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Cracking the Code for Clinical Pharmacology-Related Prescription Drug Labeling

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- The labeling examples in this presentation are provided only to demonstrate current labeling development challenges and should not be considered FDA recommended templates.
- Reference to any marketed products is for illustrative purposes only and does not constitute endorsement by the FDA.

Objectives

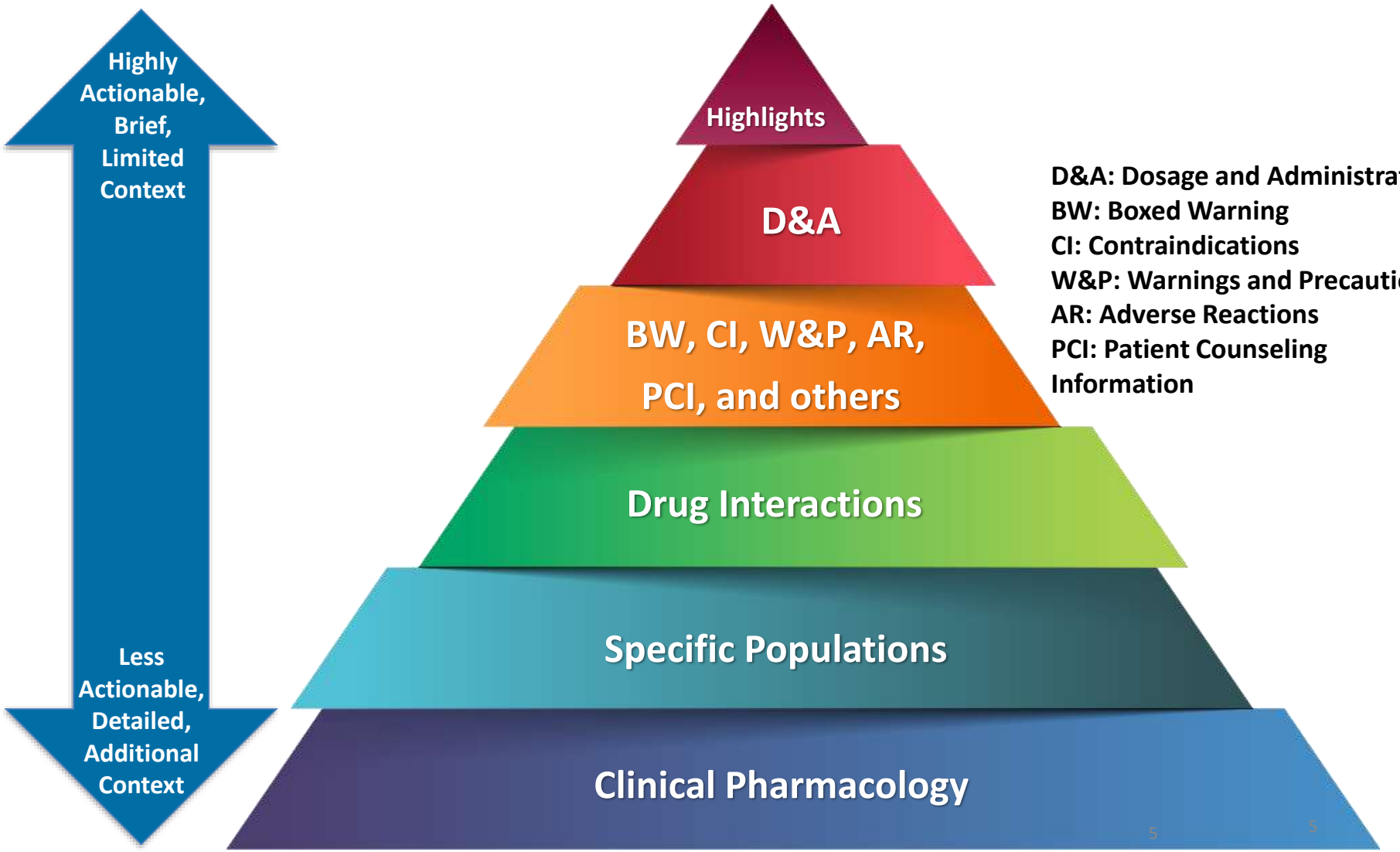
- Understand key regulations that impact clinical pharmacology content in prescription drug labeling (PDL)
- Identify alternative methods of communicating complex clinical pharmacology content
- Discuss strategies for presenting clinical pharmacology-related information in PDL for unique situations

Key PDL Regulations

- Must contain summary of essential scientific information needed for the safe and effective use of the drug[a]
- Is written for health care practitioner (HCP) audience[b]
- Must be informative and accurate[a]
- Must be updated when new information becomes available[a]
- Must not be promotional in tone, false, or misleading[a]
- Must be based whenever possible on data derived from human experience[a]

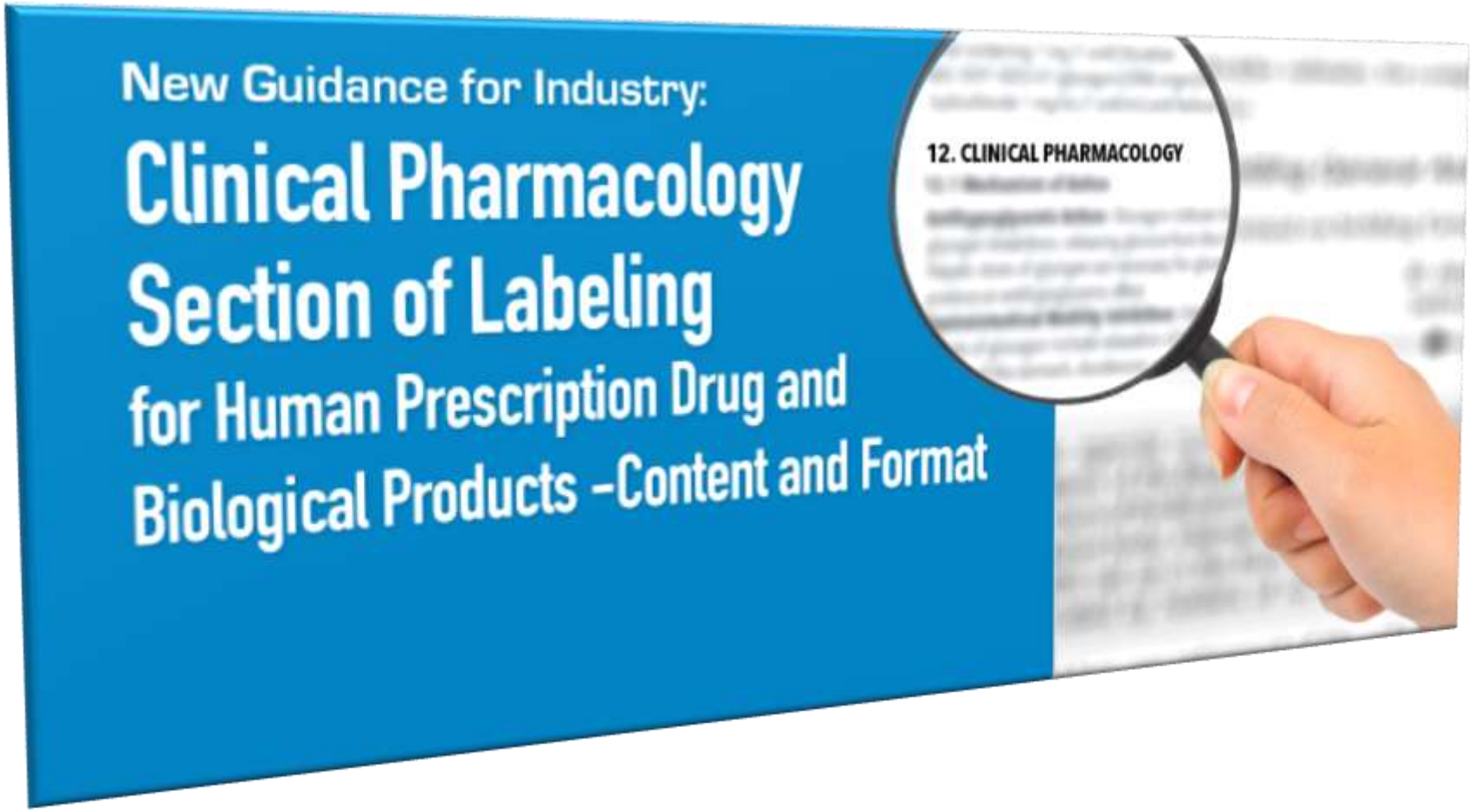
[a] 21 CFR 201.56
[b] PLR FR 71 on 1/24/2006

Clinical Pharmacology Footprint



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

Guidance Highlights



12 Clinical Pharmacology Layout*

12 CLINICAL PHARMACOLOGY

- **12.1 Mechanism of Action**
- **12.2 Pharmacodynamics**
  - Cardiac Electrophysiology
- **12.3 Pharmacokinetics**
  - Absorption
    - *Food Effect*
  - Distribution
  - Elimination
    - *Metabolism*
    - *Excretion*
  - Specific Populations
    - *Geriatric Patients*
    - *Pediatric Patients*
    - *Male and Female Patients*
    - *Racial or Ethnic Groups*
    - *Patients with Renal Impairment*
    - *Patients with Hepatic Impairment*
    - *Pregnant Women*
  - Drug Interaction Studies
- **12.4 Microbiology**
- **12.5 Pharmacogenomics**
- **12.x Additional Subsections**

***Subsection**; Heading; *Subheading*

SECTION 12 LABELING DOs & DON'Ts

DOs

- Be understandable to HCPs who may not have expertise in Clinical Pharmacology
- Include positive and pertinent negative findings that are informative for the safe and effective use of the drug
- Include information on racemate and additive effects
- Use a consistent approach to distinguish headings and subheadings within sections (e.g., underlining for headings and italics for subheadings)
- Use consistent units for all parameters and include measures of dispersion
- Include relevant component information only for fixed dose combination drugs

DON'Ts

- Use inaccurate, false,misleading or promotional information
- Use subjective wording (e.g., "fast" or "rapidly") and general terms (e.g., "systemic exposure") unless words/terms are qualified (e.g., "systemic exposure (AUC)")
- Imply or suggest unapproved indications/uses or dosing regimens
- Include of animal or in vitro information unless essential to understand dosing or drug interaction information

AUC = Area Under The Time-Concentration Curve

SECTION 12 LABELING DOs & DON'Ts

PHARMACODYNAMICS SUBSECTION

DOs

- Include PD effect(s), onset & peak, reversibility, time to stable effect
- Include effects on relevant PD biomarkers or clinical measures
- Include E-R and E-S relationships
- State if no relevant PD, E-R, or E-S data
- Include information supporting clinical impact of TDM or APA formation
- Include PD-specific drug interactions or patient characteristic effects
- Include effect on QT interval & E-R
- Use standard language if no QT effect

DON'Ts

- Include E-R analyses in a manner implying effectiveness is associated with unapproved dosages or endpoints
- Include details for negative PD-related DDI and patient characteristic effects unless clinically important
- Repeat actionable instructions related to TDM or APA included in other sections
- Include PK driven PD-drug interactions or patient characteristic effects
- Include Cardiac Electrophysiology heading if QT effect is unknown

PD = Pharmacodynamics
PK = Pharmacokinetics
E-R/S = Exposure-Response/-Safety
TDM = Therapeutic Drug Monitoring
APA = Anti-Product Antibody

SECTION 12 LABELING DOs & DON'Ts

DOs

- Include linearity, Cmax, AUC, accumulation in general PK introduction before headings
- Include rate & extent of absorption & factors affecting it under Absorption heading
- Use food-effect subheading
- Include Vd & binding under Distribution heading
- Include $t_{1/2}$ (effective), CL & contributions to CL under Elimination heading
- Include dosage associated with nonlinear $t_{1/2}$
- Include biotransformation & excretion pathways under Metabolism & Excretion subheadings
- Include active metabolite-to-parent exposure ratio & potency under Metabolism subheading

DON'Ts

- Use term "bioequivalence" or include comparative PK data
- Repeat actionable food effect instructions
- Include details regarding genetic variability in PK parameters
- Include information about metabolites unless the contribute to drug efficacy or toxicity
- Include long terminal half-life unless important from a safety or effectiveness standpoint
- Include metabolic pathways that have been ruled out unless there is uncertainty in the biotransformation pathways

Cmax = Maximum Concentration
AUC = Area Under the Time-Concentration Curve
Vd = Volume of Distribution
CL = Clearance
$t_{1/2}$ = Half-Life

SECTION 12 LABELING DOs & DON'Ts

DOs

- Include detailed information that informs the actionable recommendations in other sections
- Include essential positive and pertinent negative results from clinical studies, Pop-PK, or other M/S
- Include essential study design information that informs safe & effective prescribing
- Include potential DDI mechanisms if not covered under other headings
- List drugs or characteristics with no clinically significant[1] interaction potential as one sentence summary
- Include positive & negative DDI results from in vitro studies not assessed in clinical studies
- Use text enhancements or tabular formats to enhance readability of complex or lengthy information

SPECIFIC POPULATIONS AND DDI STUDIES HEADINGS

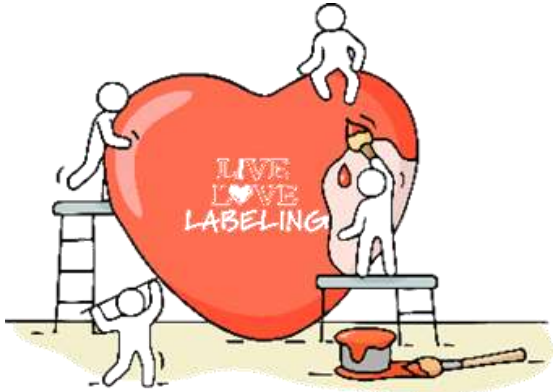
DON'Ts

- Repeat information in other PDL sections
- Include clinical implications, prevention, or management
- Include details on drugs or characteristics with no clinical significance unless it is clinically important
- Combine clinically significant[1] & nonsignificant information unless clearly identified
- Include Information regarding lactation
- Include an explicit statement that information is based on a specific analysis (e.g., Pop-PK, PBPK) if deemed adequate to make a regulatory decision in place of a clinical study unless clinically important

DDI = Drug-Drug Interaction
PDL= Prescription Drug Labeling
Pop-PK = Population Based PK Analysis
PBPK = Physiologically-Based Pharmacokinetic Modeling
M/S = Modeling and Simulation

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

Alternative Displays



12.3 Pharmacokinetics: Table

	Component Drug A	Component Drug B	Component Drug C	Component Drug D
General Information[a]				
C_{max} (mcg/mL)	31.5 ± 10.6	22.5 ± 6.4	31.5 ± 6.5	2.4 ± 1.2
AUC_{tau} (mcg*hr/mL)	342 ± 118.7	142.5 ± 48.3	175.5 ± 35.7	3.2 ± 1.8
C_{trough} (mcg/mL)	5.4 ± 2.7	0.3 ± 0.1	1.5 ± 0.6	Not available
Absorption				
T_{max} (hr)[b]	3 (1 to 4.5)	2 (1 to 4)	2.4 (1 to 3.5)	1.1 (0.6 to 2)
Effect of Food[a]				
Light meal AUC ratio[c]	1.4 (1.2, 1.6)	1.1 (0.9, 1.3)	0.9 (0.8, 1.0)	1.2 (1.1, 1.4)
High-fat meal AUC ratio[c]	1.9 (1.7, 2.2)	0.9 (0.7, 1.0)	0.9 (0.8, 1.0)	1.2 (1.1, 1.3)
Distribution				
% bound to human plasma proteins	Approximately (Approx.) 97	Approx. 98	< 8	Approx. 75
Blood-to-plasma ratio	0.8	0.7	1.0	0.6
Elimination				
$t_{1/2}$ (hr)[d]	14 ± 4.8	4.3 ± 1.4	11 ± 2.7	0.6 ± 0.3
Metabolism				
Metabolic pathway	CYP3A (major) CYP2D6 (minor)	CYP3A (major) UGT1A1 (minor)	Not significantly metabolized	CYP3A (major) CYP2C9 (minor)
Excretion				
Major route of excretion	Metabolism	Metabolism	Renal[e]	Metabolism
% of dose excreted in urine	8	7	77	< 1
% of dose excreted in feces	90	88	15	45

[a] Exposure measures are presented as mean ± SD
[b] T_{max} is presented as median (minimum to maximum)
[c] AUC ratio [fed/fasted] is presented as geometric mean (90% CI). Light meal is approx. 400 kcal, 20% fat; High-fat meal is approx. 800 kcal, 50% fat.
[d] Terminal plasma $t_{1/2}$ is presented as median ± SD
[e] Glomerular filtration and active tubular secretion

Table x. Pharmacokinetic Parameters of Drugoxide and Its Metabolites

General Information[a,b]				
		C_{max}	AUC	CV
Drugoxide exposure	Single dose	3.5 mcg/mL (1.5 to 5.3)	80.4 mcg*h/mL (48.9 to 125.7)	36% to 45%
	Steady-state[c]	4.9 mcg/mL (2.1 to 9.9)	68.3 mcg*h/mL (26.1 to 120.9)	
Dose proportionality[c]	The steady-state AUC of drugoxide increases less than dose proportionally at dosages > 50 mg (0.5 times the approved recommended dosage)			
Absorption				
Bioavailability [tablet][d]	69% to 83% compared to oral solution			
T_{max} [tablet] median (range)	4 hours (2 to 23 hours)			
Enterohepatic recycling (EHR)	• Drugoxide undergoes EHR • Multiple plasma concentration peaks were observed across the 24-hour dosing interval			
Effect of food[e] [fed/fasted] (25th to 75th percentile) *[see Dosage and Administration (2.1) and Clinical Studies (14)]*	Meal	Drugoxide AUC	M-3 AUC	M-5 AUC
	Low-fat[f]	Increased (Incr.) 40% (Incr. 22% to 68%)	Incr. 38% (Incr. 15% to 75%)	Incr. 25% (Incr. 1% to 69%)
	High-fat[g]	Incr. 53% (Incr. 30% to 81%)	Decreased (Decr.) 22% (Decr. 40% to Incr. 20%)	Decr. 51% (Decr. 72% to 27%)
Distribution				
Plasma protein binding	Drugoxide and metabolites greater than 99%			
Elimination				
Elimination $t_{1/2}$[c]	Drugoxide	M-3	M-5	
	30 hours (14 to 58 hours)	23 hours (14 to 32 hours)	56 hours (32 to 70 hours)	
Metabolism				
Primary metabolic pathways	• Oxidation: CYP3A4 • Conjugation: UGT1A1			
Active metabolites	• M-3 (N-oxide) and M-5 (N-oxide and N-desmethyl) • Both have similar in vitro pharmacological activity and steady-state concentrations as drugoxide			
Excretion[h]				
Primary excretion pathways (% dose (range))	• Feces: Approximately 73% (68% to 76%), [49% as drugoxide and 24% as metabolites] • Urine: Approximately 20% (16% to 25%), [15% as glucuronides]			

[a] The pharmacokinetics of drugoxide and its active metabolites were characterized in patients following a single dose of 100 mg Drug X after a light breakfast (e.g., a bowl of cereal with full fat milk or 2 slices of bread with cheese) unless otherwise specified

[b] Pharmacokinetic parameters are presented as geometric mean (range) unless otherwise specified

[c] Following repeat administration of 100 mg Drug X after a light breakfast on a once daily regimen for 21 days on and 7 days off

[d] Following an investigational oral solution (20 mg/mL) formulation, 80 mg (4 - 20 mg tablets) or 100 mg tablet after fasting at least 8 hours

[e] Following a single dose of 100 mg Drug X in healthy volunteers after a specified diet

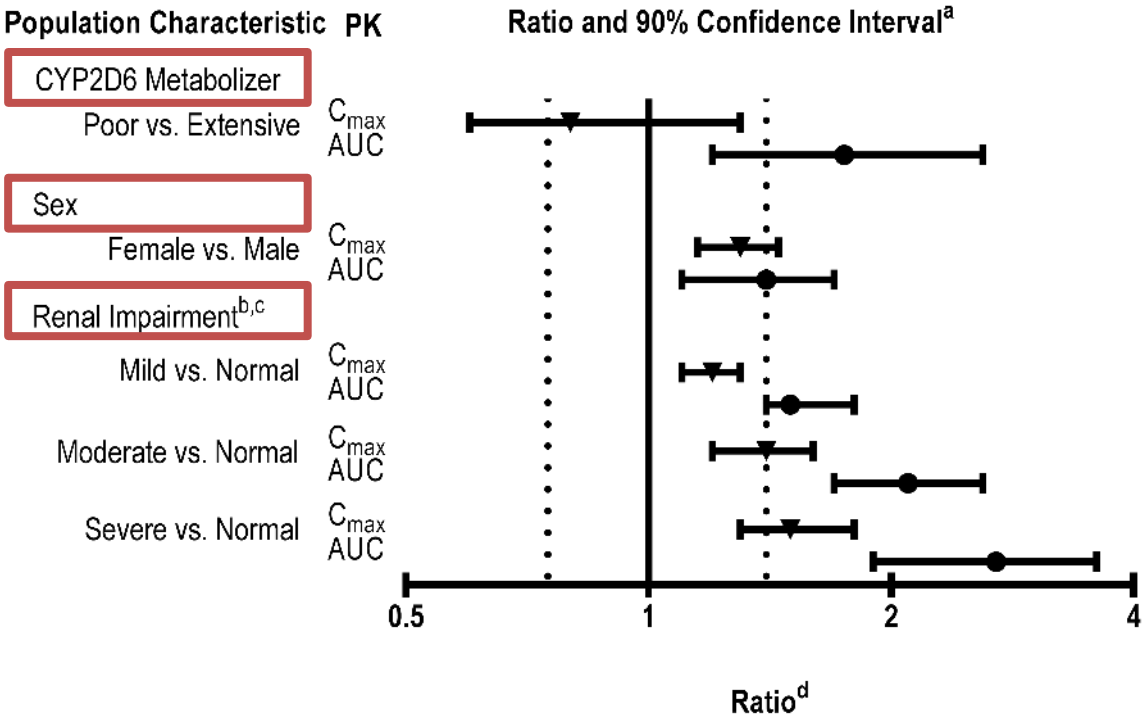
f Low-fat meal is 319 calories and 8.2 grams fat; Drug X was administered with a low-fat meal in Studies 1 and 2

[g] High-fat meal is 945 calories and 54.6 grams fat

[h] Arithmetic mean; following a single dose of 120 mg investigational radiolabeled oral solution of drugoxide in healthy fasted volunteers

Specific Populations: Figure

Table X. Established Clinically Relevant Drugoxide Exposure Changes in Specific Populations



[a] Dashed vertical lines illustrate pharmacokinetic changes that were used to inform dosing recommendations *[see DOSAGE AND ADMINISTRATION (2.1) and USE IN SPECIFIC POPULATIONS (8)]*.

[b] Degree of renal impairment was determined by Cockcroft-Gault calculated creatinine clearance (CLcr); normal (CLcr ≥ 90 mL/min), mild (CLcr 60-89 mL/min), moderate (CLcr 30-59 mL/min), and severe (CLcr 15-29 mL/min).

[c] End stage renal disease (CLcr < 15 mL/min) with or without hemodialysis was not studied.

[d] Log base 2 scale

No clinically significant changes in Drug X exposure were associated with the following population characteristics: mild to severe hepatic impairment (Child-Pugh A to C), age (18-79 years), and race (Asian and Caucasian). The pharmacokinetics of Drug X in pediatric patients is unknown.

Drug Interaction Studies: Table

Table X. Established Clinically Relevant 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.

Unique Situations

Pop-PK Analysis & M/S in PDL

- The CLINICAL PHARMACOLOGY section (Section 12) includes the majority of quantitative information from Pop-PK & M/S approaches (e.g., PBPK)
  - Include a concise description of the results of M/S approaches conducted to evaluate DDIs if they are clinically important and informative[a]
  - Should also include model design information that may inform prescribing decisions, if necessary[a]
    - Rationale for including additional contextual information should be clear[a]
  - Generally, an explicit statement that information is based upon a specific analysis (e.g., Pop-PK, PBPK) is not necessary if deemed adequate to make a regulatory decision in place of a clinical study unless clinically important

[a]21 CFR 201.56 ; FR 71 (1/24/2006); Guidance: *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*; and Draft Guidance: *Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications*

In Vitro DDI Information in PDL

- 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

Potential In Vitro DDI Formatting

Drug Interactions

Clinical Studies

In vitro

The following figure represents in vitro findings[1] that were not evaluated in clinical studies. The grey boxes include positive findings and the white boxes negative findings.

System	Inhibition		Induction		Substrate	
Cytochrome P450	1A2 3A[2] 2B6 2C8 2C9[2] 2C19 2D6[2]		1A2	3A 2B6	1A2 2C19 2D6	
Phase 2 Metabolism	UGT1A9 UGT1A4	UGT1A1 UGT1A3 UGT1A6 UGT2B7 UGT2B15			UGT1A4 UGT1A9	
Transporters	OCT2 MATE1 MATE2-K	BCRP OAT1 OAT3 OATP1B1 OATP1B3			P-gp	BCRP OCT2

1= This in vitro information is primarily utilized to inform the need for additional clinical trials and should not to be considered conclusive evidence of human drug interaction. The clinical relevance of these finds in unknown.
2=Possible time-dependent inhibition

Conclusions

- Communicate essential and accurate information for HCP to safely and effectively prescribe drugs
- Present clinical pharmacology information in a consistent manner that adheres to regulations and guidances
- Consider using alternative methods to enhance readability and clarity

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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