Enhancing the Accessibility and Utility of Drug Interaction Information in Prescription Drug Labeling

Kimpton Hotel Monaco • Washington, DC
October 16, 2019

Discussion Guide

Introduction

Clinically-significant drug interactions can have a range of clinical implications related to efficacy and safety and are estimated to account for 6–30% of all adverse drug reactions, which are a leading cause of patient morbidity and mortality.\(^1\) Prescription drug labeling (or Prescribing Information) is written for the health care practitioner audience\(^2\) and must contain a summary of the essential scientific information, including information on clinically-significant drug interactions, needed for the safe and effective use of the drug.\(^3\) Drug interaction information communicated in the Prescribing Information has a number of other users, including third-party drug information providers who maintain clinical decision support tools. Clinical decision support can range from computerized alerts to online drug information databases that guide prescribing decisions. The Prescribing Information is also used by committees responsible for the development of drug formularies as well as by payers and pharmacy benefit managers who perform drug utilization reviews.

The DRUG INTERACTIONS section (Section 7) of the Prescribing Information is the primary location for the communication of information about potential and known clinically-significant drug interactions, mechanisms of drug interactions, their clinical implications, and specific practical instructions for their prevention or management. Drug interaction information in the Prescribing Information should be presented in a clear, concise, and consistent format that supports end user interpretability and comprehension to inform clinical practice and promote the safe and effective use of drugs.

This workshop, convened by the Duke-Margolis Center for Health Policy under a cooperative agreement with FDA, aims to capture stakeholder input on factors that affect, and may potentially enhance, the utility, clarity, comprehension, and consistency of drug interaction information in the DRUG INTERACTIONS section. This workshop will be discussion-based and will explore the real-world use of drug interaction information, including how this information is curated by third-party drug information providers and used by health care providers during care delivery. The questions included in this document will guide discussion about how to provide clear, useful, consistent, and understandable information in the Prescribing Information, including information about clinically-significant drug interactions, their mechanisms and clinical implications, and instructions for preventing or managing them. Additionally, participants will be asked to respond to poll questions at the beginning of each session via the Poll Everywhere platform. Participants may respond to these questions by text message or via any web-enabled device (see instructions in Appendix 3).\(^4\) Information obtained through stakeholder discussion and participant polls will provide valuable input to FDA’s thinking about labeling practices for the DRUG INTERACTIONS section.

\(^{\text{a}}\) Responses to poll questions will remain anonymous and will be used to inform workshop discussion and FDA thinking about labeling practices for the DRUG INTERACTIONS section.
practices for the DRUG INTERACTIONS section and future recommendations to industry on how to develop this section of the Prescribing Information.

Session 1: The Real-World Uses of Drug Interaction Information

An estimated 20% of U.S. adults are taking more than three drugs concurrently. While treating these and other patients, health care providers encounter drug interaction information as part of the process of prescribing, reviewing, verifying, preparing, dispensing, and administering medications, and monitoring patients for adverse drug events. Clinical decision support tools are widely used to detect and inform providers about potential drug interactions, but health care providers access and use drug interaction information from a variety of sources.

Discussion in this session will cover how a variety of health care providers, across the spectrum of care, seek, assess, and utilize drug interaction information as it is presented in the Prescribing Information. This discussion will also inform subsequent sessions regarding the clinical relevance and utility of drug interaction information in the Prescribing Information and enhanced approaches to content development and presentation in the DRUG INTERACTIONS section.

Discussion Questions:
1. How well does the information provided in the Prescribing Information equip providers to effectively anticipate, prevent, or manage drug interactions? What additional information in the DRUG INTERACTIONS section is needed?
2. What do you consider to be essential information that should be included in the DRUG INTERACTIONS section?
3. What is your approach for assessing drug interaction risk and what type of risk information informs your prescribing decisions?
4. How do you reconcile drug interaction information from other sources that may differ from the Prescribing Information?
5. How often do you access the Prescribing Information? What other sources of drug interaction information impact your clinical practice and what makes them valuable?

Session 2: Extraction and Application of Drug Interaction Information by Drug Information Providers

Drug interaction information in the Prescribing Information is curated by third-party drug information providers to inform the development of clinical decision support tools. Drug interaction information provided through these mechanisms may be more readily accessible to health care providers and may differ from drug interaction information in the Prescribing Information in terms of clinical content, interpretation, and presentation.

Clinical decision support tools may also incorporate additional information (beyond the drug interaction information presented in the Prescribing Information) from other sources deemed clinically important. Manually extracting drug interaction information from other sources is labor intensive, and machine learning algorithms are often applied to automate the identification of drug interactions in unstructured text (e.g., text from medical literature). The Structured Product Labeling (SPL) is FDA’s standard format for the electronic exchange, between computer systems, of the Prescribing Information and provides accessible data elements and information about the drug as well as information about the
sections/subsections. SPL is also utilized by third-party information providers to inform their decision support tools.

Health care providers benefit from useful, accurate, and consistent drug interaction information presented in clinical decision support tools. This discussion will cover common approaches and resources for the extraction of drug interaction information, the utility of SPL for this purpose, as well as any differences in the extraction, content, interpretation, or presentation of drug interaction information maintained across different tools and the basis for those differences. This session will also entail discussion about the decision process to determine what additional information is included in clinical decision support tools and how this information is managed and updated.

Discussion Questions:
1. Does the current format and style of the DRUG INTERACTIONS section present any challenges with the extraction or curation of drug interaction information for clinical decision support tools? If so, please describe how and why.
2. What are the challenges with extracting drug interaction information from SPL files to inform the content of clinical decision support tools?
3. In addition to the Prescribing Information, what other sources of drug interaction information inform the content and the severity of a drug interaction in clinical decision support tools? What is the process for vetting and updating this information?
4. How do clinical decision support tools address a situation when there is not enough information in the Prescribing Information about the clinical implications to make a recommendation regarding the prevention or management of a drug interaction?

Session 3: Approaches to the Effective Presentation of Drug Interaction Information in the Prescribing Information

In a 2013 FDA advisory committee meeting, a small group of health care providers stated that the DRUG INTERACTIONS section should be easy to navigate, clinically intuitive, and should provide essential information regarding drug interactions with a clear sense of severity, risk, and prevention or management recommendations. Consistency and enhancements to content presentation in the DRUG INTERACTIONS section may contribute to increased utility, clarity, and comprehension for health care providers who rely on this information to guide prescribing practices as well as third-party information providers who curate this information to develop clinical decision support tools.

This discussion will center on preferences related to the presentation of essential drug interaction information in the DRUG INTERACTIONS section, use of enhanced presentation strategies and formats, as well as issues that may obstruct the clinical utility, comprehension, and consistency of the Prescribing Information. This session will also include a discussion on the variable information needs and preferences among diverse health care providers and potential strategies for a more inclusive presentation of drug interaction information in the Prescribing Information.

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b See FDA’s SPL resources: https://www.fda.gov/industry/fda-resources-data-standards/structured-product-labeling-resources
Discussion Questions:
1. What specific issues impact the optimal comprehension, utility, and readability of drug interaction information in the Prescribing Information?
2. What is the ideal content and format of the DRUG INTERACTIONS section of the Prescribing Information?
3. To what extent, if any, does technical language (e.g., exposure, pharmacokinetics, C<sub>max</sub>, AUC, renal clearance, substrate vs. metabolized by) impact the optimal comprehension, utility, and readability of drug interaction information in the Prescribing Information?
4. How should the drug interaction mechanism be described in the DRUG INTERACTIONS section?

Session 4: Communicating the Clinical Implications of Drug Interactions in the Prescribing Information

The clinical implications of drug interactions are key to informing prescribing decisions that prevent and mitigate drug interactions. The significance of drug interactions and any resulting clinical recommendations in the Prescribing Information are informed by a multitude of factors based on the totality of evidence reviewed by FDA, including the clinical implications of the potential interaction. According to research designed to determine the clinical significance of potential drug interactions in clinical practice, poor agreement among participants asked to rate the clinical significance of 100 potential interactions was observed. This study (Strasberg et al.), noted that there was at least some disagreement for 97 of the potential interactions presented to study participants, indicating the potential for variability in the interpretation of information included in the DRUG INTERACTIONS section among health care providers.

Discussion in this session will cover what constitutes a clinical implication and how health care providers incorporate and interpret this information, or the lack thereof, into prescribing decisions. The discussion will also focus on how clinical implications in the Prescribing Information are potentially used to categorize interaction severity in drug interaction alerts provided by clinical decision support tools.

Discussion Questions:
1. What challenges in the DRUG INTERACTIONS section, if any, affect your ability to identify the clinical implications of a drug interaction?
2. How should the DRUG INTERACTIONS section be presented so that information about the clinical implications of a drug interaction is clear and actionable?
3. What should be included in the DRUG INTERACTIONS section when there is not enough information about the clinical implications to make a recommendation regarding the prevention or management of a drug interaction?
4. How do you interpret and implement different prevention or management recommendations provided in the DRUG INTERACTIONS section regarding concomitant use of an interacting drug (e.g., 'contraindicate,' 'avoid,' 'is not recommended,' 'use with caution')?
Session 5: Synthesis Discussion and Next Steps

Discussion in this final session will cover key takeaways from the day as well as the identification of potential opportunities to provide clear, useful, and consistent drug interaction information in the Prescribing Information.

Discussion Questions:
1. What approaches discussed throughout the day may enhance communication about the mechanisms, clinical implications, and recommendations for the prevention or management of drug interactions?
2. What perspectives should FDA consider for future labeling development practices?


Appendix 1. Content and Format of the Prescribing Information

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 OVERDOSE
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.
Appendix 2. Sample Language from the Drug Interactions Section of the Prescribing Information

7 DRUG INTERACTIONS

7.1 Non-Selective Monoamine Oxidase (MAO) Inhibitors

Both DRUG X and non-selective MAO inhibitors inhibit catecholamine metabolism leading to increase catecholamines which may increase the risk of possible arrhythmias, increased heart rates, and excessive changes in blood pressure [see Warnings and Precautions (5.1)].

Concomitant use of DRUG X with non-selective MAO inhibitors is contraindicated [see Contraindications (4)]. Selective MAO-B inhibitors can be used concomitantly with DRUG X.

7.2 Effect of Other Drugs on DRUG X

Strong CYP3A Inhibitors

Concomitant use of DRUG X with a strong CYP3A inhibitor increases drugoxide plasma concentrations [see Clinical Pharmacology (12.3)], which may increase the risk of adverse reactions of DRUG X. Avoid concomitant use of DRUG X with strong CYP3A inhibitors.

Strong or Moderate CYP3A Inducers

Concomitant use of DRUG X with a strong or moderate CYP3A inducer decreases drugoxide plasma concentrations [see Clinical Pharmacology (12.3)], which may reduce DRUG X efficacy. Reduce DRUG X dosage when used concomitantly with strong or moderate CYP3A inducers, including St. John’s wort [see Dosage and Administration (2.3)].

7.3 Effect of DRUG X on Other Drugs

Drugs Metabolized by Catechol-O-Methyltransferase (COMT)

Concomitant use of DRUG X may increase the AUC of drugs metabolized by COMT, which may increase the risk of possible arrhythmias, increased heart rates, and excessive changes in blood pressure [see Warnings and Precautions (5.1)].

Reduce dosage of drugs metabolized by COMT in accordance with its approved product labelling when used concomitantly with DRUG X, and monitor heart rate, rhythm, and blood pressure in patients [see Warnings and Precautions (5.1)].

CYP2C9 Substrates

Concomitant use of DRUG X may increase plasma concentrations of CYP2C9 substrates [see Clinical Pharmacology (12.3)], which may increase the risk of toxicities of CYP2C9 substrates. Use with caution when CYP2C9 substrates where minimal concentration changes may lead to serious or life-threatening toxicities is used concomitantly with DRUG X.
Appendix 3. Poll Everywhere Instructions for Each Poll

Via Phone/Text Message

1. Text DUKEFDA175 to 22333 to join
2. Type your response to the poll displayed on screen and click send

Via Web-Enabled Device

1. Navigate to Pollev.com/DUKEFDA175
2. Choose your response to the poll displayed on screen