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

Transforming Drug Labeling to Better Translate Science to Clinical Practice

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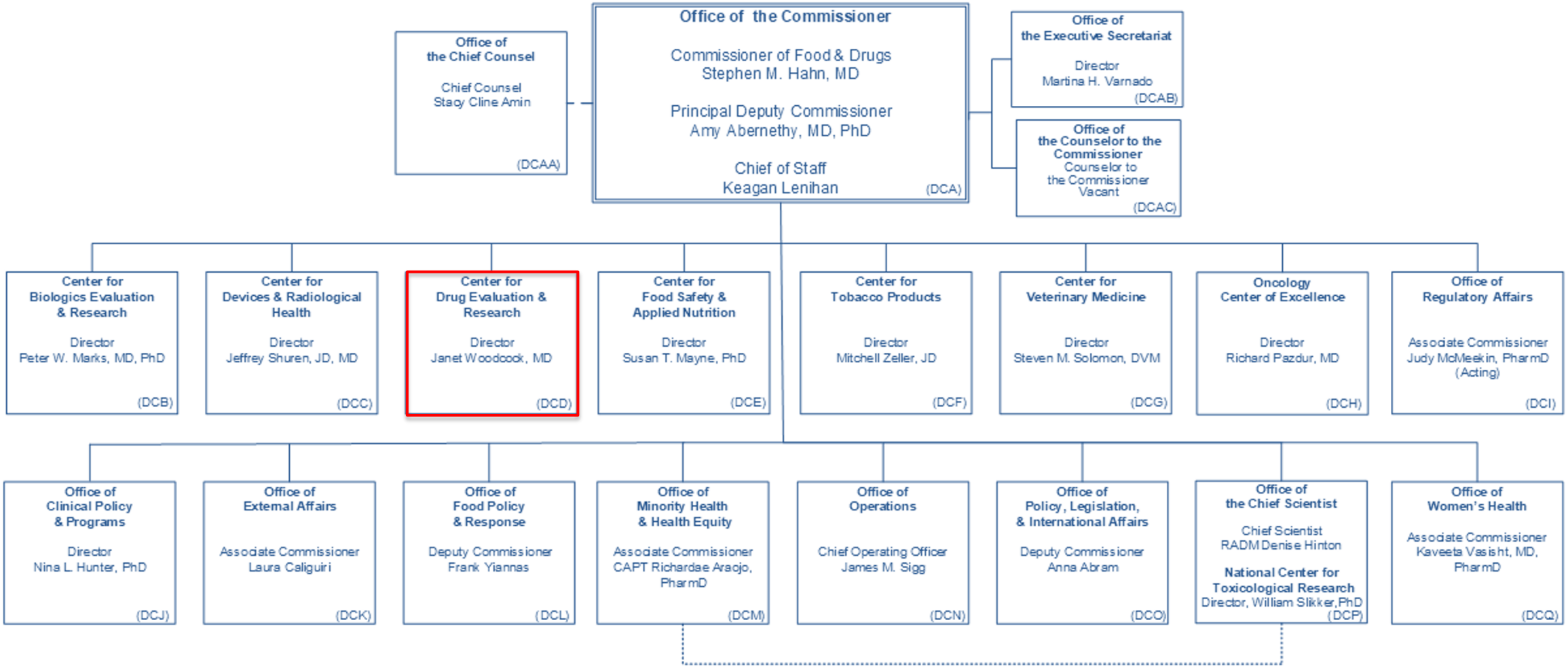
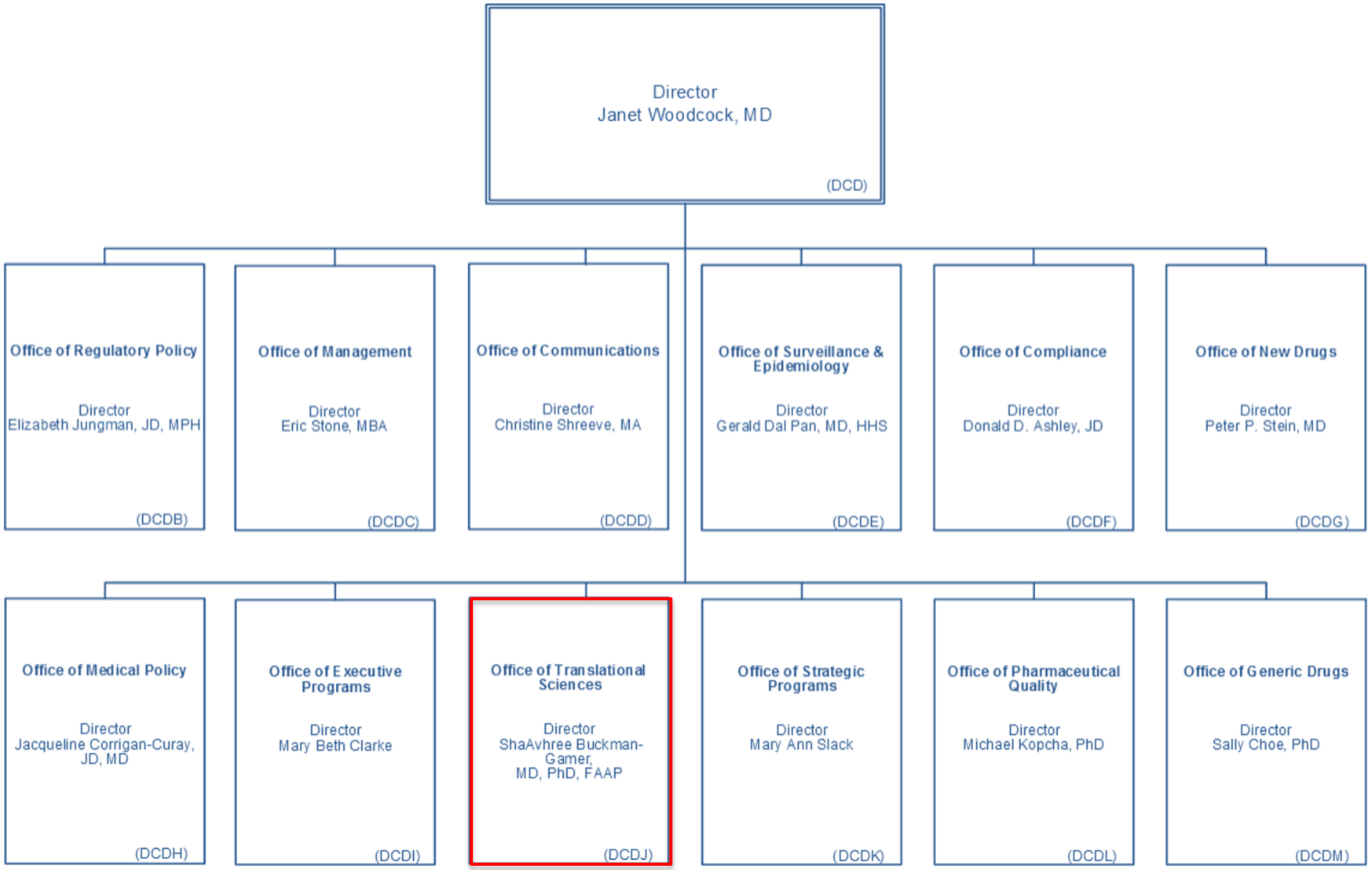
Labeling Lead, Labeling and Health Communication (LHC)
Office of Clinical Pharmacology (OCP)
Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

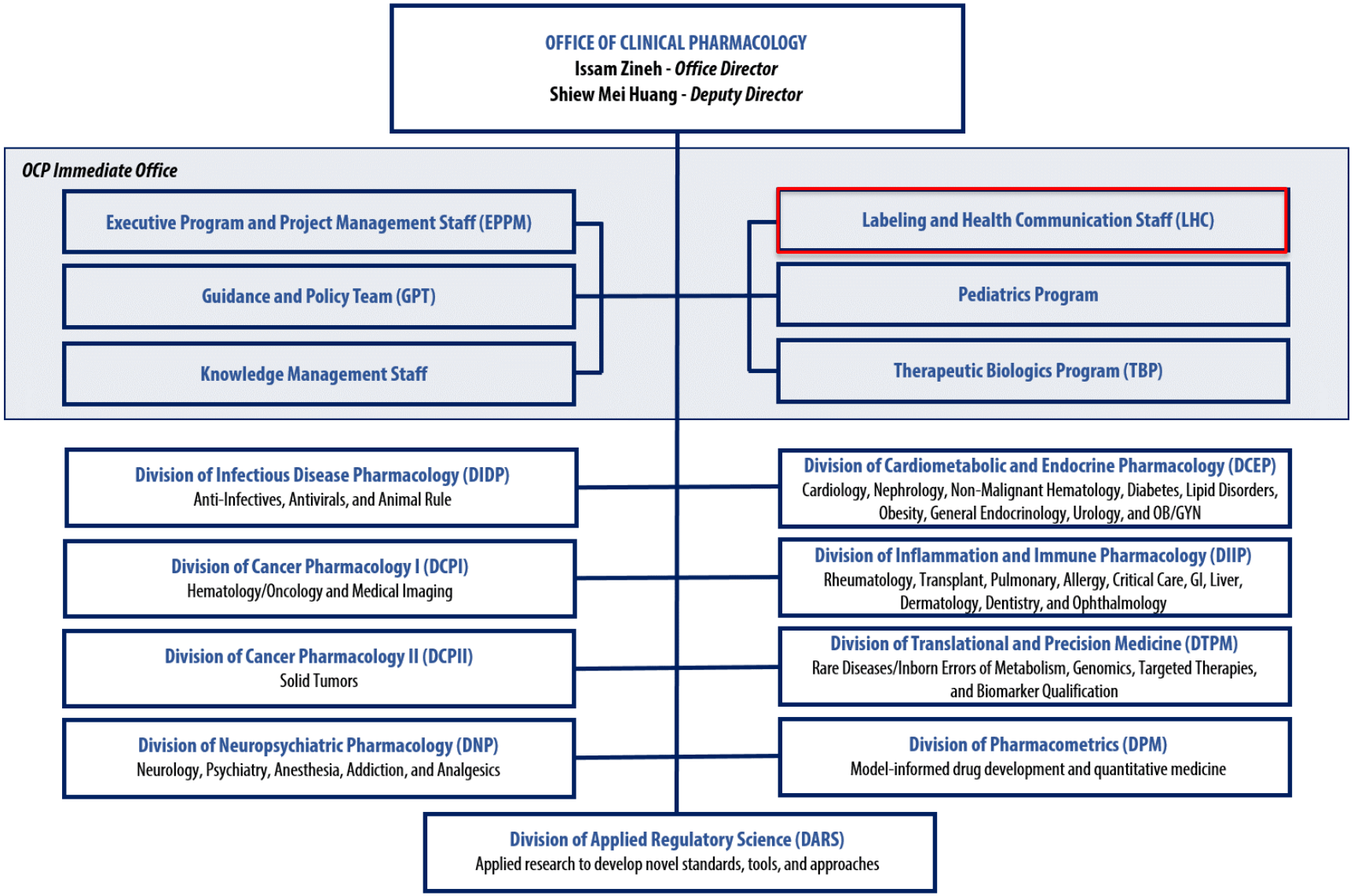
FDA Organization



CDER Organization

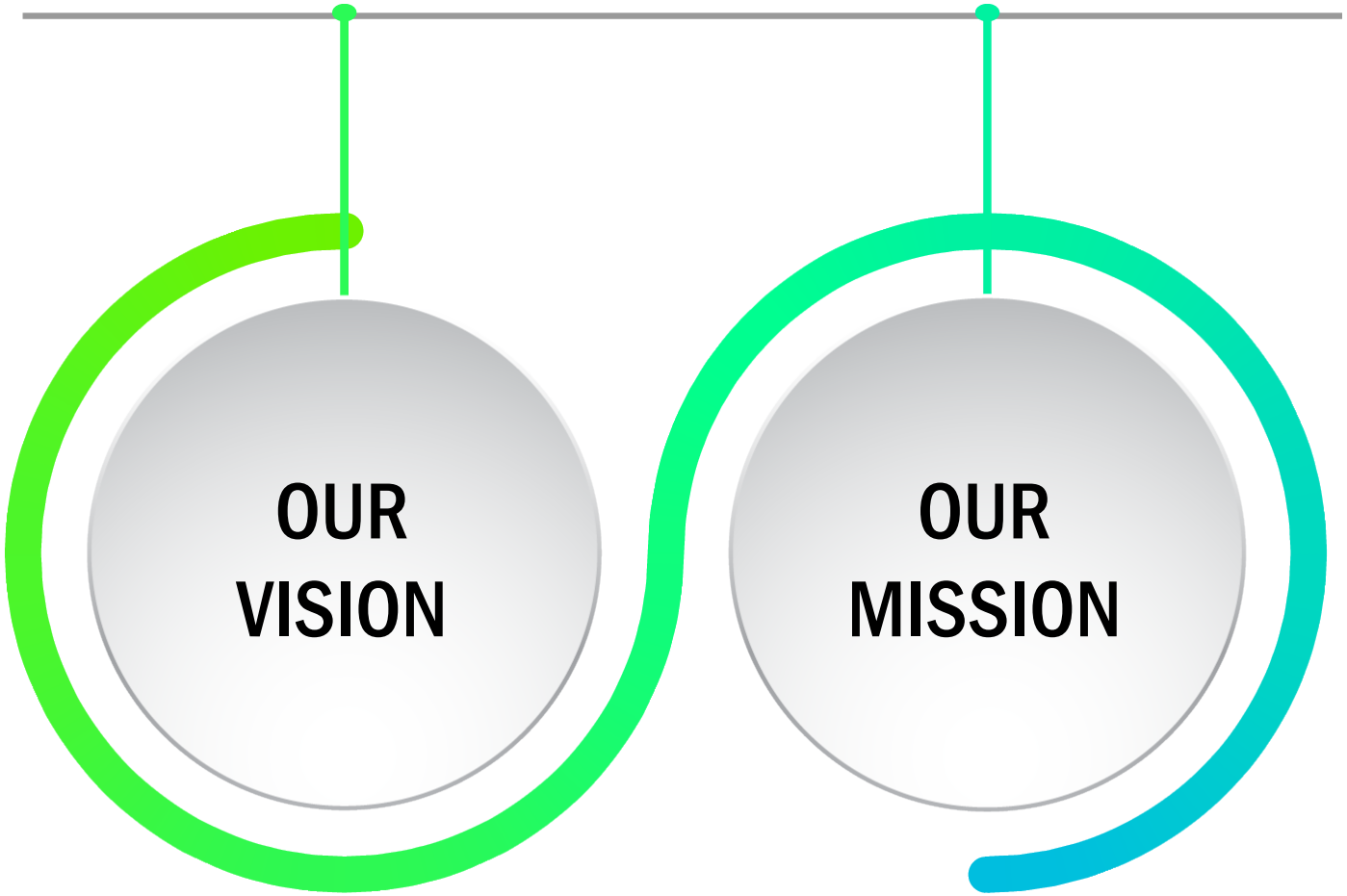


OCP Organization



Office of Clinical Pharmacology (OCP)

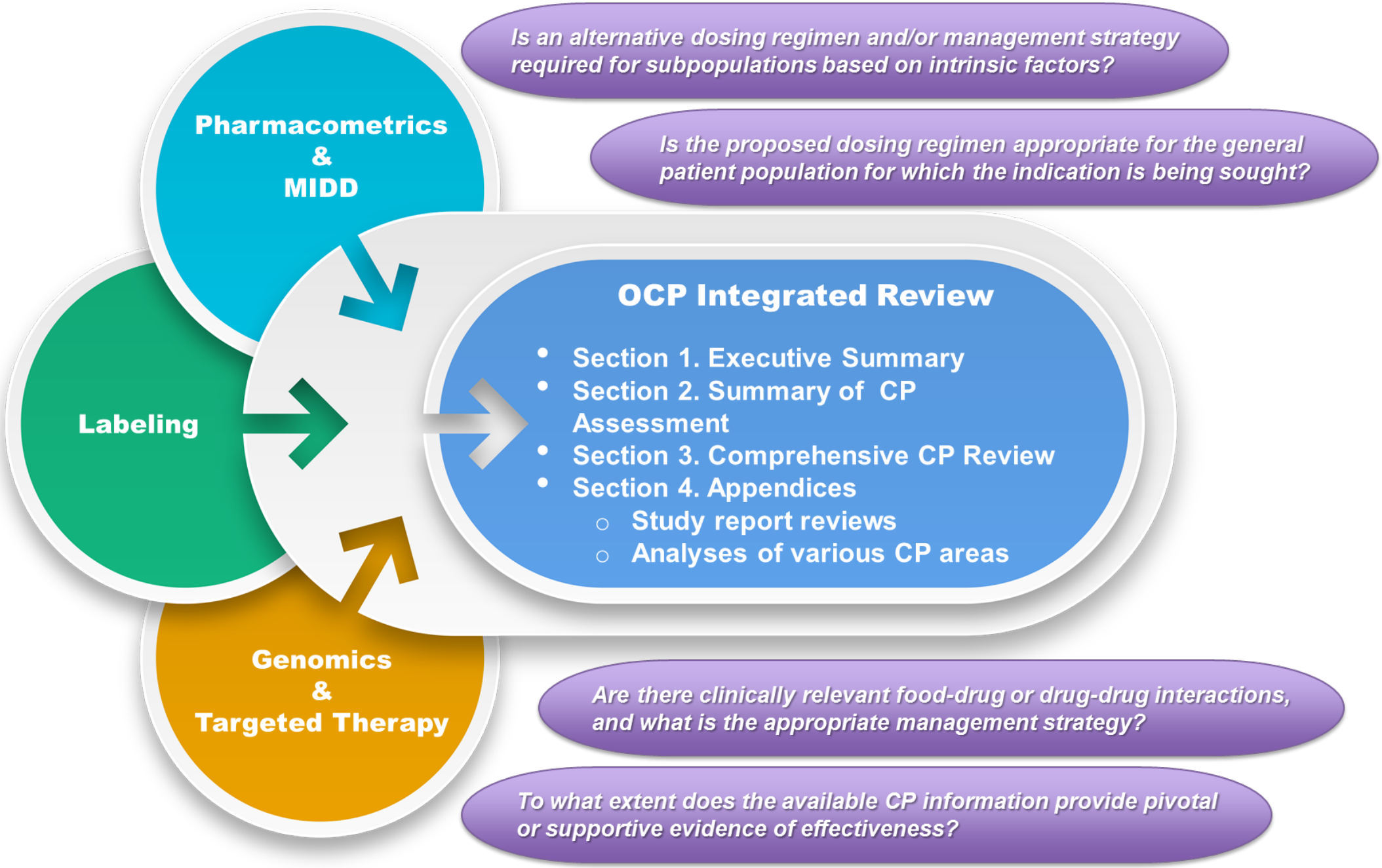
OCP is a dynamic, purpose-driven organization whose goals are to enhance drug development, promote regulatory science and innovation, and inform the optimal use of medications



Improve public health by building and translating knowledge of drug response into patient-centered regulatory decisions of the highest quality

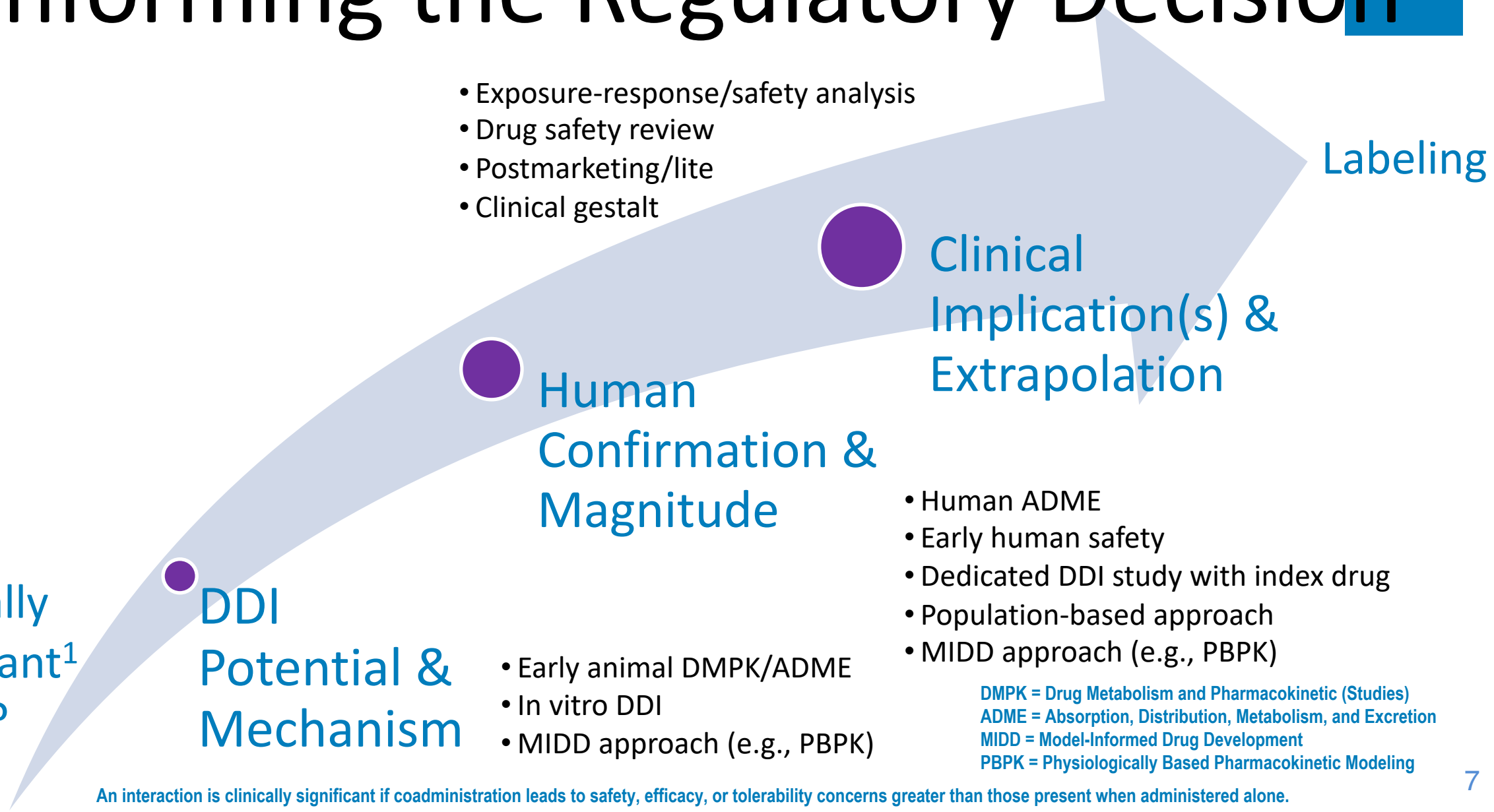
Play a pivotal role in advancing development of innovative new medicines by applying state-of-the-art regulatory science and clinical pharmacology principles

Promote therapeutic optimization and individualization through best practices in research, policy development, and drug evaluation throughout the product lifecycle



https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM073007.pdf

Informing the Regulatory Decision

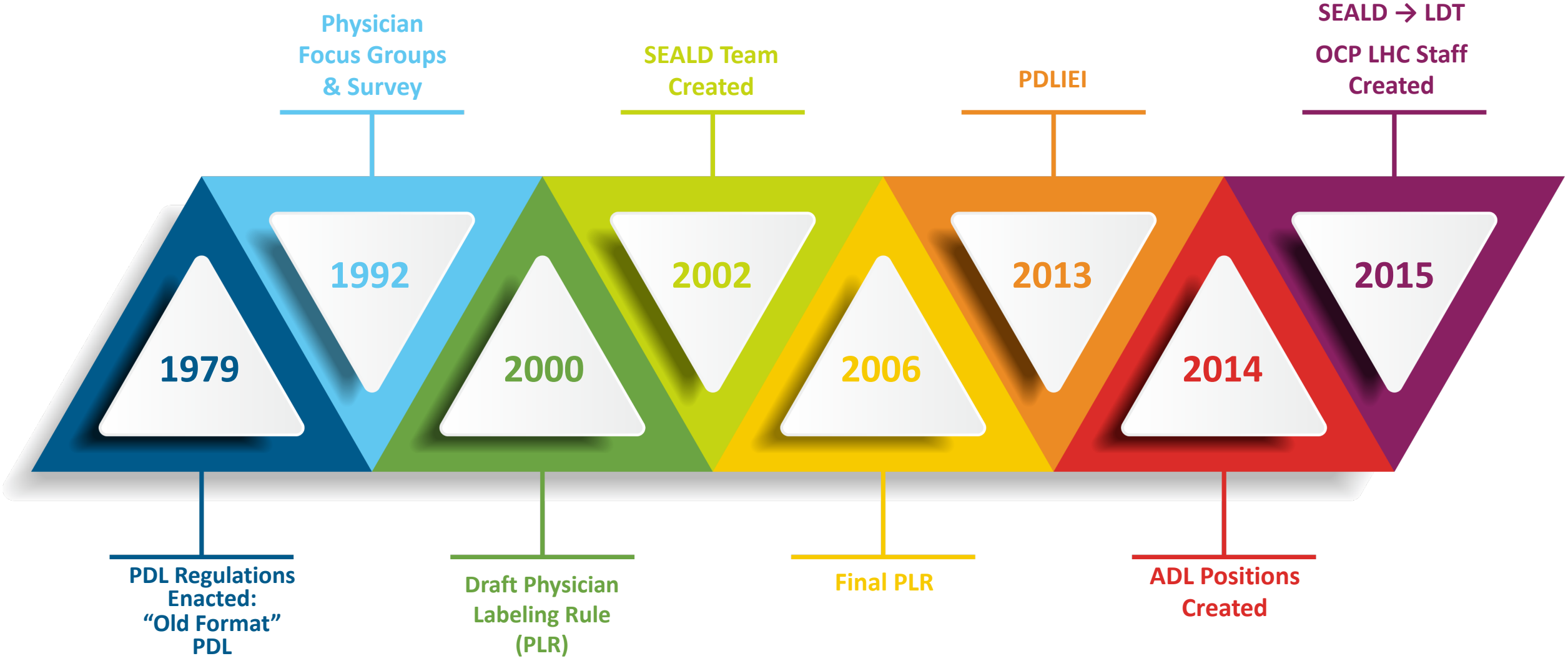


DMPK = Drug Metabolism and Pharmacokinetic (Studies)
ADME = Absorption, Distribution, Metabolism, and Excretion
MIDD = Model-Informed Drug Development
PBPK = Physiologically Based Pharmacokinetic Modeling

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


PATIENT PACKAGE INSERT
USE'S
DANGER'S
SIDE EFFECTS
OTHER EFFECTS
DOTY

Evolution of FDA PDL Initiatives



Associate Directors of Labeling (ADL); LHC= Labeling & Health Communications staff; PDL=Prescription Drug Labeling; PDLIEI=PDL Improvement & Enhancement Initiative; LDT=Labeling Development team (now the Labeling Policy Team); SEALD=Study Endpoints and Labeling Development Team

Prescribing Information 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

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.

Key US Labeling Regulations[c]

- Must contain a summary of the essential scientific information needed for the safe and effective use of the drug[a]
  - Is written for the health care practitioner (HCP) audience[b]
- Must be informative and accurate and neither promotional in tone nor false or misleading in any particular[a]
- Must be updated when new information becomes available that causes the labeling to become inaccurate, 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 1/24/2006

Key US Labeling Regulations[c]

DRUG INTERACTIONS Section

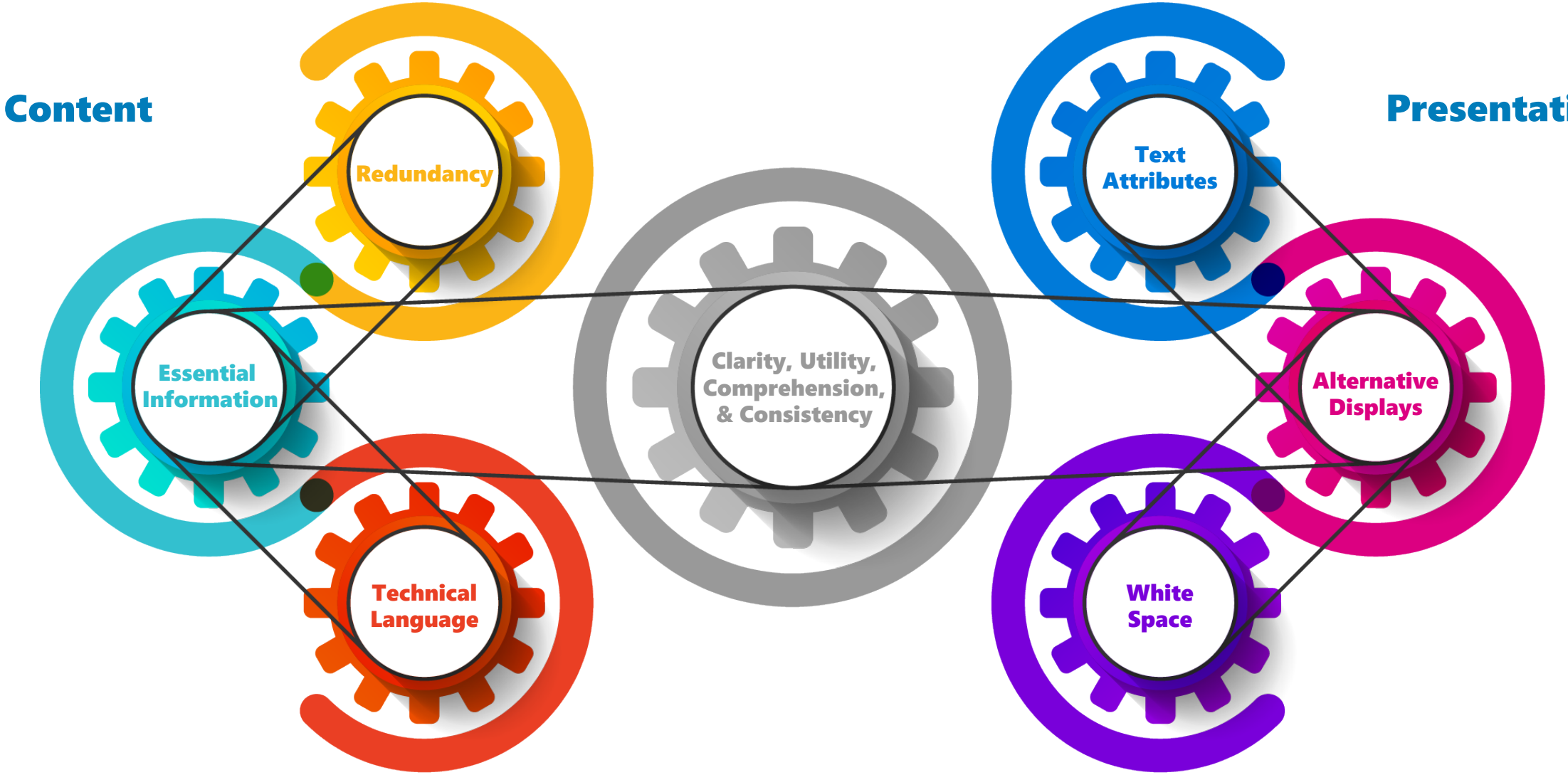
- Must contain a description of clinically significant interactions, either observed or predicted, with other prescription or over-the-counter drugs, classes of drugs, or foods (e.g., dietary supplements, grapefruit juice)
- Must contain specific practical instructions for preventing or managing them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

CLINICAL PHARMACOLOGY Section

- Must summarize what is known about the established mechanism(s) of the drug's action in humans or contain a statement about the lack of information
- Must include a description of any biochemical or physiologic pharmacologic effects of the drug or active metabolites related to the drug's clinical effect, adverse effects or toxicity
- Must include exposure-response relationships and time course of pharmacodynamic response or a statement about the lack of information
- Must describe the clinically significant pharmacokinetics of a drug or active metabolites
- Must include the results of pertinent human or in vitro pharmacokinetic studies that establish the absence of an effect

[c] 21 CFR 201.57

Strategies to Enhance Clinical Pharmacology Labeling Development



Impart Clinical Significance

- Is the information essential for the safe and effective prescribing of the drug?
- Does the content convey risk, severity, and clinical implications?
- Does it provide clinical context for essential information in a cross-referenced section of labeling?
- What non-essential contextual information should be omitted?

- Detailed PK results for healthy volunteers and patients
- Detailed PK results from unapproved dosage forms[d]
- Plasma and whole blood distribution
- Multiple volumes of distribution
- Inactive metabolite information

[d] Unapproved indications, uses, and dosages must not be implied or suggested [see 21 CFR 201.57(c)(2)(iv and v) and 21 CFR 201.57(c)(3)(ii)]

Minimize Technical Language

- Can this information be described in a simpler way?
- Is the information clinically intuitive?
- Is this informative to health care provider without clinical pharmacology expertise?
- Is additional information needed to explain the impact on safe and effective prescribing?

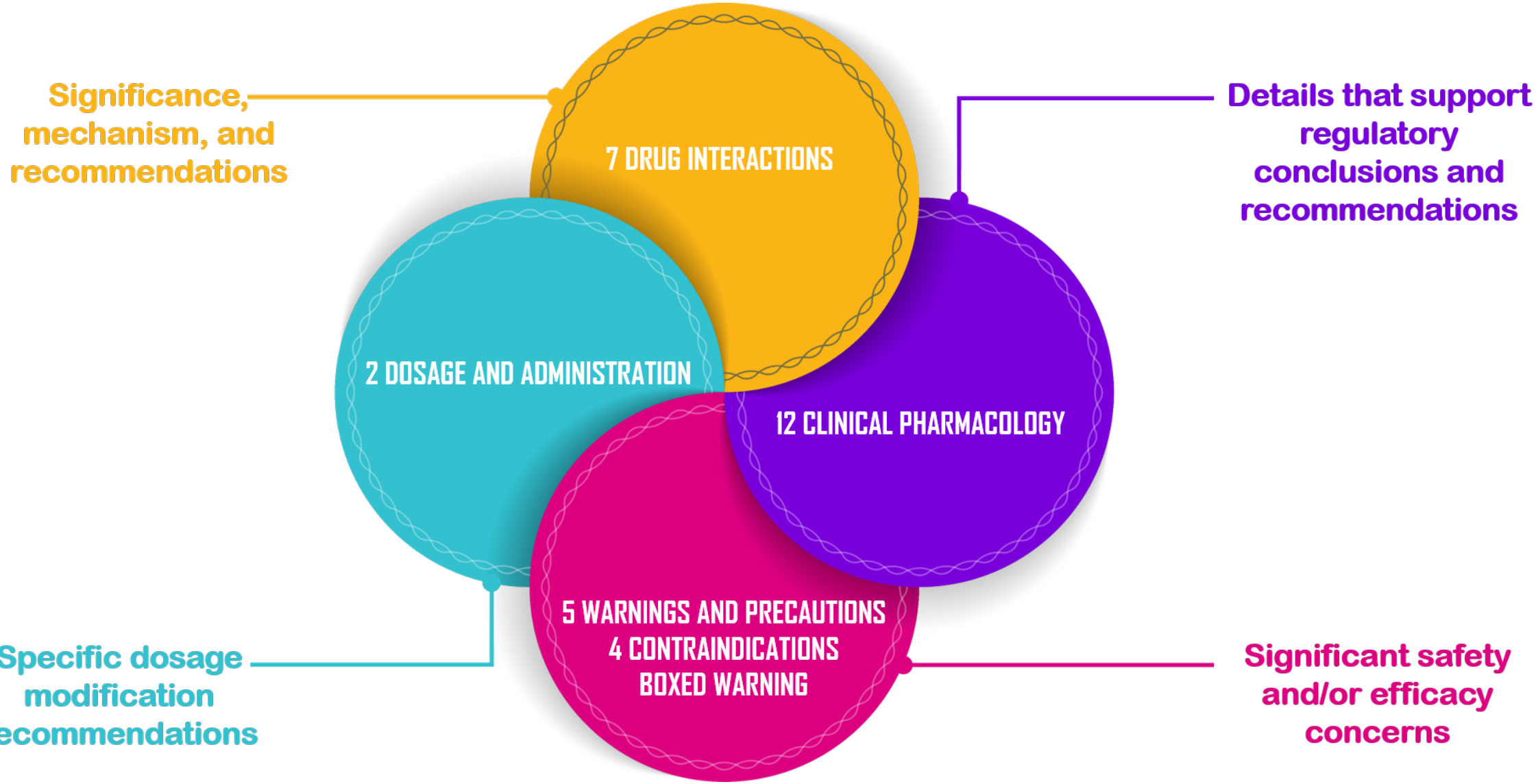
- "Drug X showed time-dependent PK with a 13% decrease in steady state clearance…"
- "Increasing the Drug X dose from 50 to 150 mg once daily resulted in a slightly less than proportional increase in drugoxide steady-state C_{max} and AUC…"
- "Drugoxide is an inhibitor of the BCRP and P-gp efflux transporters with IC_{50} values of 50 µM and 273 µM…"

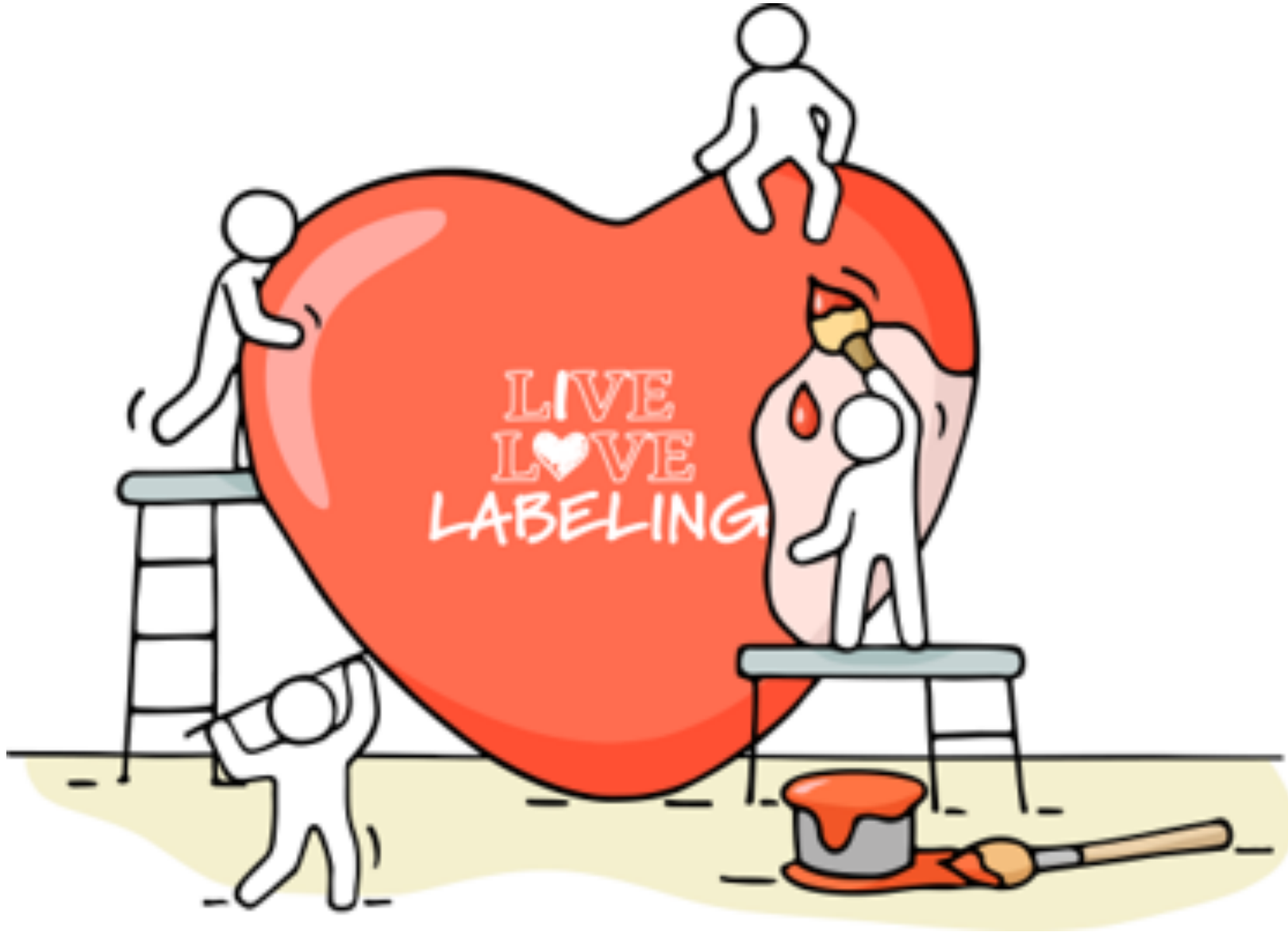
Provide Actionable Recommendations

- Are recommendations "value added" clinically?
- Are recommendations clear, specific, actionable, and practical?
- Are recommendations consistent within labeling and across labelings?
- Are recommendations aligned and supported by presented data?

- "Use with caution"
- "Monitor INR when used concomitantly with warfarin"
- "Concomitant use is not recommended" vs. "Avoid concomitant use" stated for one drug interaction

Cross Referencing Reduces Redundancy




LIVE
LOVE
LABELING

Drug Interactions 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 as Text

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on Drug X

Enhancements Used

Strong CYP3A Inhibitors

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

Drugoxide undergoes metabolism by CYP3A. Concomitant use with a strong CYP3A inhibitor increases drugoxide C_{max} and AUC which may increase 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 in a Table

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on DRUG X

Table X. Effect of Other Drugs on DRUG X

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, 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, and 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 on CYP3A4 enzymes (e.g., strong vs. moderate inhibition) depends on its brand, concentration, and preparation.
[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 in a Table

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.

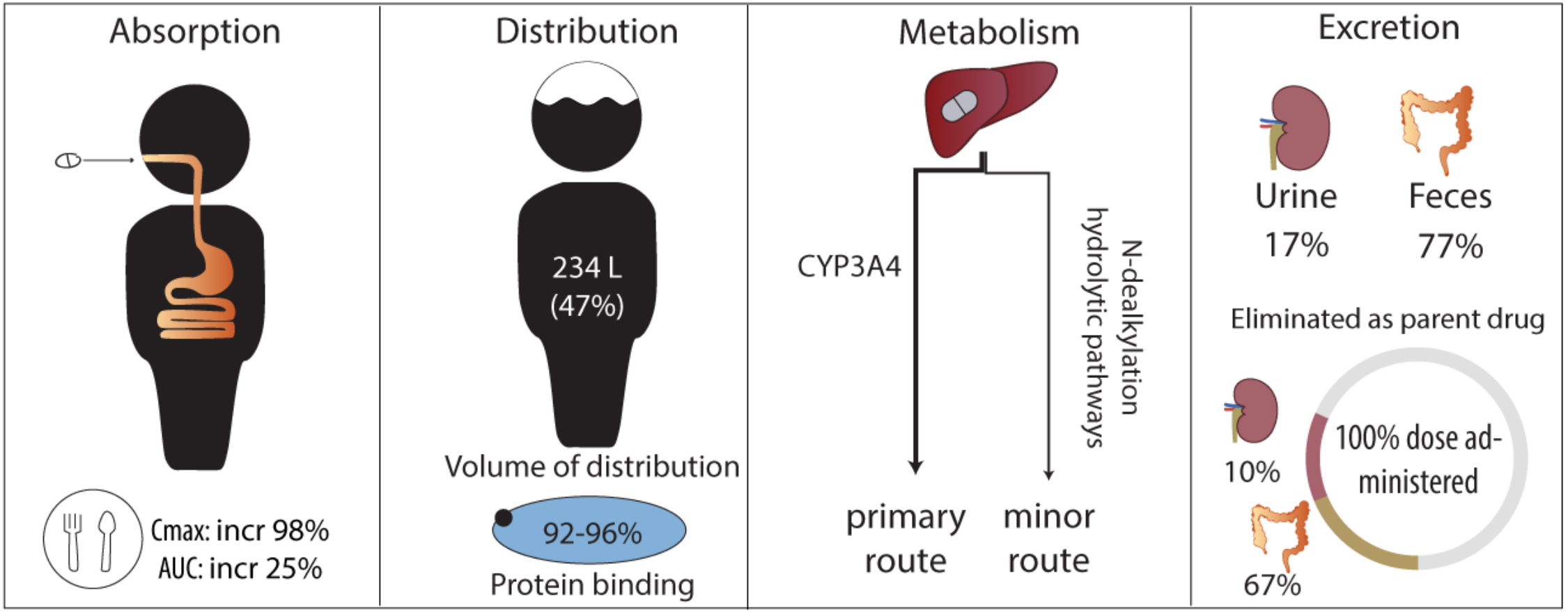
a. This table is not all inclusive; b. These data are based on drug interaction studies or predicted based upon similar characteristics to the drugs evaluated in these studies; c. ↓ = decrease, ↑ = increase; d. *[see Dosage and Administration (2.x)]*

PK Parameters in a 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

PK Parameters as a Figure?



Courtesy Giang Ho, LHC ORISE Fellow

Drug Interaction Studies as Text

Preferred Example:

12.3 Pharmacokinetics

Drug Interaction Studies

Strong CYP3A Inhibitors: Coadministration with ketoconazole (strong CYP3A inhibitor) increased drugoxide C_{max} by 1.3-fold and AUC by 2-fold.

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)]*~~.

Drug Interaction Studies in 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.

Dosage and Administration Alternative Displays

2 DOSAGE AND ADMINISTRATION

2.3 Dose Modification for Use with a Moderate CYP3A4 Inhibitor

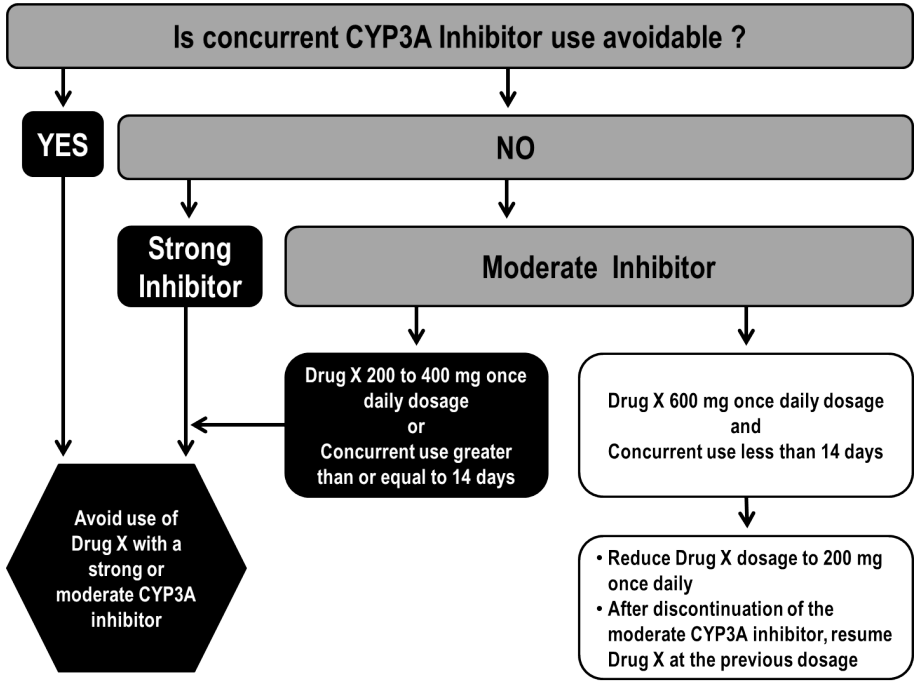
Avoid concurrent use of Drug X with moderate CYP3A inhibitors.

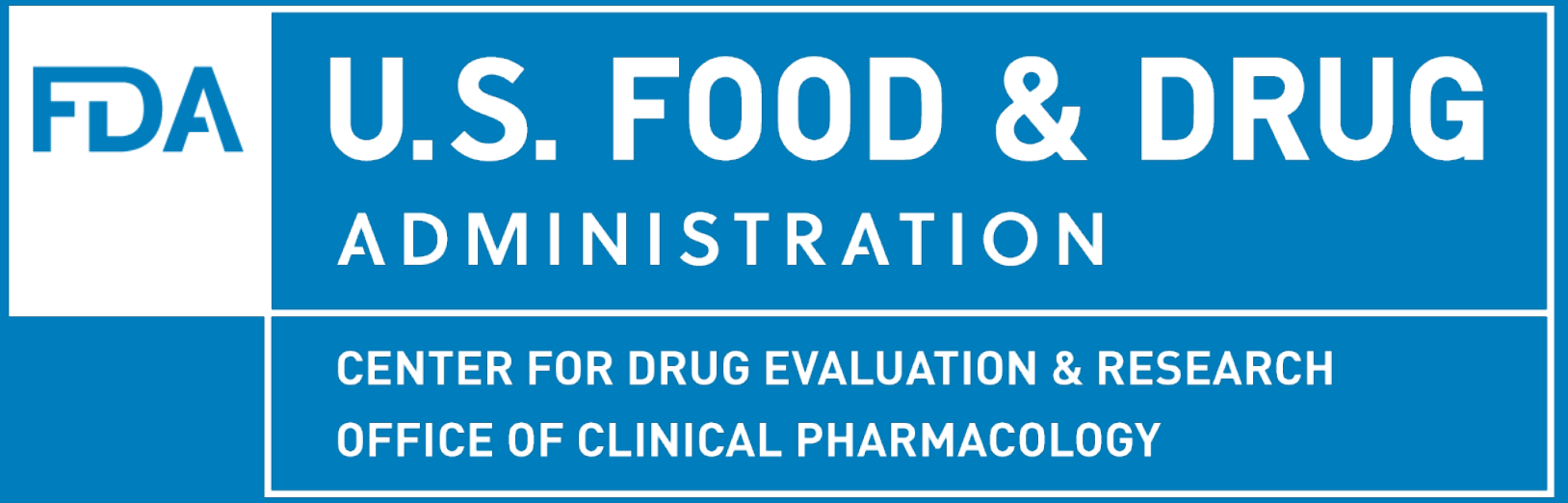
If concurrent short term (14 days or less) use of moderate CYP3A inhibitors including certain antibiotics (e.g., erythromycin, ciprofloxacin) is unavoidable for patients who are taking a Drug X 600 mg daily dosage:

- 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

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