Regulatory Education for Industry (REdI):

PRESCRIPTION DRUG LABELING - CHALLENGES AND ISSUES

Bethesda Marriott | Pooks Hill, MD | November 3-4, 2015

Strategies for Enhancing Quality, Utility, and Clarity in Drug Interaction (DDI) Labeling

A Regulatory Perspective

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

The views expressed in this presentation are personal opinion and do not reflect the official policy of the FDA

Outline

- DDI Risk
- Health care provider perception of labeling
- Enhancing clarity and readability in labeling
- Strategies for developing DDI labeling for
  - Drug Interactions (Section 7)
  - Clinical Pharmacology (Section 12)
  - Dosage and Administration (Section 2)
- Summary and tips

Medication Errors & DDI

- All drugs approved by FDA still carry risks of potentially harmful effects
  - Especially if they are used inappropriately
- Medication errors harm at least 1.5 million patients per year
  - ~400,000 are preventable
- ~11% of preventable medication errors are from harmful DDIs or drug allergies

Aspden P. Preventing Medication Errors. Washington DC: National Academies Press; 2006.
Bobb, A, et al. *Arch Intern Med*. 2004; 164(7): 785-92.

Clarity and Readability in Labeling

- Very limited published information regarding clarity, readability, and comprehension of professional labeling to healthcare providers
- Study of "Dear Doctor" letters
  - 32 letters assessed for common characteristics then rated by 10 primary care physicians
    - Rated on presentation of information, importance, and impact on prescribing behavior
  - Highest rating for special formatting
    - Highlights the adverse event, who is at risk, and what to do differently
  - Most significant deficiencies
    - The most relevant information was not easily apparent
    - Relevant information obscured by less critical information

Mazor KM, et al. *Pharmacoepidemiol Drug Saf.* 2005; 14(12):869-75

Physician Perception of Drug Interaction Information

- Some information is intuitive, generally accepted, ingrained
  - Aspirin and oral anticoagulants
- Clinicians are otherwise overwhelmed
  - Sheer number of drug interactions
  - Complexity of mechanisms and terminology

Slide Courtesy of Kellie Schoolar Reynolds, Pharm.D., Deputy Division Director, Division of Clinical Pharmacology IV
Adapted from information presented by David Juurlink (University of Toronto) at FDA Clinical Pharmacology Advisory Committee Meeting on 9/25/2013

Physician's Perception

What is wrong with DDI information in Prescribing Information?

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

Slide Courtesy of Kellie Schoolar Reynolds, Pharm.D., Deputy Division Director, Division of Clinical Pharmacology IV
Adapted from information presented by David Juurlink (University of Toronto) at FDA Clinical Pharmacology Advisory Committee Meeting on 9/25/2013

Physician's Perception

Ideal Presentation of DDI information in Prescribing Information

- 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

Slide Courtesy of Kellie Schoolar Reynolds, Pharm.D., Deputy Division Director, Division of Clinical Pharmacology IV
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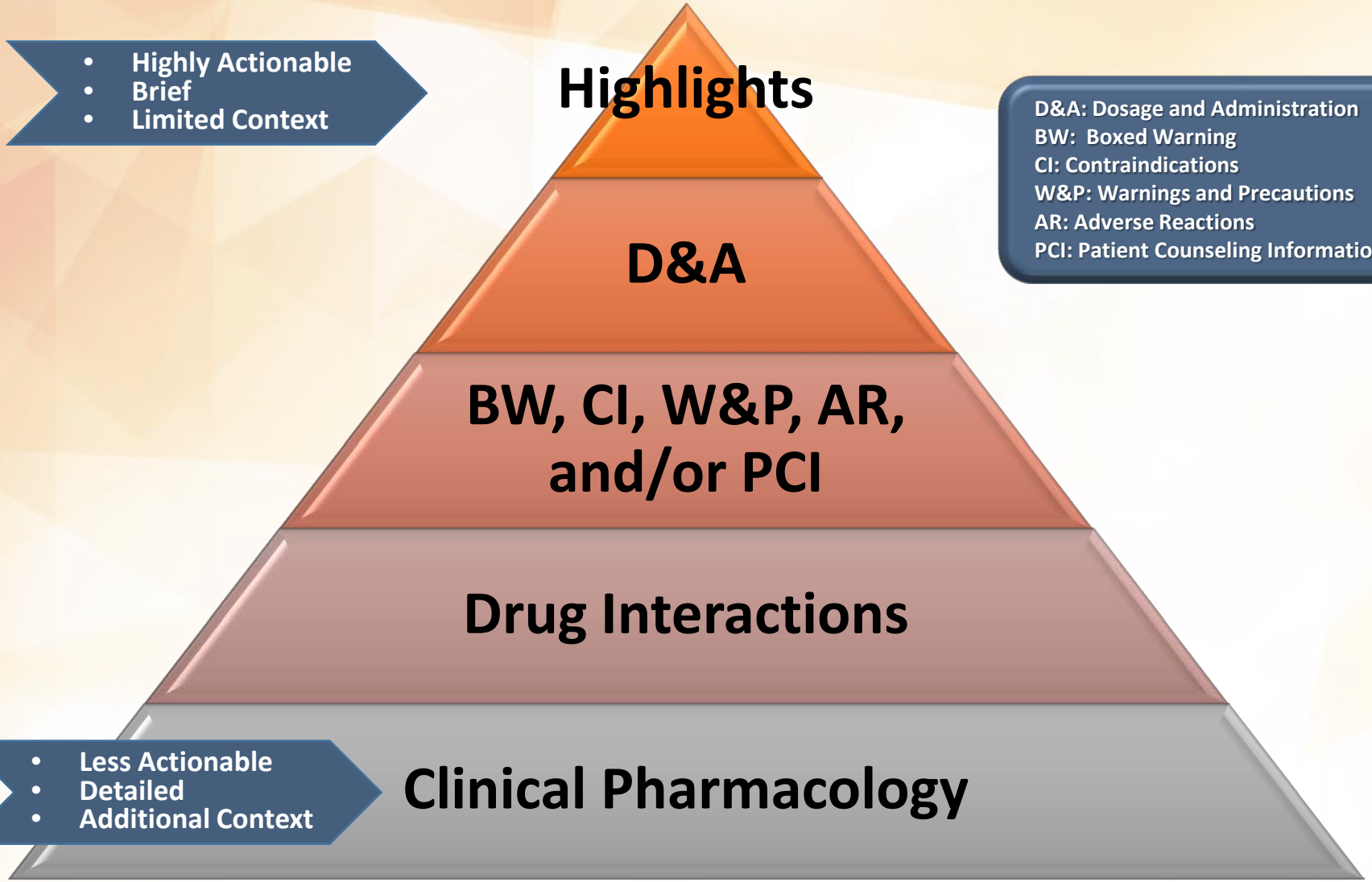
Where are DDI's in Labeling?

- Highly Actionable
- Brief
- Limited Context



D&A: Dosage and Administration
BW: Boxed Warning
CI: Contraindications
W&P: Warnings and Precautions
AR: Adverse Reactions
PCI: Patient Counseling Information

- Less Actionable
- Detailed
- Additional Context

Drug Interactions (Section 7)

- Description of the clinical implications of clinically significant interactions
  - Includes other drugs, classes of drugs, dietary supplements, and foods
- Mechanism(s) of the interaction, if known
- Actionable information
  - Indicates how to monitor for the interaction and instructions for preventing or managing it
  - Risk mitigation strategies may require a multidimensional approach
    - e.g., Clinical pharmacology, exposure-response/safety, disease and target population characteristics
- May include a list of examples representing a specific class of drugs (e.g., strong CYP3A inhibitors)

Drug Interactions (Section 7)

- The absence of an interaction should generally not appear
  - Except when commonly used together or the only drug in the class to not have the interaction
- Must also contain practical guidance on known interference of the drug with laboratory tests
- Information should be presented in the format that best accommodates the breadth and complexity of the information and ensures clarity and understanding
  - Text
  - Tables
  - Figures

Disclaimer

- The following tables and figures presented today are meant to be thought provoking and represent examples of possible formats of various DDI related information commonly found in labeling
- These examples <u>should not</u> be considered templates, limit other possible formats, or constrain the use of other information fields that may be required for a particular drug

DDI Information as Text

- Should not be so detailed and lengthy the reader skims or dismisses it
  - Include only information that informs prescribing decisions or is necessary for the safe and effective use of the drug
  - Actionable information should be clear and concise
    - Avoid vague statements such as “monitor closely” or “use with caution”
  - Use active voice
- Use font attributes, headings, bulleted lists, and shorter paragraphs to increase white space and readability wherever possible
  - Formatting suggestions are outlined in guidances to assure consistency

A sentence is a structurally independent grammatical unit of one **or** more words in speech **often** preceded **and** followed by pauses **and** in writing begun with a capital letter **and** ended with a period **or** other end punctuation.

F-K 16.0 FREI 00.0 (Very, Very Difficult to Read)

Calderon JL, et al. *Annals of Behavioral Science and Medical Education* 2007;13:20-24

A sentence:

- Is a unit of grammar with one or more words.
- It can be preceded by pauses.
- It can be followed by pauses.
- It starts with a capital letter.
- It ends with a period.
- It can end in other punctuation.

F-K 3.2 FREI 83.0 (Very Easy to Read)

DDI Information as Text (Section 7)

7 DRUG INTERACTIONS

Drugoxide undergoes metabolism by CYP3A4. Use with a strong CYP3A4 inhibitor will increase drugoxide exposure (i.e., Cmax and AUC) resulting in an increase syncope risk. Reduce the dosage of [trade name] when coadministered with strong CYP3A inhibitors (e.g., boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) [*see Dosage and Administration (2.x) and Clinical Pharmacology (12.3)*].

DDI Information as Text (Section 7)

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on [Trade name]

Strong CYP3A Inhibitors

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

Drugoxide undergoes metabolism by CYP3A4. Use with a strong CYP3A4 inhibitor will increase drugoxide exposure (i.e., Cmax and AUC) resulting in an increase syncope risk [*see Warnings and Precautions (5.x) and Clinical Pharmacology (12.3)*].

The following are some examples of Strong CYP3A Inhibitors: boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole.

DDI Information as a Table (Section 7)

7 DRUG INTERACTIONS

Tables X and Y include drugs which demonstrated a clinically important drug interaction with drugoxide that affect drugoxide or drugs co-administered with drugoxide, respectively.

Table X. Established and Other Potentially Clinically Relevant Interactions Affecting Drugoxide	
Strong CYP3A4 Inhibitors	
Clinical Implications:	Increased the exposure of drugoxide compared to the use of [trade name] alone that may result in hypotension and syncope *[see Warnings and Precautions (5.x) and Clinical Pharmacology (12.3)]*
Prevention or Management:	Reduce the [trade name] dosage [see *Dosage and Administration* (2.x)]
Examples:	Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole
Strong CYP3A4 Inducers	
Clinical Implications:	Decreased the exposure of drugoxide compared to the use of [trade name] alone that may lead to reduced efficacy *[see Clinical Pharmacology (12.3)]*.
Prevention or Management:	Increase the [trade name] dosage *[see Dosage and Administration (2.x)]*.
Examples:	Carbamazepine, phenytoin, rifampin, St. John's wort
Benzodiazepines	
Clinical Implications:	Increased sedation and orthostatic hypotension *[see Warnings and Precautions (5.x)]*
Prevention or Management:	Monitor sedation and blood pressure. Adjust the benzodiazepine dosage accordingly.
Examples:	Alprazolam, clonazepam, diazepam, lorazepam, triazolam

Column Headings Not Ideal

- Tables with column headings force up and down reading
  - Uncomfortable when table cells contain large amounts of text

Table X: Clinically Important Drug Interactions with Drugoxide:

Concomitant Drug Name or Drug Class	Clinical Rationale	Clinical Recommendation
Strong CYP3A4 Inhibitors (e.g., Drug A, Drug B, Drug C…) or strong CYP2D6 inhibitors (e.g., Drug D, Drug E, Drug F…)	The concomitant use of [trade name] with strong CYP 3A4 or CYP2D6 inhibitors increased the exposure of drugoxide *[see Clinical Pharmacology (12.3)]*.	With concomitant use of [trade name] with a strong CYP3A4 inhibitor or CYP2D6 inhibitor for more than 14 days, reduce the [trade name] dosage *[see Dosage and Administration (2.x)]*.
Strong CYP3A4 Inducers (e.g., Drug G, Drug H, Drug I…)	The concomitant use of [trade name] and Drug E decreased the exposure of drugoxide *[see Clinical Pharmacology (12.3)]*.	Avoid use of [trade name] in combination with Drug E and other inducers of CYP3A4 for greater than 14 days *[see Dosage and Administration (2.x)]*.
Antihypertensive Drugs	Due to its alpha adrenergic antagonism, drugoxide has the potential to enhance the effect of certain antihypertensive agents.	Monitor blood pressure and the adjust dosage accordingly *[see Warnings and Precautions (5.x)]*.

Antimicrobials/Antivirals

7 DRUG INTERACTIONS

7.1 Potential for Drug Interaction

Drugoxide is an inhibitor of the drug transporters P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of coadministered substrates for these transporters.

7.2 Established and Potentially Significant Drug Interactions

Table X provides a listing…

Table X: Potentially Significant Drug Interactions: Alteration in Dosage May Be Recommended Based on Drug Interaction Studies or Predicted Interaction[a]

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	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)		It is recommended to separate antacid and [trade name] administration by 4 hours.
H_2-receptor antagonists (e.g., Drug C)		H_2-receptor antagonists may be administered simultaneously with or 12 hours apart from [trade name] at a dosage that does not exceed dosages comparable to Drug C x mg twice daily.
Proton-pump inhibitors (e.g., Drug D)		Proton-pump inhibitor dosages comparable to Drug D xx mg or lower can be administered simultaneously with [trade name] under fasted conditions.
Antiarrhythmics: Drug F	↑ Drug F	Therapeutic concentration monitoring of Drug F is recommended when coadministered with [trade name]
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 [trade name] with Drug L is not recommended.

a. This table is not all inclusive; b. ↓ = decrease, ↑ = increase

Clinical Pharmacology (Section 12)

- Pharmacokinetics subsection (12.3) should include descriptive information related to mechanisms of DDI and brief details of the relevant drug interaction studies
  - ADE(ME) Headings
    - Clinically relevant mechanistic information regarding metabolic pathways, transporter systems, and genetic polymorphisms
  - Drug Interaction Studies heading
    - Informs actionable recommendations in Drug Interactions (Section 7)
    - Should include pertinent positive and negative results from clinical DDI studies
      - Ideally expressed as geometric mean change (CI90%) [min to max] of relevant PK exposures (e.g., AUC, Cmax, Cmin, Tmax)
    - A list of studied drugs with no clinically relevant interaction potential may be summarized in one or more sentences
    - Study design information that may inform prescribing decisions

Clinical Pharmacology (Section 12)

- Pertinent positive and negative results from vitro studies may also be provided if it
  - Informs prescribing decisions
  - Contributes to the overall mechanistic understanding of an investigational agents drug interaction potential in the absence of clinical drug interaction information
- DDI studies with a clinically significant impact on PD that is independent of PK changes may be described in the Pharmacodynamics subsection (12.2)
- Information should be presented in the format that best accommodates the breadth and complexity of the information and ensures clarity and understanding
  - Text
  - Tables
  - Figures

DDI Information as Text (Section 12)

12.3 Pharmacokinetics

Drug Interaction Studies

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

DDI Information as Text (Section 12)

12.3 Pharmacokinetics

Drug Interaction Studies

Strong CYP3A Inhibitors: The Cmax and AUC_{inf} of drugoxide increased by 1.3 and 2-fold, respectively, following coadministration of drugoxide at the approved recommended dosage with ketoconazole [*see Dosage and Administration (2.x), Drug Interactions (7.x)*]

DDI Information as a Table (Section 12)

Table X. Established Clinically Relevant Interactions Affecting Drugoxide *[Note in this example clinically relevant findings are found in the table and those that are not are listed in a sentence]*			
Concomitant Drug (Dosage)	Drugoxide Dosage	Ratio (90% CI) of Exposure Measures of Drugoxide Combination/No Combination [minimum to maximum][a]	
		Cmax	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]

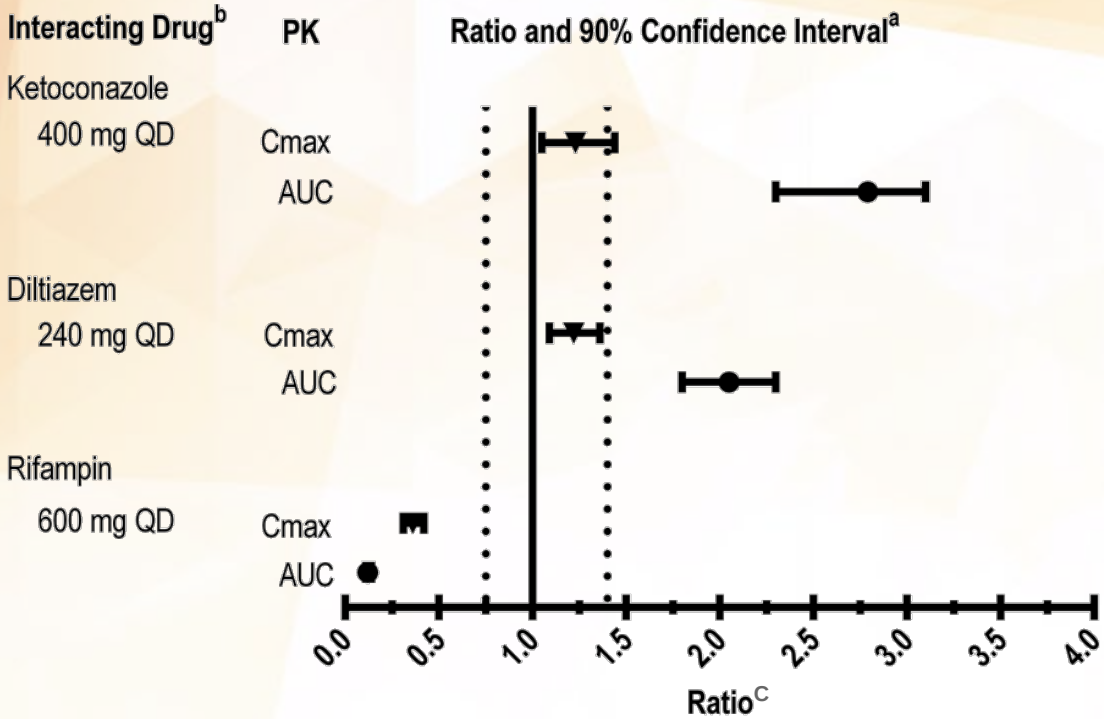
a= *[see Dosage and Administration (2.x) and Drug Interactions (7)]*

No clinically significant changes in exposure were observed for drugoxide when coadministered with the following concomitant medications in drug interaction trials: Drug A, Drug B and Drug C.

DDI Information as a Figure (Section 12)

Table X. Established Clinically Relevant Interactions Affecting Drugoxide

[Note in this example clinically relevant findings are found in the table and those that are not are listed in a sentence]



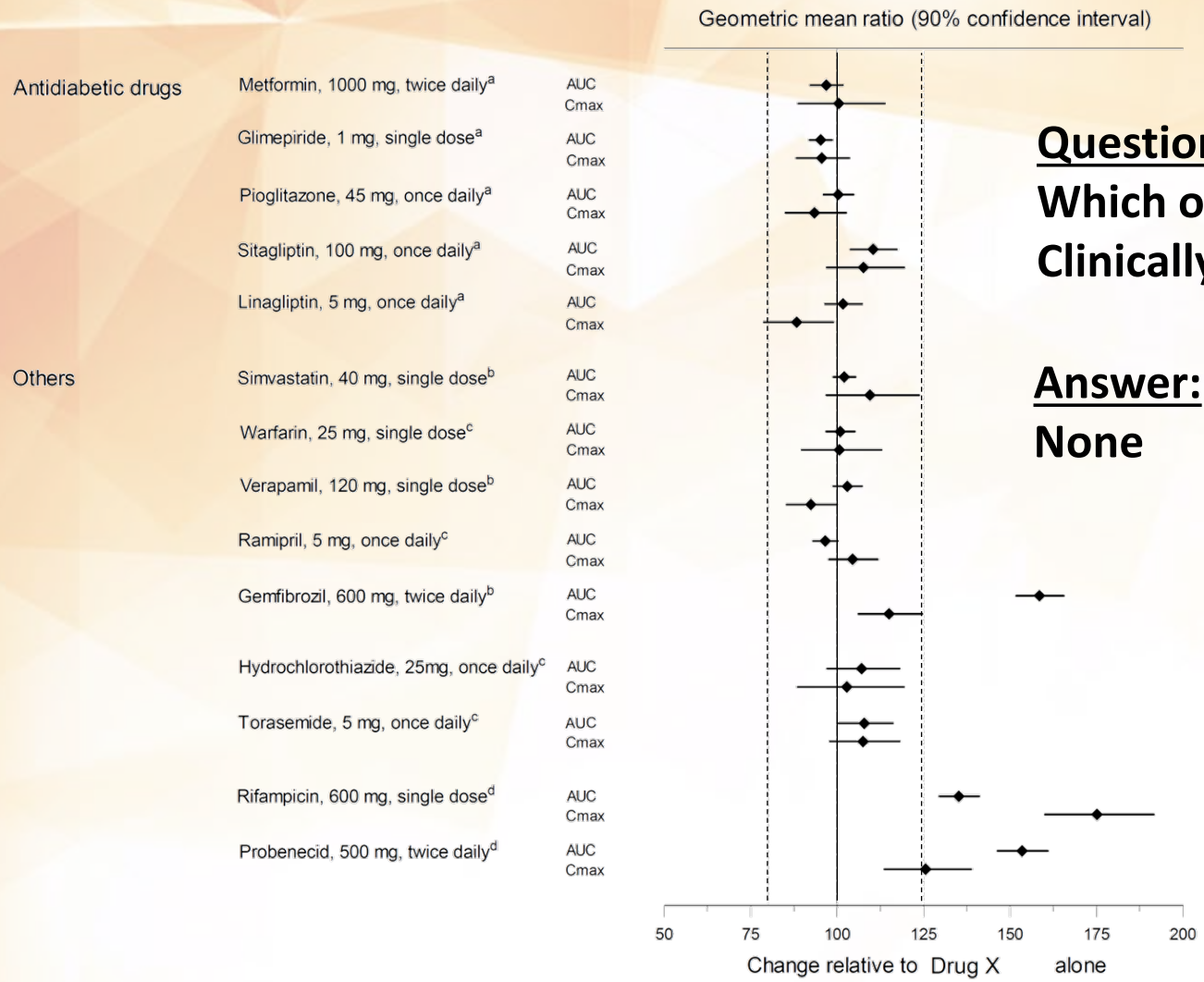
a= Dashed vertical lines illustrate pharmacokinetic changes that were used to inform dosing recommendations *[see Dosage and Administration (2.1) and Drug Interactions (7)]*

b= Drugoxide 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 the following concomitant medications in drug interaction trials: Drug A, Drug B and Drug C.

Clearly Identify Significant DDI Effects in Text, Tables, and Figures



Question:

Which of these DDI's are Clinically significant?

Answer:

None

[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

Dosage and Administration (Section 2)

- Includes information about DDI that have important implications for a drug's dosage regimen
  - Dosage adjustments, timing of dose relative to dosing of another drug
- May need to consider multiple dosage mitigation scenarios
  - Starting or stopping both or individual components of the DDI
  - Initiating therapy vs. steady state
  - Drug/population characteristics
    - Concurrent therapy may only last short time (e.g., antibiotics/ antifungal)
    - Titrated regimen
    - Therapeutic drug monitoring possible
    - Is the proposed dosage mitigation strategy too complicated for the patient (e.g., elderly)
- Focus on precision medicine may result in the need to communicate more complex dosage modification strategies based on several factors

DDI Information as Text (Section 2)

2.x Dosage Modifications for Concomitant Use with Strong CYP3A Inhibitors

Decrease the dosage of [trade name] by 50% to 10 mg twice a day when coadministered with drugs that are strong inhibitors of CYP3A *[see Drug Interactions (7.x) and Clinical Pharmacology (12.3)]*

Multidimensional Approach (Section 2)

2.x Dosage Modifications for Concomitant Use with Strong CYP3A Inhibitors

Concomitant use of strong CYP3A inhibitors which would be taken chronically (e.g., ritonavir, indinavir, nelfinavir, saquinavir, boceprevir, telaprevir, nefazodone) is not recommended

For short-term use (treatment for 7 days or less) of strong CYP3A inhibitors (e.g., antifungals and antibiotics) consider interrupting [trade name] therapy until the CYP3A inhibitor is no longer needed

Complex Dosage Mitigation Strategy (Section 2)

Table X: Dosage Adjustment Table for Patients Taking CYP2D6 Inhibitors, CYP3A4 Inhibitors, or CYP3A4 Inducers for Greater Than 2 Weeks

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	662	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	662	600 mg	12
			Yes	Yes	No	Avoid Use	NA
			No	No	Yes	400 mg	6

INH= inhibitor; IND= inducer; NA= not applicable

Tips for Communicating DDI Related Information in Labeling

- Communicate with the Agency early and often
  - Don’t wait until the final stages of an NDA/BLA review
- The rationale for proposed DDI related labeling and mitigation strategies should be clearly stated in the NDA/BLA application’s clinical pharmacology summary
- Provide sufficient detail in labeling to inform prescribing decisions regarding a DDI
  - Actions should be clear and specific
  - Clinically significant DDI should be clearly identified
  - Avoid redundancy between DDI related labeling sections
  - Brevity encouraged
- Use white space, text attributes, tables, and figures where appropriate to enhance readability, clarity and utility

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

Questions?

Regulatory Education for Industry (REdI):

PRESCRIPTION DRUG LABELING - CHALLENGES AND ISSUES

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Describing Clinically Significant Drug Interactions in WARNINGS AND PRECAUTIONS Section

Eric Brodsky, M.D.
Associate Director, Labeling Development Team
Office of New Drugs, Center for Drug Evaluation and Research
Food and Drug Administration (FDA)

Disclaimer

- The views and opinions expressed in this presentation represent those of the presenter, and do not necessarily represent an official FDA position.
- The labeling examples in this presentation are fictitious and are provided only to demonstrate current labeling development challenges.

W&P Section: Clinically Significant DI With Two Drug Classes – ENVARSUS XR

5.9 Risk of Rejection with Strong CYP3A Inducers and Risk of Serious Adverse Reactions with Strong CYP3A Inhibitors

The concomitant use of strong CYP3A inducers may increase the metabolism of tacrolimus, leading to lower whole blood trough concentrations and greater risk of rejection. In contrast, the concomitant use of strong CYP3A inhibitors may decrease the metabolism of tacrolimus, leading to higher whole blood trough concentrations and greater risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see Warnings and Precautions (5.6, 5.10)]* Therefore, adjust ENVARSUS XR dose and monitor tacrolimus whole blood trough concentrations when coadministering ENVARSUS XR with strong CYP3A inhibitors (e.g., telaprevir, boceprevir, ritonavir, ketoconazole, itraconazole, voriconazole, clarithromycin) or strong CYP3A inducers (e.g., rifampin, rifabutin) *[see Dosage and Administration (2.3) and Drug Interactions (7.2)].*

W&P Section: Clinically Significant DI With Multiple Drugs - VITEKTA

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

The concomitant use of VITEKTA and other drugs may result in known or potentially significant drug interactions, some of which may lead to *[see Drug Interactions (7)]:*

- Loss of therapeutic effect of VITEKTA and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs or elvitegravir.

See Table 4 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations *[see Drug Interactions (7)]*. Consider the potential for drug interactions prior to and during VITEKTA therapy; review concomitant medications during VITEKTA therapy; and monitor for the adverse reactions associated with the concomitant drugs.