

FDA Oncology Center of Excellence Project Renewal: Engaging the Oncology Community to Update Product Labeling for Older Oncology Drugs



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ABSTRACT

The FDA conducts independent reviews of scientific data obtained with investigational drug products to ensure that they are safe and effective. As a result of this process, FDA-approved product labeling is generated that is considered one of the most trusted sources of information for use of an approved drug. But FDA approval is only the beginning of the life cycle of a new drug; the first oncology drugs now have more than 7 decades of clinical experience in the postmarketing setting. Due, in part, to lack of incentives, some companies may not seek inclusion of new data, other than new safety information, in FDA-approved product labeling. Ensuring that product labeling provides adequate directions for use is important for all drugs, including older therapies that may form the

backbone of many standard combination regimens for pediatric and adult cancers. Project Renewal is an FDA Oncology Center of Excellence pilot program that leverages expertise from the clinical and scientific oncology communities to review published literature and generate a drug-specific product report summarizing data that may support updates to FDA-approved product labeling. This article provides a broad overview of Project Renewal's collaborative pilot process for identifying and assessing literature supporting potential labeling updates, while engaging the oncology community to increase awareness of FDA's evidentiary standards and deliberative processes used when considering the addition of new indications and dosing regimens to product labeling.

Introduction

The FDA-approved product labeling is a summary of information verified during FDA's independent, unbiased review of pharmaceutical quality, nonclinical and clinical pharmacology, and clinical study data. In 2006, the Physician Labeling Rule (PLR) was published, creating a consistent content and format for product labeling, including highlights of prescribing information, a table of contents, and 17 discrete sections intended to improve healthcare providers' ability to locate important prescribing information (**Table 1**). The most updated version of FDA product labeling for each approved product is available to the public online (1).

Following initial FDA approval, additional data are typically generated about a drug product in the postmarketing setting. New safety information must be included in product labeling by the drug company when it is essential for the safe and effective use of the drug or required by statute. FDA encourages additional updates to product labeling, including new uses and dosing regimens where appropriate

evidence exists, to ensure that labeled information is clinically meaningful and scientifically accurate. Independent of FDA, other deliberative bodies may identify new indications or modified uses for inclusion in drug compendia or clinical practice guidelines (e.g., Micromedex DrugDex, National Comprehensive Cancer Network, etc.), leading to disparities between compendia or guidelines and FDA-approved product labeling.

FDA and companies are obligated to ensure product labeling contains essential scientific information, is not misleading, and provides accurate directions for use. When a drug patent expires, generic drug products can be approved whose product labels are essentially copies of the reference listed drug (RLD, i.e. the innovator drug), with the exception of some information that may be left out if under another patent or exclusivity. Unfortunately, there are limited incentives for a company with a reference listed drug to update the FDA-approved product labeling when not required, such as to update content and format requirements, or add new uses or dosing regimens. This may be because off-label uses are often reimbursed by insurers for oncology drugs through compendia or guideline listings. Informed by discussion at a National Academies of Sciences, Engineering, and Medicine meeting in 2019 (2), the FDA Oncology Center of Excellence (OCE) has initiated a pilot program entitled Project Renewal, to address outdated labeling by assessing publicly available information that may support updates to FDA-approved product labeling (3).

Project Renewal is a collaboration that leverages clinical and scientific expertise in the oncology community to identify and assess publicly available data with the aim of improving product labeling for healthcare providers. This pilot program provides an opportunity for both external oncology experts and early-career scientists and oncologists to gain first-hand experience in the selection, curation, and evaluation of published information according to FDA's evidentiary requirements. In addition to assessing and updating the product

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Table 1. Comparison of “old” FDA labeling format and contemporary PLR format.

Old format ^a	PLR format ^b
Description	Highlights of prescribing information
Clinical pharmacology	Product names, other required information
Indications and usage	Boxed warning
Contraindications	Recent major changes
Warnings	Indications and usage
Precautions	Dosage and administration
Adverse reactions	Dosage forms and strengths
Drug abuse and dependence	Contraindications
Overdosage	Warnings and precautions
Dosage and administration	Adverse reactions
How supplied	Drug interactions
	Use in specific populations
Optional sections:	
Animal pharmacology and/or animal toxicology	Full prescribing information: contents
Clinical studies	Full prescribing information
References	Boxed warning
	(i) Indications and usage
	(ii) Dosage and administration
	(iii) Dosage forms and strengths
	(iv) Contraindications
	(v) Warnings and precautions
	(vi) Adverse reactions
	(vii) Drug interactions
	(viii) Use in specific populations
	(ix) Drug abuse and dependence
	(x) Overdosage
	(xi) Description
	(xii) Clinical pharmacology
	(xiii) Nonclinical toxicology
	(xiv) Clinical studies
	(xv) References
	(xvi) How supplied/storage and handling
	(xvii) Patient counseling information

Note: Appendix B: Guidance for industry labeling for human prescription drug and biological products - implementing the PLR content and format requirements (Feb 2013).

^aAs required by 21 CFR 201.56(e) and 201.80.

^bAs required by 21 CFR 201.56(d) and 201.57.

labeling of older cancer drugs based on their continuing importance in current clinical practice, Project Renewal provides transparency on FDA’s evaluation process and creates an opportunity to maximize the awareness and utility of drug labeling as an information resource for healthcare providers.

Assessing Current Stakeholder Knowledge and Product Labeling Use

One of the initial efforts of Project Renewal has been to better understand the oncology community’s knowledge and use of FDA product labeling. Project Renewal conducted structured interviews assessing healthcare providers’ level of access to and perceived utility of FDA-approved labeling compared with alternative sources of prescription drug information, such as Micromedex, UpToDate, and LexiComp. The survey included oncologists, advanced practice pro-

viders, registered nurses, and pharmacists, with engagement facilitated by collaborations with several professional organizations, including the American Association for Cancer Research (AACR), the American Society of Clinical Oncology (ASCO), the Association of Physician Assistants in Oncology, the Advanced Practitioner Society for Hematology and Oncology, and the Oncology Nursing Society. Thirty-nine individuals participated in one-on-one interviews. Interviewees ranged in experience from recent graduates of clinical training programs to healthcare providers with more than 35 years of experience in oncology. Practice settings varied from small physician-owned practices to major academic institutions and large integrated healthcare delivery systems located across a range of both remote and metropolitan geographic areas.

Results of these focused interviews supported that the sample of healthcare providers queried trusted the scientific integrity of FDA-approved product labeling and some relied on information in product labeling in their healthcare practice. Survey results suggested that providers were more likely to use FDA-approved product labeling for decision-making if they (i) lacked access to alternative sources of prescription drug information, (ii) practiced in a rural geographic location, or (iii) operated in a small practice of five or fewer oncologists. Although urban and larger oncology practices more frequently reported using alternative drug information sources, such as peer-reviewed published literature and subscription software (e.g., Micromedex and UpToDate), most subscription services obtain a large portion of their information from FDA-approved product labeling. Acknowledging the small sample size and other limitations inherent in a survey, results were supportive of the goal of Project Renewal: providing the most up-to-date information in FDA-approved product labeling where feasible.

What Project Renewal Is (and Is Not)

Project Renewal is an ambitious initiative to develop a standardized process of evaluating publicly available scientific information in the context of applicable laws, regulations, and guidance to determine whether revisions to FDA-approved product labeling are justified and needed. Project Renewal targets product labeling for a prioritized set of older oncology drugs, many of which are components of multi-agent, potentially curative regimens commonly used in the United States. This process primarily relies on publicly available information to support proposed product labeling changes, such as inclusion of contemporary dosing regimens for approved or new uses, new drug interactions, or use in patients with organ dysfunction. Project Renewal also provides an opportunity to ensure FDA product labeling is consistent with current FDA statutes, regulations, and guidance on content and format requirements for drug labeling, which can aid healthcare providers in efficiently navigating drug information.

The focus of Project Renewal is not to update product labeling with all possible or reported uses, but rather to identify currently unlabeled uses, which could be supported by published studies meeting FDA’s regulatory standard of substantial evidence of effectiveness (4–7). Project Renewal prioritizes oncology drugs with decades of clinical experience and postmarketing safety data and allows flexibility in the type and quantity of data used to conduct the benefit–risk assessment supporting a recommendation for inclusion of new uses and dosing regimens. Project Renewal will not be used to modify FDA-approved product labeling for drugs initially approved in the past 15 years. Such newer drugs have less accumulated safety experience. Furthermore, full clinical study reports with digital datasets are expected to be

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	Key activities
<p style="text-align: center;">A</p> <p style="text-align: center;">Candidate drug list (CDL) prioritization and off-label uses selection</p>	<ul style="list-style-type: none"> • Identify and prioritize potential oncology products into the CDL • Engage reference listed drug holders to confirm participation in Project Renewal • Identify and select potential off-label uses for each product
<p style="text-align: center;">B</p> <p style="text-align: center;">Stakeholder engagement</p>	<ul style="list-style-type: none"> • Identify and onboard research team members (RTMs) to evaluate evidence and discuss clinical use • Identify and onboard oncology fellows to support identifying and evaluating scientific literature
<p style="text-align: center;">C</p> <p style="text-align: center;">Labeling evidence evaluation process (LEEP)</p>	<ul style="list-style-type: none"> • Identify and evaluate publicly available literature on selected off-label use(s), summarized in a draft product report • Discuss clinical use and the evidence to support potential labeling updates through a series of LEEP meetings • Finalize the product report, summarizing available evidence and labeling considerations
<p style="text-align: center;">D</p> <p style="text-align: center;">Documentation and closeout</p>	<ul style="list-style-type: none"> • Deliver final product report and draft labeling considerations to FDA for independent review • Document labeling considerations and decisions in a repository • Capture lessons learned about Project Renewal processes for continual process improvement • Publish findings from labeling updates, as appropriate

Figure 1.
Key activities of the Project Renewal process.

available for regulatory review of new uses for drugs approved in the more contemporary drug development era.

Project Renewal is intended to improve outdated FDA product labeling. It does not aim to be, nor will it be, a replacement for drug compendia or clinical guidelines. It is not expected that Project Renewal will find sufficient published information to establish substantial evidence of effectiveness for all off-label uses that are included in the drug compendia. Project Renewal will not consider cost, payment, or coverage decisions in product labeling considerations.

The Project Renewal Process

Project Renewal includes four subprocesses:

- (i) Candidate drug list (CDL) prioritization and selection of off-label uses,
- (ii) Engagement with the oncology clinical and scientific community,
- (iii) Labeling evidence evaluation process (LEEP), and
- (iv) Documentation and closeout.

The Project Renewal process (Fig. 1) will be continually refined, standardized, and optimized by implementing lessons learned throughout the pilot phase and continuing into future operations. Following receipt of each Project Renewal product report, the FDA will perform an independent assessment and request submission of a supplemental application from the drug company.

CDL Prioritization and Selection of Off-label Uses

FDA independently identified and prioritized a list of marketed, off-patent oncology drug products to include in Project Renewal based on several criteria, including their importance in current clinical practice and time since initial approval (initial approval prior to 2005). Each company with the reference listed drug is contacted to obtain their agreement to participate in Project Renewal. The first seven oncology drug products included in Project Renewal are listed in Table 2.

To maximize FDA resources, Deloitte Consulting, LLC, provided contractor support for project management, process design and improvement, and formation of external scientific teams in collaboration with the AACR. For each selected drug product, Deloitte and external experts identify the need for labeling updates, including potential off-label uses or dosing regimens, for further evaluation based on the highest level of evidence category (e.g., level 1 or level A) across several compendia (8). Scientific literature providing evidence to support changes to the product labeling is identified through citations listed within compendia supplemented by a python-based

Table 2. Project renewal CDL.

Drugs selected for inclusion in Project Renewal: years 1 and 2	
Drug	Date of initial U.S. approval
Fluorouracil	April 1962
Cisplatin	December 1978
Capecitabine	April 1998
Daunorubicin	December 1979
Oxaliplatin	August 2002
Temozolomide	August 1999
Fludarabine	August 1974

tool that leverages PubMed and captures reports of both “positive” and “negative” studies. In addition to studies supporting new uses, published literature is identified for reassessment of the appropriateness of approved indications, dosing regimens, clinical safety information, and other aspects of product labeling (e.g., nonclinical information).

Engagement with the Oncology Clinical and Scientific Community

On the basis of potential off-label uses selected, and following a screening process to rule out relevant conflicts of interest, research team members (RTM) consisting of external oncologists, hematology and/or oncology fellows from Accreditation Council for Graduate Medical Education (ACGME)-accredited institutions, and other subject matter experts are assembled. Deloitte retained AACR as a key collaborator, leveraging the Association’s scientific expertise and network of basic, translational, and clinical science researchers.

One advantage of Project Renewal is that it facilitates interchange between FDA and external healthcare providers and scientists participating as RTMs. In collaboration with the AACR, the Project Renewal team identifies basic scientists and healthcare providers from academic institutions and professional organizations to provide feedback on the disease-specific standard of care for the identified off-label uses and to comprehensively review clinical data from published studies. A variety of external expertise is needed; RTMs include healthcare providers across oncology subspecialties, clinical pharmacologists, as well as other scientific experts. This broad-based approach allows the FDA to obtain the collective insight of healthcare providers and clinical pharmacologists both in evaluation of available data and how drugs are currently used in the clinical setting. All selected RTMs are educated on the Project Renewal process and provided with FDA-approved product labeling and off-label uses identified from the compendia review.

A limited number of structured interviews with practicing healthcare providers not participating as RTMs is conducted for each drug chosen for inclusion in Project Renewal to ensure diverse representation of opinions across geographic regions and oncology practice settings. These oncologists are selected by a third-party vendor who verifies their role as a healthcare provider through National Provider Identifier search. Interview questions are tailored for each product on the basis of the selected off-label uses identified. Interview results provide further insight into selected and potential additional indications, appropriateness of current dosing recommendations (including preparation and administration), safety signals, and other aspects of drug use not included in the FDA-approved product labeling. Structured interviews can reinforce, and in some cases, redirect the RTM’s research and evidence evaluation and can be used to identify nuances for each off-label use that may require additional evaluation.

LEEP

The LEEP consists of a series of meetings between FDA, RTMs, and Deloitte team members that occur over several months to address regulatory questions raised by RTMs and provide FDA’s advice on statutory and regulatory requirements. During this process, publicly available information, predominately peer-reviewed articles, is evaluated by RTMs to determine the strength of the evidence that may support inclusion of specific off-label uses, dosing regimens, and other safety and pharmacologic information into revised product labeling.

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With respect to new indications, the quality of individual studies is evaluated against the statutory and regulatory requirements further clarified in FDA guidance (6, 7). For instance, elements of an adequate and well-controlled trial are assessed, including the ability to isolate the treatment effect of the drug from other variables, control for potential sources of bias, and the presence or absence of robust, statistically significant, and clinically meaningful efficacy results that are based on objective endpoints used for the approval of cancer drugs (9).

The context of Project Renewal is unique in the quantity of available information, as drugs in the market for decades have a large amount of safety data and many published trials across multiple disease types. Importantly, evidence of effectiveness refers not just to the quality of an individual study, but to the quantity of available evidence across independent studies, which taken together, can provide substantial evidence based on the totality of data. Following literature review and input from RTMs, a drug-specific product report is generated by the Project Renewal team that includes a summary of the team's evaluation of the scientific evidence supporting specific product labeling considerations. At the close of LEEP, the product report and considerations for proposed product labeling revisions are submitted to FDA as one source of information to support their independent labeling review.

Documentation and Closeout

During documentation and closeout, important lessons learned and decisions made by RTMs and Deloitte are documented and indexed as the basis for continual process improvement over time. At the completion of the pilot program, a streamlined, repeatable process will be established that may allow for efficient scaling to multiple products per year. Standardization of this strategy is intended to result in a transparent and consistent approach to update the product labeling of older marketed, off-patent drug products based on current scientific knowledge.

Independent FDA Assessment and Request for Revised Product Labeling

After LEEP meetings, the product report (with considerations for revisions to the FDA-approved product labeling) is provided to FDA for its independent assessment of adherence to current labeling requirements and identification of limitations in the data. The product report is just one resource that the FDA will use during their independent labeling review, and FDA may include additional evidence when creating their final recommendations to ensure product labeling contains essential scientific information, is not misleading, and provides adequate directions for use. FDA then sends FDA-reviewed draft labeling to the reference listed drug company along with a letter requesting submission of a supplemental application. The company is encouraged to submit the FDA-reviewed product labeling, with or without further modifications, in their supplemental marketing application(s). The Project Renewal process is intended to facilitate submissions by companies, with a goal to reduce burden and maximize the efficiency of review of supplemental applications submitted to update older oncology product labeling.

Fostering Education

A lasting benefit of Project Renewal is the incorporation of health-care providers and scientists unfamiliar with regulatory review into

ongoing educational efforts between AACR and FDA in the area of regulatory science. Project Renewal RTMs play a critical role in evaluating the published information and provide practical perspective when interacting with FDA review staff. In developing the product report, RTMs receive a hands-on and in-depth experience with the regulatory assessment process, including a direct view of the manner in which FDA evaluates evidence. In addition, RTMs see how cancer clinical trials have evolved over the past decades, reinforcing the value of rigorous study design, isolating variables to ensure interpretability, and other key elements of modern clinical research. This unique experience supports broader efforts by OCE to introduce the clinical and scientific community to FDA's role in cancer drug development and evidence evaluation, complementing ongoing OCE collaboration with other organizations, including the NCI/Cancer Therapy Evaluation Program, the ASCO, the American Society of Hematology, and the Society for Immunotherapy of Cancer, among others (10).

Conclusion

FDA-approved product labeling is a trusted source of essential scientific and clinical information intended to ensure safe and effective use of drug products. FDA's OCE created Project Renewal to address barriers to updating older oncology product labeling to include more current prescribing information, while providing an opportunity to engage and educate the oncology community on product labeling. Project Renewal is an ambitious initiative, and FDA's OCE will reevaluate the program's impact and scalability after gaining experience with several oncology drug products. Initial feedback from those participating in Project Renewal indicates that the collaboration with external clinical experts, scientists, and postdoctoral trainees has created an engagement and educational experience that adds lasting value in and of itself.

Authors' Disclosures

L.B. Burke reports personal fees from Deloitte during the conduct of the study. G.D. Demetri reports personal fees from Deloitte Consulting during the conduct of the study and full disclosure of personal interactions outside this work as follows: scientific consultant with sponsored research to Dana-Farber (Bayer, Pfizer, Novartis, Epizyme, Roche/Genentech, Loxo Oncology, AbbVie, GlaxoSmithKline, Janssen, PharmaMar, Daiichi Sankyo, and Adaptimmune), scientific consultant (GlaxoSmithKline, EMD-Serono, Sanofi, ICON plc, MEDSCAPE, Mirati, WCG/Arsenal Capital, Polaris, MJ Hennessey/OncLive, C4 Therapeutics, Synlogic, and McCann Health), consultant/SAB member with minor equity holding (G1 Therapeutics, Caris Life Sciences, Erasca Pharmaceuticals, RELAY Therapeutics, Bessor Pharmaceuticals, Champions Biotechnology, Caprion/HistoGeneX, and Ikena Oncology), member of board of directors and scientific advisory board consultant with minor equity holding (Blueprint Medicines and Translate BIO), patents/royalties (Novartis royalty to Dana-Farber for use patent of imatinib in GIST), and nonfinancial interests (AACR Science Policy and Government Affairs Committee Chair and Alexandria Real Estate Equities). No disclosures were reported by the other authors.

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