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

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## INTRODUCTION AND WORKSHOP PURPOSE

Drug interactions (DIs) are a significant source of preventable adverse reactions in the United States (US). For example, a retrospective chart review of 437 adverse reactions over an 11-month period at a large university hospital found that 26% (40/154) of adverse reactions that led to hospital admission and that were at least probably related to drug exposure were attributable to a drug-drug interaction.[1] In a meta-analysis of thirteen observational studies examining DIs, the median DI prevalence rates for hospital admissions and hospital visits were 1.1% and 0.1% respectively; however, among patients with adverse reactions, the median DI prevalence rates for hospital admissions and hospital visits were 22% and 9%, respectively.[2]

Information regarding the DI risks of prescription drugs have increased in breadth and complexity over the past several decades, which might make it more difficult for health care practitioners (HCPs) to find and effectively apply specific DI information in practice. Furthermore, multiple private- and public-sector organizations, including the US Food and Drug Administration (FDA), are involved in reducing the risk of DIs by identifying clinically significant drug-drug, drug-food, or drug-substance interactions and communicating them to HCPs. HCPs apply this information to reduce and manage DI risks (for example, by lowering the drug dosage or using alternative drugs).

During drug development, studies are conducted to identify clinically significant DIs between the investigational drug and other drugs, foods, or dietary supplements. A drug developer then submits DI information to the FDA as part of a New Drug Application (NDA) or a Biologics License Application (BLA). As part of their NDA or BLA, a drug developer

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develops and submits proposed Prescribing Information (PI) that includes essential DI information for the safe and effective use of the drug. As part of the NDA or BLA review process, the FDA then reviews and may further revise DI information in PI, within the context of the entire body of evidence submitted, before taking regulatory action. Following the FDA's regulatory approval of an NDA or BLA, the FDA makes the approved PI available online at Drugs@FDA ([www.fda.gov/drugsatfda](www.fda.gov/drugsatfda)) and through structured product labeling (SPL) files [e.g., National Library of Medicine's DailyMed ([https://dailymed.nlm.nih.gov](https://dailymed.nlm.nih.gov)), FDA's FDALabel ([https://nctr-crs.fda.gov/fdalabel/ui/search](https://nctr-crs.fda.gov/fdalabel/ui/search))].  After drug approval, if there is new DI information from the post-marketing setting, the drug developer can submit a supplement to their NDA or BLA to add additional DI information to the PI, or the FDA can either request, or in certain cases require, the drug developer to add the DI to the PI.

Third-party drug information publishers can use the PI as a resource for publishing DI information used by HCPs to support clinical decision making and drug dispensing.  DI information is also found within third-party clinical decision support software (CDSS) including applications within electronic health record (EHR) systems and drug developers' publications.  Drug developers, scientists, and HCPs explore potential new DI signals throughout the lifecycle of a drug via research, studies, and clinical observations reported in the medical literature. Third-party drug information publishers might incorporate updated DI information in their drug information resources based on this additional postmarketing experience, which might not yet be included in PI at that time. However, the curation and presentation of DI information can differ across drug information resources. Therefore, new or updated DI information might be described and presented differently to HCPs depending on the drug information resources they reference.

In clinical settings, HCPs rely on a combination of their own knowledge and experience, the PI, and other drug information resources to identify, reduce the risk of, and manage DIs. Differences in health care settings and health information technology (HIT), as well as differences in HCP preferences related to DI resources, impact how HCPs access and apply DI information. PI developers and third-party drug information publishers should consider these factors when designing DI information resources to assist HCPs in reducing the risk of DIs and managing DIs in clinical practice.

The FDA, through its public health mission to assure the safe and effective use of drugs that are marketed in the US, helps to ensure that PI communicates essential DI information. To obtain input on how to best communicate DI information in PI, including the DRUG INTERACTIONS section, the FDA and Duke-Margolis convened a stakeholder workshop in October 2019 and a follow-on meeting in December 2019.[5] Meeting participants included academic physicians, retail and clinical pharmacists, nurse practitioners, academic researchers, drug database publishers, drug developers, informaticists, and representatives from the FDA. The following is a summary of participant feedback from these meetings. Statements below are attributable to non-FDA meeting participants unless otherwise noted.

### CHALLENGES AND POTENTIAL SOLUTIONS FOR MANAGING DRUG INTERACTIONS IN THE CLINICAL SETTING

*Challenges Reducing the Risk of Drug Interactions and Managing Drug Interactions*

Numerous factors can impact how DI information is communicated, accessed, and used to reduce the risk of and manage DIs. HCPs (for example, physicians, pharmacists, physician assistants, nurse practitioners, and nurses) are involved in drug selection, prescribing, dispensing, preparation, and administration of prescription drugs, and each HCP group might require and process DI information differently in their varied roles. Additionally, a HCP's practice setting might influence their DI information needs. Workshop participants reported that HCPs routinely face time pressures that necessitate easily accessible and succinct DI information to inform their clinical decision making. Specialized providers (for example, cardiologists, oncologists, endocrinologists, and others) might prefer more detailed DI information within their field from multiple sources. The delivery of clear and consistent DI information is often complicated by the HCPs' reliance on varied reference resources (for example, PI, third-party drug information databases, medical literature) that might include different DI information as discussed above.

Generally, HCPs interpret DI information in PI as it applies to their clinical specialty and target patient population. It is challenging for HCPs to incorporate DI information into their clinical decision making when DI information is vague or inconsistent; when recommendations are not clinically actionable (for example, "use with caution"); or when DI scenarios are complex, such as the need to understand the additional impact of organ

impairment and/or genetic polymorphisms on a DI. Issues with the utility of DI information are compounded by the fact that DI information is often limited for specific patient populations (such as pediatric and geriatric populations) because dedicated DI studies are not routinely conducted in these populations. Meeting participants noted that more frequent and consistent inclusion of DI information for these populations in PI and other third-party drug information databases might improve the ability of HCPs to reduce the risk of DIs and better manage DIs across care settings and patient populations.

Variations in infrastructure across different health care settings also influence the availability and accessibility of DI information. Large academic health systems might have DI resources that may be unavailable to other facilities such as federally qualified health centers (FQHCs). Funding can influence the availability of HIT (such as CDSS) and staff services (such as on demand pharmacy consultations or DI information services) for supporting access to DI information.

### *The Role of Health Information Technology – Drug Information Databases, Electronic Health Records, and Clinical Decision Support Software*

Third-party DI information is commonly compiled from the approved PI and other sources (including the medical literature and treatment guidelines) and is frequently tailored to individual health care systems. Third-party DI information is provided to HCPs through tools including CDSS and searchable drug information databases. While HIT offers important tools for communicating DI information, how developers create and maintain tools affects their quality and utility. The description of the clinical effect(s) of DIs as well as clinical recommendations about reducing the risk of DIs or managing DIs might vary among third-party drug information databases, especially when DI information has not been fully characterized. For example, when PI does not clearly convey the DI risk or seriousness, or does not provide an actionable management strategy because a DI has not been fully characterized, third-party drug information publishers might provide additional context and recommendations depending on their internal policies and clinical experts. Sometimes, the additional context and recommendations provided may diverge from PI and may be inconsistent among different third-party drug information databases.

Furthermore, different EHR vendors and EHR user interfaces include algorithms that trigger DI alerts and present DI information at the point of care in different ways. When resources

permit, clinic- or hospital-based HCPs might work with EHR vendors and health care administrators to tailor DI alerts to the appropriate clinical context. Context-dependent alerts are triggered based on patient data within an EHR. However, such capability varies among EHR systems and interfaces. Participants indicated that without well-tailored alerts, HCPs might experience alert fatigue—reduced responsiveness to software-based alerts intended to communicate important DI information. Alert fatigue results from repeated exposure to low-value or false-positive alerts. Accordingly, developing algorithms that focus more on clinically significant DI alerts that include actionable recommendations, where possible, might help to ameliorate alert fatigue.

*Potential Solutions*

Third-party drug information publishers, health systems, drug developers, and the FDA can take steps to improve the way they characterize and communicate information to help HCPs reduce the risk of DIs and manage DIs. Participants suggested drug information publishers work with one another, as well as with academic and regulatory stakeholders, to establish a public-private partnership (PPP) to promote access to consistent DI information across publications and platforms. Participants also recommended the FDA work with drug developers and others to provide guidance on how to develop and submit PI with more succinct, clinically relevant, and interpretable DI information (for example, by characterizing DIs using standardized seriousness levels similar to those found in treatment guidelines). To support this effort, a PPP can develop a method for determining DI seriousness, as well as recommendations about when, where, and how this information is presented within PI and how third-party drug information publishers communicate it across their drug information platforms. The FDA and other stakeholders can   additionally convene public meetings or other forums to discuss approaches to enhance communication of DI information. Furthermore, while HIT differs among clinical settings, HCPs and their organizations can more broadly share knowledge and best practices about designing effective DI alerts that reduce alert fatigue and promote safe prescribing, dispensing, and utilization of prescription drugs.

## THE ROLE OF PRESCRIBING INFORMATION IN COMMUNICATING DRUG INTERACTION INFORMATION AND SUGGESTIONS FOR IMPROVEMENT

PI is one of many sources through which HCPs obtain DI information. However, HCPs generally rely on other sources of DI information more frequently than they refer to PI, including information from third-party information publishers. At the workshop and follow-up meeting, stakeholders noted several issues with PI that might impact its utility and lead to reliance on alternative sources of DI information. This section discusses attendee concerns with PI with respect to clarity, density, format, and reliability.

### Clarity of the Presented DI Information

Workshop participants indicated that DI information must be communicated consistently and unambiguously to support HCPs in clinical decision making across diverse care settings and patient populations. DI information should be actionable and easily understood; workshop participants noted that clinical recommendations presented in a consistent format within PI are broadly desired by healthcare providers but frequently lacking. For example, terms like "use with caution" and "clinically significant" appear frequently within PI, but their meanings might be ambiguous without additional context describing the clinical impact and seriousness. Likewise, although the term "contraindicated" is clearly defined by FDA regulations (specifically, situations in which the drug should not be used because the risk of use clearly outweighs any possible therapeutic benefit), it is sometimes interpreted and implemented inconsistently among HCPs. For example, the term "contraindicated" might be incorrectly interpreted as communicating theoretical risk as opposed to the known evidence-based risk that clearly outweighs any possible therapeutic benefit. Furthermore, inconsistencies can occur when PI for respective interacting drugs includes discordant information, or when PI is internally inconsistent. Finally, some stakeholders recommended that if no clinically significant DIs are known, the DRUG INTERACTIONS section can include a statement on the absence or lack of DI information to avoid ambiguity.

DI information included in PI must be clear so HCPs can quickly consult and apply DI information in clinical practice. Some approaches to improve clarity might be simple. For instance, participants suggested better defining and specifying the interacting drug classes. For example, instead of referencing "all oral medications" or "anticholinergic drugs"

sponsors can consider if a narrower scope of drugs should be referenced, if appropriate ("anticholinergic drugs" can refer to drugs with a primary anticholinergic mechanism or to other drugs with anticholinergic effects, such as antipsychotics). Sometimes a broad interacting drug class is  referenced in the PI, but examples of interacting drugs are limited to those that are severe. For example, CYP3A substrates might be indicated as an interacting drug class but only CYP3A substrates with a narrow therapeutic index are cited as examples.

Furthermore, there is no standardized process for characterizing different levels of DI seriousness or severity. Participants at the workshop discussed the benefits and limitations of a centralized process for characterizing the seriousness or severity of DIs based on several factors such as a DI's incidence or likelihood, anticipated clinical effects, and potential mitigation strategies. Participants suggested that a national panel of experts might establish a process for characterizing levels of seriousness or severity for DI within PI. However, such an approach might have drawbacks. For example, standardizing DI seriousness or severity might unintentionally contribute to providers ignoring or minimizing those DIs that are characterized as less-severe or lower-priority but are nonetheless clinically significant. Finally, PI might characterize the quality of evidence supporting determinations about DI seriousness or severity (and clinical recommendations) in cases where evidence is available as well as in cases where evidence is limited or lacking.

*Density*

Densely written PI can be difficult to use in clinical practice. Workshop participants noted that when essential information within PI is eclipsed by what they perceive as information that is not directly related to the safe and effective use of the prescription drug, HCPs often reference alternate resources. In resource-limited practice settings, particularly when patient-facing time is short and clinical pharmacy staff are unavailable, PI, when densely-written, can be difficult to navigate to quickly access pertinent DI information as compared to using more streamlined third-party DI information resources. Workshop participants indicated that drug developers and the FDA can take steps to reduce unnecessary or overly technical DI information in PI. For example, PI might not need to include clinical recommendations that are part of standard medical care (for example, recommendation to

monitor international normalized ratio when this is already part of routine care for patients taking warfarin). Furthermore, some stakeholders suggested that it might be unnecessary to include certain information in PI, like routine specific pharmacokinetic values that are primarily contextual and pharmacodynamic interactions considered general medical knowledge (for example, that administering two sedatives will increase drowsiness).

Although FDA regulations do not require drug developers to include examples of interacting drugs within a drug class in the PI, participants provided input on whether to and how to incorporate specific examples of interacting drugs within a drug class in the DRUG INTERACTIONS section of PI (for example, a list of strong CYP3A inhibitors). Further, participants noted that, for certain drugs with uncommon or unique DI mechanisms, it might be useful to reference all known interacting drugs within a drug class in PI because the information might not be readily accessible in other resources. However, given that multiple new drugs are approved every year and DI information is updated for many drugs in the postmarketing setting, the list of interacting drugs within a class in PI can become outdated. Some participants stated that HCPs could misinterpret interacting drug examples included in the DRUG INTERACTIONS section because they might incorrectly assume that lists are comprehensive within that class. Some participants suggested that while listing all possible DI examples within in class in PI may be impractical, a list of frequently co-administered drugs within a class which might cause DIs might be helpful. However, participants added that it might be challenging to determine and track changes among frequently co-administered drugs. Other participants suggested that because the seriousness of DIs frequently depends on the therapeutic context and patient population, HCPs might benefit from referring to examples in resources other than PI, especially resources tailored to their practice area. Including a comprehensive list of interacting drug examples within a drug class can also unnecessarily increase the length and density of DI information within PI, which might reduce readability. Furthermore, examples of interacting drugs within a class are often not updated or are included inconsistently in PI, and are readily available in other drug information resources. The majority of participants preferred including text in the PI that contain a link to an FDA website of vetted interacting drug examples within a drug class without including any examples of interacting drugs in PI. Few participants preferred including a complete list of FDA-vetted examples within a

class, whereas others preferred including only a few representative examples within a class in PI.

Some participants suggested that links within PI to additional non-essential contextual information in the application or publicly available FDA reviews on Drugs@FDA might reduce excessive DI information and redundancy while providing supplemental information.

## *Format*

The format in which DI information is presented in PI also impacts its utility. Participants strongly suggested including succinct and actionable DI information in tables or lists, as well as ordering DI information by seriousness or severity. A few participants suggested listing DI information alphabetically. Some participants suggested grouping DI information in the DRUG INTERACTIONS section by clinical effects (for example, 7.1 Life-Threatening Drug Interactions, 7.2 Serious But Not Life-Threatening Drug Interactions, 7.3 Other Clinically Significant Drug Interactions). Participants also indicated that tables are preferred when there are more than five DIs in the DRUG INTERACTIONS section or if DI information is complex.

Some participants favored including all DI-related information in one section of PI. Such a section might include practical instructions for preventing and managing clinically significant DIs (including dosage modifications due to DIs and contraindications to use with other drugs or foods); descriptions of clinically significant DIs, DI mechanisms, DI clinical effects; and descriptions and results of negative and positive DI studies. However, other participants recommended that DI information be distributed in different parts of the labeling because different sections are used by different stakeholders. Participants also considered whether publishing PI in three versions—including versions for HCPs, for patients, and for comprehensive reference—might best address format, length, and different end-user needs.

Workshop participants provided several additional recommendations related to format and organization of DI information in the PI:

- Graphics within PI should be purposeful and clear and indicate values and scales to improve utility. For example, participants indicated that reading forest plots on a log scale is difficult.

- When the frequency of DI-related adverse reactions is described, both relative and absolute increases in frequency should be indicated.

Participants recommended using terms in the PI such as "prescribers", "healthcare providers", or "healthcare practitioners" instead of "physicians" when DI information is relevant to a broad group of HCPs.

Human factors research can inform efforts to reformat PI so that PI applies to varied HCPs and their clinical practice. For example, some HCPs might more frequently search electronic text for key terms and might overlook relevant context when what workshop participants described as excessive DI information is included in PI.

The FDA can consider providing guidance to industry regarding the content and format of the DRUG INTERACTIONS section of PI to promote a consistent labeling approach. Guidance might discuss the meaning of terms. For example, the FDA can help further define and differentiate the terms "avoid concomitant use" and "concomitant use not recommended". However, developing standardized DI terms might require additional planning and consideration.

*Reliability*

Routine updating of PI by drug developers can ensure the utility of PI. HCPs and others expressed concern that DI information in PI might not be up-to-date and might not be consistent among other DI information resources. Participants noted that updating PI can address out-of-date information, particularly frequently updated information about metabolic or transporter system-based DIs. Updating PI might involve including new drug-food, drug-cannabis, drug-tobacco product, drug-dietary supplement, drug-condition, and drug-gene interaction information. The FDA can consider working with industry stakeholders to systematically update DI information in PI, perhaps for the 100 most frequently prescribed drugs.

## CONCLUSION

Based on the information provided by the participants in this workshop, the authors draw several overarching conclusions. The need for and use of DI information and tools developed to support HCPs in reducing the risk of DI's and managing them likely differ among HCPs. This can depend on the providers' roles and responsibilities, the patient populations they treat, and their preferences. Furthermore, the need for and use of DI information and tools depends on the health care settings and staff familiarity with DI information, facility resources, provider time constraints, and availability and uptake of HIT. These factors affect the availability, accessibility, and application of DI information.

The workshop participants indicated that drug developers, third-party drug information publishers, researchers, and regulators should work collaboratively, perhaps through a PPP, to advance clear and reliable communication of clinically significant DI information for a broad range of HCPs.  The FDA can encourage clear and concise presentation of clinically significant DI information in PI during the regulatory review process. The FDA can also continue to collaborate with drug developers, third-party drug information publishers, and HCPs as they create, use, and apply DI information in PI and other drug information resources. Further, drug developers and FDA can improve the communication of DI in the PI by recommending consistent format and organization, focusing on clinical relevance of DI information, including action-orientated elements where possible, hyperlinking to additional non-required information, and routinely updating DI information. Improving the communication of DI information through clear, up-to-date, and clinically relevant PI supports health care decision making across practice areas and helps to protect public health through safe and effective use of drugs.

## ACKNOWLEDGEMENTS

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