Cross Labeling Oncology Drugs in Combination Regimens

Guidance for Industry

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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TABLE OF CONTENTS

I. INTRODUCTION 1

II. BACKGROUND AND SCOPE 2

III. PROCEDURES FOR CROSS LABELING APPLICATION SUBMISSIONS 2

A. Timing for Cross Labeling Regulatory Submissions 2

B. Regulatory Submissions 3

IV. CONTENT OF LABELING 3

Contains Nonbinding Recommendations

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

This guidance represents 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 office responsible for this guidance as listed on the title page.

I. INTRODUCTION

Drug approvals in oncology often build on treatment effects by adding drugs[2] to current regimens or by combining investigational drug products in a combination regimen, creating new regimens with greater efficacy. 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. *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.

The purpose of this guidance is to describe the Food and Drug Administration's (FDA's) current recommendations about including relevant information in labeling for oncology drugs[3] 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. This guidance also does not address circumstances in which a drug product and a biological product packaged separately constitute a cross-labeled combination product as defined in 21 CFR 3.2(e).

[1] This guidance has been prepared by the Oncology Center of Excellence in cooperation with the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) 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. 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. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

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

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

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; the intent is not to include all of the same information in labeling for each drug in the combination regimen.

The scope of this guidance is limited to oncology drugs for which (1) the applicant owns or has a right of reference[4,5] to the data demonstrating the safety and effectiveness of the new combination regimen for treatment of an oncological disease, (2) the applicant submits an application to 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.

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 the evidence establishing the contribution of each drug in the combination regimen, in their proposal for cross labeling a new oncology drug combination regimen in a pre-new drug application/biologics license application meeting or a pre-supplemental new drug application/biologics license application meeting.

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

[5] This guidance does not address use of the pathway described by section 505(b)(2) of the FD&C Act, which could facilitate cross labeling of two or more drug products regulated under the FD&C Act that are administered in a combination regimen. See the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999). When final, this guidance will represent the Agency's current thinking on this topic. There are certain regulatory considerations (e.g., patents and exclusivity) for applications submitted through the 505(b)(2) pathway, but discussion of those considerations is beyond the scope of this guidance.

- 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 their applications.

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.[6]

- Applicants seeking cross labeling may reference another application's data 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 of authorization authorizing a right of reference from the appropriate application holder.

  – The application that is being referenced by the applicant should already be filed by FDA.[7]

  – Applicants should annotate each section in their application that is being cross-referenced to another application.

IV. CONTENT OF LABELING

This section of the guidance summarizes cross labeling considerations for selected sections in the Full Prescribing Information. This section is not intended to be exhaustive. An applicant that 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 recommendations for specific sections and subsections of labeling, applicants should refer to FDA's Prescription Drug Labeling Resources website.[8]

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

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

[7] See, for example, 21 CFR 314.101, CBER SOPP 8401: Administrative Processing of Original Biologics License Applications (BLA) and New Drug Applications (NDA).

[8] See https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources.

of the combination regimen, as noted below, as well as information that would be limited to the individual drug.[9]

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.

In general, the brand or trade name should be used for the applicant's drug that is the subject of the original application, and the established name (for a biological product, the proper name) should be used for the other products 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: 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 (for a biological product, the 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 text, as appropriate.

  – DOSAGE AND ADMINISTRATION section:

    - Although this section should identify the other drug or drugs in the combination regimen,[10] in general, information should be limited to the recommended dosage for the applicant's drug as used in the combination regimen. Dosage information for other drugs in the combination regimen should be provided by statements that refer the reader to the Prescribing Information for the other drugs, as appropriate; however, if the combination regimen dosing is complex or if the Prescribing Information for the other drugs does not contain the necessary dosing information, the recommended dosages of each drug in the combination regimen should be specified in this section.

    - Dosage modification instructions generally should be limited to the applicant's drug unless there are adverse reactions *associated with the combination regimen* that would require dosage modifications for the other drug or drugs in the combination regimen that are not described in the Prescribing Information for the other drug or drugs.

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

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

    - The preparation and administration information generally should be included only for the applicant's drug.

  – CLINICAL STUDIES section: The clinical trial descriptions and results for the combination regimen should be consistent in the Prescribing Information for each cross-labeled drug in the combination regimen.

- Safety 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 that were not seen with the use of the applicant's drug alone. Examples include but are not limited to the following:

  – WARNINGS AND PRECAUTIONS section: This section should include information unique to the combination regimen, based on the potentiation or development of 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 should ordinarily not be included in the applicant's drug labeling.

  – ADVERSE REACTIONS section: The *Clinical Trials Experience* subsection should include adverse reactions observed in the trial or trials supporting approval of the cross-labeled combination regimen. In general, the percentage of subjects with a serious adverse reaction or fatal adverse reaction should be reported for those subjects treated with the combination regimen. The percentage of subjects treated with the combination regimen who required permanent discontinuation, dosage interruption, or dosage reduction should be reported, including specific information for the applicant's drug when dosage modification and data collection methodologies permit these determinations.

  – PATIENT COUNSELING INFORMATION section: 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).

  – BOXED WARNING (if applicable)
  – DOSAGE FORMS AND STRENGTHS
  – CONTRAINDICATIONS
  – DRUG INTERACTIONS
  – USE IN SPECIFIC POPULATIONS
  – OVERDOSAGE
  – DESCRIPTION

- CLINICAL PHARMACOLOGY
- NONCLINICAL TOXICOLOGY
- REFERENCES
- HOW SUPPLIED/STORAGE AND HANDLING