COMMENTARIES

Translation of Drug Interaction Knowledge to Actionable Labeling

Mongthuong T. Tran[1] and Joseph A. Grillo[1,*]

This paper focuses on the effective communication of drug interaction information in US prescription drug labeling. There are important implications and unique challenges related to drug interaction information, including the translation of scientific data into clinical recommendations and presentation of its breadth and complexity. This paper highlights strategies to enhance communication in labeling of essential drug interaction–related information to healthcare providers regarding the safe and effective use of a drug.

BACKGROUND

Unanticipated, unrecognized, or mismanaged drug interactions (DIs) are major contributors to preventable morbidity and mortality. DIs are estimated to represent 3–5% of preventable in-hospital adverse reactions[1] and are recognized as an important contributor to emergency department visits and hospital admissions.[2] A retrospective study reported 26% of total hospital admissions directly due to adverse drug reactions involved a DI.[3]

DIs may be complicated, not well elucidated, and lead to suboptimal therapy with reduced efficacy or increased drug-related toxicities. Understanding how to safely avoid, mitigate, or manage DIs is critical to patient care. However, in a recent cross-sectional study of 895 final-year European medical students, Brinkman *et al.*[4] observed that the students had the lowest knowledge scores for DIs and contraindications. Furthermore, a 2016 newspaper investigation reported that when their investigators attempted to fill prescriptions that had potentially dangerous interactions at 255 community pharmacies in the United States, 52% dispensed the drugs without warning the patient of the potential risk.[5] These findings highlight the importance of effective communication of DI-related information to the healthcare provider.

DI-RELATED INFORMATION IN US PRESCRIPTION DRUG LABELING

A key source for information regarding the interaction profile of a drug in the United States is the prescribing information (PI) portion of prescription drug labeling, which is also referred to as the package insert. The PI is the primary mechanism by which the US Food and Drug Administration (FDA) and drug manufacturers communicate essential information to healthcare providers regarding the safe and effective use of a drug per the Code of Federal Regulations ((CFR) 21 CFR 201.56 (a)(1)). In addition to the specific requirements on content and format of labeling for human prescription drug and biological products that are codified in the CFR, the FDA also publishes Guidances for Industry, which represent its current thinking on a topic but are not binding on the FDA or the public.

Comprised of 17 major sections, the PI is based on the totality of evidence derived from a comprehensive review and analysis by the FDA of the new drug application or biologics license application submitted by an applicant. Following regulatory review and approval, the PI is available directly to providers and informs tertiary drug information sources and clinical decision support tools, which may be more readily accessible.

The majority of DI information in the United States PI is found in the DRUG INTERACTIONS and CLINICAL PHARMACOLOGY sections. In particular, the DRUG INTERACTION section is a highly utilized section by healthcare providers.[6] The DRUG INTERACTIONS section presents clinically relevant regulatory conclusions regarding the existence and mitigation of DIs, and the CLINICAL PHARMACOLOGY section describes detailed scientific information to support these conclusions. Additional pertinent information may also be found in other PI sections, such as DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, OR WARNINGS AND PRECAUTIONS.

DI information in labeling should inform prescribing decisions regarding pharmacokinetic (PK) or pharmacodynamic interactions by including clinically relevant findings and regulatory conclusions, if

[1]Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA. *Correspondence: Joseph A. Grillo (joseph.grillo@fda.hhs.gov)

Received February 22, 2019; accepted March 6, 2019. doi:10.1002/cpt.1427

appropriate, for such information as metabolic and transport pathways, clinically important metabolites, clinical implications of clinically significant DIs and genetic polymorphisms, and recommended risk mitigation strategies.

Although the PI contains DI information required by regulation, inconsistencies with translating scientific data into clinical recommendations and presenting the breadth and complexity of DI-related information may still exist. For example, conveying clinical implications of exposure changes driving interactions, method for providing representative examples of interacting drugs, and informing additional pathway implications or variability of an individual drug when representing DI as a group. As conveyed at the 2013 advisory committee meeting hosted by the FDA Office of Clinical Pharmacology, the desire is to communicate clinical pharmacology information, including DIs, in a manner that is more clinically intuitive and free of unnecessary information.[7] Other unique challenges that impact effective communication may be attributed to the ever-changing nature of DI information that is difficult to capture in a timely way, the diverse understanding of underlying pharmacology of metabolic-based and transporter-based DIs, inconsistent labeling development, and differences between PI and tertiary DI information sources.

STRATEGIES TO ENHANCE COMMUNICATION OF DI-RELATED INFORMATION IN US PRESCRIPTION DRUG LABELING

DI information should be communicated in an actionable and informative manner to healthcare providers who may not have specific expertise in clinical pharmacology.

- DI information should be clear and include essential details for safe and effective prescribing of a drug.
- Consistent and deliberate use of terminology in labeling is important to minimize ambiguity or confusion within and across PIs.
- DI information should be devoid of any technical jargon and distilled into what is clinically relevant.
- In general, DI information should be presented in the format that enhances readability and best accommodates its breadth and complexity to ensure clarity and understanding (e.g., font and text attributes, bullets, headings, white space, and tables). For example, **Figure 1** displays a representative example that effectively conveys extensive information in the DRUG INTERACTIONS section.

DRUG INTERACTIONS Section of US PI

Regulation 21 CFR 201.57(c)(8)(i) and FDA guidance[8] state that the DRUG INTERACTIONS section describe clinically significant interactions, either observed or predicted, with other prescription or over-the-counter drugs, classes of drugs, or foods (e.g., dietary supplements and grapefruit juice); include specific practical instructions for preventing or managing the DI; the mechanism of the DI (if known); and the clinical implication of the DI. An interaction is clinically significant if concomitant use of drugs leads to safety, efficacy, or tolerability concerns greater than those present when the drugs are administered alone. In general, DIs should be listed in the order of clinical importance.

The clinical implication of a DI is essential to convey as it links the mechanism of the interaction to a safety, efficacy, or tolerability concern that impacts the provider's decision making on therapeutic individualization and optimization for patients. Changes in relative drug concentrations or other PK parameters alone do not sufficiently establish a clinical implication, and therefore, the PK changes should be linked with a clinical concern (e.g., reduced efficacy or increased bleeding risk). Information regarding the absence of a DI should generally not appear in this section, unless this information is clinically relevant for the healthcare provider (e.g., if a drug does not have the same interaction as other drugs in the same class).

Strategies to prevent or manage these DIs should be actionable, specific, and practical to the healthcare provider, such as contraindicate concomitant use, avoid concomitant use, temporarily discontinue

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)]*.
Strong CYP3A Inducers[b]	
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.

[a] Strong inhibitors increase the AUC of sensitive index substrates of a given metabolic pathway by ≥ 5-fold.
[b] Strong inducers decrease the AUC of sensitive index substrates of a given metabolic pathway by ≥ 5-fold

Figure 1 Representative example of drug interaction information in a tabular format in the DRUG INTERACTIONS section of the prescribing information. The following table is meant to be a representative example of a possible format and should not be considered a template, limit other possible formats, or constrain the use of other information fields that may be required for a particular drug. Drug X is the proprietary name and drugoxide is the generic name. AUC, area under the curve; CYP, cytochrome P450.

interacting drug, modify dosage, and monitor specific safety or efficacy parameters. Specific statements using active voice (e.g., monitor serum creatinine or increase dose) are more informative than ambiguous or vague statements (e.g., use caution or adjust dose). Standardization of "avoidance" terms (e.g., avoid, do not recommend, use if benefits outweigh the risk) will provide consistency and clarity for the healthcare provider.

CLINICAL PHARMACOLOGY Section of US PI

Regulation 21 CFR 201.57(c)(13)(i) and FDA guidance[9] state the CLINICAL PHARMACOLOGY section should include the results of clinical and *in vitro* studies (e.g., of metabolism or interaction) and other pertinent analyses that establish the presence or absence of a clinically significant DI. Clinical information can include data and results from prospective clinical DI studies, population PK analyses, modeling and simulations (e.g., physiologically-based PK modeling), postmarketing reports, or data extrapolated from other information. Once deemed sufficient to inform a regulatory decision in place of a dedicated clinical study, population analyses or modeling and simulation approaches generally do not need to be referenced as the source of data (e.g., "Based on physiologically-based pharmacokinetic modeling…").

Clinically significant study results can be presented in the CLINICAL PHARMACOLOGY section as text or in a table or figure depending on the number of studies and the level of detail needed for clarity and understanding. **Figure 2** displays representative examples of tabular and figure presentations in this PI section. DI information should include only those study features that are essential for the safe and effective use of a drug. The relative change in exposure can be presented as a percentage or a fold change with a clinically meaningful measure of variability/dispersion, such as range. For example, although 90% confidence intervals are useful for regulatory review, the minimum and maximum potential exposure change may be more informative to the healthcare provider. Tables and figures should clearly state the reference arm and display the relative change in key PK exposure measures.

In vitro information should establish the absence of a DI effect or characterize protein binding, metabolic, and transporter pathways in the absence of clinical information. *In vitro* information alone does not establish a significant DI and, therefore, is rarely presented in the DRUG INTERACTIONS section. Generally, *in vitro* information that is superseded by clinical data should not be reported. However, in rare cases, *in vitro* studies may be included to provide additional context for related clinical studies.

Studied drugs with no clinically significant interaction potential should be listed in a summary sentence without any study details. To minimize redundancy of information appropriately presented elsewhere in labeling, specific regulatory conclusions and actionable instructions regarding a DI should not be repeated in the CLINICAL PHARMACOLOGY section.

CONCLUSION

DIs contribute to preventable morbidity and mortality and may not be fully understood by healthcare providers. How well information regarding the safe and effective use of a drug is ultimately communicated to the prescribing provider in labeling is a key element of a drug development program. Appropriate presentation of DI information in the PI is critical to enable interpretation and translation of this information for individualized

(a)

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Drug interaction studies

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]	
		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]

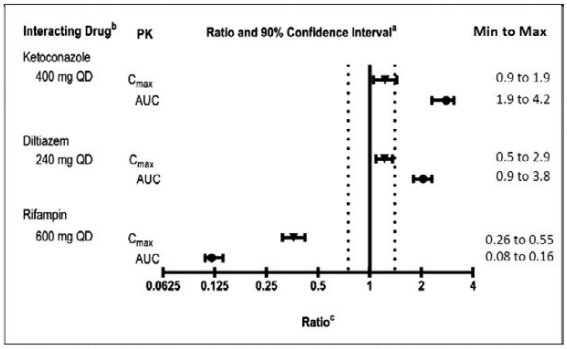
(b)

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Drug interaction studies

Table X. Clinically Significant Interactions Affecting Drugoxide



a Dashed vertical lines illustrate pharmacokinetic changes that were used to inform dosing recommendations
b Drug X administered as a 60 mg single dose.
c Log base 2 scale

Figure 2 Representative example of drug interaction information as either a tabular (**a**) and figure (**b**) format in the CLINICAL PHARMACOLOGY section of the prescribing information. The following table and figure are meant to be a representative example of a possible format and should not be considered a template, limit other possible formats, or constrain the use of other information fields that may be required for a particular drug. Drug X is the proprietary name and drugoxide is the generic name. AUC, area under the curve; CI, confidence interval; C_{max}, peak plasma concentration; PK, pharmacokinetic.

patient care. This presentation can be optimized by communicating essential information in a clear, concise, nontechnical manner and leveraging the use of text attributes and creative formatting techniques.

FUNDING
No funding was received for this work.

CONFLICT OF INTEREST
The authors declared no competing interests for this work.

DISCLAIMER
The contents of this article reflect the views of the authors and should not be construed to represent the US Food and Drug Administration (FDA)'s views or policies. No official support or endorsement by the FDA is intended or should be inferred. The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the FDA.

1. Leape, L.L. *et al.* Systems analysis of adverse drug events. ADE Prevention Study Group. *JAMA* **274**, 35–43 (1995).
2. Raschetti, R. *et al.* Suspected adverse drug events requiring emergency department visits or hospital admissions. *Eur. J. Clin. Pharmacol.* **54**, 959–963 (1999).
3. McDonnell, P.J., Jacobs, M.R., Monsanto, H.A. & Kaiser, J.M. Hospital admissions resulting from preventable adverse drug reactions. *Ann. Pharmacother.* **36**, 1331–1336 (2002).
4. Brinkman, D.J. *et al.* Hospital admissions resulting from preventable adverse drug reactions. *Clin. Pharmacol. Ther.* **101**, 281–289 (2017).
5. Roe, S., Long, R. & King, K. Pharmacies miss half of dangerous drug combinations. *Chicago Tribune* <http://www.chicagotribune.com/> (2016). Accessed February 22, 2019.
6. Sullivan, H.W., O'Donoghue, A.C. & Aikin, K.J. Primary care physicians' use of FDA-approved prescription drug labels. *J. Am. Board Fam. Med.* **27**, 694–698 (2014).
7. US Food and Drug Administration (FDA). FDA Advisory Committee Meeting Transcript. Advisory committee for pharmaceutical science and clinical pharmacology (ACPS-CP); 210–294, <https://bit.ly/2QK9z4s> (2013). Accessed February 22, 2019.
8. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications: Guidance for Industry. Draft Guidance. October 2017. <https://bit.ly/2BRNbI7> (2017). Accessed February 22, 2019. When finalized, the guidance may be found at <https://bit.ly/2SYdmRF>.
9. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format: Guidance for Industry. December 2016. <https://bit.ly/2VcXesb> (2016). Accessed February 22, 2019.

Clopidogrel as a Perpetrator of Drug–Drug Interactions: A Challenge for Quantitative Predictions?

Manthena V.S. Varma[1,*], Yi-an Bi[1], Sarah Lazzaro[1] and Mark West[1]

Clopidogrel perpetrates pharmacokinetic interactions primarily due to time-dependent inhibition (TDI) of cytochrome P450 (CYP)2C8 by a circulating metabolite, clopidogrel acyl-β-D-glucuronide (Clop-Gluc).[1] Additionally, Clop-Gluc is a reversible inhibitor of organic anion transporting polypeptide (OATP)1B1 *in vitro*. Given many CYP2C8 substrates show hepatic uptake via OATP1B1, clopidogrel interaction mechanisms and inhibition potential at clinical doses have been debated—particularly with the quantitative predictions of dasabuvir–clopidogrel interactions.[2,3] Here, we summarize clinical data and evaluate mechanistic models to further our understanding of clopidogrel interactions.

Gemfibrozil and clopidogrel are recommended inhibitors to probe CYP2C8 activity *in vivo*.[4] Gemfibrozil is metabolized by uridine 5′-diphosphate glucuronosyltransferase 2B7 to form gemfibrozil acyl-β-D-glucuronide (Gem-Gluc), whereas clopidogrel is an ester prodrug that converts to an inactive carboxylic acid (~ 85% of dose), which is further glucuronidated to form Clop-Gluc. Both Gem-Gluc and Clop-Gluc show CYP2C8 TDI, and parent-metabolite pairs also inhibit OATP1B1 *in vitro*.[1,5]

EFFECT OF CLOPIDOGREL ON CYPs—CLINICAL EVIDENCE

Clopidogrel inhibits CYP2C8 to a moderate-to-strong degree (area under the curve (AUC) ratio 2–5) and weakly (AUC ratio 1.25–2) inhibits CYP2B6 and CYP2C19 at a loading dose of 300 mg (**Figure 1**). Relatively lower effects are noted with 75 mg maintenance dose. On the other hand, gemfibrozil 600 mg b.i.d. increased AUC of daprodustat and dasabuvir by ~ 19-fold and 11-fold,

[1]Pharmacokinetics, Dynamics, and Metabolism, Medicine Design, Worldwide R&D, Pfizer, Inc., Groton, Connecticut, USA. *Correspondence: Manthena V.S. Varma (manthena.v.varma@pfizer.com)

Received December 13, 2018; accepted February 8, 2019. doi:10.1002/cpt.1398