Cross Labeling Oncology Drugs in Combination Regimens

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Marc Theoret at 301-796-4099, or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Cross Labeling Oncology Drugs in Combination Regimens Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

Drug[2] approvals in oncology often build on treatment effects by adding drugs to current regimens or by combining investigational drug products in a combination regimen,[3] creating new regimens with greater efficacy. Traditionally, applicants have not requested changes to the labeling of a previously approved drug to describe how to use that drug in a new regimen (*cross labeling*).[4] However, there has recently been an increasing number of applications[5] that have

[1] This guidance has been prepared by the Oncology Center of Excellence in cooperation with the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drug* or *drugs* include both human drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and therapeutic biological products licensed under section 351 of the Public Health Service Act.

[3] For the purpose of this guidance, a *combination regimen* refers to two or more drugs that are marketed separately, where at least one of the drugs has an approved indication for the combination based upon one or more adequate and well-controlled clinical trials. For the purposes of this guidance, codevelopment of two or more new investigational drugs for use in combination has the meaning described in the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination* (June 2013). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[4] Although this guidance uses the term *cross labeling* with respect to combination regimens that may include a drug and a biological product, this guidance is not intended to address the circumstances under which a drug and biological product labeled for such combined use constitute a cross-labeled combination product as described at 21 CFR 3.2(e)(3) and (4). Combination products governed by 21 CFR part 3 may have additional regulatory requirements not addressed in this guidance.

[5] The term *application* in this guidance refers to a new drug application under section 505 of the FD&C Act (21 U.S.C. 355) or a biologics license application under section 351 of the Public Health Service Act (42 U.S.C. 262) or an efficacy supplement to such application.

proposed cross labeling for oncology drug combination regimens. The purpose of this guidance is to describe FDA's current recommendations about including relevant information in labeling for oncology drugs[6] approved for use in a combination regimen, including important considerations for cross labeling of these drugs. This guidance does not address all issues that might arise relating to labeling for oncology drugs for use in a combination regimen. Applicants proposing cross labeling for oncology drug combination regimens should contact the review division for information on cross labeling of their individual products.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND AND SCOPE

For the purposes of this guidance, *cross labeling* is defined as inclusion of information in approved product labeling of two or more oncology drug products approved in a combination regimen for a specific indication. Cross labeling of two or more drugs administered in a combination regimen can provide clear, consistent, and accessible information to guide the safe and effective use of the cross-labeled drugs in a regimen for oncological disease or diseases. The intent of cross labeling is to provide information in product labeling for the drugs used in a combination regimen that is complementary and consistent, and not to include all of the same information in labeling for each drug in the combination regimen.

FDA frequently used overall response rates as the basis of approval for oncology drugs in the 1970s before moving to other outcome measures. Most oncology clinical trials continue to measure an overall response rate as a key outcome measure to assess effectiveness and inform clinical decision-making. As malignancies generally do not spontaneously regress, response rates can be attributed to the treatment intervention and not to the natural history of the disease. When FDA evaluates applications with cross labeling, the consistency of overall response rates being reported in historical and current clinical trials may enable an estimation of the contribution of the treatment effect for each drug in an oncology drug combination regimen.

The scope of this guidance is limited to oncology drugs for which (1) the applicant owns or has a right of reference[7] to the data demonstrating the safety and effectiveness of the new combination regimen for an oncological disease, (2) the applicant submits an application to the FDA that includes labeling for the use of the drug in this new combination regimen, and (3) the application provides evidence to support the contribution of the applicant's drug to the overall treatment effect of the combination regimen.

[6] For the purpose of this guidance, *oncology drugs* refer to drugs indicated for the treatment of malignant diseases.

[7] *Right of reference* has the same meaning as defined in 21 CFR 314.3.

The recommendations in this guidance are not intended for drugs outside its scope. Applicants in non-oncology therapeutic areas should contact the applicable review division if they wish to discuss whether cross labeling may be appropriate for their application.

III. PROCEDURES FOR CROSS LABELING APPLICATION SUBMISSIONS

A. Timing for Cross Labeling Regulatory Submissions

- Applicants should discuss the proposed content of the planned application, including their proposal for cross labeling a new oncology drug combination regimen in a pre-new drug application (NDA)/biologics license application (BLA) meeting or a pre-supplemental NDA/BLA (sNDA/sBLA) meeting.

- Ideally, cross labeling for each drug identified in the combination regimen will occur at the same time. However, approval of separate applications for cross-labeled drugs may occur in sequence, as applicants may have different timelines for submitting an application.

B. Regulatory Submissions

- Each applicant seeking cross labeling for a drug used in a combination regimen with one or more other drugs must submit an original application or efficacy supplement for cross labeling.[8]

- Applicants seeking cross labeling may reference data included in another application that demonstrate the treatment effect of the combination regimen if the applicant is the application holder for each drug in the combination regimen or if the applicant obtains a letter authorizing a right of reference from the appropriate application holder.

IV. CONTENT OF LABELING

This section of the guidance summarizes cross labeling considerations for selected sections in the Full Prescribing Information part of the labeling. This section is not intended to be exhaustive. An applicant who wishes to submit an application for cross labeling of an oncology drug approved for use in a combination regimen should consult with the appropriate oncology prescription drug review division about the specific issues raised by the application. For specific sections and subsections of labeling, applicants should refer to FDA's labeling regulations[9] and guidance recommendations.[10]

[8] See 21 CFR 314.50, 314.70, 601.2, and 601.12.

[9] See 21 CFR 201.56(d) and 201.57.

[10] See the guidance for industry *Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements* (February 2013).

For each new drug submitted in an original application as a separately packaged product intended for use in a combination regimen with one or more new drugs or with one or more approved drugs, the new drug's labeling should include information on the safe and effective use of the combination regimen, as noted below, as well as information that would be limited to the individual drug.[11]

For an approved drug, proposed changes to the approved labeling should include information on the safe and effective use of the drug in combination with the other drug or drugs in the combination regimen.

Below are recommendations that an applicant should consider when submitting an application for cross labeling.

- Indications and Usage, Dosage and Administration, and Clinical Studies sections:

  – Indications and Usage (Section 1): The indication for the combination regimen should be the same for all drugs approved for use in the combination regimen, except that (1) the applicant's drug should be listed first in the combination regimen and (2) the established name or proper name should be used for the other drugs in the combination regimen. This order and naming format should be used in all combination regimen-related labeling changes.

  – Dosage and Administration (Section 2): Although this section should identify the other drug or drugs in the combination regimen,[12] in general only the recommended dosage for the applicant's drug with respect to the combination regimen should be included. Dose modification instructions generally should be limited to the applicant's drug unless there are adverse reactions that would require dose modification for the other drug or drugs in a combination regimen. The preparation and administration information generally should be included only for the applicant's drug.

  – Clinical Studies (Section 14): The description of the clinical studies for the combination regimen should be similar in the labeling for all drugs for which a cross labeling application has been submitted.

- Information about the other drug or drugs in the combination regimen should be included in both the applicant drug's labeling and the labeling for the other drug or drugs in the regimen when the combination regimen raises significant new safety issues compared with use of the applicant's drug alone. Examples include but are not limited to the following:

[11] See the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination*.

[12] See the guidance for industry *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format* (March 2010).

  - Warnings and Precautions (Section 5): Should include information unique to the combination regimen, based on synergistic or novel clinically significant adverse reactions and/or risks. Information about warnings and precautions attributed solely to the other drug or drugs in the combination regimen usually should be omitted from the applicant's drug labeling.

  - Adverse Reactions (Section 6): The Clinical Trials Experience subsection for the cross-labeled combination regimen indication should include adverse reactions observed in the trial or trials supporting approval of this indication.

  - Patient Counseling Information (Section 17): Information regarding the combination regimen that a health care provider should convey to patients or caregivers should be limited to unique toxicities and unique preparation and administration instructions relevant to the combination regimen.

- The following sections generally should include only information relevant to the applicant's drug (and not the other drug or drugs used in the combination regimen); however, there may be exceptions (e.g., when the pharmacokinetics of one drug in a combination regimen are altered by another drug in the regimen).

  - Dosage Forms and Strengths (Section 3)
  - Contraindications (Section 4)
  - Drug Interactions (Section 7)
  - Use in Specific Populations (Section 8)
  - Overdosage (Section 10)
  - Description (Section 11)
  - Clinical Pharmacology (Section 12)
  - Nonclinical Toxicology (Section 13)
  - References (Section 15)
  - How Supplied/Storage and Handling (Section 16)