTransporterInteractingDrugs

HealthCare Provider Focused Drug Interaction Site



Filter boxes to find examples of drugs and other substances within selected pathways

Use filters in this box or use the search box ("Search") that is directly below to refine the results.

CYP strong inhibitor: 2C8	CYP moderate inhibitor	CYP weak inhibitor
CYP strong inducer	CYP moderator inducer	CYP weak inducer
CYP sensitive substrate	CYP moderate sensitive substrate	
Transporter inhibitor	Transporter substrate	

Clear Filters

Search: Export Excel Show 10 entries

Drug or Other Substance	CYP Strg INH	CYP Mod INH	CYP WK INH	CYP Strg IND	CYP Mod IND	CYP WK IND	CYP SENS SUB	CYP Mod SENS SUB	TRNSP INH	TRNSP SUB
gemfibrozil	2C8 strong inhibitor								OAT3; OATP1B1; OATP1B3 inhibitor	

Showing 1 to 1 of 1 entries (filtered from 218 total entries) Previous 1 Next

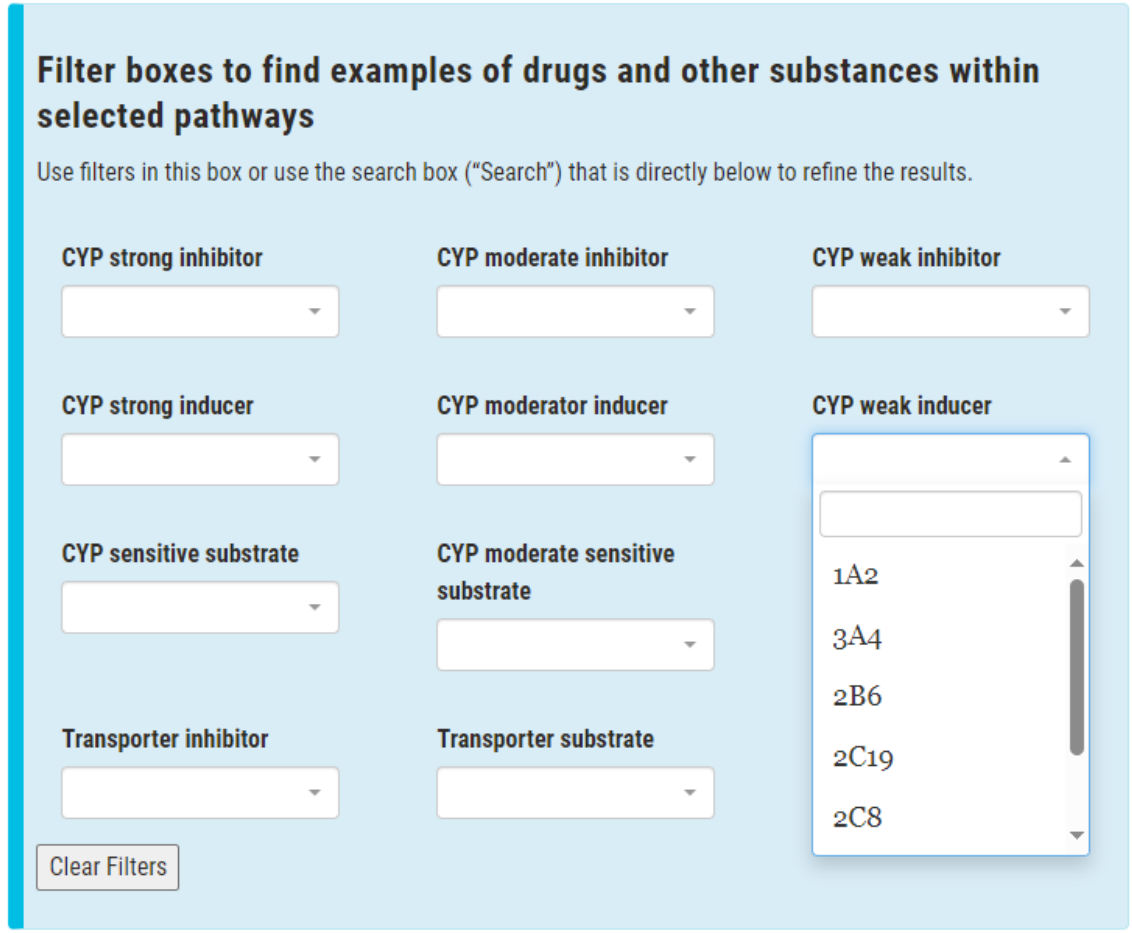
- Examples* of drugs that interact with CYP enzymes & transporter systems
- Searchable
- All relevant information in one table

https://www.fda.gov/CYPandTransporterInteractingDrugs

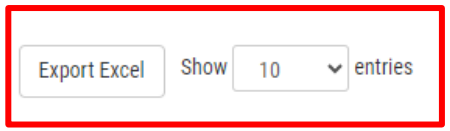
*These examples were evaluated and compiled by FDA as an optional resource for healthcare professionals to consult when reviewing information in the DRUG INTERACTIONS section of the approved U.S. Prescribing Information (PI) in clinical practice.

How to Use

Dropdown Filters



Freeform Search



Download results or entire database

How to Optimize Searches

- To refine your search for interacting examples use the filters and/or the search box
- When using the search box…
  - include the name of the drug substance rather than the name of the drug product or the proprietary name
    - e.g., “Atorvastatin” instead of “atorvastatin calcium tablets” or “Lipitor.”
  - Remember that the search ignores the symbols: ., (,), ‘, -, and /
    - e.g., “St. John’s wort” or “St John s wort” will return the same result
- The filters and search box operate using the “and” function
  - Use of two or more filters or the combination of filters with the search box returns results that meet both criteria

Special Situations: Smaller Screens

Drug or Other Substance	CYP Strg INH	CYP Mod INH	CYP WK INH	CYP Strg IND	CYP Mod IND	CYP WK IND
⊕ gemfibrozil	2C8 strong inhibitor					

Showing 1 to 1 of 1 entries (filtered from 218 total entries)

Previous 1 Next

Drug or Other Substance	CYP Strg INH	CYP Mod INH	CYP WK INH	CYP Strg IND	CYP Mod IND	CYP WK IND
⊖ gemfibrozil	2C8 strong inhibitor					

CYP SENS SUB

CYP Mod SENS SUB

TRNSP INH OAT3; OATP1B1; OATP1B3 inhibitor

TRNSP SUB

12.3 PK Subsection Content

- Must describe the clinically significant pharmacokinetics of a drug or active metabolites, (i.e., pertinent absorption, distribution, metabolism, and excretion parameters).
  - Information regarding bioavailability, the effect of food, minimum concentration (Cmin), maximum concentration (Cmax), time to maximum concentration (Tmax), area under the curve (AUC), pertinent half-lives (t1/2), time to reach steady state, extent of accumulation, route(s) of elimination, clearance (renal, hepatic, total), mechanisms of clearance (e.g., specific enzyme systems), drug/drug and drug/food (e.g., dietary supplements, grapefruit juice) pharmacokinetic interactions (including inhibition, induction, and genetic characteristics), and volume of distribution (Vd) must be presented if clinically significant.
  - Information regarding nonlinearity in pharmacokinetic parameters, changes in pharmacokinetics over time, and binding (plasma protein, erythrocyte) parameters must also be presented if clinically significant.
  - This section must also include the results of pharmacokinetic studies (e.g., of metabolism or interaction) that establish the absence of an effect, including pertinent human studies and in vitro data.
  - Dosing recommendations based on clinically significant factors that change the product's pharmacokinetics … that appear in other sections … must not be repeated in this subsection, but the location of such recommendations must be referenced.

12.3 PK Subsection DI Information as Text

12.3 Pharmacokinetics

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Strong CYP3A4 inhibitors: Drugazide mean Cmax increased 3.2-fold and AUC by 3.5-fold following itraconazole (strong CYP3A4 inhibitors) 200 mg twice daily for one day then daily for 10 days and a single dose of drugazide 100 mg on Day 6.

Moderate CYP3A4 inhibitors: Drugazide mean Cmax is predicted to increase by 1.4-fold and AUC by 2.1-fold following concomitant administration of fluconazole (moderate CYP3A4 inhibitor) with drugazide 100 mg daily.

Strong CYP3A4 inducers: drugazide 100 mg mean Cmax decreased by 67% and AUC by 86% following rifampicin (strong CYP3A4 inducer) 600 mg daily for 10 days and a single dose of rivoceranib 100 mg on Day 8.

12.3 PK Subsection DI Information as Text

12.3 Pharmacokinetics

Drug Interaction Studies

In Vitro Studies

CYP450 Enzymes: Drugazide is a CYP1A2, CYP3A4, and CYP2D6 substrate, but is not a substrate of, CYP2B6, CYP2C8, CYP2C9, CYP2C19. Drugazide is an inhibitor of CYP1A2, CYP2B6, and CYP3A4, but not CYP2C8, CYP2C9, CYP2C19, and CYP2D6. Drugazide is an inducer of CYP1A2 and CYP 3A4, but not CYP2B6.

Glucuronidation Enzymes: Drugazide is a UGT1A1 substrate, but is not a substrate of, UGT1A3, UGT1A4, UGT1A6, UGT1A9, and UGT2B7 Drugazide is an inhibitor of UGT1A1, UGT1A4, UGT1A9, and UGT2B7, but not UGT1A3 or UGT1A6.

Transporter Systems: Drugazide is a P-gp and BRCP substrate, but is not a substrate of OATP1B1, OATP1B3, and OCT1. Drugazide is an inhibitor of P-gp, BCRP, OCT2, and OCT1, but not OATP1B1, OATP1B3, OAT1, OAT3, MATE1, MATE2- K, or bile salt export pump (BSEP).

12.3 PK Subsection DI Information Alternative Displays

Table

12.3 Pharmacokinetics

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Table X: Clinically Significant Drug Interactions That Affect Drugazide

Concomitant Drug (Dosage) [Interacting class]	Drugazide Dosage	Ratio (90% CI) [minimum to maximum] of Drugazide Exposure Measures Combination/No Combination	
		C_{max}	AUC
Ketoconazole (400 mg QD) [Strong CYP3A Inhibitor]	60 mg single dose	Increase 1.2-fold (1.1, 1.4) [0.9 to 1.9]	Increase 2.8 -fold (2.3, 3.1) [1.9 to 4.2]
Diltiazem (240 mg QD) [Moderate CYP3A Inhibitor]		Increase 1.2-Fold (1.1, 1.4) [0.5 to 2.9]	Increase 2.1-Fold (1.8, 2.3) [0.9 to 3.8]
Rifampin (600 mg QD) [Strong CYP3A Inducer]		Decrease 64% (58%, 69%) [45% to 74%]	Decrease 88% (86%, 89%) [84% to 92%]

Other Drugs: No clinically significant differences in drugazide pharmacokinetics were observed when used concomitantly with Drug-A, Drug-B, Drug-C.

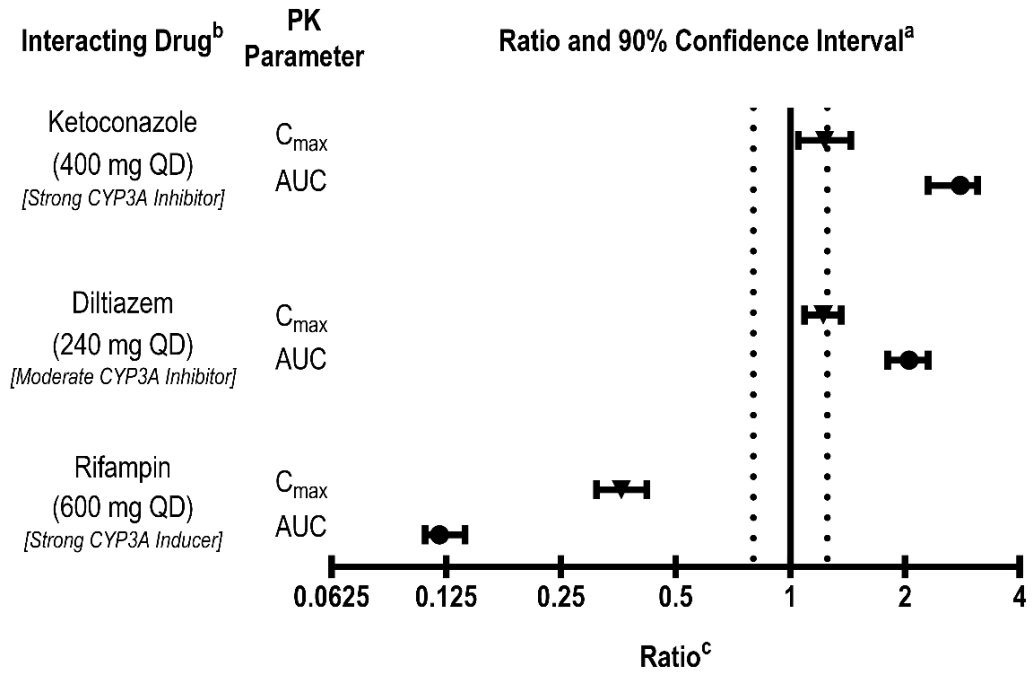
Figure

12.3 Pharmacokinetics

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

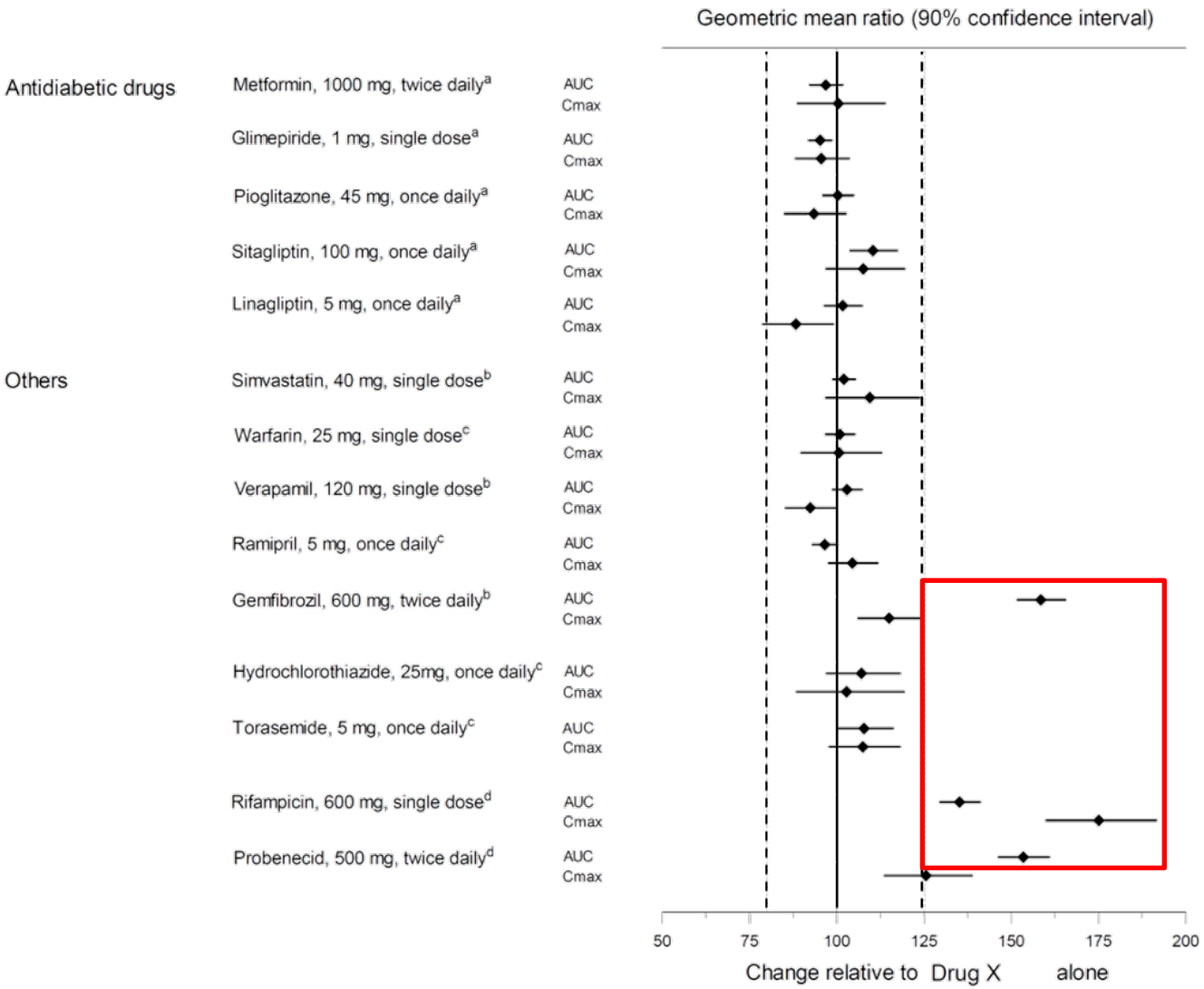
Figure X: Clinically Significant Drug Interactions That Affect Drugazide



a= Dashed vertical lines represent 0.8 to 1.25 equivalence range
b= Drug X administered as a 60 mg single dose
c=Log base 2 scale

Other Drugs: No clinically significant differences in drugazide pharmacokinetics were observed when used concomitantly with Drug-A, Drug-B, Drug-C.

“Significance” Can Be Confusing in Some Figures



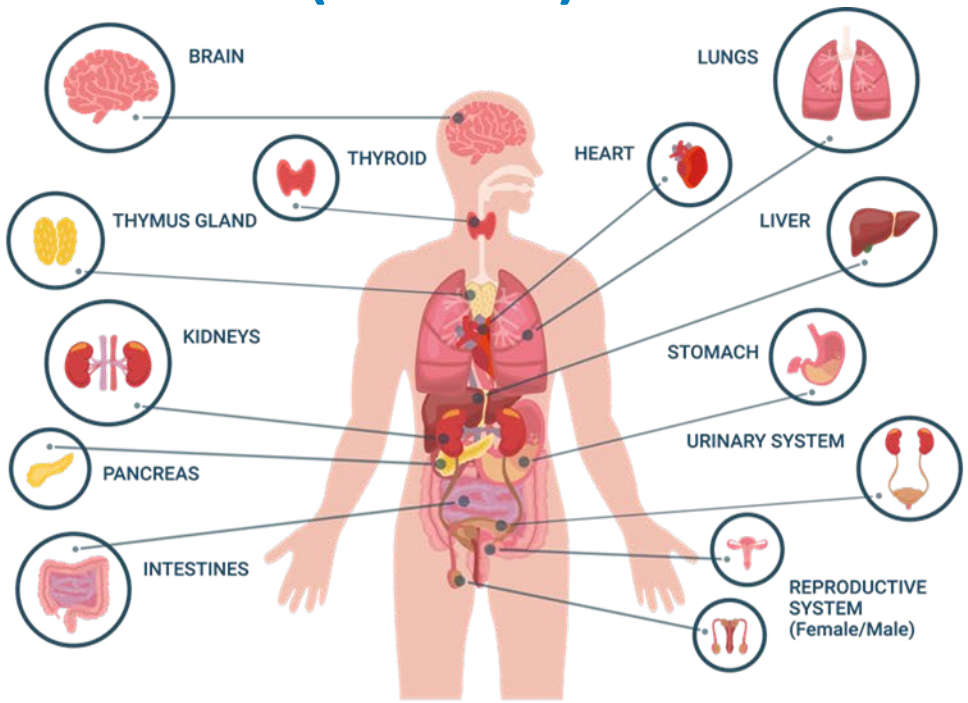
- **Statistically different but not clinically significant**
- **Will not be in the DRUG INTERACTIONS section**

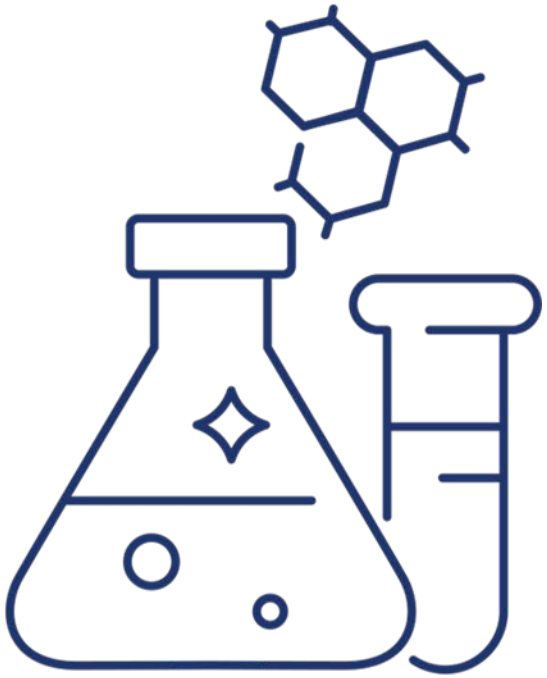
[a] Drug X ,100 mg, once daily; [b] Drug X, 50 mg, single dose; [c] Drug X ,50 mg, once daily; [d] Drug X 25 mg, single dose

Polling Questions

1. Have you heard the term Physiologically-Based Pharmacokinetic Modeling (PBPK) in your clinical practice environment?
   a) Yes
   b) No
2. Do you feel comfortable critically evaluating PBPK-based information found in the PI for use in your clinical practice environment?
   a) Yes
   b) No

Physiologically-Based Pharmacokinetic Modeling (PBPK)





Drug Specific Parameters

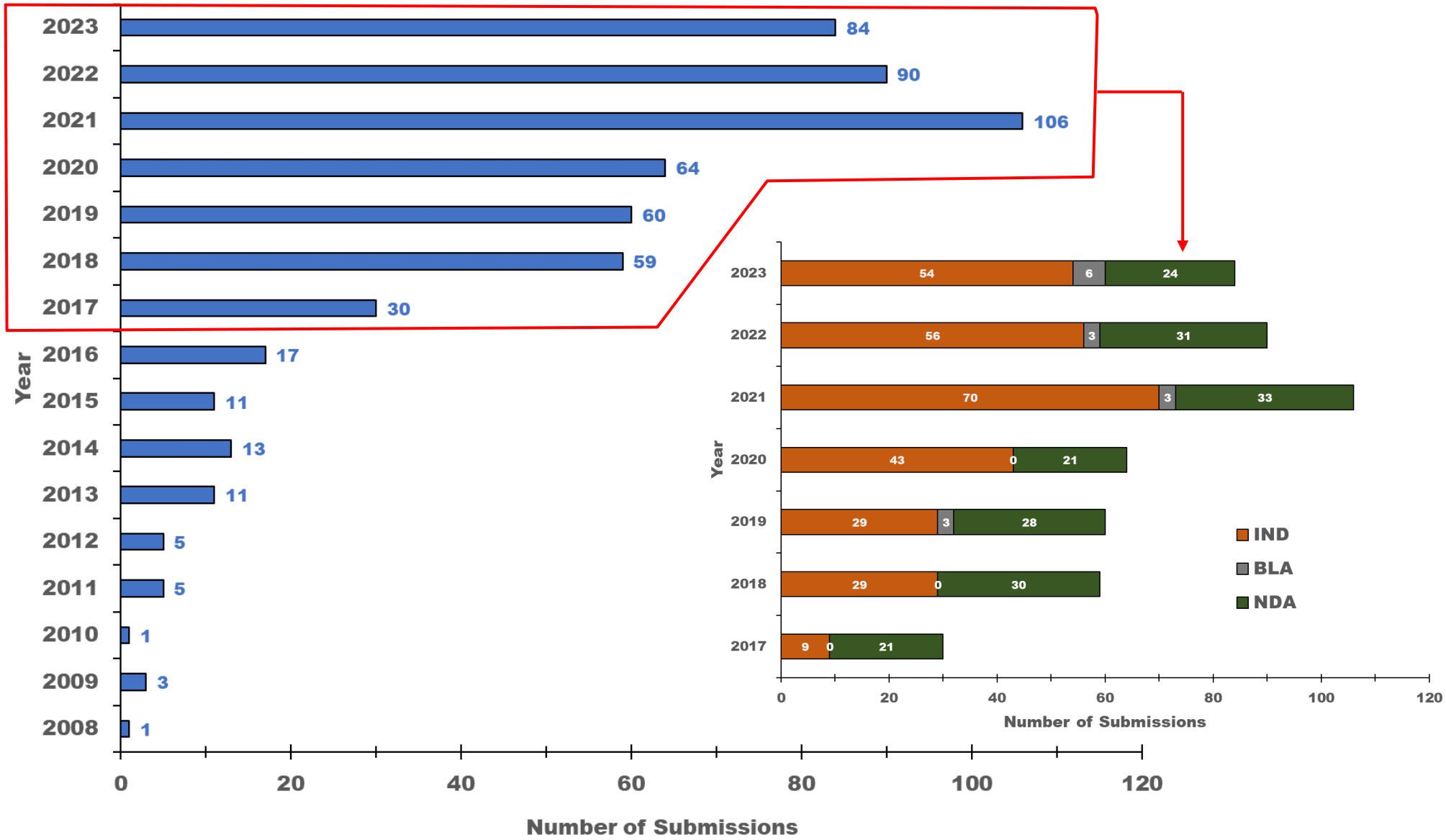
Physiology

Chemistry

PBPK Modeling

Predict → Learn → Confirm

PBPK Submissions 2008-2023*



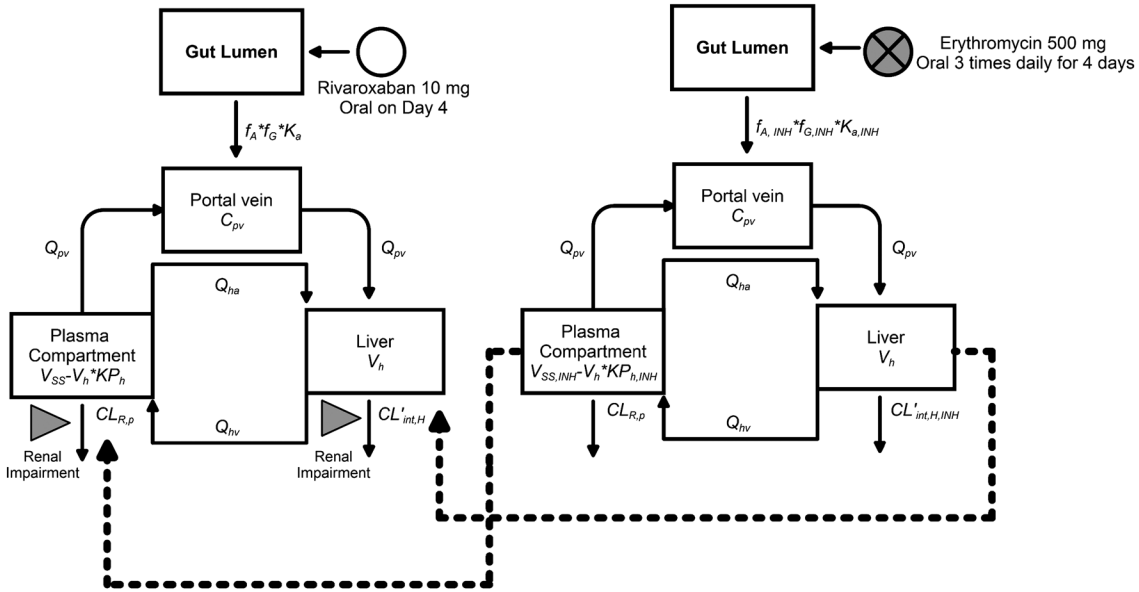
* Ending Dec 15, 2023

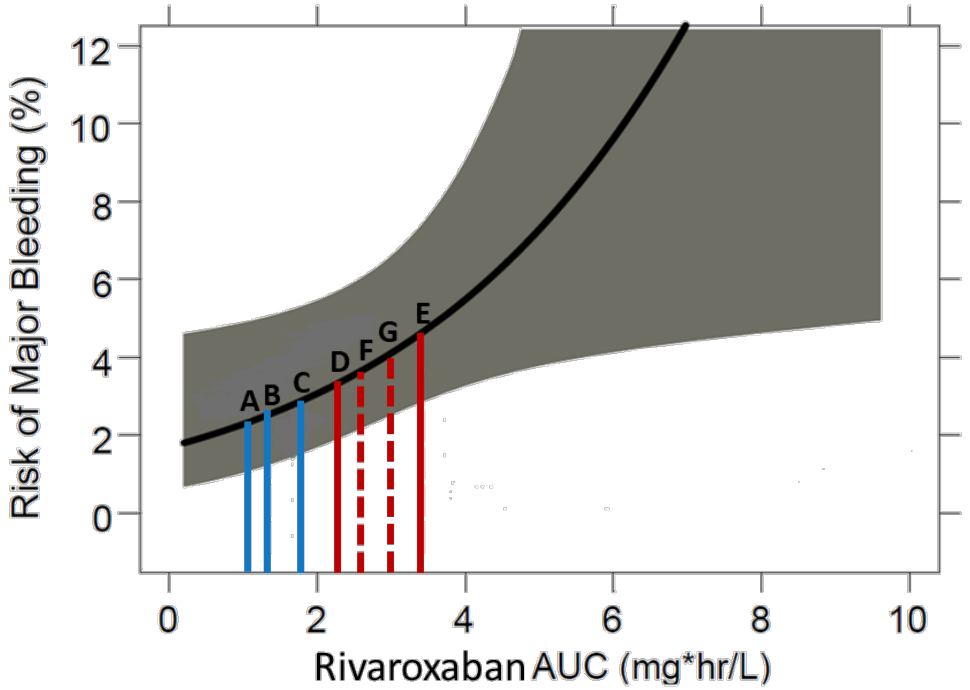
Submissions By Therapeutic Class 2017-2023*

* Ending Dec 15, 2023

PBPK to Predict a Complex Disease-DI Scenario

- PBPK model simulating rivaroxaban (DOAC) pharmacokinetics in young or older subjects with normal or impaired renal function ± erythromycin (P-gp and moderate CYP3A4 inhibitor)
- Pgp renal and sex effects added later





A= Normal RF, No Inhibitor
B= Normal RF, + Erythromycin [~1.3 fold ↑]
C= Mild RI, No Inhibitor [~1.4 fold ↑]

D= Severe RI, No Inhibitor [~1.6 fold ↑]
E= Mod HI, No Inhibitor [~2.3 fold ↑]
"↑ Monitoring &/or Avoid Use"

Predicted
F= Older, Mild RI, + Erythromycin [~1.9 fold ↑]
G= Older, Mod RI, + Erythromycin [~2.2 fold ↑]

Mild RI, + Erythromycin [~1.8 fold ↑]
Mod RI, + Erythromycin [~2 fold ↑]

"Should not be used unless the potential benefit justifies the potential risk"

Predicted
Older, ♂, Mod RI, + Erythromycin [~2.9 fold ↑]

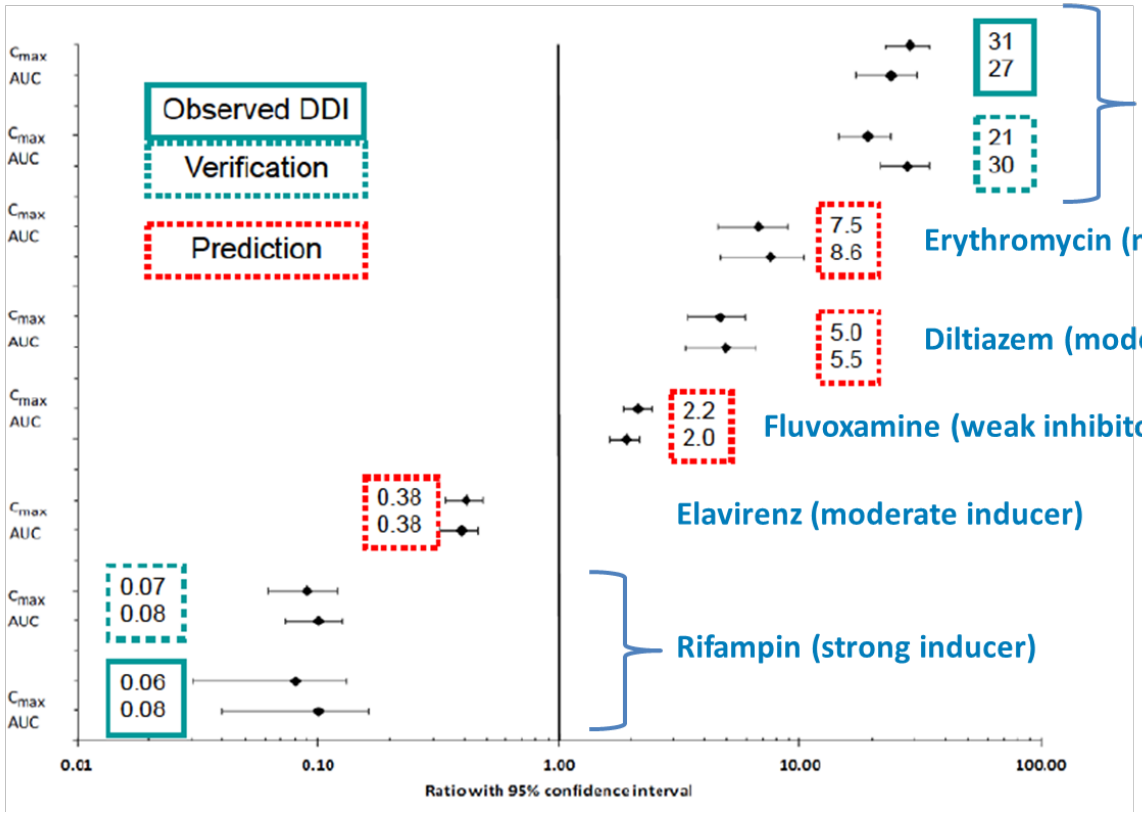
DOAC= direct oral anticoagulant
Exposure-Response Graphic adapted from https://bit.ly/3OwuaIQ

Janssen Pharmaceuticals, Inc. XARELTO (rivaroxaban) package insert. Titusville, NJ; 2021.
Grillo JA, et. al. Biopharm Drug Dispos. 2012;33(2):99-110. doi:10.1002/bdd.1771
V. Hsu, et al. Clin Pharmacol Ther. 2014; 95 (S1): S19.

PBPK to Predict DI & Reduce Trial Burden

Ibrutinib
(kinase inhibitor)

PBPK-simulated and observed C_{max} and AUC ratios (mean and 95% confidence interval)



Applicant simulations and FDA analysis informed prescription drug labeling (PDL) and provided decision support for potential dose staggering and dose reduction mitigation strategies

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205552Orig1s000ClinPharmR.pdf

PBPK to Predict DI in a Vulnerable Population

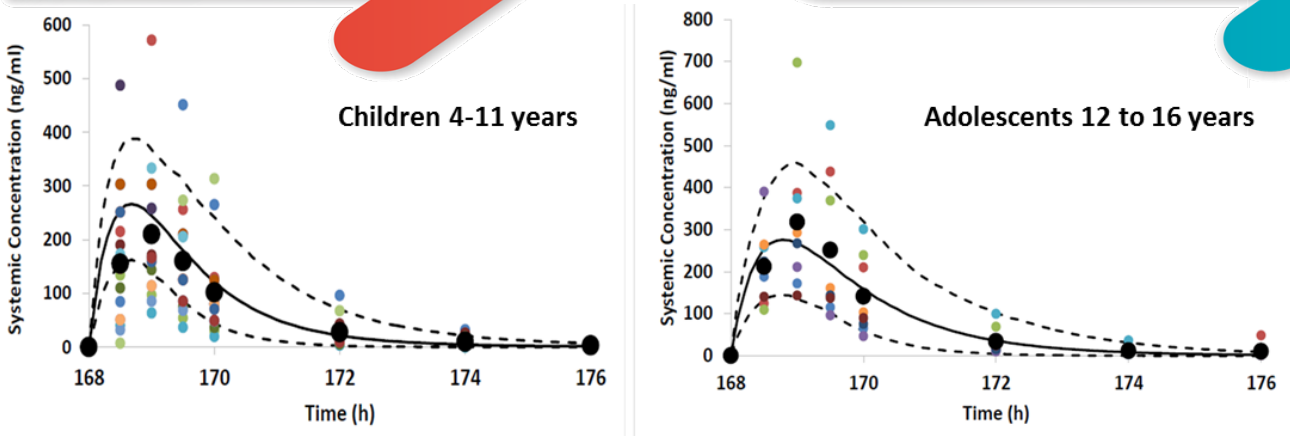
Deflazacort (corticosteroid)

Model Development
- Physicochemical & in vitro ADME data
- Literature-based clinical data

Model Verification
- Adult CLA & RIF DDI study
- SD & MD PK study in children & adolescents

Model Application
- Predict DDI in children & adolescents

Applicant proposed a model that predicted exposure of active 21-desDFZ in children & adolescents following coadministration of deflazacort and strong or moderate CYP3A4 inhibitors/ inducers



Drug	Children		Adolescents	
	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio
Clarithromycin (7.5 mg/kg)	**1.97**	**3.85**	**2.14**	**4.31**
Fluconazole (6 mg/kg)	**1.96**	**3.61**	**2.10**	**3.97**

Applicant simulations and FDA analysis informed PDL and provided decision support for revised dose mitigation strategies in children, and adolescents

SD= single dose; MD = multiple dosing; CLA= Clarithromycin; RIF=Rifampicin; DFZ=Deflazacort

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208684,208685Orig1s000ClinPharmR.pdf

2020 HCP Labeling Semi-Structured Interviews

70 semi-structured qualitative interviews of 35 primary care physicians and 35 physicians from a wide range of specialties using fictitious PI examples

PCP= Primary care physician

CP= Clinical Pharmacology

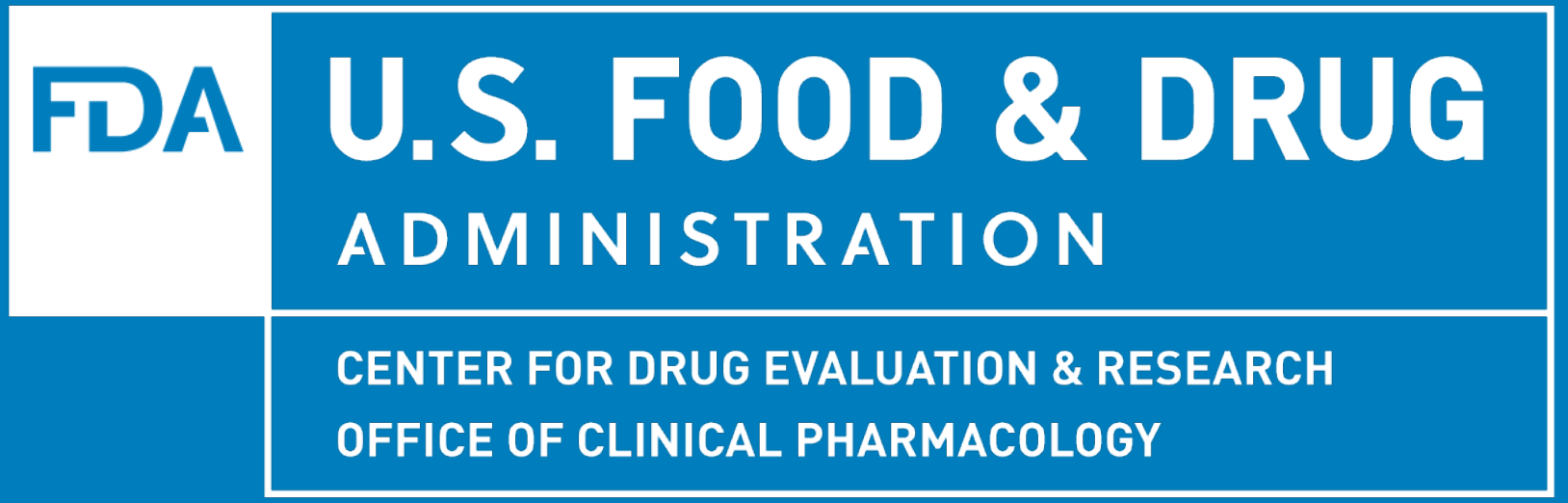
- 46% of PCP & 69% of Specialists cited the Drug Interactions (7) section as among the most useful
- Some sections, such as the CP section, can be confusing and include a lot of information some of which is complicated
- 52% of PCP and 57% of specialists said they would look in the CP section for results of positive and pertinent negative results from population analyses or other modeling
  - In approximately 25% of the interviews, participants asked the moderator to clarify the meaning of either
    - Population analyses or other modeling
    - Simulation approaches that evaluate drug interactions
    - Positive and pertinent negative results from specific clinical pharmacology studies

Sullivan HW, Squire C, Aikin KJ, Tzeng J, Ferriola-Bruckenstein K, Brodsky E, Trentacosti AM, Johnson M. Physicians' use of and preferences for FDA-approved prescribing information. *Res Social Adm Pharm.* 2021 Aug 1:S1551-7411.

Unpublished data from Sullivan HW, et. al, 2020 with permission of the authors.

Closing Thoughts

- DIs are a major contributor to preventable morbidity and mortality
- The US PI describes clinically significant DIs, provides essential context from studies and modeling and offers recommendations for prevention and management
- FDA online resource allows HCPs to view which drugs or foods are within a specific CYP- or transporter-based drug interacting class through filter and free form searching
  - Provide feedback: ocp@fda.hhs.gov
- The use of PBPK modeling in the assessment of DI risk is increasing
  - Elevating awareness of PBPK modeling among healthcare providers is crucial
  - Clinicians can be a valuable resource to “modelers” to inform complex disease related physiology and provide a real-world perspective during model development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