

ENHANCING INFORMATION ABOUT OLDER PRESCRIPTION DRUGS

CAN DRUG LABELING BE MODERNIZED?

INTRODUCTION

This white paper presents a policy proposal designed to enhance the quality and utility of information about older prescription drugs. The proposal outlined below is a “straw man” intended to generate discussion and foster creative solutions rather than assert any definitive answer to the problem of outdated prescription drug information. To that end, this white paper describes a potential pathway to bring labeling in line with high quality, real-world practice. However, it is widely known that, today, labeling is not the only, or most frequently used, source of up-to-date information used by practitioners. Therefore, this paper also presents a series of additional considerations for policymakers to contemplate. The scope of this proposal extends to older drugs, both brand and generic, that are 15 years past initial approval that have outdated labeling, either due to the absence of critical information about drug safety or effectiveness or the presence of inaccurate prescribing instructions.

An effort to modernize information about older prescription drugs can have a number of benefits. First, it can correct inaccurate information that is currently contained on some product labels, thereby averting a public health hazard. Second, it can enhance the dissemination of high quality information about approved drugs and lead to greater confidence in the use of drugs for indications beyond those that were initially approved. Third, it can remove an impediment to reimbursement in certain disease settings where labeling is currently used to guide payment decisions. And finally, it can establish greater clarity around the use of real-world evidence (RWE) to inform regulatory decision-making.

CONTRIBUTORS*

ANGELA GREEN
*Memorial Sloan Kettering
 Cancer Center*

LINDA HOUSE
Cancer Support Community

MICHAEL SHEA
Friends of Cancer Research

MARK STEWART
Friends of Cancer Research

JOSEPHINE TORRENTE
Hyman, Phelps & McNamara, P.C.

* In addition to the contributors listed, the FDA and Association for Accessible Medicines (AAM) reviewed and commented on this document.

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BACKGROUND ON PRESCRIPTION DRUG LABELING

A prescription drug product's labeling (also known as the "professional labeling" or "package insert") is a compilation of information about the drug product that is written for a health care practitioner audience.¹ Federal regulations state that labeling must contain "a summary of the essential scientific information needed for the safe and effective use of the drug," and that it must be "informative and accurate."² The content of labeling is written by drug manufacturers, but must be approved by the Food and Drug Administration (FDA) to ensure that it meets standards laid out in regulations.³

Under the 1984 Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act (FDCA), generic drug labeling necessarily relies on the brand name drug labeling as a matter of product approval. The Hatch-Waxman Amendments established the modern generic drug industry and required "sameness" for generics with the brand-name drug counterpart in all material respects. The statute mandates that generic drug products have the same active ingredients, strength, dosage, indications, and safety labeling as the reference drug. In fact, the Hatch-Waxman statute's whole premise is that generic drugs are materially indistinguishable from their brand-name counterparts, and so naturally must bear labeling that "is the same as the labeling approved for the [brand-name] drug" on which the generic product's approval is based.⁴ In enacting the Hatch-Waxman Amendments, Congress provided that FDA cannot approve an abbreviated new drug application (ANDA) if, with certain exceptions not relevant to this paper (e.g., patent carve-outs), the labeling proposed for the generic drug is not the same as the labeling approved for the listed drug.⁵ Those requirements subsequently were incorporated into FDA's regulations.⁶

When it is kept up to date, labeling represents the most authoritative drug-related information that is available to prescribers. However, for both brand name as well as generic drugs, labeling often falls out of date when new information emerges in the post-market setting. When sections of FDA-approved labeling become outdated they may lose value for prescribers and fail to communicate essential information about drugs to patients and physicians. In such cases, and even if labeling is kept up to date, prescribers routinely use other information such as peer-reviewed treatment guidelines in making decisions for patients.

Older drugs may be particularly susceptible to outdated product labeling, especially with regard to the "effectiveness" portions of labeling, including information relating to dosage and clinical studies. Both brand name and generic drug companies have an ongoing responsibility to report safety information to FDA, and the Agency has the authority to order changes relating to new safety information for both brand name and generic drugs.⁷ Manufacturers of products that will soon lose or have already lost marketing exclusivity or patent protection often lack an incentive to maintain up-to-date labeling actively. In some cases, brand name manufacturers of older drugs will voluntarily withdraw their products from the market, leaving only generic manufacturers (if generic versions of the drug exist) to maintain labeling. However, some parts of

FDA-approved labeling routinely fall out of date even when products are still being actively marketed by the innovator company. The result is that most older drugs have aspects of FDA-approved labeling that need to be modernized to prevent the dissemination of incorrect information and to enable the communication of information pertinent to safe and effective prescribing.

BACKGROUND ON ADDITIONAL SOURCES OF INFORMATION USED BY PRACTITIONERS

It is important to acknowledge that there are many sources of information about medicines upon which prescribers routinely rely for patient care, especially for oncology drugs. Especially once drugs have been on the market for longer periods of time, prescribers turn to high quality sources of evidence beyond the FDA-approved labeling. These sources include:

- **Clinical practice guidelines and compendia.** Specialty societies and evidence-based practice organizations synthesize uses of drugs in areas such as oncology where therapies change rapidly. For example, the development of the National Comprehensive Cancer Network (NCCN) Guidelines “is an ongoing and iterative process, which is based on a critical review of the best available evidence and derivation of recommendations by a multidisciplinary panel of experts in the field of cancer.”⁸ According to NCCN, “Because new data are published continuously, it is essential that the NCCN Guidelines also be continuously updated and revised to reflect new data and clinical information that may add to or alter current clinical practice standards.”⁹
- **Peer-reviewed medical journal articles.** In recognition of their potential public health value to prescribers, FDA has promulgated guidance on manufacturer dissemination of peer-reviewed medical journal articles.¹⁰
- **Real world evidence.** FDA has recently noted that “[t]he incorporation of ‘real-world evidence’—that is, evidence derived from data gathered from actual patient experiences, in all their diversity— in many ways represents an important step toward a fundamentally better understanding of states of disease and health.”¹¹

Thus, aside from FDA-approved labeling, there are other sources of information that aid prescribers in making evidence-based treatment decisions.

SCOPE OF THIS WHITE PAPER

The proposal outlined in this white paper is intended to facilitate practitioner access to enhanced information about drugs initially approved at least 15 years ago (referred to as “older drugs” in this paper). The proposal is intended to apply to the following scenarios involving these older drugs:

- 1 The NDA for an older drug is still active but the drug’s labeling is missing critical information about drug safety or effectiveness or contains incorrect prescribing instructions.
- 2 The NDA for an older drug has been withdrawn or discontinued for reasons other than safety or effectiveness.

WHY LABELING FALLS OUT-OF-DATE

Given the speed with which new, clinically-relevant information emerges in the post-market setting, it is impossible for approved labeling to be perfectly aligned with high quality real-world practice. However, there are many circumstances in which information that is essential to the safe and effective use of prescription drugs remains absent from labeling years after that information has been identified. Some of the reasons for why labeling may fall out of date are listed below.

- **Sponsor-initiated labeling updates.** With the exception of certain safety updates that the FDA can require manufacturers to make under the Food and Drug Administration Amendments Act of 2007 (FDAAA),¹² many types of labeling changes are made at a drug manufacturer’s discretion. For example, new indications are generally added to labeling only if a drug manufacturer decides to pursue marketing authorization in a new treatment setting.¹³ Factors such as the cost of preparing supplemental applications and the presence of generic competition may erode incentives for manufacturers to update labeling in a proactive manner.
- **Perceptions about the quality of post-market evidence.** The source of new evidence about a drug will often predict whether a drug manufacturer will submit a supplement to incorporate that evidence into labeling. Studies in the published literature to which a drug manufacturer does not have a right of reference, rather than manufacturer-sponsored studies, may serve as evidence supporting an application. However, there may be concerns that the quality of evidence from the literature is not high enough to support marketing approval. The regulatory standard for approval is the same for new drug applications and supplements.

- **Healthcare providers obtain information from other high-quality sources.** As discussed previously, there is a recognition by some practitioners that there may be other sources of information that synthesize clinical data, such as peer reviewed literature and practice guidelines, that are outside of FDA-approved labeling.
- **Withdrawal or discontinuation of a New Drug Application.** A brand name drug's manufacturer may withdraw a drug from the market if the cost of continued expenditures is not financially sound or consistent with corporate responsibility. When a drug has been withdrawn, its manufacturer is no longer involved in maintaining product labeling. Such withdrawals often take place if a drug has lost significant market share to generic competitors. The FDA will allow generic versions of a withdrawn drug to continue to be marketed if the agency finds that the drug was not withdrawn for reasons of safety or effectiveness.¹⁴ Confusion then arises over how generic versions of a withdrawn drug can maintain updated labeling, given the statutory requirement that a generic product must have the "same" labeling as the generic's reference listed drug (RLD).¹⁵
- **Compendia-based reimbursement.** A Medicare policy dating back to 1993 permits reimbursement of an off-label use of a cancer drug if that use is deemed medically accepted by one or more federally-designated compendia.¹⁶ Unlike many other conditions, where reimbursement is closely tied to approved labeling, special accommodation was made in oncology due to the severity of the disease, the time-sensitive nature of treatment decisions, and the fact that many anti-cancer agents have activity in multiple cancer types, but may only be approved for a portion.¹⁷ The resulting compendia-based reimbursement paradigm in oncology has enabled Medicare coverage of drugs for indications separate from their initial FDA approval. This program circumvents regulatory delays and drug manufacturer inaction to optimize patient access to cancer care. However, some have raised concerns that the current reimbursement scheme in oncology has caused an increase in the amount of uncertainty about the evidence supporting drug use generally, due to a lack of transparency and consistency among compendia.^{18, 19}

THE PUBLIC HEALTH IMPACT OF OUTDATED LABELING

Maintaining authoritative sources of information about prescription drugs, including FDA-approved labeling, is an important public health objective. When such labeling becomes outdated it loses its value for prescribers and inhibits the FDA's ability to validate accurate and reliable information about drugs to patients and physicians and may serve as the conduit of incorrect information.

- **Outdated labeling prevents important information from reaching prescribers.** Labeling is the FDA's primary means of validating information about drugs, and in some cases, it is updated with new urgent information about drug safety. Due to perceptions that labeling is outdated, prescribers may fail to consult labeling, missing important updates such as black box warnings. This was seen in the case of cisapride, a drug used to treat symptoms of nighttime heartburn, when a revised label warning of life-threatening adverse events did not change prescribing behavior.²⁰ If such information is not gleaned in FDA-approved labeling, it is important for other sources of information to capture it.
- **Outdated labeling contributes to the dissemination of incorrect information.** The information contained in approved labeling is ingrained into medical decision-making: it frequently informs clinical practice guidelines, payment decisions, decision support in electronic health records, and physician teaching materials. The failure to maintain accurate labeling may result in the spread of such information to other decision-making resources.
- **Outdated labeling may decrease reliance on high quality information.** As labeling falls out of date, its status as a useful resource may decline, causing prescribers to rely instead on other sources of information. Over-reliance on sources other than labeling, such as compendia, may result in misplaced confidence in some off-label uses. While compendia recommend many strongly-supported uses of drugs, they have also been shown to recommend uses that are supported by far less rigorous evidence.²¹
- **Outdated labeling hinders communication of combination and repurposed products.** Many older drug products whose labeling has fallen out of date are part of combination regimens with newer agents. The inclusion of a combination therapy on one product's label but not another's may lead to prescriber confusion. Similarly, there is a low likelihood that repurposed uses of older drugs will be incorporated onto product labeling.
- **The number of drugs with outdated labeling will increase in coming years.** The number of drugs with outdated labeling will likely increase as manufacturers choose to voluntarily withdraw their products from the market. In many cases, generic versions of those drugs remain available, leading to confusion over how to maintain up-to-date labeling in the absence of a reference listed drug. As of 2013, there were over 430 cases of approved drugs for which no brand-name product remains on the market.²²

CURRENT REGULATORY PATHWAYS TO UPDATE LABELING

The following section outlines current regulatory pathways for drug manufacturers to update product labeling after a product has been approved.

Prior Approval Supplements²³

Innovator drug manufacturers seeking to make a change to product labeling for their own approved drug must submit a supplemental new drug application (sNDA) to the FDA. A sNDA can come in the form of a Prior Approval Supplement (PAS) or a Changes Being Effected (CBE) supplement. The type of supplement that should be submitted depends on the magnitude of the intended labeling change. The FDA defines a “major” change as one “that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.” The Agency defines a “moderate” change as one that has “a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.”

- **Major changes to labeling are required to be submitted to the FDA through a PAS.** The FDA must review the changes requested in a PAS before the applicant can implement the requested changes. The following changes to labeling are considered major changes: the addition of new indications; the addition of clinical pharmacology data; the addition of pharmacoeconomic claims; or the addition of claims of superiority to another drug product.
- **Moderate changes to labeling are required to be submitted to the FDA through a CBE supplement.** Unlike a PAS, a CBE supplement does not require prior approval from the FDA before a change can be implemented. Moderate changes to labeling that may be submitted through a CBE include: the addition of an adverse event; the addition of a precaution arising out of a post-marketing study; or the clarification of the administration statement to ensure proper administration of the drug product.

The 505(b)(2) Pathway—“Literature-based” 505(b)(2)s

A 505(b)(2) application is a type of new drug application “where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference.”²⁴ Both innovator and generic companies can avail themselves of this type of application. The 505(b)(2) pathway originated in the 1984 Hatch-Waxman Amendments, which also created the 505(j) pathway for ANDAs. The central component of the 505(b)(2) pathway is that it permits the FDA to rely for approval of an NDA on data not developed by the applicant. This is in direct contrast to the traditional 505(b)(1) pathway, which is used by manufacturers that have full right of reference to the underlying data in the application.

In some cases, a manufacturer can add new information to product labeling by submitting a 505(b)(2) new drug application. The manufacturer can do this by submitting a “literature-based 505(b)(2),” which relies in part on clinical evidence from published literature to which the manufacturer does not have a right of reference. A manufacturer may submit a literature-based 505(b)(2) to support a number of aspects of the

application, including any of the following: a new dosing regimen, a new combination product, or a new indication for a previously approved drug. In the same manner, a generic drug applicant can add information to its labeling by submitting a 505(b)(2) supplement to its ANDA.

LIMITATIONS OF EXISTING PATHWAYS

Despite the mechanisms that currently exist for drug manufacturers to revise product labeling, sponsors do not always keep the labeling for many drugs up to date. In particular, existing pathways rely on sponsors to incorporate new information onto the labeling of older products, but those sponsors have either lost interest in maintaining product labeling or have exited the market altogether.

- **Current pathways may be too resource intensive for sponsors of older drug products.** Sponsors of older drug products who lack incentives to update labeling may view existing pathways to update labeling as too burdensome to warrant expenditure of the substantial resources needed to submit supplements.
- **Published literature is rarely used to support new drug applications.** The 505(b)(2) pathway exists to allow manufacturers to add indications and other information to product labels using published literature. However, it is rarely used; a recent study found that approximately 3% of 505(b)(2) applications are literature based.²⁵
- **No clear pathway exists to update the labeling of drugs with withdrawn NDAs.** When a drug product has been withdrawn, the product's manufacturer no longer has any mechanism for maintaining product labeling. Generic products relying for approval on an NDA that has been withdrawn are generally required under current law to have the same labeling as the reference product, despite the fact that the reference product's labeling has become static. In many cases, no clear pathway exists for these generic products to undergo the steps necessary to bring their labeling up to date. While the 505(b)(2) pathway is available to generic applicants it may be outside of their business model and come with additional responsibilities that are unpalatable.

PROPOSED APPROACH TO UPDATE LABELING

The following proposal seeks to facilitate timely labeling updates by lowering the barriers to supplemental new drug applications. Since one of the primary reasons labeling becomes outdated is limited incentives for manufacturers to update labels once innovator exclusivity either has expired or is close to expiring, this proposal seeks to provide manufacturers with the raw materials to submit supplemental applications and thereby make the submission of such applications less burdensome. In addition, this proposal provides a novel method of enabling generic manufacturers to update product labeling in cases where the brand name reference listed drug that the generic product relies upon has been withdrawn from the market. In such circumstances, it is essential that FDA manage the review of new clinical data and maintain the sameness requirement, whereby all generic labeling changes at once after an FDA order.

STEP 1**FDA IDENTIFIES PRODUCTS THAT MAY HAVE OUTDATED LABELS**

The FDA may identify one or more drug products whose labeling is missing critical information about drug safety or effectiveness or includes outmoded prescribing instructions.

STEP 2:**SPONSOR AGREEMENT**

The FDA will notify the sponsor(s) of drugs identified in Step 1 and proceed if agreement to pursue revised labeling is obtained. Where drugs identified in Step 1 have an active or discontinued NDA, the sponsor referred to in this step is the holder of the RLD NDA; where the RLD has been withdrawn, the sponsor(s) referred to in this step is/are one or more ANDA holder(s).

STEP 3:**FDA WORKS WITH STAKEHOLDERS TO REVIEW AVAILABLE POST-MARKET EVIDENCE**

The FDA may enter into cooperative agreements or contracts with private entities to review the available evidence concerning drugs identified in Step 1. The Agency may seek public input concerning such evidence (including, as determined appropriate by the Secretary, holding public meetings), and should seek input from each sponsor of the approved application for such drug.

STEP 4:**FDA DETERMINES WHETHER AVAILABLE EVIDENCE MEETS EXISTING STANDARDS**

The FDA may determine, with respect to a drug identified in Step 1, whether the evidence reviewed in Step 3 is sufficient to meet existing regulatory standards for revising the labeling of the drug.

STEP 5:**INITIATION OF UPDATE PROCESS PER FEDERAL REGISTER NOTICE OR OTHER COMMUNICATION**

The FDA publishes a Federal Register notice or other communication that:

- Summarizes the findings supporting the determination of the Agency that the available evidence is sufficient to meet the standards under section 505 of the FDCA for amending the labeling of the drug as an additional indication for the drug;
- States the modifications to the labeling that should be made;
- Describes the process under Step 6 for approving modifications to the labeling of the drug.

STEP 6:

SUBMISSION OF SUPPLEMENTAL DRUG APPLICATION PER FEDERAL REGISTER NOTICE OR OTHER COMMUNICATION

The sponsor of a selected drug in Step 1 may submit a supplemental application to the FDA that includes a statement that such application is submitted in response to a notice referred to in Step 5; and which also states that it seeks to modify the labeling of the drug in accordance with the statement of the FDA in the relevant notice. The following three scenarios involving supplemental applications are envisioned:

- ❶ If the NDA for a drug identified in Step 1 has not been withdrawn and the manufacturing of such drug has not been discontinued, a supplemental new drug application may be submitted by the holder of the NDA.
- ❷ If the NDA for a drug identified in Step 1 has not been withdrawn, but the manufacturing of such drug has been discontinued for other than safety or effectiveness reasons, a supplemental new drug application may be submitted by the holder of the NDA.
- ❸ If the NDA for a drug identified in Step 1 has been withdrawn for other than safety or effectiveness reasons, a supplemental new drug application may be submitted under Section 505(b)(2) by the sponsor of a generic version of such drug. Following the submission of the supplement, the FDA would request that any other generic products relying on the same withdrawn RLD amend their labeling to conform to the changes made in supplement.

CONSIDERATIONS FOR POLICYMAKERS

As mentioned in the introduction to this white paper, the proposal outlined in this document is intended to serve as a "straw man" to generate discussion around the topic of outdated labeling. There are existing unanswered questions regarding the proposal, which policymakers should contemplate moving forward.

- **Avoid undercutting the current sNDA process.** How can a program to facilitate updated product labeling avoid the unintended consequence of undercutting the current sNDA process? In other words, if the FDA facilitates labeling updates for certain older drugs, will it lower the incentive for manufactures of newer products to submit labeling updates through sNDAs?
- **Decrease the regulatory burdens for sponsors to participate in labeling updates.** To what degree would the sponsors of brand name drugs nearing the end of exclusivity or generic drugs be willing to submit supplements to update product labeling? What impediments exist? Could a new incentive structure for supplements remove these impediments?

- **Establish guardrails to protect reimbursement of off-label use.** In order to be successful, a program to update outdated labeling will need to avoid the unintended consequence of motivating payers to end compendia-based reimbursement. What guardrails can be established to safeguard the payment of off-label use?
- **Maintain the same labeling for the RLD and all versions of the generic drug.** The Hatch-Waxman Amendments require the labeling of all generic drugs to be the same as the RLD. How will FDA ensure that the RLD and all versions of the generic drug remain the same at all times in order to avoid prescriber confusion?
- **Consideration of additional policy options.** In the event that the proposal outlined in this white paper is infeasible, alternative policy proposals need to be developed. In addition to labeling updates, FDA could partner with evidence-based practitioner groups and medical journals to serve as a consolidator and validator of high quality clinical trials and real-world evidence. This would allow the FDA to evaluate clinical evidence in cases where sponsors choose not to update the non-safety portions of the labeling. Policymakers could also consider options to allow the FDA to publish, through the Federal Register or otherwise, corrections to outdated labeling that could then be communicated directly to clinicians.

APPENDIX
 OUTDATED LABELING CASE STUDY: CISPLATIN

Cisplatin is a platinum-based chemotherapy originally approved in 1978. It is now off patent and is marketed widely by a number of separate generic manufacturers. The new drug application (NDA) for the reference listed drug (RLD) has been discontinued. As a result, generic cisplatin, which is used in dozens of treatment regimens for both solid tumors and hematologic malignancies, has outdated labeling that is unlikely to be revised. A comparison of the current labeling for generic cisplatin and recommended preferred uses in clinical practice guidelines highlights the divergence between current labeling and real-world practice.

Appendix Figure 1. Comparison of Most Recent Cisplatin Labeling and NCCN Category 1 Uses of Cisplatin

Tumor setting	FDA-Approved Uses on Labeling	NCCN-Recommended Preferred Category 1 Uses	Number of NCCN Preferred Category 1 Uses
Bladder	✓	✓	5
Bone		✓	1
Cervical		✓	3
Esophageal and Esophagogastric Junction		✓	6
Gastric		✓	4
Head and Neck		✓	31
Hepatobiliary		✓	3
Malignant Pleural Mesothelioma		✓	3
NSCLC		✓	3
Ovarian	✓	✓	1
Small Cell Lung Cancer		✓	1
Testicular	✓	✓	5
Sources FDA-approved labeling for cisplatin available on FDA’s website, ANDA: 018057; Company: HQ SPCLT PHARMA; Link: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/018057s079lbl.pdf . NCCN Drugs and Biologics Compendium, entry for cisplatin.			

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- ² See 21 C.F.R. § 201.56
- ³ Lindstrom J. Sources of Drug Information: FDA-Approved Labeling and Other Official FDA Sources. *Dermatol Ther.* 2009;22:246-56.
- ⁴ 21 U.S.C. § 355(j)(2)(A)(v) (emphasis added).
- ⁵ See 21 U.S.C. §355(j)(4)(G); see also 21 U.S.C. §355(j)(2)(A)(v) (requiring that ANDAs include information to show the labeling proposed for the generic drug is the same as the labeling approved for the listed drug).
- ⁶ See 21 C.F.R. §314.94(a)(8) (providing that ANDAs must include labeling that is the same as labeling approved for listed drug and must include [a] statement that the applicant's proposed labeling ... is the same as the labeling of the reference listed drug except for differences annotated and explained under paragraph (a)(8)(iv) of this section).
- ⁷ See, e.g., U.S. FDA, FDA announces enhanced warnings for immediate-release opioid pain medications related to risks of misuse, abuse, addiction, overdose and death available at <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm491739.htm>.
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²³ The information in this section was drawn from the following guidance document: US Food and Drug Administration. Guidance for Industry: Changes to an Approved NDA or ANDA. April 2004.

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