Guidance for Industry

Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

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

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Clinical/Medical

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TABLE OF CONTENTS

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I. INTRODUCTION

This guidance is the first in a planned series of cancer endpoint guidances. It provides recommendations to applicants on endpoints for cancer clinical trials submitted to the Food and Drug Administration (FDA) to support effectiveness claims in new drug applications (NDAs), biologics license applications (BLAs), or supplemental applications.[2] It also provides background information and discusses general regulatory principles. The endpoints discussed in this guidance are for drugs to treat patients with an existing cancer. This guidance does not address endpoints for drugs to prevent or decrease the incidence of cancer.

The FDA is developing guidance on oncology endpoints through a process that includes public workshops and discussions before the FDA's Oncologic Drugs Advisory Committee (ODAC).[3] Each subsequent guidance will focus on endpoints for specific cancer types (e.g., lung cancer, colon cancer) to support drug approval or labeling claims.

FDA's guidance documents, including this guidance, 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.

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[1] This guidance has been prepared by the Division of Drug Oncology Products and the Division of Biologic Oncology Products in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and biological products unless otherwise specified.

[3] Transcripts are available at http://www.fda.gov/cder/drug/cancer_endpoints/default.htm.

II. BACKGROUND

Clinical trial endpoints serve different purposes. In conventional oncology drug development, early phase clinical trials evaluate safety and identify evidence of biological drug activity, such as tumor shrinkage. Endpoints for later phase efficacy studies commonly evaluate whether a drug provides a clinical benefit such as prolongation of survival or an improvement in symptoms. The following sections discuss the general regulatory requirements for efficacy and how they have influenced endpoint selection for the approval of cancer drugs. Later sections describe these endpoints in more detail and discuss whether they might serve as measures of disease activity or clinical benefit in various clinical settings.

A. Regulatory Requirements for Effectiveness

The requirement that new drugs show effectiveness is based on a 1962 amendment to the Federal Food, Drug, and Cosmetic Act. This law requires substantial evidence of effectiveness and specifies that this evidence must be derived from adequate and well-controlled clinical investigations. Similarly, the Public Health Service Act requires biological products to be safe, pure, and potent. Clinical benefits that have supported drug approval have included important clinical outcomes (e.g., increased survival, symptomatic improvement) but have also included effects on established surrogate endpoints (e.g., blood pressure, serum cholesterol).

The accelerated approval regulations (21 CFR part 314, subpart H and 21 CFR part 601, subpart E), promulgated in 1992, allow use of additional endpoints for approval of drugs or biological products that are intended to treat serious or life-threatening diseases and that either demonstrate an improvement over available therapy or provide therapy where none exists. In this setting, the FDA may grant approval based on an effect on a surrogate endpoint that is *reasonably likely* to predict clinical benefit ("based on epidemiologic, therapeutic, pathophysiologic, or other evidence"). Such surrogates are less well-established than surrogates in regular use, such as blood pressure or cholesterol for cardiovascular disease. A drug is approved under the accelerated approval regulations on condition that the manufacturer conducts clinical studies to verify and describe the actual clinical benefit. If the postmarketing studies fail to demonstrate clinical benefit or if the applicant does not demonstrate due diligence in conducting the required studies, the drug may be removed from the market under an expedited process. In the following discussion, the term *regular approval* denotes the longstanding route of drug approval based on the demonstration of clinical benefit. That term is distinguished from *accelerated approval*, which is associated with use of a surrogate endpoint that is reasonably likely to predict benefit.

The evidence critical for supporting drug approval, including the preferred number of clinical trials, is discussed in the guidance for industry *FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products*[4] and in the FDA Modernization Act of 1997.[5] In most

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

[5] http://www.fda.gov/cder/fdama/default.htm

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