TARGETED THERAPIES


FDA News Release: FDA approves Zelboraf and companion diagnostic test for late-stage skin cancer, August 17, 2011.

FDA News Release: FDA approves Xalkori with companion diagnostic for a type of late-stage lung cancer, August 26, 2011.

Department of Health and Human Services, Food and Drug Administration, Draft Guidance on Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination, December 2010

Department of Health and Human Services, Food and Drug Administration, Draft Guidance on In Vitro Companion Diagnostic Devices, July 14, 2011.
Targeted Cancer Therapies

Key Points

Targeted cancer therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules involved in tumor growth and progression (see Questions 1 and 2).

Because scientists call these specific molecules “molecular targets,” therapies that interfere with them are sometimes called “molecularly targeted drugs,” “molecularly targeted therapies,” or other similar names (see Question 1).

Targeted cancer therapies that have been approved for use in specific cancers include drugs that interfere with cell growth signaling or tumor blood vessel development, promote the specific death of cancer cells, stimulate the immune system to destroy specific cancer cells, and deliver toxic drugs to cancer cells (see Questions 4 and 5).

The National Cancer Institute’s Molecular Targets Laboratory is working to identify and evaluate molecular targets (see Question 8).

1. What are targeted cancer therapies?

Targeted cancer therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules involved in tumor growth and progression. Because scientists often call these molecules “molecular targets,” targeted cancer therapies are sometimes called “molecularly targeted drugs,” “molecularly targeted therapies,” or other similar names. By focusing on molecular and cellular changes that are specific to cancer, targeted cancer therapies may be more effective than other types of treatment, including chemotherapy and radiotherapy, and less harmful to normal cells.

Many targeted cancer therapies have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of specific types of cancer (see details in Questions 4 and 5). Others are being studied in clinical trials (research studies with people), and many more are in preclinical testing (research studies with animals).

Targeted cancer therapies are being studied for use alone, in combination with other targeted therapies, and in combination with other cancer treatments, such as chemotherapy.

2. How do targeted cancer therapies work?

Targeted cancer therapies interfere with cancer cell division (proliferation) and spread in different ways. Many of these therapies focus on proteins that are involved in cell signaling pathways, which form a complex communication system that governs basic cellular functions and activities, such as cell division, cell movement, cell responses to specific external stimuli, and even cell death. By blocking signals that tell cancer cells to grow and divide uncontrollably, targeted cancer therapies can help stop cancer progression and may induce cancer cell death through a process known as apoptosis. Other targeted therapies can cause cancer cell death directly, by specifically inducing apoptosis, or indirectly, by stimulating the immune system to recognize and destroy cancer cells and/or by delivering toxic substances directly to the cancer cells.

The development of targeted therapies, therefore, requires the identification of good targets—that is, targets that are known to play a key role in cancer cell growth and survival. (It is for this reason that targeted therapies are often referred to as the product of “rational drug design.”)

For example, most cases of chronic myeloid leukemia (CML) are caused by the formation of a gene called BCR-ABL. This gene is formed when pieces of chromosome 9 and chromosome 22 break off and trade places. One of the changed chromosomes resulting from this switch contains part of the ABL gene from chromosome 9 fused to part of the BCR gene from chromosome 22. The protein normally produced by the ABL gene (Abl) is a signaling molecule that plays an important role in controlling cell proliferation and usually must interact with other signaling molecules to be active. However, Abl signaling is always active in
The protein (Bcr-Abl) produced by the \textit{BCR-ABL} fusion gene. This activity promotes the continuous proliferation of CML cells. Therefore, Bcr-Abl represents a good molecule to target.

3. \textbf{How are targeted therapies developed?}

Once a target has been identified, a therapy must be developed. Most targeted therapies are either small-molecule drugs or \textit{monoclonal antibodies}. Small-molecule drugs are typically able to diffuse into cells and can act on targets that are found inside the cell. Most monoclonal antibodies cannot penetrate the cell’s \textit{plasma membrane} and are directed against targets that are outside cells or on the cell surface.

Candidates for small-molecule drugs are usually identified in studies known as drug screens—\textit{laboratory tests} that look at the effects of thousands of test compounds on a specific target, such as Bcr-Abl. The best candidates are then chemically modified to produce numerous closely related versions, and these are tested to identify the most effective and specific drugs.

Monoclonal antibodies, by contrast, are prepared first by immunizing animals (typically mice) with purified target molecules. The immunized animals will make many different types of antibodies against the target. Next, spleen cells, each of which makes only one type of antibody, are collected from the immunized animals and fused with myeloma cells. Cloning of these fused cells generates cultures of cells that produce large amounts of a single type of antibody, known as a monoclonal antibody. These antibodies are then tested to find the ones that react best with the target.

Before they can be used in humans, monoclonal antibodies are “humanized” by replacing as much of the animal portion of the antibody as possible with human portions. This is done through \textit{genetic engineering}. Humanizing is necessary to prevent the human immune system from recognizing the monoclonal antibody as “foreign” and destroying it before it has a chance to interact with and inactivate its target molecule.

4. \textbf{What was the first target for targeted cancer therapy?}

The first molecular target for targeted cancer therapy was the cellular \textit{receptor} for the female sex \textit{hormone estrogen}, which many \textit{breast cancers} require for growth. When estrogen binds to the \textit{estrogen receptor} (ER) inside cells, the resulting hormone-receptor complex activates the expression of specific genes, including genes involved in cell growth and proliferation. Research has shown that interfering with estrogen’s ability to stimulate the growth of breast cancer cells that have these receptors (ER-positive breast cancer cells) is an effective treatment approach.

Several drugs that interfere with estrogen binding to the ER have been approved by the FDA for the treatment of ER-positive breast cancer. Drugs called selective estrogen receptor modulators (SERMs), including \textit{tamoxifen} \textsuperscript{7} and \textit{toremifene} (Fareston\textsuperscript{®}) \textsuperscript{2}, bind to the ER and prevent estrogen binding. Another drug, \textit{fulvestrant} (Faslodex\textsuperscript{®}) \textsuperscript{3}, binds to the ER and promotes its destruction, thereby reducing ER levels inside cells.

\textit{Aromatase inhibitors} (AIs) are another class of targeted drugs that interfere with estrogen’s ability to promote the growth of ER-positive breast cancers. The \textit{enzyme} aromatase is necessary to produce estrogen in the body. Blocking the activity of aromatase lowers estrogen levels and inhibits the growth of cancers that need estrogen to grow. AIs are used mostly in women who have reached \textit{menopause} because the ovaries of \textit{premenopausal} women can produce enough aromatase to override the inhibition. Three AIs have been approved by the FDA for the treatment of ER-positive breast cancer: \textit{Anastrozole} (Arimidex\textsuperscript{®}) \textsuperscript{4}, \textit{exemestane} (Aromasin\textsuperscript{®}) \textsuperscript{3}, and \textit{letrozole} (Femara\textsuperscript{®}) \textsuperscript{4}.

5. \textbf{What are some other targeted therapies?}

Targeted cancer therapies have been developed that interfere with a variety of other cellular processes. FDA-approved targeted therapies are listed below:

Some targeted therapies block specific enzymes and growth factor receptors involved in cancer cell proliferation. These drugs are also called \textit{signal transduction} inhibitors.

\textit{Imatinib mesylate} (Gleevec\textsuperscript{®}) \textsuperscript{2} is approved to treat gastrointestinal stromal tumor (a rare cancer of the gastrointestinal tract), certain kinds of leukemia, dermatofibrosarcoma protuberans, myelodysplastic/myeloproliferative disorders, and systemic mastocytosis. The drug targets several members of a class of proteins called \textit{tyrosine kinase} enzymes that participate in signal transduction. These enzymes are overactive in some cancers, leading to uncontrolled growth. It is a small-molecule drug, which means that it can pass through cell membranes and reach targets inside the cell.
Dasatinib (Sprycel®) is approved to treat some patients with CML or acute lymphoblastic leukemia. The drug is a small-molecule inhibitor of several tyrosine kinase enzymes.

Nilotinib (Tasigna®) is approved to treat some patients with CML. The drug is another small-molecule tyrosine kinase inhibitor.

Trastuzumab (Herceptin®) is approved for the treatment of certain types of breast cancer as well as some types of gastric or gastroesophageal junction adenocarcinoma. The therapy is a monoclonal antibody that binds to the human epidermal growth factor receptor (HER-2). HER-2, a receptor with tyrosine kinase activity, is expressed at high levels in some breast cancers and also some other types of cancer. The mechanism by which trastuzumab acts is not completely understood, but one likely possibility is that by binding to HER-2 on the surface of tumor cells that express high levels of HER-2, it prevents HER-2 from sending growth-promoting signals. Trastuzumab may have other effects as well, such as inducing the immune system to attack cells that express high levels of HER-2.

Lapatinib (Tykerb®) is approved for the treatment of certain types of advanced or metastatic breast cancer. This small-molecule drug inhibits several tyrosine kinases, including the tyrosine kinase activity of HER-2. Lapatinib treatment prevents HER-2 signals from activating cell growth.

Gefitinib (Iressa®) is approved to treat patients with advanced non-small cell lung cancer. This small-molecule drug is restricted to use in patients who, in the opinion of their treating physician, are currently benefiting, or have previously benefited, from gefitinib treatment. Gefitinib inhibits the tyrosine kinase activity of the epidermal growth factor receptor (EGFR), which is overproduced by many types of cancer cells.

Erlotinib (Tarceva®) is approved to treat metastatic non-small cell lung cancer and pancreatic cancer that cannot be removed by surgery or has metastasized. This small-molecule drug inhibits the tyrosine kinase activity of EGFR.

Cetuximab (Erbitux®) is a monoclonal antibody that is approved for treating some patients with squamous cell carcinoma of the head and neck or colorectal cancer. The therapy binds to the external portion of EGFR, thereby preventing the receptor from being activated by growth signals, which may inhibit signal transduction and lead to antiproliferative effects.

Panitumumab (Vectibix®) is approved to treat some patients with metastatic colon cancer. This monoclonal antibody attaches to EGFR and prevents it from sending growth signals.

Temsirolimus (Torisel®) is approved to treat patients with advanced renal cell carcinoma. This small-molecule drug is a specific inhibitor of a serine/threonine kinase called mTOR that is activated in tumor cells and stimulates their growth and proliferation.

Everolimus (Afinitor®) is approved to treat patients with advanced kidney cancer whose disease has progressed after treatment with other therapies, patients with subependymal giant cell astrocytoma who also have tuberous sclerosis and are unable to have surgery, or patients with pancreatic neuroendocrine tumors that cannot be removed by surgery, are locally advanced, or have metastasized. This small-molecule drug binds to a protein called immunophilin FK binding protein-12, forming a complex that in turn binds to and inhibits the mTOR kinase.

Vandetanib (Zactima™) is approved to treat patients with metastatic medullary thyroid cancer who are ineligible for surgery. This small-molecule drug binds to and blocks the growth-promoting activity of several tyrosine kinase enzymes, including EGFR, several receptors for vascular endothelial growth factor receptor (VEGF), and RET.

Other targeted therapies modify the function of proteins that regulate gene expression and other cellular functions.

Vorinostat (Zolinza®) is approved for the treatment of cutaneous T-cell lymphoma (CTCL) that has persisted, progressed, or recurred during or after treatment with other medicines. This small-
molecule drug inhibits the activity of a group of enzymes called histone deacetylases (HDACs), which remove small chemical groups called acetyl groups from many different proteins, including proteins that regulate gene expression. By altering the acetylation of these proteins, HDAC inhibitors can induce tumor cell differentiation, cell cycle arrest, and apoptosis.

**Romidepsin (Istodax®)** is approved for the treatment of CTCL in patients who have received at least one prior systemic therapy. This small-molecule drug inhibits members of one class of HDACs and induces tumor cell apoptosis.

**Bexarotene (Targretin®)** is approved for the treatment of some patients with CTCL. This drug belongs to a class of compounds called retinoids, which are chemically related to vitamin A. Bexarotene binds selectively to, and thereby activates, retinoid X receptors. Once activated, these nuclear proteins act in concert with retinoic acid receptors to regulate the expression of genes that control cell growth, differentiation, survival, and death.

**Alitretinoin (Panretin®)** is approved for the treatment of cutaneous lesions in patients with AIDS-related Kaposi sarcoma. This retinoid binds to both retinoic acid receptors and retinoid X receptors.

**Tretinoin (Vesanoid®)** is approved for the induction of remission in certain patients with acute promyelocytic leukemia. This retinoid binds to and thereby activates retinoic acid receptors.

Some targeted therapies induce cancer cells to undergo apoptosis (cell death).

**Bortezomib (Velcade®)** is approved to treat some patients with multiple myeloma. The drug is also approved for the treatment of some patients with mantle cell lymphoma. Bortezomib causes cancer cells to die by interfering with the action of a large cellular structure called the proteasome, which degrades proteins. Proteasomes control the degradation of many proteins that regulate cell proliferation. By blocking this process, bortezomib causes cancer cells to die. Normal cells are affected too, but to a lesser extent.

**Pralatrexate (Folotyn®)** is approved for the treatment of some patients with peripheral T-cell lymphoma. Pralatrexate is an antifolate, which is a type of molecule that interferes with DNA synthesis. Other antifolates, such as methotrexate, are not considered targeted therapies because they interfere with DNA synthesis in all dividing cells. However, pralatrexate appears to selectively accumulate in cells that express RFC-1, a protein that may be overexpressed by some cancer cells.

Other targeted therapies block the growth of blood vessels to tumors (angiogenesis). To grow beyond a certain size, tumors must obtain a blood supply to get the oxygen and nutrients needed for continued growth. Treatments that interfere with angiogenesis may block tumor growth.

**Bevacizumab (Avastin®)** is a monoclonal antibody that is approved for the treatment of glioblastoma. The therapy is also approved for some patients with non-small cell lung cancer, metastatic breast cancer, metastatic colorectal cancer, and metastatic kidney cancer. Bevacizumab binds to VEGF and prevents it from interacting with receptors on endothelial cells, blocking a step that is necessary for the initiation of new blood vessel growth.

**Sorafenib (Nexavar®)** is a small-molecule inhibitor of tyrosine kinases that is approved for the treatment of advanced renal cell carcinoma and some cases of hepatocellular carcinoma. One of the kinases that sorafenib inhibits is involved in the signaling pathway that is initiated when VEGF binds to its receptors. As a result, new blood vessel development is halted. Sorafenib also blocks an enzyme that is involved in cell growth and division.

**Sunitinib (Sutent®)** is another small-molecule tyrosine kinase inhibitor that is approved for the treatment of patients with metastatic renal cell carcinoma, gastrointestinal stromal tumor that is not responding to imatinib, or pancreatic neuroendocrine tumors that cannot be removed by surgery, are locally advanced, or have metastasized. Sunitinib blocks kinases involved in VEGF signaling, thereby inhibiting angiogenesis and cell proliferation.
**Pazopanib (Votrient®)** is approved for the treatment of patients with advanced renal cell carcinoma. Pazopanib is a small-molecule inhibitor of several tyrosine kinases, including VEGF receptors, c-kit, and platelet-derived growth factor receptor.

Some targeted therapies act by helping the immune system to destroy cancer cells.

**Rituximab (Rituxan®)** is a monoclonal antibody that is approved to treat certain types of B-cell non-Hodgkin lymphoma and, when combined with other drugs, to treat chronic lymphocytic leukemia (CLL). The therapy recognizes a molecule called CD20 that is found on B cells. When rituximab binds to these cells, it triggers an immune response that results in their destruction. Rituximab may also induce apoptosis.

**Alemtuzumab (Campath®)** is approved to treat patients with B-cell CLL. The therapy is a monoclonal antibody directed against CD52, a protein found on the surface of normal and malignant B and T cells and many other cells of the immune system. Binding of alemtuzumab to CD52 triggers an immune response that destroys the cells.

**Otfatumub (Arzerra®)** is approved for the treatment of some patients with CLL that do not respond to treatment with fludarabine and alemtuzumab. This monoclonal antibody is directed against the B-cell CD20 cell surface antigen.

**Ipilimumab (Yervoy™)** is approved to treat patients with unresectable or metastatic melanoma. This monoclonal antibody is directed against cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), which is expressed on the surface of activated T cells as part of a “checkpoint” to prevent a runaway immune response. By inhibiting CTLA-4, ipilimumab stimulates the immune system to attack melanoma cells.

Another class of targeted therapies includes monoclonal antibodies that deliver toxic molecules to cancer cells specifically.

**Tositumomab and 131I-tositumomab (Bexxar®)** is approved to treat certain types of B-cell non-Hodgkin lymphoma. The therapy is a mixture of monoclonal antibodies that recognize the CD20 molecule. Some of the antibodies in the mixture are linked to a radioactive substance called iodine-131. The 131I-tositumomab component delivers radioactive energy to CD20-expressing B cells specifically, reducing collateral damage to normal cells. In addition, the binding of tositumomab to the CD20-expressing B cells triggers the immune system to destroy these cells.

**Ibritumomab tiuxetan (Zevalin®)** is approved to treat some patients with B-cell non-Hodgkin lymphoma. The therapy is a monoclonal antibody directed against CD20 that is linked to a molecule that can bind radioisotopes such as indium-111 or yttrium-90. The radiolabeled forms of Zevalin deliver a high dose of radioactivity to cells that express CD20.

**Denileukin diffitox (Ontak®)** is approved for the treatment of some patients with CTCL. Denileukin diffitox consists of interleukin-2 (IL-2) protein sequences fused to diphtheria toxin. The drug binds to cell surface IL-2 receptors, which are found on certain immune cells and some cancer cells, directing the cytotoxic action of the diphtheria toxin to these cells.

Cancer vaccines and gene therapy are often considered to be targeted therapies because they interfere with the growth of specific cancer cells. Information about these treatments can be found in the following National Cancer Institute (NCI) fact sheets, which are available online or by calling NCI’s Cancer Information Service (see below):

— Biological Therapies for Cancer includes information about monoclonal antibodies and cancer vaccines.

— Cancer Vaccines contains information on vaccines intended to treat cancer, as well as those intended to prevent it.

— Gene Therapy for Cancer discusses research with genetic material in developing cancer therapies, including risks, benefits, and ethical issues.
6. What impact will targeted therapies have on cancer treatment?

Targeted cancer therapies give doctors a better way to tailor cancer treatment, especially when a target is present in some but not all tumors of a particular type, as is the case for HER-2. Eventually, treatments may be individualized based on the unique set of molecular targets produced by the patient’s tumor. Targeted cancer therapies also hold the promise of being more selective for cancer cells than normal cells, thus harming fewer normal cells, reducing side effects, and improving quality of life.

Nevertheless, targeted therapies have some limitations. Chief among these is the potential for cells to develop resistance to them. In some patients who have developed resistance to imatinib, for example, a mutation in the BCR-ABL gene has arisen that changes the shape of the protein so that it no longer binds this drug as well. In most cases, another targeted therapy that could overcome this resistance is not available. It is for this reason that targeted therapies may work best in combination, either with other targeted therapies or with more traditional therapies.

7. Where can I find information about clinical trials of targeted therapies?

The list below provides links to active clinical trials of FDA-approved targeted therapies. Because trials begin and end regularly, it is possible that, at any given time, a particular drug will not have any trials available. If you are viewing this fact sheet online, drug names are links to search results for trials in NCI’s clinical trials database. For information about how to search the database, see “Help Using the NCI Clinical Trials Search Form.” The database includes all NCI-funded clinical trials and many other studies conducted by investigators at hospitals and medical centers in the United States and other countries around the world.

**Targeted Cancer Therapies Being Studied in Clinical Trials:**

- Alemtuzumab (Campath®)
- Alitretinoin (Panretin®)
- Anastrozole (Arimidex®)
- Bevacizumab (Avastin®)
- Bexarotene (Targretin®)
- Bortezomib (Velcade®)
- Cetuximab (Erbitux®)
- Dasatinib (Sprycel®)
- Denileukin diftitox (Ontak®)
- Erlotinib hydrochloride (Tarceva®)
- Everolimus (Afinitor®)
- Exemestane (Aromasin®)
- Fulvestrant (Faslodex®)
- Gefitinib (Iressa®)
- Ibritumomab tiuxetan (Zevalin®)
- Imatinib mesylate (Gleevec®)
- Ipilimumab (Yervoy™)
- Lapatinib ditosylate (Tykerb®)
- Letrozole (Femara®)
- Nilotinib (Tasigna®)
- Ofatumumab (Arzerra®)
- Panitumumab (Vectibix®)
- Pazopanib hydrochloride (Votrient®)
- Pralatrexate (Folotyn®)
- Rituximab (Rituxan®)
- Romidepsin (Istodax®)
- Sorafenib tosylate (Nexavar®)
- Sunitinib malate (Sutent®)
- Tamoxifen
- Temsirolimus (Torisel®)
- Toremifene (Fareston®)
- Tositumomab and 131I-tositumomab (Bexxar®)
- Trastuzumab (Herceptin®)
- Tretinoin (Vesanoid®)
Vandetanib (Zactima™) 76
Vorinostat (Zolinza®) 77

8. What are some resources for more information?

NCI’s Molecular Targets Laboratory 26 (MTL), part of NCI’s Center for Cancer Research (CCR), is working to identify and evaluate molecular targets that may be candidates for drug development. The initial goal of the MTL is to facilitate the discovery of compounds that may serve as bioprobes for functional genomics, proteomics, and molecular target validation research, as well as leads or candidates for drug development.

NCI’s Chemical Biology Consortium 26 (CBC) facilitates the discovery and development of new agents to treat cancer. The CBC is part of the NCI Experimental Therapeutics Program, which is a collaborative effort of CCR and NCI’s Division of Cancer Treatment and Diagnosis.

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Related NCI materials and Web pages:

- Angiogenesis Inhibitors Therapy 80 Fact Sheet
- Cancer Clinical Trials 81 Fact Sheet
- Understanding Cancer Series: Targeted Therapies Tutorial 82
- What You Need To Know About™ Cancer 83

How can we help?

We offer comprehensive research-based information for patients and their families, health professionals, cancer researchers, advocates, and the public.

- Call NCI’s Cancer Information Service at 1–800–4–CANCER (1–800–422–6237)
- E-mail us at cancergovstaff@mail.nih.gov
- Order publications at http://www.cancer.gov/publications or by calling 1–800–4–CANCER

Glossary Terms

acetylation (a-SEH-tih-LAY-shun)

A chemical reaction in which a small molecule called an acetyl group is added to other molecules. Acetylation of proteins may affect how they act in the body.

acute lymphoblastic leukemia (uh-KYOOT LIM-foh-BLAS-tik loo-KEE-mee-uh)

An aggressive (fast-growing) type of leukemia (blood cancer) in which too many lymphoblasts (immature white blood cells) are found in the blood and bone marrow. Also called acute lymphocytic leukemia and ALL.

acute promyelocytic leukemia (uh-KYOOT PRO-MY-eh-loh-SIH-tik loo-KEE-mee-uh)

An aggressive (fast-growing) type of acute myeloid leukemia in which there are too many immature blood-forming cells in the blood and bone marrow. It is usually marked by an exchange of parts of chromosomes 15 and 17. Also called APL and promyelocytic leukemia.

adenocarcinoma (A-den-oh-KAR-sih-NOH-muh)
Opportunities and Challenges in the Development of Experimental Drug Combinations for Cancer

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It is becoming increasingly evident that cancers are dependent on a number of altered molecular pathways and can develop diverse mechanisms of resistance to therapy with single agents. Therefore, combination regimens may provide the best hope for effective therapies with durable effects. Despite preclinical data to support this notion, there are many challenges to the development of targeted combinations including scientific, economic, legal, and regulatory barriers. A discussion of these challenges and identification of models and best practices are presented with intent of aiding the research community in addressing real and perceived barriers to the development of combination therapies for cancer.

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Cancers are dependent on many altered molecular pathways and use multiple mechanisms of immune resistance such that single-agent therapies alone may not provide long-lasting benefit for most patients. Even dramatic objective responses to single agents are commonly short-lived as evolving mutations in the agent’s primary target or changes in a downstream effector lead to drug resistance and cancer progression. For example, the median duration of response to vemurafenib (ROS185426, RG7204, or PLX4032), a highly selective mutant BRAF inhibitor under development for BRAF mutant metastatic melanoma, is approximately 7 months despite an initial response rate of 81% (1). Although it has been reported that some patients in this first cohort are still responding more than 2 years after initial treatment (2), the majority of responses are temporary and incomplete. In addition, analyses of tissues from relapsed patients and laboratory studies with cell lines are identifying several mechanisms of resistance to highly selective BRAF inhibition (3,4,5). These studies and other reports support the hypothesis that drug combinations will be necessary to provide long-term tumor control for most patients. These considerations recapitulate infectious disease paradigms in which combination therapies for disorders such as HIV/AIDS and tuberculosis are the rule rather than the exception. Potential combinations of anticancer agents include a variety of permutations of experimental agents and/or standards of care (eg, chemotherapy, targeted agents, and immunomodulators). Evidence from animal tumor models indicates that the therapeutic effects of certain drug combinations may exceed those of monotherapies. Before phase II or phase III studies of combination therapies can be initiated, rational preclinical models should guide clinical trial design and may illuminate issues such as dosing regimens (administering two drugs concomitantly or sequentially), drug interactions affecting pharmacokinetics, and interactive toxic effects. In addition, new approaches to phase I studies of combination therapies should be considered to improve efficiency and increase our understanding of how best to test agents in combination (6).

Despite evidence of the potential for improved benefit when two anticancer agents are combined (7-10), the majority of cancer drugs follow development pathways as single agents, resulting in substantial failure rates. Roughly, 90% of the oncology drugs that entered clinical testing between 1993 and 2002 ultimately did not receive US Food and Drug Administration (FDA) approval (11). Oncology therapeutic strategies that incorporate rationally designed drug combinations at earlier stages of development may have the potential to substantially improve this disappointing track record. Numerous challenges exist in developing research approaches for combination therapy, particularly for agents developed by multiple institutions, both academic and pharmaceutical based (12-17). For example, in addition to the scientific challenges inherent in optimizing drug combinations, productive collaborations can be challenged by economic considerations, issues related to contract terms including intellectual property, and a range of logistical obstacles. Mechanisms are needed to efficiently identify the potential therapeutic advantage in the combination of select anticancer drugs, drive decision making about the prioritization of rational combination trials, and then implement the clinical development of high-priority combinations efficiently. Clinical trial design for combination therapies is complex, and there is no one-size-fits-all approach; however, new and more flexible development models described here and in previous reports may simplify the process (16). Regulatory and safety considerations, such as concerns about unexpected toxic effects, are barriers to clinical development and approval. Some of these barriers are perceived rather than real, but perception can (and has) become reality. Overcoming these
barriers will take cooperation among the regulatory bodies, the academic community, and the private sector.

The economic environment for the commercial development of combination therapies is an overarching challenge. Drug development is primarily funded by the private sector; thus, business considerations play a role. Efficacy must outweigh the increased cost and development complexity of a combination product. Importantly, partnerships between companies (risk sharing and profit sharing business models) as well as between sectors (academia, industry, and government) can leverage resources and mitigate risk and have become more common for these reasons. Other solutions include improved preclinical research, innovative trial design, rational intellectual property and legal approaches, and more frequent interactions with regulatory agencies.

The need for new more effective cancer treatments has never been greater. Cancer is the second-most common cause of death in the United States; in 2010, it was estimated that more than half a million Americans died of cancer, or more than 1500 people per day (18). Given the opportunities and challenges for combination therapies for cancer, the Melanoma Research Alliance hosted the session, “Developing Experimental Drug Combinations: Opportunities and Challenges” as part of the Melanoma Research Alliance Annual Scientific Retreat held February 24–26, 2010, in Las Vegas, NV. Whereas the potential value of combinatorial therapies applies to all cancer types, the incidence of melanoma has risen faster than any other cancer during the last three decades (19), and is particularly relevant because of the recent monotherapies that statistically significantly slow disease progression and improve overall survival but infrequently produce long-term remission in patients. These monotherapies include kinase inhibitors such as vemurafenib and immunotherapies such as ipilimumab (anti-cytotoxic T-lymphocyte antigen-4). Precedent for the development of combinatorial therapies of cancer comes from the cure of most childhood leukemias with combinations of agents, which displayed only transient antitumor effects on their own. Thus, a discussion of the opportunities and challenges to developing combination therapies for melanoma in particular, and cancer in general, was held among representatives from academia, industry, and government with the goal of accelerating the delivery of new tools and treatments to patients. The discussion prepared the Melanoma Research Alliance for a continuing dialogue on these issues, the summary of which is presented here.

**Scientific Considerations**

New treatment opportunities for melanoma fall into two broad categories as follows: immunotherapy targeting specific regulatory molecules for the antitumor immune response and molecularly targeted pathway inhibition. Melanoma is one of the most responsive human cancers to immune modulation and has become the prototype for developing cancer immunotherapies (20), which may be applicable in a broader setting. Furthermore, mechanisms of carcinogenesis depending on aberrant intracellular signaling have been well characterized in many cancers with BRAF being the most common kinase mutation in melanoma identified to date (21). Thus, opportunities for combined therapies in cancer include combinations of molecularly targeted agents (eg, a highly selective BRAF inhibitor with a MEK inhibitor), combinations of two or more immunotherapies (eg, vaccines plus immune modulating antibodies or two immunomodulatory antibodies), combinations of signaling inhibitors with immunotherapy, or combinations of an experimental agent with standards of care (eg, radiotherapy and chemotherapy). In addition, new insights into the tumor microenvironment suggest opportunities to combine agents, which directly target the tumor cell and nontransformed cells in the tumor stroma.

A first key step in the pursuit of combination therapies is to show compelling scientific and medical rationale, that is, the potential for increased efficacy with limited toxicity. The development stage of the individual agents (what is known and not known about the drugs) will affect the approach used for the combination and is summarized in Table 1. Rigorous preclinical studies, including appropriate animal models and toxicity studies, are required to assess the potential of a combinatorial regimen and to set the stage for clinical trial design. Kwak et al. (22) proposed guidelines for the identification of potential combinations of molecularly targeted agents on the basis of biological and preclinical data. Also, prospects for melanoma combination therapies were recently summarized by Ascierto et al. (23) who described combinations of agents that could be useful for melanoma as well as scientific considerations for testing these combinations and more general considerations for combination therapy development.

In academia, basic and preclinical studies can be impeded by a lack of access to commercial and investigational agents. The US National Cancer Institute (NCI) has created several resources to facilitate research in the area of drug combinations. To address the need for commercially available agents for in vitro use, NCI developed COMBO plates for in vitro combination studies. These 96-well plates containing all commercial FDA-approved anticancer drugs are available at no cost to academic investigators. Another resource is the NCI 60, a platform incorporating 60 tumor cell lines that is being used to investigate the effects of two-drug combinations for all commercially available anticancer agents. NCI will make the results of these studies available to academic investigators for further hypotheses-driven research (24).

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<th>Drug development</th>
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<td>Drug A Early</td>
<td>Combination opportunity is theoretical</td>
<td>Dose, efficacy, and toxicity of at least one compound is well defined</td>
</tr>
<tr>
<td>Drug A Late</td>
<td>Dose, efficacy, and toxicity of at least one compound is well defined</td>
<td>Combination opportunity on the basis of a solid understanding of the dose, efficacy, and toxicity of each agent as a monotherapy</td>
</tr>
</tbody>
</table>

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A third NCI resource is the Chemical Biology Consortium, an initiative created to facilitate drug discovery and development of new investigational agents for cancer. A limitation of these in vitro screens is the increased biologic complexity of in vivo tumors that depend on nontransformed components of the tumor microenvironment. Nevertheless, the in vitro combinatorial screens provide a rapid means of empirically identifying candidate drug pairs that can be further tested using in vivo cancer models.

Organ site cancers are not a single disease and identifying subpopulations of patients most likely to benefit and/or are least likely to incur serious toxic effects from a particular drug or combination increases the probability of success. In melanoma, for example, several different subtypes have been identified on the basis of common genetic mutations, in molecules such as BRAF, NRAS, PTEN, cKIT, and GNAQ (23). The development of companion diagnostics to identify patients who will benefit from agents targeting aberrant molecular pathways, although sometimes costly, may be an important component in developing both monotherapies and combination therapies for cancer.

**Clinical Trial Design**

Clinical trial design for combination therapies is complex, and there is no uniform approach (6). Trial design for a combination must be driven by preclinical studies, the characteristics of the individual compounds, and the patient population of interest. Three typical combination scenarios and clinical trial design recommendations are summarized in Table 2. When the combination of two drugs demonstrates potential antitumor activity but neither drug has single-agent activity (Scenario 1), there are three variables that should be optimized: 1) the ratio of the drugs, 2) the dose of each drug in the combination, and 3) the administration regimen (A with B, A before B, or B before A). The variables of drug ratio and overall dose require a phase I trial using a factorial design followed by either a single-arm phase II design with a fixed ratio and dose and concomitant administration. Alternatively, one could adaptively vary the ratio and/or dose of each drug on the basis of interim analyses to improve the efficiency of the trial. When one drug is active (A), but potentially modulated by the administration of a second drug which by itself is inactive (B) (Scenario 2), one should consider a phase I design in which the dose of A is fixed and the dose of B is modulated, and vice versa, to explore the influence of the inactive drug on the safety, efficacy, and pharmacodynamics of the active compound. A randomized phase II design (A vs AB) should follow, as recently recommended by the NCI's Investigational Drug Steering Committee (26).

The most common scenario is that both drugs are active independently, but the combination is expected to be more effective than either agent alone (Scenario 3). A phase I dose-seekig trial should ideally be designed around a testable hypothesis. For example, 1) both drugs can be given at full dose, 2) one drug modulates the pharmacokinetics of the other, 3) one drug modulates the pharmacodynamics of the other, or 4) one drug increases the toxicity of the other. If there is a possible pharmacokinetic interaction (eg, one may decrease the clearance of the other), consider starting at 25%–50% of the standard dose of one drug and the full dose of the other. The pharmacokinetics of one drug should therefore be evaluated with and without the second and rapidly escalate it if there is no evidence for interaction. If there is a possible pharmacodynamic interaction (eg, one may increase the toxicity of the other), consider designing the trial such that patients receive one drug alone in the first treatment cycle, followed by the combination.

A phase I trial might not be necessary under certain circumstances. Preclinical data may suggest that a pharmacokinetic interaction is unlikely, as indicated by in vitro studies and knowledge of metabolism and transport of both drugs. In addition, a drug combination may go straight into a phase II study if in vivo animal studies showed that both drugs can safely be given together at the full dose without increased toxicity compared with monotherapy. If there is no formal phase I trial, the safety of the full dose of the combination should be tested as an initial cohort in the phase II study.

**Legal Issues**

Legal issues are often cited as barriers to the development of combination therapies. This is particularly true when the therapeutic agents come from different sources, such as separate biopharmaceutical companies or academic centers. Yet, there are very few true legal barriers. In reality, other tensions such as patent, regulatory, and transactional dynamics are sometimes expressed in legal terms. Agreements between partners can nevertheless be delayed by these perceived barriers.

A frequent source of contention is the struggle to define which party will own the rights to any invention developed during the
course of research to develop a combinatorial strategy. In fact, such inventions are rare, and it is highly unlikely that they will measurably affect the exclusivity or economic value of the combination therapy being developed. Freedom to operate, in fact, protects both patent holders of each component, and thus, the definition of rights is straightforward to resolve by contract if the parties are reasonable.

In addition to intellectual property, sources of possible contention include the division of expenses and profit, proposals for exclusive arrangements, disagreements about commercial strategy, and the complexity of combination product pricing. Uncertainty about the commercial potential of combination regimens and the potential impact of combination therapy development on single agents can also negatively influence negotiations. In general, the greatest barrier to agreement on combination therapy is the desire of one party to extract more value from the partnership than is warranted by its contribution to the collaboration. This potential barrier results when the negotiation is viewed as a zero-sum exercise, with an economic winner and a loser. However, collaborations can create added value for each partner, particularly when there is strong preclinical data supporting enhanced efficacy for combination therapy. First, the probabilities of ultimate success in FDA approval (and therefore the market) increase, thereby mitigating the risk of financial losses associated with development paths that ultimately fail. Second, a more effective regimen has a longer market life cycle because it is not as easily displaced by other agents competing for the same market.

Resources provided by the NCI Cancer Therapy Evaluation Program (CTEP) may facilitate research on combination therapies involving sponsors from different sectors. CTEP holds collaborative development agreements with more than 80 industry partners for more than 100 investigational agents, as well as clinical trial agreements with academic institutions, consortia, and cooperative groups. CTEP developed a template agreement language for these multisector collaborations that addresses data sharing and intellectual property. Provisions were included to ensure access to data by all parties who provided agents and the use of the data for scientific and regulatory purposes that is consistent with the development of a single agent. In addition, there is an option for each collaborator to receive fully paid, co-exclusive or nonexclusive royalty-free licenses to any inventions from the combination studies (27). Best practices specific to academic-industrial partnerships have also been produced by the Government-University-Industry Research Roundtable of the National Academies (28), the Association of University Technology Managers (29), and other groups. Despite the perception to the contrary, it is extremely rare to have antitrust concerns in the development of combination therapies between two companies unless there is an exclusive arrangement that would prohibit one partner from developing combinations with the products of third companies. A final perceived barrier is the fear of product liability. Liability is rarely a major factor in oncology clinical trials designed for patients with advanced treatment-refractory disease, because these patients are more likely to accept some risk of toxicity for a potential clinical benefit (30). Liability issues become more important in trials designed for otherwise healthy at-risk individuals or those with early-stage cancer. The development of enhanced biomarkers predictive of recurrence in patients with stage I-III cancers would allow for identification of high-risk individuals, thereby diminishing liability risks for the development of combinatorial adjuvant therapies. Detailed and properly explained clinical trial consent documents would also minimize the liability risk in trials designed for otherwise healthy at-risk individuals or patients with early-stage cancer.

**Regulatory Concerns**

Regulatory considerations are of paramount importance in the development of combination therapies for cancer. The expense, complexity, and time needed to prove that a combination product is both superior to the standard care and to monotherapy with each agent are substantial barriers to development (15). A major issue that the FDA should address stems from the fact that companies considering development of combinations of agents are often in the process of developing one or more of the components as single agents. Under these circumstances, there is a concern that unexpected toxic effects associated with the combination will either slow the concurrent development of the single agent or create new liability (14). The FDA does not currently have a mechanism for single-agent indemnification, that is, attributing an adverse event (toxicity) to one component of a combinatorial treatment regimen but not the other. Furthermore, the FDA has not clearly articulated policies of toxicity review and drug labeling that would allow single-agent development to proceed unfettered by toxic effects, which only arise when the agent is used in a novel combination. Although there have been varying interpretations of the FDA combination rule, it is intended for drugs combined in one physical form. The agency is creating a guidance document on regulatory policies specific to combination regimens composed of experimental drugs and has recently solicited relevant commentary from the public on draft guidance (31).

Because combinatorial strategies will always be easier to develop when one of the components is already approved as a single agent, accelerated approval of single agents would dramatically enhance the development of combinatorial approaches to treat cancer, an important aspect distinct from the conventional consideration of making promising agents more available to cancer patients. Enhancements in the accelerated review process that allow for market approval contingent on a postmarketing phase III study would, therefore, have important benefits for the approval process for combinatorial therapies.

To address the regulatory issues that may cause unnecessary delay in the drug development process, sponsors should have discussions with regulatory agencies about novel development approaches and the level of preclinical evidence needed before a clinical trial is initiated and frequently throughout the course of the trial. Improved FDA guidance, including the draft guidance recently announced, will enhance development efforts for combination therapies for cancer.

**Conclusions**

Recent scientific advances have led to the development of promising individual therapeutic agents, but it is becoming increasingly
clear that tumor cells have redundant prosurvival pathways that will need to be overcome through combination treatments. In addition to scientific and clinical issues, numerous operational challenges including economic, legal, and regulatory hurdles exist in developing combination therapies, particularly when different sponsors are involved. Although some barriers are only perceived, these difficulties can be addressed through the use of smart practices and creative approaches. Combination therapy development can be facilitated through improved preclinical research to predict the best therapeutic strategies, thereby reducing the complexity and cost of clinical trials; innovative clinical trial design, including modeling and simulation studies; early and frequent discussions with regulatory agencies to discuss novel developmental approaches; increased collaborations between industry, government, and academia; and risk sharing and profit sharing business models. New molecularly targeted agents and immunotherapies provide many promising options for combination strategies which, in addition to refined FDA guidance, will help speed the development of more effective treatments to end suffering and death from cancer.

References


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Targeted Agents: The Rules of Combination

Eunice L. Kwak, Jeffrey W. Clark, and Bruce Chabner

Abstract

The success of molecularly targeted agents (MTA) in the treatment of cancer has led to the investigation of their use in combination with other MTAs and with conventional chemotherapies. An overview of the MTAs that have emerged as Food and Drug Administration–approved drugs is presented, along with a framework for the consideration of how MTAs can best be combined to maximize therapeutic effect.

During the past decade, molecularly targeted agents (MTA) have become the primary focus of therapeutic cancer research. The lure of molecular targets is derived from several factors: the strong rationale of a target that represents a selective advantage for tumor killing as compared with normal tissue toxicity, the relative ease of high-throughput screening against molecular entities, and the potential for refinement of leads through screening against molecular, cellular, and animal models. Further support for this effort has come from the demonstration that certain tumors in humans are addicted to signals from mutant or amplified receptors (1), such as the epidermal growth factor receptor (EGFR; ref. 2), and undergo rapid apoptosis upon pathway inhibition. Even when the MTA has no discernible effect on tumor size, it may drastically alter tumor metabolism, block survival signals from receptor-linked pathways such as phosphatidylinositol 3-kinase (PI3K), and lower the threshold for apoptosis (3). The value of MTAs may thus increase dramatically when they are used with cytotoxic agents.

Although there have been active investigation of MTAs as monotherapy, there have been fewer explorations of MTA combinations in human clinical trials. From a biological standpoint, solid tumors often contain mutations in multiple genes (4), but the significance of these “accessory” mutations for survival and proliferation remains unproven. In addition, because the widespread development and use of MTAs has been a relatively recent event, hormonal therapy notwithstanding, there are few MTAs whose properties are understood well enough as single agents to have proceeded on to development as combination therapy. In this report, we will explore additional challenges for MTA combinations in human tumor therapy. We will first summarize the clinical successes of single-agent MTAs, and then examine the rationale, strategies, and experience to date for MTA combinations. From this discussion, we will address the “rules” that seem logical for further development of MTA combinations.

Single-Agent Experience with Molecularly Targeted Drugs

A growing number of MTAs have gained Food and Drug Administration approval and have become standard of care for specific tumors (Table 1). These agents have ranged from antibodies with a high degree of selectivity for their targets to small-molecule kinase inhibitors with broader spectrums of target-inhibitory activity. The targets of these agents may reside in the tumor cell itself, or may exist in the tumor’s microenvironment. Although some of these drugs are used in combination with cytotoxic drugs, they have each shown activity as single agents.

As a generalization, none of the drugs, with the possible exception of imatinib, are curative as single agents. Furthermore as single agents, the small molecules, such as sunitinib, the EGFR inhibitors, and imatinib, have greater activity than monoclonal antibodies in the more common solid tumors. Many such agents are available or in development, with varying degrees of specificity for their targets. The most striking responses have been seen in cancers with “oncogene addiction.” That is, the growth and survival of the cancer is completely dependent on the signal that is inhibited by the targeted agent (1). However, even in the most successful example of an oncogene-addicted tumor, chronic myelogenous leukemia (CML), whereas the majority of patients experience a long-lasting hematologic and cytogenetic remission, eradication of BCR-ABL–positive cells occurs in <20% of patients, and there is a constant overall relapse rate of 1% to 2% per year (5).

Single-adding mutations are rare in solid tumors. Non–small cell lung cancer with activating mutations in exons 19 or 21 of the EGFR (6), exon 11 mutations in C-KIT–positive gastrointestinal stromal tumor (GIST; ref. 7), and C-MET-mutant hereditary papillary renal cell carcinoma (RCC; ref. 8) are the rare exceptions. Although therapy with erlotinib or imatinib can produce previously unimagined responses in EGFR-mutant non–small cell lung cancers or GIST, respectively, monotherapy with these targeted agents produces few complete remissions, and these are usually of 3 to 6 months in duration. Similarly, in the case of clear cell RCC, in which von Hippel-Lindau mutations are responsible for the up-regulation
of proangiogenic signals such as vascular endothelial growth factor and platelet-derived growth factor, inhibition of angiogenesis with agents such as sunitinib is only partially effective (9).

Therefore, it is likely that the broadest potential of targeted therapies in solid tumors will not be as single agents in the rare addicted cancers, but in combinations that allow rational inhibition of the multiple pathways that contribute to tumorigenesis. Up to this point, the advanced development of MTAs has largely been devoted to their combination with well-established cytotoxic drug combinations in advanced disease, such as bevacizumab with fluorouracil/leucovorin/oxaliplatin (FOLFOX) in metastatic colon cancer. The next step will be the exploitation of rational combinations of MTAs in advanced disease. Furthermore, the principle of MTA effectiveness in combination with cytotoxics has been established in the adjuvant setting, as shown by trastuzumab with taxol-based combinations in breast cancer. Meanwhile, the role of MTA combinations in the adjuvant setting, in which there may be a more realistic opportunity for cure, will likely become an active area of investigation.

### Rules for Trials of Combinations of Targeted Agents

The dearth of clinical experience with combinations of MTAs makes it impossible to offer any definitive rules for combination therapy. A variety of rationales for constructing combinations can be proposed, and these can be assigned a priority based on biological evidence and preclinical experiments in model systems. It must be remembered, however, that no preclinical system, whether it be human tumor cells in culture or human xenografts in mice, or genetically engineered tumors in mice, has a track record for predicting success in humans (10), and that model tumors simply represent models of their own specific biology, no more and no less. With that caveat, the following rules are proposed.

**Based on the single-agent experience described above, the best chances of success will be realized when both agents in a combination inhibit separate pathways known to be critical to the survival of the tumor.** Combinations might be based on knowledge that activation of an alternative pathway confers resistance to hormonal therapy or signal inhibition. Cell and animal tumor experiments suggest that activation of alternative pathways may circumvent the inhibition of a primary signaling receptor such as EGFR or HER2/neu (11, 12). For example, resistance to estrogen-targeted therapy in breast cancer can be mediated by activation of the PI3K pathway in human breast cancer cells (13). Trastuzumab- or tamoxifen-resistant cells in culture regain sensitivity in the presence of inhibitors of the PI3K pathway (14), such as the direct PI3K inhibitor LY 294002 or mTOR inhibitors of the rapamycin class.

An example of collateral pathway activation as a mechanism of resistance has recently come to light in the studies of EGFR inhibitors. Engelman and colleagues found that amplification of C-MET circumvents the antitumor effects of EGFR inhibition in otherwise sensitive lung cancer cells carrying an activating mutation in EGFR (11). They found examples of C-MET amplification in gefitinib-resistant human tumors, and showed that sensitivity to gefitinib could be restored by exposing cells concurrently to a C-MET inhibitor and gefitinib, thus providing an example of concurrent dependence on two distinct targets. Although this activating C-MET amplification was found in only 4 of 18 resistant tumor samples, it may herald the discovery of a generalizable finding in other solid tumors. The combination of EGFR and C-MET inhibitors could represent a logical approach to overcoming resistance in carefully selected patients.

Another example in which inhibition of separate pathways resulted in enhanced antitumor activity was shown in glioblastoma cell lines in which the PI3K pathway and Ras/mitogen-activated protein kinase pathways were targeted in combination. PI3K-regulated integrin-linked kinase was inhibited using integrin-linked kinase antisense oligonucleotides or small interfering RNA, whereas Ras/mitogen-activated protein kinase signaling was targeted with small molecule inhibitors of either Raf or MEK. Inhibition of both pathways resulted in synergistic decreases in colony formation and increases in apoptosis (15). Thus, the clinical use of agents targeting the PI3K pathway used in conjunction with Ras pathway inhibition could lead to improved outcomes in glioblastoma or other diseases whose growth and survival are dependent on multiple pathways.

**Mutations conferring drug resistance may produce new versions of the same target resulting in reduced sensitivity to a given MTA’s inhibitory effect: combination therapy may inhibit multiple alternate forms of the target.** Perhaps the most straightforward case will be a combination of agents based on an understanding of resistance to a single agent. Thus, a clear and strong case can be made for combining imatinib and dasatinib, either given together or in sequence, as the primary treatment of CML. The mutations in BCR-ABL that confer resistance to imatinib have been carefully defined by molecular studies of patients failing imatinib treatment. All but two of these mutations are susceptible to dasatinib (16). Interestingly, according to preliminary results, the T315I mutation which confers resistance to both imatinib and dasatinib is sensitive to another class of drugs, the Merck aurora kinase inhibitor (17). Should all three drugs be given together, or is dasatinib or the aurora kinase inhibitor alone sufficient? At this point, it is unclear that either of the newer drugs has equal activity to imatinib in nonmutated BCR-ABL–driven disease. If one were to extrapolate the success of multiple reverse transcriptase inhibitors in AIDS, the combination strategy would be worth evaluating in CML. The alternative of using imatinib first and waiting for resistance to develop before using the other drugs is less likely to be curative, as one would be facing a resistant tumor with a single agent, or two agents, rather than three. The overlapping toxicities of the three drugs, however, might present a problem for their concurrent use. Thus, sequential use of two or three drugs against CML might be a more feasible strategy. Similar preliminary evidence of C-KIT kinase mutations causing resistance to imatinib therapy in GIST might lead to combination therapies, although the case is less certain in this tumor because sunitinib, which is active in imatinib-resistant GIST (18), may be acting through a second, unrelated mechanism (angiogenesis).

Despite the appeal of a combination therapy approach in preventing the emergence of resistance mutations in CML, it is unclear whether the above strategy would yield more cures. There is clinical and in vitro evidence that the leukemic stem cell population is relatively resistant to imatinib and dasatinib,
<table>
<thead>
<tr>
<th>Name of compound</th>
<th>Target(s)</th>
<th>Class of molecule</th>
<th>Approved indications (References)</th>
<th>Date of first approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib (Gleevec, Novartis)</td>
<td>ABL, BCR-ABL, PDGFR, C-KIT</td>
<td>Small-molecule inhibitor</td>
<td>CML: chronic phase, newly diagnosed; chronic phase after IFN-α failure; blast crisis, accelerated phase (34) Ph+ALL: relapsed or refractory MDS/MPD ASM HES/CEL DP</td>
<td>May 2001</td>
</tr>
<tr>
<td>Dasatinib (Sprycel, Bristol-Myers Squibb)</td>
<td>BCR-ABL, SRC family, C-KIT, EPHA2, PDGFRA, PDGFRβ, PDGFRα, PDGFRβ, C-KIT, FLT3, Colony-stimulating factor receptor type 1 (CSF-1R), Glial cell line–derived neurotrophic factor receptor (RET)</td>
<td>Small-molecule inhibitor</td>
<td>CML: chronic, accelerated, blast phase, with intolerance or resistance to imatinib (16) Ph+ALL: refractory to imatinib (36)</td>
<td>June 2006</td>
</tr>
<tr>
<td>Sunitinib (Sutent, Pfizer)</td>
<td>VEGFR1, VEGFR2, and VEGFR3, PDGFRα and β, C-KIT, FLT3</td>
<td>Small-molecule inhibitor</td>
<td>GIST: refractory or intolerant to imatinib (18) RCC: first-line metastatic (9)</td>
<td>January 2006</td>
</tr>
<tr>
<td>Sorafenib (Nexavar, Onyx/Bayer)</td>
<td>VEGFR-2, VEGFR-3, PDGFR-β, FLT-3, RET, C-Raf, B-raf, VEGF</td>
<td>Small-molecule inhibitor</td>
<td>RCC: second line (37) HCC: advanced disease (38)</td>
<td>December 2005</td>
</tr>
<tr>
<td>Bevacizumab (Avastin, Genentech)</td>
<td>Antibody</td>
<td>CRC: metastatic, first-or second-line with 5-fluorouracil-based chemotherapy (39) NSCLC (nonsquamous): unresectable or metastatic with carboplatin and paclitaxel (40)</td>
<td>February 2004</td>
<td></td>
</tr>
<tr>
<td>Rituximab (Rituxan, Genentech)</td>
<td>CD20</td>
<td>Antibody</td>
<td>NHL, B cell: CD20 + relapsed or refractory low-grade or follicular; diffuse with anthracycline-based chemotherapy regimen (41)</td>
<td>November 1997</td>
</tr>
<tr>
<td>Bortezomib (Velcade, Millennium Pharmaceuticals)</td>
<td>Proteasome inhibitor</td>
<td>Small-molecule inhibitor</td>
<td>Multiple myeloma: relapsed disease after 2 prior treatments, with resistance to last prior treatment (42)</td>
<td>May 2003</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin, Genentech)</td>
<td>HER2</td>
<td>Antibody</td>
<td>BrCA: HER2-overexpressing metastatic, prior chemotherapy; adjuvant in HER2-overexpressing node-positive in combination with a regimen containing doxorubicin, cyclophosphamide, paclitaxel; metastatic in combination with paclitaxel (43)</td>
<td>October 1998</td>
</tr>
<tr>
<td>Cetuximab (Erbitux, Bristol-Meyers Squibb)</td>
<td>EGFR</td>
<td>Antibody</td>
<td>CRC: metastatic, single agent or in combination with irinotecan (44) SCC head and neck: locally advanced disease in combination with radiation therapy; recurrent or metastatic disease after platinum failure (45)</td>
<td>February 2004</td>
</tr>
<tr>
<td>Panitumumab (Vectibix, Amgen)</td>
<td>EGFR</td>
<td>Antibody</td>
<td>CRC: metastatic, chemotherapy refractory (46)</td>
<td>September 2006</td>
</tr>
</tbody>
</table>

(Continued on the following page)
and therefore, even concurrent use of multiple agents targeting the same molecule may not be adequate to counteract the mechanisms responsible for the intrinsic resistance of the stem cell population (19, 20).

**Combinations of inhibitors might be designed that attack sequential steps in a single pathway.** This concept has a rational basis in experiments with antimetabolite chemotherapy, in which sequential inhibitors of purine and pyrimidine biosynthesis were synergistic in selected animal tumors (21). There is no rigorous proof of this concept in human trials, but the availability of multiple inhibitors of a single pathway raises the possibility of exploring this strategy in the clinic. Indeed, the concept of sequential inhibition underlies many recent studies of the PI3K pathway, which mediates survival and antiapoptotic signals generated from activation of cell surface receptors such as HER2, EGFR, C-MET, or the insulin-like growth factor receptor (12, 22, 23). Blocking both the receptor and the downstream PI3K pathway may produce supra-additive effects. Even downstream within the PI3K pathway, there is experimental evidence that would support the simultaneous use of inhibitors at multiple points. For instance, treatment of glioma cells in vitro with rapamycin alone resulted in AKT activation, likely through the disruption of negative feedback signals. Simultaneous inhibition of both PI3K and mTOR was able to prevent the AKT activation and overcome resistance to mTOR inhibition alone (24).

Another interesting possibility for “sequential” therapy is presented by lapatinib and trastuzumab. In preclinical experiments with breast cancer cells, these drugs together were more potent in decreasing cell survival than either drug alone (25). Lapatinib recently received Food and Drug Administration approval on the basis of results of a phase III trial of capcitabine alone versus capcitabine plus lapatinib in patients with HER2-positive metastatic breast cancer that had progressed on previous trastuzumab therapy. Of the approximately 400 patients on the study, the half who received lapatinib and capcitabine experienced a significantly longer time-to-progression and higher response rate than those who received capcitabine alone (27.1 versus 18.6 weeks; 23.7% versus 13.9%, respectively; ref. 26). Why lapatinib is active in patients resistant to trastuzumab is currently unclear. It may be that trastuzumab-resistant cells signal through alternative HER1 or HER3 receptor activation, independent of HER2, but these positive clinical findings suggest that the optimal use of other receptor-directed antibodies may require the blockade of ancillary mechanisms.

There are negative aspects to the blockade of sequential steps in a pathway. Sequential combinations are unlikely to overcome resistance related to the activation of alternative pathways, and could have additive toxicities, as was observed for bevacizumab and sorafenib, both inhibitors of the vascular endothelial growth factor pathway (27).

**The combination of a targeted agent and a second drug that modulates the target function has strong appeal.** A pertinent example is the combined use of trastuzumab or imatinib and 17-AAG, a HSP90 inhibitor. HSP90 serves a chaperone function, protecting key intracellular proteins against degradation and inducing the folding of mutant proteins. Preclinical experiments have shown that 17-AAG blocks HSP90 interaction with its client proteins and induces the rapid turnover of the clients, such as HER2 (28) and other oncogenic tyrosine kinases (29), including BCR-ABL. Clinical trials are ongoing to test the ability of 17-AAG and related compounds to enhance response and overcome resistance to trastuzumab in breast cancer, and imatinib in CML.

**The combination of agents that target different functional pathways (e.g., survival and angiogenesis) might have additive or synergistic activity.** The biotechnology industry has now discovered inhibitors for a variety of other functions that contribute to the survival of most tumor cells. These targets include proteins involved in angiogenesis and antiapoptotic proteins of the BH3 family, including BCL-2 and survivin (30, 31). Antiapoptotic drugs and antiangiogenic agents are of general interest as modulators of the response to both cytotoxic and targeted agents. The rationale for adding an antiangiogenic agent can be generalized to virtually any tumor and any targeted drug. One notable trial in RCC combined bevacizumab and erlotinib, an EGFR inhibitor

### Table 1. Food and Drug Administration–approved molecularly targeted drugs (Cont’d)

<table>
<thead>
<tr>
<th>Name of compound</th>
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<th>Class of molecule</th>
<th>Approved indications (References)</th>
<th>Date of first approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib (Iressa, Astra-Zeneca)</td>
<td>EGFR</td>
<td>Small-molecule inhibitor</td>
<td>NSCLC: advanced, chemotherapy-refractory (47)</td>
<td>May 2003</td>
</tr>
<tr>
<td>Erlotinib (Tarceva, Genentech)</td>
<td>EGFR</td>
<td>Small-molecule inhibitor</td>
<td>NSCLC: locally advanced or metastatic chemotherapy-refractory Pancreatic cancer: unresectable or metastatic first-line (48)</td>
<td>November 2004</td>
</tr>
<tr>
<td>Lapatinib (Tykerb, GlaxoSmithKline)</td>
<td>EGFR HER2</td>
<td>Small-molecule inhibitor</td>
<td>BrCA: advanced or metastatic HER2 overexpressing breast cancer after chemotherapy and trastuzumab failure (26)</td>
<td>March 2007</td>
</tr>
<tr>
<td>Temsirolimus (Torisel, Wyeth)</td>
<td>mTOR</td>
<td>Rapamycin analogue</td>
<td>RCC: advanced disease (49)</td>
<td>May 2007</td>
</tr>
</tbody>
</table>

Abbreviations: CML, chronic myelogenous leukemia; NHL, non–Hodgkin’s lymphoma; CRC, colorectal cancer; NSCLC, non–small cell lung cancer; BrCa, breast cancer; SCC, squamous cell carcinoma; HCC, hepatocellular carcinoma. PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor.
with minimal activity in this disease. The preliminary trial of the combination showed an improvement in response rate over bevacizumab alone (32), but final results of the randomized trial are still pending.

The ongoing development of multitargeted small molecule inhibitors allows one molecule to provide inhibition of several pathways, for instance, proapoptotic/antiproliferative signals along with antiangiogenic activity. This prompts the question of the relative benefits of treatment with multiple drugs hitting single pathways (e.g., erlotinib and bevacizumab) versus single drugs hitting multiple pathways (e.g., ZD6474, a combined EGFR and vascular endothelial growth factor receptor inhibitor; ref. 33). Although there is no data comparing the two approaches head-to-head, one can imagine that the potential for advantages in single multitargeted agents will lie in the potency and specificity of a particular agent for the proteins that it inhibits. If the MTA is too “dirty” in its inhibitory spectrum, increased side effects may result, and this may prevent treatment with therapeutic doses of drug, thus compromising target inhibition. Broad-spectrum activity may also limit the ability to further combine a given multitargeted agent with additional chemotherapeutic or targeted agents. Nonetheless, the clinical care of patients would be simplified if therapy could be administered as a single drug effectively inhibiting multiple relevant targets with minimal additional toxicities.

Challenges to Combination Therapy with MTAs

Clearly, the potential for MTA combinations designed to modulate different aspects of the same or different targets brings tremendous promise for the improved therapy of cancer. There are, however, a number of challenges that need to be overcome for this to become a reality. For instance, the targeted agents attractive for combination therapy are frequently produced by different sponsors. There often is little financial incentive for one pharmaceutical sponsor to support clinical trials combining its agent with an agent(s) from another sponsor, particularly in early phase trials. Even if a compelling scientific rationale for the combination prevails, prolonged negotiations are required to reach an agreement between the different sponsors and academic partners. Measures proposed to facilitate these types of collaborations have included assigning a central role to the National Cancer Institute/Cancer Therapy Evaluation Program in fostering combination trials of targeted agents from different sponsors. Another solution is the inclusion of such potential combination clinical trials in master agreements between sponsors and academic centers. Although not insurmountable, continued efforts encouraging cooperation between pharmaceutical companies to facilitate these studies are needed.

Another challenge to combination therapy with MTAs is the heightened potential for pharmacokinetic interactions between small molecule kinase inhibitors. This is due to the high percentage of these agents that are substrates for the p450 system, especially CYP3A4, a major player in the hepatic metabolism of MTAs. The potential for adverse pharmacokinetic interactions is further compounded by the large number of other drugs that are either inhibitors or inducers of these enzymes. Given the relative newness of MTAs, there have been few examples of careful clinical evaluation of pharmacokinetic interactions and how these interactions affect the administration of combination therapy to patients.

Combinations of MTAs also raise issues about the optimal design of clinical trials so as to obtain the most information about the relative roles of each agent separately as well as in combination. Some of the guideposts in combining chemotherapeutic agents (e.g., avoidance of overlapping toxicities or response rate end points as indicators of activity) might not be available when combining targeted agents that are cytostatic rather than cytotoxic. For instance, the criteria for MTA activity may be stable disease rather than disease shrinkage; however, this will be complicated by variable growth rates of tumors and may require that patients are followed longer on study, increasing the overall duration and cost of clinical trials.

Given the difficulty in evaluating clinical activity, pharmacodynamic studies to assess the effect of an agent on its target are essential components of MTA trials. Although such studies increase in complexity when attempting to evaluate two or more targets, pharmacodynamic end points in combination trials become particularly important in assessing the minimal effective doses needed for target modulation. This information is especially useful if the agents under study are well-tolerated because there may not be a maximum tolerated dose in the traditional sense to guide “optimal” dosing. Unfortunately, the acquisition of pharmacodynamic data is not only associated with increased complexity, but increased costs and potentially increased risks to the patient. For instance, repeat biopsies of tumor tissue raise both ethical and patient acceptance issues that must be considered. Even if pretreatment and posttreatment biopsies of tumors could be obtained, the optimal use of limited tissue to address the effect of MTAs on multiple targets must be determined. Furthermore, routine sample processing and preservation protocols may be inadequate for pharmacodynamic studies on pretreatment and posttreatment tumor specimens. For example, many small molecule inhibitors lead to changes in protein phosphorylation, thus, phosphorylation status may be an important pharmacodynamic assay. However, because the phosphorylation of proteins can change very rapidly upon removal from the patient, biopsy tissue may need immediate and tailored processing.

Finally, in evaluating the effect of targeting specific genes or proteins, ideally, one would stratify tumors for study on the basis of presence/activation or absence of the target rather than the histology of the tumor. This, however, would require patient recruitment and physician collaboration across different academic groups representing different cancer types, thus increasing the complexity of trial implementation.

Conclusion

This is an exciting time in cancer drug development, and the promise of combination therapy using MTAs is only beginning to emerge. The most informative clinical trials will be designed by careful consideration of cellular targets and preclinical models of their function. Nonetheless, unanticipated results are bound to surface in the clinical setting, and we should look on these as opportunities to expand our understanding of the basic biology of cancer.
Development of Rational Drug Combinations with Investigational Targeted Agents

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INTRODUCTION AND BACKGROUND
Recent research advancements have identified molecular mechanisms underlying cancerous transformation and growth, leading to a new generation of therapies. Key signaling intermediates and genetic mutations associated with oncogenic cell-cycle regulation have been identified as specific targets for the development of new therapies that would be less toxic and more effective than currently available interventions. Progress has also been made in the understanding of how extracellular factors, such as hormones and growth factors, can influence the progression of tumor growth. For example, targeted agents against human epidermal growth factor receptor 2 (trastuzumab) and Abl (imatinib) have altered the natural history of the diseases in populations for which they were initially developed. However, in cases of other cellular targets, such as epidermal growth factor receptor (EGFR) in colorectal cancer and mammalian target of rapamycin (mTOR) in renal cell cancer, clinical results have been more modest.

The challenge facing the development of safer and more effective therapies can lie both with the specificity of new targeted agents and with the complexity of disease biology, which usually involves multiple redundancies and pathway crosstalk. By selectively and specifically inhibiting one aspect of tumor cell growth or survival, the therapeutic effect may be lessened by concomitant upregulation of another aspect of the same pathway or by the development of acquired resistance through activation of a compensatory pathway. For example, clinical data suggest that Met pathway activation can compensate in lung tumors when EGFR signaling is inhibited [1], whereas inhibition of mTOR with rapamycin analogs results in an increase in Akt signaling [2] that may reduce the overall therapeutic effect. Given the limited number of approved targeted agents, most rational combinations will require dosing of two or more (as yet) unapproved new molecular entities (NMEs). The strong scientific rationale for such combinations warrants a re-examination of our current developmental model and suggests that a new developmental model may, in select circumstances, facilitate evaluation of two investigational agents in combination.

The existing combination rule (21CFR300.50) provides

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one mechanism for approval of the combination of two investigational agents, typically by the demonstration, in a phase III trial, of the contribution of each agent to the claimed effects of the combination, compared with standard-of-care (SOC) therapy. However, there may be circumstances in which there is sufficient evidence to consider alternatives to the standard phase III factorial trial design or to consider alternative criteria for the regulatory burden of proof necessary for approval of the combination of two investigational targeted therapies. The objective of this panel is to explore specific examples and criteria in which an alternative regulatory process to the existing combination rule would be appropriate and feasible and thus could be adopted by developers.

**BENEFIT TO PATIENTS**

Any new model for the development of investigational agents must have as its ultimate goal an improvement in the therapeutic benefit to patients, both in terms of the efficacy and safety profile of the product and in terms of the efficiency of the drug development process itself. The putative benefits to patients include the potential for combination therapies to synergistically target tumors and therefore be more effective than a single agent alone. One of the theoretical benefits of combination targeted therapies is that, by the inherent nature of their specificity, toxicities may be minimized relative to broader spectrum agents. Employing two targeted agents versus a single multitargeted agent may allow for a dose reduction of either/both agent(s), thereby reducing toxicity while potentially maintaining or improving efficacy. There is also the possibility of achieving better safety profiles while using two agents with specific known targets rather than employing a single agent with multiple known and unknown targets. Thus, one criterion for the development of combination targeted therapies is that the toxicities of each individual agent are either nonoverlapping or merely additive in combination rather than synergistic, making it easier to monitor and manage in the clinic.

An estimated 20% of adult cancer patients are medically eligible for a cancer clinical trial, yet accrual rates remain at about 3%. These rates are even lower for ethnic and racial minorities as well as for young adult cancer patients, who have higher cancer mortality rates than the general population. The 2NME strategy has the potential to improve both the number and the quality of cancer clinical trials, enhancing the access of new targeted therapeutics to cancer patients. In addition to matching likely responders to these treatments, the potential 2NME approach would benefit patients where evidence suggests a therapeutic benefit for a highly refractory patient population or where no approved therapy exists but there exists a biological rationale for efficacy. The high unmet medical needs of these patients could support an alternative developmental model of two agents.

Finally, it should be acknowledged that the goal of all participants in the drug development process, including the research community, pharmaceutical industry, and regulatory agencies, is to expedite the availability of safe and effective therapies to the intended patient populations. The developmental models discussed below are an attempt to achieve this goal, without compromising existing regulatory standards that protect the safety of patients.

**EXAMPLES AND DECISION-MAKING CRITERIA OF 2NME DEVELOPMENT PLAN**

In order to explore specific examples and decision-making criteria of conditions when approval of the combination of two NMEs would be appropriate and feasible, we have made certain general assumptions about the 2NMEs, which are listed below:

- **Strong biological rationale for the 2NME combination**, for example, selective inhibition of two targets in the same pathway or inhibition of a primary and compensatory pathway.
- **Biological indicators for likely responders in a patient population** (i.e., paired markers to indicate that the pathway is actually altered in a patient population).
- **Evidence of synergy of the 2NME combination in in vitro cell lines and greater activity of the 2NME combination compared with the activity of either agent alone in in vivo nonclinical models**.
- **Nonclinical characterization of the toxicity profile of each individual agent according to current International Conference on Harmonization guidelines suggesting nonsynergistic toxicity.**
- **Thorough characterization of potential drug–drug interactions of the 2NME combination to minimize the potential for additive or synergistic toxicities.**

**POTENTIAL SCENARIOS FOR THE DEVELOPMENT OF 2NMEs**

**Synthetic Lethality**

Synthetic lethality refers to situations in which each NME is individually inactive or minimally active except in genetically defined models (e.g., a specific background mutation). The specific genetic background where each individual NME is active may not be broadly representative of the disease population. However, when the 2NMEs are used in combination, they exhibit highly potent activity, and further, this activity is detected in multiple representa-
tive model systems (various cell lines and animal models). In this example, the minimal activity of each agent alone precludes a regulatory process for single-agent approval and supports evaluation of an alternative developmental model for the 2NME combination. In these cases, we propose limiting data collection about each individual agent to phase I studies.

The rationale is that the individual NMEs are not being proposed as single agents, with their use being limited to the proposed combination therapy only. Also, it is perhaps more informative to learn of the risks and benefits associated with the combination rather than each individual agent because the combination has different molecular targets than each agent individually.

Proposed development plan:

1. Thorough characterization of the safety profile and maximum-tolerated dose of each individual agent in phase I studies. The decision to proceed with a phase Ib trial would be based on whether the observed exposure–toxicity relationship of each drug as a single agent is adequate to consider combination therapy feasible.
2. Evaluation of the safety profile of the 2NME combination and appropriate dose selection criteria for each agent in the combination (phase Ib). An expansion cohort may be used to demonstrate evidence of activity for the combination, such as tumor shrinkage.
3. Demonstration of proof of concept for the 2NME combination in phase II trial compared with each agent alone and with the SOC. Surrogate efficacy endpoints (i.e., response rate) may be used if appropriate for decision making in the face of compelling antitumor activity.
4. Standard phase III design comparing the 2NME combination with the SOC.

Coenhancement

Coenhancement refers to scenarios in which each NME is modestly active as an individual agent in model systems, but the combination is highly active in the exact same model systems. Therefore, a multiple-arm phase II trial may be sufficient to demonstrate the advantage of the combination, and allow for a two-arm phase III trial comparing the combination with the SOC.

Proposed development plan:

1. In this scenario, the proposed phase I/Ib development plan would be identical to that described above, with the objective of providing adequate characterization of the safety profile of each individual agent and the 2NME combination as well as the appropriate dose selection for each agent in the 2NME combination.

2. Demonstration of proof of concept with a four-arm comparison of the 2NME combination with each agent alone and with the SOC during phase II of development. An adaptive trial design might be employed initially testing the 2NME combination versus the SOC, with addition of the single-agent arms once evidence of activity for the 2NME combination was obtained.
3. Proof of concept for the combination, and the contribution of each agent to the combination, would be determined without exposing the large numbers of patients typically required for phase III trials to therapeutic agents with minimal activity.

Unienhancement

This case of enhancement refers to scenarios in which one of the NMEs is inactive or minimally active in model systems, the other NME is modestly active in the same model systems, but the combination is highly potent in the model systems. An example of this situation is when the minimally active NME’s role is to prevent resistance. In this situation, it is likely that the more active NME will require greater scrutiny and should be studied as a single agent in phase II trials. In contrast, the minimally active agent may not require study as a single agent beyond initial phase I studies. Therefore, the proposed modifications to the development plan would be similar to those of “coenhancement.”

CONCLUSION

There is a clear need to modify the current regulatory approval process such that it is more in alignment with the reality of new therapies in development, including the use of multiple therapies that target different molecular pathways. In addition to the specific scenarios sketched above, whenever feasible, combining of clinical trials (i.e., phase Ib–II or phase II–III) should also be considered to enhance clinical development timelines.

There are other facets of this issue that require further discussion, such as determining the optimal doses of the agents in the combination, labeling and packaging to ensure safe and effective usage, etc. Nevertheless, the issue of combinatorial therapies holds great promise for the future of cancer treatment. Enhanced understanding of complex signaling pathways that are misregulated in human cancer both provides an opportunity and presents various challenges to advance cancer therapeutics. To take full advantage of this opportunity, drug development must evolve past the current norm of targeted agents, either as individual agents effective in small patient groups or by empirically adding to the current SOC, to develop targeted agents to be used in rational combinations.
FDA RESPONSE

The conventional approach to cancer drug development has concentrated on the evaluation of single-agent therapies to determine efficacy and safety. Subsequently, the drug is evaluated in advanced stages of a malignancy or in combination regimens adding the new drug to approved drugs. Emerging knowledge on the molecular mechanisms of malignancies, however, may require greater use of multiple drug combinations. Each component of a drug combination could target different parts of complex molecular pathways involved in tumor development. Interest in combining two unapproved drugs with a strong biological rationale may expedite the development of new treatment regimens for serious and life-threatening diseases.

The “combination rule” (21 CRF 300.5) refers to fixed drug combinations (i.e., drugs that are physically combined) and states that the contribution of each agent to the combination must be demonstrated. To demonstrate the contributions of specific drugs in these fixed combinations, randomized, factorial clinical trials are usually performed (e.g., drug A versus drug B versus the combination of drug A and drug B).

Individual drugs are commonly combined in oncology treatment regimens (e.g., doxorubicin, bleomycin, vinblastine, and dacarbazine; mechlorethamine, vincristine, procarbazine, and prednisone; cyclophosphamide, doxorubicin, vincristine, and prednisone). Although factorial trial designs aimed at evaluating the individual contributions of separate drugs used in combination have been recommended, these drug regimens are not the subject of the combination rule.

Issues related to the codevelopment of two investigational drugs for cancer include:

1. The amount of toxicologic data for each individual drug and the drugs in combination needed prior to the initiation of clinical studies.
2. The mechanistic rationale or animal model data needed to justify use of the investigational drugs in combination at various stages of development.
3. The rationale needed for omission of a factorial design in demonstration of effectiveness.

Although a factorial trial design is frequently used to evaluate fixed combinations, other data, including compelling mechanistic data (e.g., animal or in vitro data) may provide sufficient rationale for regulatory approval of fixed combinations or of two investigational drugs used together. The acceptance of mechanistic data would be in the setting of a highly significant treatment benefit and a favorable benefit-to-risk assessment.

The use of multiple unapproved drugs in combination will also be investigated in therapeutic areas other than oncology. The U.S. Food and Drug Administration recognizes that a clear regulatory pathway is required and that further public discussion and formal guidance in this area are required.

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REFERENCES

Economics of New Oncology Drug Development
Joseph A. DiMasi and Henry G. Grabowski

ABSTRACT

Purpose
Review existing studies and provide new results on the development, regulatory, and market aspects of new oncology drug development.

Methods
We utilized data from the US Food and Drug Administration (FDA), company surveys, and publicly available commercial business intelligence databases on new oncology drugs approved in the United States and on investigational oncology drugs to estimate average development and regulatory approval times, clinical approval success rates, first-in-class status, and global market diffusion.

Results
We found that approved new oncology drugs to have a disproportionately high share of FDA priority review ratings, of orphan drug designations at approval, and of drugs that were granted inclusion in at least one of the FDA’s expedited access programs. US regulatory approval times were shorter, on average, for oncology drugs (0.5 years), but US clinical development times were longer on average (1.5 years). Clinical approval success rates were similar for oncology and other drugs, but proportionately more of the oncology failures reached expensive late-stage clinical testing before being abandoned. In relation to other drugs, new oncology drug approvals were more often first-in-class and diffused more widely across important international markets.

Conclusion
The market success of oncology drugs has induced a substantial amount of investment in oncology drug development in the last decade or so. However, given the great need for further progress, the extent to which efforts to develop new oncology drugs will grow depends on future public-sector investment in basic research, developments in translational medicine, and regulatory reforms that advance drug-development science.

INTRODUCTION

Although progress has been made in treating many forms of cancer, there remains a strong medical need for substantial improvement. This makes the complex economics of new oncology drug development an important area to research. In recent years, rising prices and growing expenditures on oncology drugs have caused significant concern among payers and patients. At the same time, and likely due in part to expanded market opportunities, some data indicate that the development of new, often targeted, oncology therapies has recently been growing significantly. The extent to which markets will grow in the future, however, is uncertain because sponsors may face increasing resistance to what are perceived to be high and unsustainable prices, increasing competition if a substantial number of new therapies enter the market, and smaller market sizes for highly targeted therapies.

Incentives to develop new therapies also depend on the costs, risks, and length of new drug development. Pharmaceutical research and development (R&D) costs in general have been estimated to be high and rising substantially over time. Costs (at least clinical phase expenditures) have also been shown to differ by therapeutic class. Unfortunately, to date, not enough information has been available to reliably estimate R&D costs for oncology drugs. A good deal of information, however, can be gathered on other metrics of the drug development process for oncology drugs. This article will review information on the markets for new oncology drugs and present new data on the length and risks of new oncology drug development.

METHODS

To analyze various aspects of the development, regulatory, and market characteristics of new oncology drugs, we
utilized a variety of data sources. Information on new drug US clinical development and approval times were obtained from public sources and company surveys, and were complied for a Tufts Center for the Study of Drug development (CSDD) database. The US clinical phase is defined here as the time from first filing of an investigational new drug application (IND) with the US Food and Drug Administration (FDA) to study a new drug in humans to first submission to the FDA of a new drug application (NDA) or biologic license application (BLA) for marketing approval of the new drug. The approval phase is the time from first submission of an NDA or BLA to approval of the application for marketing. With regard to these development and approval times, we focus attention on therapeutic drugs and biologics that had first obtained FDA approval for US marketing from 1990 through 2005. We examined both new chemical entities and therapeutically significant new biologics. For the sake of brevity in expression, we refer to all of these compounds as new drugs. We have public NDA/BLA submission and approval dates for all of these new drugs, and dates of first IND filing (which have been validated with the FDA) for 95% of these compounds.

We analyzed clinical approval success rates based on information obtained from a publicly available business intelligence database (IMS Health’s ReD Focus) for the 20 largest pharmaceutical firms in terms of pharmaceutical sales in 2005, with supplementary information from other commercial business intelligence databases. Given the lengthy development process, only compounds that had entered clinical testing through 2002 were included in the phase transition probability analyses. Their status was tracked through the first half of 2006. In addition, because a relatively large share of the compounds that initiated clinical testing during the latter half of the success rate analysis period are still active, a separate analysis for the 1998 through 2002 period would be questionable. Instead, to obtain a sense for the direction and extent of changes over time we compared results for the entire 1993 to 2002 period with results for the 1993 to 1997 period.

A number of studies of drug industry success rates have used statistical inference techniques (mainly survival analysis) to account for the right-censoring of the data. However, given the relatively recent experience of the compounds we considered here and the length of the development process for many drugs, a significant number of compounds that we examined had not yet reached their final fate (abandonment or marketing approval), thereby making these statistical approaches somewhat unreliable. Therefore, we estimate success and phase attrition rates in a mechanistic manner. Specifically, we calculated phase transition probabilities by dividing the number of molecules that completed a given phase and entered the next phase by the difference between the number of molecules that entered the phase and those still in the phase at the time of the analysis. Such an approach should provide reasonable estimates of phase transition probabilities because the lengths of individual phases are short relative to total development times. The accuracy depends on an implicit assumption that those drugs that are still active at the time of analysis will proceed to later phases more or less in the same proportions as the estimated transition probabilities. The overall clinical success rate is then determined as the product of the phase transition probabilities. Clinical success is defined as US regulatory approval for marketing.

Data on market and other characteristics of new drug launches were obtained from IMS Health’s New Product Focus database used for a study of the quality and quantity of worldwide new drug introductions. This database reports drug launches in 68 countries since 1982. The data examined includes new biologic products, but it excludes diagnostic tests (except for radiopaques), radiologicals, over-the-counter drugs, combination vaccines, polyclonal antibodies, and biologic extracts. Launch dates were used to determine whether a new drug launch was for a first-in-class drug. Therapeutic classes for this analysis were chosen based on a unique combination of the four-digit level Anatomic Therapeutic Classification (ATC) and five-digit level Uniform System of Classification (USC) codes. The ATC and USC system are the same for many therapeutic classes, but when they differed, as a general principle the most disaggregate class from these two sources was used.

RESULTS

We first examined the number and regulatory characteristics of new oncology drug approvals in the Unites States since 1990. Table 1 lists the 68 new oncology drugs approved for marketing in the United States from 1990 to 2005, along with their NDA/BLA submission and approval dates. The FDA also approved 434 other new drugs (as defined herein) during this period. Seventy-nine percent of the approved new oncology drugs are traditional small-molecule compounds (78% of the other new drugs approved during the study period are also small molecules). If we narrow the focus on large-molecule approvals to the most common types of approved “biotech” products (recombinant proteins and monoclonal antibodies [mAbs]; excluding, for example, purified biologics), we find that 18% of the oncology drug approvals and 15% of the other drug approvals are biotech products under this definition. The biotech share of all drug approvals increased over time for both oncology and other drugs, although the rate of increase was faster for oncology drugs. The biotech shares were 8% and 9% during 1990 to 1993 for oncology and other drugs, respectively. However, the biotech shares rose to 29% and 24% during 2002 to 2005 for oncology and other drugs, respectively.

From a regulatory perspective, the oncology drugs differ markedly from other new drug approvals. As Table 2 indicates, 71% of the oncology drug approvals were given a priority review rating by the FDA, in contrast to 40% for other new drugs. Nearly half of the oncology drugs were initially approved with an orphan drug indication, while less than one in five other drugs had orphan drug status at first approval. Finally, sponsors of oncology drugs were much more often able to take advantage of at least one of the FDA’s programs to speed development (subpart E, accelerated approval, fast track). Close to half of the approved oncology drugs had some expedited access status during development, as opposed to only 13% for the other new drugs approved during the study period.

Oncology Drug Development Times

As noted, oncology drugs are disproportionately given priority ratings by the FDA, which carries with it a performance goal for faster review of marketing applications. This is reflected in the approval phase means shown in Figure 1. The FDA reviewed oncology drugs, on average, 6 months faster than other drugs. We also noted that oncology drugs were more likely to be able to take advantage of FDA expedited access programs during development. However, despite this fact, difficulties in recruiting patients and longer times needed to establish efficacy (particularly if survival is an end point) for oncology drug clinical trials can help explain why we found US clinical development times to be a year and a half longer for oncology drugs. For the period analyzed, oncology drugs took, on average, 1 year longer to move from the initiation of clinical testing in the United States to US regulatory marketing approval. Development and approval phase times are lower for medians, but the comparative results are similar. Median approval phase times are 0.3 years shorter for oncology drugs (1.0 v 1.3 years), whereas median clinical phase times are 1.5 years longer for oncology drugs (7.8 v 6.3 years).

Technical Success Rates for Oncology Drug Development

To examine technical success rates and phase transition rates for investigational oncology and other drugs, we obtained data on the pipelines of the 20 pharmaceutical firms with the most...
Table 1. New Oncology Compounds Approved in the United States, 1990-2005

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Sponsor</th>
<th>NDA Submission Date</th>
<th>NDA Approval Date</th>
</tr>
</thead>
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<tr>
<td>Alemtuzumab</td>
<td>Campath</td>
<td>Berlex</td>
<td>12/23/1999</td>
<td>5/7/2001</td>
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<tr>
<td>Bortezomib</td>
<td>Velcade</td>
<td>Millennium</td>
<td>1/21/2003</td>
<td>5/13/2003</td>
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<td>Xeloda</td>
<td>Roche</td>
<td>10/31/1997</td>
<td>4/30/1998</td>
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<tr>
<td>Cetuximab</td>
<td>Erbitux</td>
<td>Imclone</td>
<td>8/14/2003</td>
<td>2/12/2004</td>
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<tr>
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<td>Leucatin</td>
<td>Ortho</td>
<td>12/21/1991</td>
<td>2/26/1993</td>
</tr>
<tr>
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<td>Ontak</td>
<td>Ligand</td>
<td>12/9/1997</td>
<td>2/5/1999</td>
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<tr>
<td>Gancitoxan</td>
<td>Niladron</td>
<td>Hoechst Marion Roussel</td>
<td>3/7/1994</td>
<td>9/19/1996</td>
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<tr>
<td>Ibritumomab</td>
<td>Zevalin</td>
<td>Ides</td>
<td>10/20/1997</td>
<td>2/19/2002</td>
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<td>Imatinib mesylate</td>
<td>Gleevec</td>
<td>Novartis</td>
<td>2/27/2001</td>
<td>5/10/2001</td>
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<tr>
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<td>Nilotinib</td>
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<td>12/16/1999</td>
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<td>Bayer/DNx</td>
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<td>8/13/1998</td>
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<td>Zometa</td>
<td>Novartis</td>
<td>12/21/1999</td>
<td>8/20/2001</td>
</tr>
</tbody>
</table>

Abbreviation: NDA, new drug application.
pharmaceutical sales in 2005. We were able to identify 838 drugs that had entered the clinical testing pipeline for the first time anywhere in the world from 1993 to 2002. Of these drugs, 175 (21%) were investigated for oncology indications. A somewhat higher proportion of the investigational oncology drugs are large molecules (28%) than is the case for the approved drugs noted herein. The oncology drugs tended to be investigated for more indications than was the case for other investigational drugs. Whereas 46% of other investigational drugs were tested for more than one indication before an approval for marketing, 57% of the oncology drugs were investigated for multiple indications. More notably, nearly one third of the oncology drugs (32%) were tested in at least four indications, whereas only 9% of the other drugs were examined in four or more indications before an original approval for marketing.

Figure 2 shows estimated clinical phase transition probabilities for investigational oncology drugs that first entered clinical testing from 1993 to 1997 and 1993 to 2002. The results indicate that one half of the oncology drugs that entered the expensive phase III clinical testing phase never make it to US regulatory approval (although, the approval rate is somewhat higher when the longer timeframe for drugs entering clinical testing is considered). The product of the phase transition probability estimates yields an estimate of the clinical approval phase III testing is notably lower for oncology drugs. Overall, though, the approval success rates for drugs entering the clinical testing pipeline are essentially the same.

The results in Figure 2 are for all oncology drugs that were in the firms’ clinical testing pipelines at some point. The data include compounds that were licensed in at some point in development by one of the firms and a smaller proportion of drugs that these firms licensed out to firms outside of the group of 20. Drugs that are licensed may have somewhat higher success rates than those that are developed entirely under the auspices of a given firm (self-originated) because of due diligence prescreening and because they tend to be licensed after the drugs had progressed to later clinical phases. Figure 3 shows estimates of phase transition probabilities and the overall clinical approval success rate for self-originated oncology drugs compared with the results for all oncology drugs. The self-originated compounds have a slightly lower approval success rate than is the case for all oncology drugs.

Finally, we examined transition probability and success rate results for oncology drugs compared with all other drugs. The results in Figure 4 cover all drugs for the entire 1993 to 2002 period. Oncology drugs have a higher likelihood of progressing to later clinical phases, but the success rate once drugs reach expensive phase III testing is notably lower for oncology drugs. Overall, though, the approval success rates for drugs entering the clinical testing pipeline are essentially the same.
Biotech products, particularly mAbs, have become increasingly prevalent in oncology investigational drug pipelines. The data for the 20 firms examined here are too limited with regard to mAbs to provide reliable success rate estimates. However, for a recent analysis of biopharmaceutical R&D costs, DiMasi and Grabowski examined clinical approval success rates for 522 recombinant proteins and mAbs that first entered clinical testing from 1990 to 2003 for what is likely either the population or something close to the population of such products. More than half (54%) of the mAbs in this data set were examined for oncology indications. The clinical approval success rate for the biotech products in aggregate was 30%, but only 19% for mAbs. Further analysis of that data set shows that the estimated success rate for the subset of oncology mAbs is also 19%. The data do suggest, however, an increasing trend in success rates for mAbs in general.

**Market Attributes and Diffusion of Oncology Drugs: Comparative Trends**

In a recent article, Grabowski and Wang examine trends in various attributes of worldwide new drug introductions over the period 1982 to 2003. In particular, they consider trends in drug “innovativeness” as indicated by the number of first-in-class introductions. These are essentially new drugs with a novel mechanism of action. Second, they consider trends in the global diffusion of worldwide new drug introductions. In particular, they define a new drug as global when it is launched in a majority of the world’s largest drug markets. Global diffusion is an indicator of both commercial as well as therapeutic importance. They also focus on the growth in biotech products and orphan drug products, two groups of products with increasing impact on the biopharmaceutical industry over the last two decades.

One key finding of the Grabowski and Wang analysis is that the number of first-in-class drug introductions has been increasing over time. This contrasts with a downward trend in overall new drug introductions that has been discussed by many observers. This latter trend has been cited as evidence for the declining research productivity of the pharmaceutical industry in recent years. However, this view must be qualified by the positive trend in drug innovativeness, as reflected by the increasing number of first-in-class products. Of course, therapeutic benefits are also obtained from follow-on introductions in a new drug class as well as by combination therapies involving new and established drugs. Significant drug progress occurs both by introduction of novel new classes and by the evolution of products in these classes after the first mover is introduced. However, first-in-class drug introductions represent important milestones in documenting the extent of drug innovation over time.

A second major finding of the Grabowski and Wang analysis is the increasing global character of new drug introductions. Grabowski and Wang found that nearly half (47%) of all 1993 to 2003 new drug introductions were launched in a majority of the G7 countries. (The G7 countries were chosen as a relevant benchmark because they constitute the largest seven drug markets in terms of sales. These countries are the United States, Japan, the United Kingdom, Germany, France, Italy, and Canada.) This compares to 37% for the 1982 to 1992 period. Furthermore, a prior study of new drug introductions for the 1970 to 1983 period found that only 24% of new drugs were characterized as global entities.

Grabowski and Wang also found that biotech drugs account for a rising portion of all new drugs over the 1982 to 2003 period. The rapid growth of biotech compounds is reflected in the fact that biotech drugs accounted for only 4% of worldwide introductions in the period 1982 to 1992, but this increased to 16% in the 1993 to 2003 period. Furthermore, more than half of these biotech compounds originated in US firms. The growth of biotech drugs is particularly significant because they have been a major source of both first-in-class and global drugs. They also have a strong presence in the oncology class.

In this review article, we are particularly interested in how oncology drugs compare with other therapeutic classes with respect to these drug industry attributes considered in the Grabowski and Wang analysis. In this regard, Table 3 provides a breakdown of the distribution of new drugs by therapeutic areas and various subcategories using Grabowski and Wang’s sample of 919 worldwide introductions for the 1992 to 2003 period. All therapeutic areas with 5% or more of the total number of new drug introductions total are listed separately. The remaining areas with small numbers of introductions are combined into the miscellaneous category.

**Table 3. Therapeutic Area Distribution of New Drugs for 1982-2003 Worldwide New Drug Introductions**

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>All New Drugs</th>
<th>Global New Drugs</th>
<th>First-in-Class New Drugs</th>
<th>Biotech New Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td>130</td>
<td>57</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>128</td>
<td>45</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Systemic anti-infectives</td>
<td>127</td>
<td>62</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Oncology</td>
<td>99</td>
<td>52</td>
<td>21</td>
<td>25</td>
</tr>
<tr>
<td>Alimentary tract and metabolism</td>
<td>86</td>
<td>29</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Musculoskeletal system</td>
<td>70</td>
<td>28</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Blood and blood-forming organs</td>
<td>59</td>
<td>24</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>57</td>
<td>21</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Dermatologicals</td>
<td>49</td>
<td>21</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>118</td>
<td>49</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>654</strong></td>
<td><strong>259</strong></td>
<td><strong>75</strong></td>
<td><strong>59</strong></td>
</tr>
</tbody>
</table>

**NOTE.** Worldwide introductions by year are obtained from the IMS New Product Focus database. A global new drug is defined as a new drug introduced in a majority of the G7 countries. A first-in-class new drug is defined as the first drug introduction in a specific five-digit Uniform System of Classification category or a four-digit Anatomic Therapeutic Classification category, based on information contained in the IMS databases. Biotech drug classification is based on IMS designation in its New Product Focus database. A few drugs are classified into more than one therapeutic area so category totals may not equal the sum of the specific therapeutic areas.
Table 3 indicates that oncology was the fourth largest therapeutic area in terms of the number of worldwide introductions (99) behind the CNS, cardiovascular, and systemic anti-infective categories. At the same time, the Table shows that oncology drugs had the most first-in-class and biotech drugs. It also ranked third in terms of global new drug introductions across all the therapeutic area categories. (The miscellaneous category is not included in this comparison, given that it’s a conglomerate of many smaller drug categories.)

It is instructive to consider the share of oncology drugs that embody these various attributes compared with other major drug classes. Consider this information for the four largest therapeutic areas in Table 3: the CNS, cardiovascular, anti-infective, and oncology categories. Oncology is particularly distinguished by the large percentage of its new drug introductions that were first-in-class. Over the 1992 to 2003 period, 21% of oncology introductions were first-in-class entities, as compared with less than 10% of the introductions in the other three classes. This figure also shows that more than half of all oncology introductions were classified as global drugs as compared with 35% to 49% of the drugs in the other three therapeutic areas.

The results in Table 3 demonstrate that the oncology therapeutic area has been a focal point for the introduction of innovative first-in-class compounds with a high rate of global diffusion. Oncology also has been an increasing focus of biotech drug R&D. As can be seen from the data in Table 3, 25% of oncology drug approvals are based on biotechnology techniques, compared with 5% or less in the three other major classes. This is a striking difference. Biotech products are an important driver of strong innovative performance observed for the oncology class in recent years.

**Orphan Drug Act and Oncology Drugs**

The oncology drug class has benefited from the passage of the Orphan Drug Act in 1983. The Act specifically applies to illness or conditions with a prevalence of less than 200,000 individuals. This Act created a number of incentives designed to spur R&D investment for rare conditions and illnesses. First, the Act instructed the FDA to implement new protocols to facilitate orphan drug approvals, or advanced counseling to create a more effective R&D process. Second, Congress created a 50% tax credit for clinical trial expenditures for orphan drug designations. Third, a 7-year marketing exclusivity was granted for FDA-designated orphan drug indications, apart from any patent protection that existed on these drugs.

These provisions have been an important catalyst for the development of oncology drugs for rarer forms of cancer. As noted herein, nearly half of the oncology drugs introduced had an orphan indication approved at the time of initial marketing approval. Once again, this is a much higher percentage than what is observed for other drugs. In an earlier analysis of the first dozen years of the US Orphan Drug Act, the authors found that a total of 502 approved drugs and clinical drug candidates obtained orphan drug designation from the FDA. The leading indication category was cancer with 89 drug entities (17.7% of all drugs that received an orphan drug designation).

Grabowski has analyzed the distribution of sales for 27 orphan drugs introduced in the 1990 to 1994 period. While there are a few orphan products with large annual sales, the median orphan drug in this sample had peak annual worldwide sales of only $29.5 million. The median nonorphan introduction over this same period had peak global sales of $236 million.

The group of 27 orphan compounds introduced from 1990 to 1994 included six cancer treatments (the largest indication category). All of these six drugs also received a priority drug rating from the FDA as well as orphan drug designation. (The six cancer drug introductions receiving orphan drug approval over the 1990-1994 period were al-tretamine, cladribine, fludarabine phosphate, idarubicin, pentostatin, and teniposide.) These six orphan therapies had peak global sales that ranged from $2 million to $103 million. The median and mean global peak sales for this set of orphan cancer treatments were $12 million and $27 million, respectively.

The Orphan Drug Act clearly has been an important stimulant of new cancer treatments for small patient populations with correspondingly modest levels of sales. Orphan drugs can realize a positive return on investment with smaller sales levels than can non-orphan products given their very different economics. First, as discussed, they have much smaller up-front R&D costs, with typically smaller sized clinical trials and the special tax credits. In addition, orphan drugs often have fewer competitors and are typically prescribed primarily by specialists. Hence, they tend to have lower promotional and distribution costs.

**Commercial Significance of Oncology Drugs**

As in the case of other therapeutic categories, the distribution of sales for cancer drugs is highly skewed. Although the oncology class includes a number of orphan drug compounds, it also has many drugs that are in the top ranks of all drug products. These are products with annual worldwide sales in excess of $1 billion. With an increased knowledge of the molecular basis of cancer, the oncology class has been characterized in recent years by the introduction of therapeutically important monoclonal antibodies and other targeted pharmaceutical agents. These include rituximab, trastuzumab, imatinib, and bevacuzimab. All of these drugs have reached the market between 1997 and 2004. These are now among the leading drug therapies ranked in terms of sales.

The oncology drug class is the fastest growing therapeutic category of all the major drug classes in terms of market sales. The rapid growth of the cancer area is reflected in the annual sales of the top 200 pharmaceuticals. Med Ad News chronicles this each year. Our analyses of development candidates and marketed products abstracts from the supportive care products used to ameliorate adverse effects such as anemia, neutropenia, and nausea and vomiting that are frequently experienced with treatments of diseases such as cancer and AIDS. It is worth noting that the leading biologically derived drugs for anemia and neutropenia have also experienced rapid growth in recent years. For example the supportive care products for the two conditions (for example, Procrit/Eprex [epoetin alfa; Amgen, Thousand Oaks, CA], Aranesp [darboepoetin alfa; Amgen], Epogen [epoetin alfa; Amgen], and Neulasta/Neupogen [Pegfilgrastim/Filgrastim; Amgen] had global sales of $14.3 billion in 2005 compared with $7.6 billion in 2001), according to the MedAd News’ Surveys of 200 Best-Selling Prescription Drugs for these years. The Med Ad list of the top 200 selling pharmaceuticals for 2001 included 14 cancer drugs with a total of $10.5 billion dollars worldwide sales.

There was only one single drug entity (Taxol; paclitaxel; Bristol-Myers Squibb, New York, NY) that had sales in excess of $1 billion. By contrast, the 2005 list of top 200 pharmaceuticals had $23.5 billion in total cancer drug sales with 11 of 18 cancer drugs on the list with sales in excess of $1 billion.
The rapid growth of sales in the cancer area has been driven by the fast uptake of targeted breakthrough drug products such as Rituxan (rituximab; Genentech, South San Francisco, CA), Gleevec (imatinib mesylate; Novartis, East Hanover, NJ), Herceptin (trastuzumab; Genentech), and Avastin (bevacizumab; Genentech). These four products by themselves accounted for $8.4 billion in worldwide sales in 2005 and were the four largest selling cancer treatments in the first quarter of 2006. There is also evidence of a strong pipeline of targeted therapies in development in both the biotechnology and pharmaceutical industry. This is being fostered by the increasing knowledge base emanating from basic biomedical research as well as a favorable economic environment for drug innovations in the oncology therapeutic area. Hence, the continued introduction of innovative new oncology products is likely to occur over the foreseeable future.

CONCLUSION

In comparison with other new drugs, new oncology drugs tend to be distinctly different in terms of regulatory status and development metrics. A substantial majority of first approvals for marketing of oncology drugs (71%) have received priority reviews of their marketing applications from the FDA for drugs approved in the United States from 1990 to 2005. This compares with the 40% rate at which other new drugs received a priority review status from the FDA. Approved oncology drugs have also had a disproportionately higher share of orphan drug approvals, and approved oncology drugs were able to take advantage of FDA programs to speed development at a rate that was 3.5 times higher than that for other new drugs.

Despite more often obtaining regulatory advantages from programs to speed clinical development and regulatory review of marketing applications, US clinical development times and total times from the start of US clinical testing to marketing approval were longer, on average, for oncology drugs than for other drugs approved from 1990 to 2005. The recent efforts by the FDA to establish new approaches to assess the efficacy and safety of investigational drugs through its Critical Path Initiative hold the promise of shorter development times for oncology and other drugs. Of particular relevance for oncology drugs is the Critical Path Initiative’s goal to find and validate new biomarkers.

Although we found that oncology and other drugs had marketing approval success rates for drugs entering the clinical testing pipeline that were similar, a higher percentage of oncology drugs failed after entering phase III testing than did other drugs. Phase III is generally the most expensive clinical development phase. If all other things were equal, this result would imply higher average development costs for oncology drugs (taking into account the costs of drug failures). Methods to better prioritize the choice of investigational oncology drugs for a transition from phase II to phase III testing could yield substantial gains. As has been suggested elsewhere, a greater investment in gathering appropriate information in phase I and II trials can help achieve this objective. The full capitalized cost per approved new drug (cash flow plus time costs) depends on out-of-pocket expenditures, approval success and phase attrition rates, and development and regulatory approval times. On the basis of data obtained from a commercial business intelligence database, Adams and Brantner estimated the R&D cost per approved new drug for development that occurred primarily during the 1990s to be 20% higher for oncology drugs compared to the average for all drugs ($1,042 million compared to $868 million), although they also provide an estimate for breast cancer development that is 30% below average. However, their cost differentials by therapeutic class were based solely on differences in estimated clinical approval and phase transition rates, and development times. (Through a number of simulation experiments, DiMasi demonstrates the extent to which R&D cost estimates are sensitive to changes in clinical approval and phase transition rates, and development times.) They did not have data on differences in cash flows by class. To our knowledge, there have been no published studies with enough data on oncology drug R&D cash flows to provide estimates of average oncology out-of-pocket R&D costs. A number of factors determine out-of-pocket expenditures, including discovery costs; R&D costs for chemistry, manufacturing, and controls; the costs of providing clinical testing supplies; infrastructure costs; the complexity of treating patients with the conditions investigated; the number of subjects tested per indication; and the number of indications investigated before approval. We currently know very little about most of these factors, although results presented here suggest that oncology drugs tend to be tested in many more uses before first marketing approval than is the case for drugs in general.

Despite the considerable hurdles in developing new oncology drugs, the new oncology drugs that have been approved in recent years have been relatively novel and commercially successful. The evidence indicates that approved oncology drugs were more often first-in-class and diffused more widely to major international markets than was the case for drugs in other classes. Nonetheless, the need for new therapies that are more effective and safe is still substantial. The incentives and scientific opportunities to develop highly effective and safer oncology drugs in the future will depend critically on public-sector investment in basic research, developments in translational medicine, and regulatory reforms that advance drug-development science.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Data analysis and interpretation: Joseph A. DiMasi, Henry G. Grabowski
Manuscript writing: Joseph A. DiMasi, Henry G. Grabowski
Final approval of manuscript: Joseph A. DiMasi
REFERENCES

overall survival,” said Richard Pazdur, M.D., director of the Office of Oncology Drug Products in the FDA’s Center for Drug Evaluation and Research. “In March, we

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Zelboraf was reviewed under the FDA’s priority review program that provides for an expedited six-month review of drugs that may offer major advances in

“This has been an important year for patients with late-stage melanoma. Zelboraf is the second new cancer drug approved that demonstrates an improvement in

The BRAF protein is normally involved in regulating cell growth, but is mutated in about half of the patients with late-stage melanomas. Zelboraf is a BRAF inhibitor

Zelboraf is specifically indicated for the treatment of patients with melanoma whose tumors express a gene mutation called BRAF V600E. The drug has not been studied in patients whose melanoma tests negative for that mutation by an FDA approved diagnostic.

Zelboraf is being approved with a first-of-a-kind test called the cobas 4800 BRAF V600 Mutation Test, a companion diagnostic that will help determine if a patient’s melanoma cells have the BRAF V600E mutation.

The BRAF protein is normally involved in regulating cell growth, but is mutated in about half of the patients with late-stage melanomas. Zelboraf is a BRAF inhibitor that is able to block the function of the V600E-mutated BRAF protein.

“This has been an important year for patients with late-stage melanoma. Zelboraf is the second new cancer drug approved that demonstrates an improvement in overall survival,” said Richard Pazdur, M.D., director of the Office of Oncology Drug Products in the FDA’s Center for Drug Evaluation and Research. “In March, we approved Vemurafenib (vemurafenib), another new treatment for late-stage melanoma that also showed patients live longer after receiving the drug.”

Zelboraf was reviewed under the FDA’s priority review program that provides for an expedited six-month review of drugs that may offer major advances in treatment or that provide a treatment when no adequate therapy exists. Zelboraf and the companion BRAF V600E test are being approved ahead of the drug’s Oct. 28, 2011 goal date and the companion diagnostics’ Nov. 12, 2011 goal date.

Zelboraf’s safety and effectiveness were established in a single international trial of 675 patients with late-stage melanoma with the BRAF V600E mutation who had not received prior therapy. Patients were assigned to receive either Zelboraf or dacarbazine, another anti-cancer therapy. The trial was designed to measure overall survival (the length of time between start of treatment and death of a patient).

The median survival (the length of time a patient lives after treatment) of patients receiving Zelboraf has not been reached (77 percent still living) while the median survival for those who received dacarbazine was 8 months (64 percent still living).

“Today’s approval of Zelboraf and the cobas test is a great example of how companion diagnostics can be developed and used to ensure patients are exposed to highly effective, more personalized therapies in a safe manner,” said Alberto Gutierrez, Ph.D., director of the Office of In Vitro Diagnostic Device Evaluation and Safety in the FDA’s Center for Devices and Radiological Health.

The FDA’s approval of the cobas 4800 BRAF V600 Mutation Test was based on data from the clinical study that also evaluated the safety and effectiveness of Zelboraf. Samples of a patient’s melanoma tissue were collected to test for the mutation.

The most common side effects reported in patients receiving Zelboraf included joint pain, rash, hair loss, fatigue, nausea, and skin sensitivity when exposed to the sun. About 26 percent of patients developed a skin-related cancer called cutaneous squamous cell carcinoma, which was managed with surgery. Patients treated with Zelboraf should avoid sun exposure.

Zelboraf is being approved with a Medication Guide to inform health care professionals and patients of Zelboraf’s potential risks.

In July 2011, the FDA issued a new draft guidance to facilitate the development and review of companion diagnostics. The guidance, currently available for public comment, is intended to provide companies with guidance on the agency’s policy for reviewing a companion diagnostic and the corresponding drug therapy.

Melanoma is the leading cause of death from skin disease. The National Cancer Institute estimated that 68,130 new cases of melanoma were diagnosed in the United States during 2010; about 8,700 people died from the disease.

Zelboraf is marketed by South San Francisco based-Genentech, a member of the Roche Group. The cobas 4800 BRAF V600 Mutation Test is manufactured by Roche Molecular Systems in Pleasanton, Calif.

For more information:

FDA: Office of Oncology Drug Products

FDA: Office of In Vitro Diagnostics

FDA: Draft Guidance – In Vitro Companion Diagnostic Devices

FDA: Approved Drugs: Questions and Answers

NCI: Melanoma

CDC: Skin Cancer

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The U.S. Food and Drug Administration today approved Xalkori (crizotinib) to treat certain patients with late-stage (locally advanced or metastatic), non-small cell lung cancers (NSCLC) who express the abnormal anaplastic lymphoma kinase (ALK) gene.

Xalkori is being approved with a companion diagnostic test that will help determine if a patient has the abnormal ALK gene, a first-of-a-kind genetic test called the Vysis ALK Break Apart FISH Probe Kit. It is the second such targeted therapy approved by the FDA this year.

This ALK gene abnormality causes cancer development and growth. About 1 percent to 7 percent of those with NSCLC have the ALK gene abnormality. Patients with this form of lung cancer are typically non-smokers. Xalkori works by blocking certain proteins called kinases, including the protein produced by the abnormal ALK gene. Xalkori is a pill taken twice a day as a single-agent treatment.

"The approval of Xalkori with a specific test allows the selection of patients who are more likely to respond to the drug," said Richard Pazdur, M.D., director of the Office of Oncology Drug Products in the FDA's Center for Drug Evaluation and Research. "Targeted therapies such as Xalkori are important options for treating patients with this disease and may ultimately result in fewer side effects."

Xalkori's safety and effectiveness were established in two multi-center, single-arm studies enrolling a total of 255 patients with late-stage ALK-positive NSCLC. A sample of a patient's lung cancer tissue was collected and tested for the ALK gene abnormality prior to study enrollment. The studies were designed to measure objective response rate, the percentage of patients who experienced complete or partial cancer shrinkage. Most patients in the studies had received prior chemotherapy.

In one study, the objective response rate was 50 percent with a median response duration of 42 weeks. In another, the objective response rate was 61 percent with a median response duration of 48 weeks.

The FDA based its approval of the Vysis ALK Break Apart FISH Probe Kit on data from one of the studies.

Xalkori was reviewed under the FDA's priority review program, which provides for an expedited six-month review of drugs that may offer major advances in treatment or that provide a treatment when no adequate therapy exists.

Xalkori is being approved under the FDA's accelerated approval program, which allows the agency to approve a drug to treat a serious disease based on clinical data showing that the drug has an effect on an endpoint that is reasonably likely to predict a clinical benefit to patients. The program is designed to provide patients with earlier access to promising new drugs, followed by further studies to confirm the drug's clinical benefit.

Xalkori and the companion Vysis ALK Break Apart FISH Probe Kit were approved ahead of the drug's Sept. 30, 2011, FDA review goal date and the companion diagnostics' Sept. 28, 2011, review goal date.

"The trend in oncology research continues towards targeted therapies," said Alberto Gutierrez, Ph.D., director of the Office of In Vitro Diagnostic Device Evaluation and Safety in the FDA's Center for Devices and Radiological Health. "This test is an example of the important role companion diagnostics play in determining that the safest and most effective treatments are promptly delivered to patients living with serious and life-threatening diseases."

The most common side effects reported in patients receiving Xalkori included vision disorders, nausea, diarrhea, vomiting, swelling (edema), and constipation. Vision disorders included visual impairment, flashes of light, blurred vision, floaters, double vision, sensitivity to light, and visual field defects. Xalkori use has also been associated with inflammation of the lung tissue (pneumonitis), which can be life-threatening. Patients with treatment-related pneumonitis should permanently stop treatment with Xalkori. The drug should not be used in pregnant women.

In July 2011, FDA issued a draft guidance industry on the agency's policy for reviewing a companion diagnostic and the corresponding drug therapy. The guidance is currently available for public comment.

Xalkori is marketed by New York City-based Pfizer. The Vysis ALK Break Apart FISH Probe Kit is marketed by Abbott Molecular Inc. of Des Plaines, Ill.

For more information:

- FDA: Office of Oncology Drug Products
- FDA: Office of In Vitro Diagnostics
- FDA: Draft Guidance – In Vitro Companion Diagnostic Devices
- FDA: Approved Drugs: Questions and Answers
- NCI: Non-small cell lung cancer

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.
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For questions regarding this draft document contact (CDER) Colleen Locicero 301-796-1114.

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Guidance for Industry¹

Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination

This draft guidance, when finalized, will represent the Food and Drug Administration’s (FDA’s) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist sponsors in the codevelopment² of two or more novel (not previously marketed) drugs to be used in combination to treat a disease or condition. The guidance provides recommendations and advice on how to address certain scientific and regulatory issues that will arise during codevelopment. It is not intended to apply to development of fixed-dose combinations of already marketed drugs or to development of a single new investigational drug to be used in combination with an approved drug or drugs. The guidance is also not intended to apply to vaccines, gene or cellular therapies, blood products, or medical devices.³

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.

¹ This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.
² Codevelopment herein refers to the concurrent development of two or more drug products with the intent that the products be used in combination to treat a disease or condition.
³ For purposes of this guidance, the term drug includes therapeutic biological products that are regulated by CDER. Consult the Therapeutic Biologics web page for further information on the types of biological products to which this guidance applies: www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/default.htm
Combination therapy is an important treatment modality in many disease settings, including cancer, cardio-vascular disease, and infectious diseases. Recent scientific advances have increased our understanding of the pathophysiological processes that underlie these and other complex diseases. This increased understanding has provided further impetus for new therapeutic approaches using combinations of drugs directed at multiple therapeutic targets to improve treatment response or minimize development of resistance. In settings in which combination therapy provides significant therapeutic advantages, there is growing interest in the development of combinations of investigational drugs not previously developed for any purpose.

Because the existing developmental and regulatory paradigm focuses primarily on assessment of the effectiveness and safety of a single new investigational drug acting alone, or in combination with an approved drug, FDA believes guidance is needed to assist sponsors in the codevelopment of two or more unmarketed drugs. Although interest in codevelopment has been most prominent in oncology and infectious disease settings, codevelopment also has potential application in other therapeutic settings. Therefore, this guidance is intended to describe a high-level, generally applicable approach to codevelopment of two or more unmarketed drugs. It describes the criteria for determining when codevelopment is an appropriate option, makes recommendations about nonclinical and clinical development strategies, and addresses certain regulatory process issues.

III. DETERMINING WHETHER CODEVELOPMENT IS AN APPROPRIATE DEVELOPMENT OPTION

Concurrent development of two or more novel drugs for use in combination generally will provide less information about the safety and effectiveness of the individual drugs than would be obtained if the individual drugs were developed alone. How much less will vary depending on a variety of factors, including the stage of development at which the individual drug components cease to be studied independently. For example, in codevelopment scenarios in which rapid development of resistance to monotherapy is a major concern, it may not be possible or appropriate to obtain clinical data for the individual components of the combination beyond phase 1 testing. Because codevelopment will generally provide less information about the safety and effectiveness of the individual drugs, it will present greater risk compared to development of an individual drug. Therefore, FDA believes that codevelopment should ordinarily be reserved for situations that meet the following criteria:

- The combination is intended to treat a serious disease or condition.
- There is a compelling biological rationale for use of the combination (e.g., the agents inhibit distinct targets in the same molecular pathway, provide inhibition of both a primary and compensatory pathway, or inhibit the same target at different binding sites to decrease resistance or allow use of lower doses to minimize toxicity).
- A preclinical model (in vivo or in vitro) or short-term clinical study on an established biomarker suggests that the combination has substantial activity and provides greater than...
additive activity or a more durable response (e.g., delayed resistance) compared to the individual agents alone.

- There is a compelling reason for why the agents cannot be developed individually (e.g., monotherapy for the disease of interest leads to resistance and/or one or both of the agents would be expected to have very limited activity when used as monotherapy).

FDA recommends that sponsors consult with FDA on the appropriateness of codevelopment before initiation of clinical development of the combination.

IV. NONCLINICAL CODEVELOPMENT

A. Demonstrating the Biological Rationale for the Combination

The biology of the disease, pathogen, or tumor type should be sufficiently understood to provide a plausible biological rationale for the use of combination therapy to treat the disease or condition. For example, in an oncology setting the biological rationale may be to intervene at different steps in the cell proliferation pathway. The biological rationale for a combination anti-infective therapy may be to target different metabolic pathways or different steps in the replication cycle of the pathogen to reduce the chance of developing resistance to the therapy or increase efficacy in treating disease caused by resistant organisms (e.g., multidrug-resistant atypical tuberculosis).

Sponsors should develop evidence to support the biological rationale for the combination in an in vivo (preferable) or in vitro model. The model should compare the activity of the combination to the activity of the individual components. Ordinarily, the model should demonstrate that, compared to the individual components, the combination has substantial activity and provides greater than additive activity or a more durable response in a pathophysiological process considered pertinent to the drug’s intended use in humans. An animal model of activity generally would not be necessary. However, if there is an animal model relevant to the human disease, valuable activity data, as well as information about the relative doses of the drugs, might be obtained from evaluating the combination in that model.

B. Nonclinical Safety Characterization

For detailed recommendations regarding nonclinical safety characterization for two or more investigational drugs to be used in combination, sponsors should consult the recently revised International Conference on Harmonisation (ICH) Guidance on Nonclinical Safety Studies. Section XVII of that guidance (Combination Drug Toxicity Testing) includes a discussion of nonclinical safety studies appropriate in a combination drug development setting involving two early stage entities. The ICH guidance defines early stage entities as compounds with limited clinical experience (i.e., phase 2 studies or less), so the discussion is specifically applicable to the

V. CLINICAL CODEVELOPMENT

This section provides a general roadmap and guiding principles for concurrent clinical development of two or more investigational drugs to be used in combination. It includes recommendations for characterizing the clinical safety and effectiveness of the combination and, to the extent needed or possible, the individual components of the combination.

Note: The appropriate review division should always be consulted on the specifics of a given clinical development program.

A. Early Human Studies (Phase 1)

The main objectives of early studies in humans are to characterize the safety and pharmacokinetics of the individual components and then the combination and to provide data to support appropriate dosing for the combination in phase 2 testing.

1. Safety of the Individual Components

Whenever possible, the safety profile of each individual drug should be characterized in phase 1 studies in healthy volunteers in the same manner as would be done for development of a single drug, including determination of the maximum tolerated dose (MTD), the nature of the dose limiting toxicity (DLT), and pharmacokinetic parameters. If there is a useful measure (e.g., biomarker) of pharmacologic activity, it will also be important to determine dose-response for that measure. If testing in healthy volunteers is not possible (e.g., if nonclinical data suggest a drug may be genotoxic or otherwise unacceptable for studies in healthy volunteers), the safety profile of the individual drugs should be evaluated in patients with the disease of interest. These safety data will guide decisions in later studies about starting doses, dose escalation increments, and final dose selection.

If it is not possible to characterize the safety of the individual drugs in humans (e.g., where drug toxicity prevents use of healthy volunteers and monotherapy would be unethical in patients with the disease of interest), the sponsor should conduct nonclinical studies of the combination to support initial dosing of the combination in humans. The nonclinical data for the combination should include pharmacokinetic (absorption, distribution, metabolism, and excretion) and toxicokinetic data and appropriate biomarker/target inhibition, if relevant.
2. Safety and Dosing of the Combination

For initial human effectiveness studies of the combination, the combination starting dose, dosing escalation intervals, and doses to be used in dose-response studies should be determined based on phase 1 safety data for the individual components, if available. If phase 1 safety data for the components are unavailable, nonclinical data for the combination will be needed to determine the initial combination dose in humans (see previous paragraph). Phase 1 safety studies of the combination could also be conducted — for example, sequential testing in which subjects get drug A, then drug B, then AB — to support dosing in subsequent studies.

B. Clinical Pharmacology

The sponsor should conduct the same clinical pharmacology studies for each of the individual drugs in the combination as would be done if the drugs were being developed separately. In general, such studies include the assessment of bioavailability, characterization of pharmacokinetics, mass balance, the evaluation of effects of intrinsic (such as renal impairment and hepatic impairment) and extrinsic (such as food effect and drug interactions) factors on pharmacokinetics or pharmacodynamics, and exposure-response. Studies to address intrinsic and extrinsic factors could be conducted with the combination instead of the individual drugs.

The evaluation of drug interaction potential follows the same sequence as in other development programs; results of in vitro drug metabolism and drug transporter studies inform the need for in vivo drug interaction studies. The role of pharmacogenomics should be investigated and incorporated into the combination drug development plan to identify potential sources of pharmacokinetic or pharmacodynamic variability.

Dose-response should be evaluated for each drug of the combination. The results of such studies should be used to determine doses to further explore for the combination. If the drug products cannot be administered alone, various doses of each drug administered as the combination should be assessed.

If one drug has no activity or minimal activity by itself, dose-response should be assessed when the drug products are administered in combination using a number of doses of the active drug and the inactive drug. The same approach should be used in evaluating dose-response for the combination of drugs where each drug has minimal activity when used alone.

In addition to evaluating dose-response, response should be evaluated with respect to systemic drug concentration to provide insight into efficacy and safety as a function of drug exposure. Concentration-response assessments should be done in both phase 2 and phase 3 trials. To increase exposure ranges in phase 3 and to further assess dose-response, the incorporation of more than one dose of each of the drugs used in the combination in the phase 3 trials should be considered.
C. Proof of Concept Studies (Phase 2)

In general, phase 2 testing should accomplish the following to the extent needed for a given combination (e.g., to the extent not sufficiently established by existing data):

- Demonstrate the contribution of each component of the combination to the extent possible and needed (given available nonclinical and pharmacologic data);
- Provide evidence of the effectiveness of the combination; and
- Optimize the dose or doses of the combination for phase 3 trials.

The amount and types of clinical data needed and appropriate study designs will vary depending on the nature of the combination being developed, the disease, and other factors. For the types of combinations contemplated by this guidance, it will often be inappropriate to use monotherapy treatment arms in studies of the disease of interest, or it will be possible to administer the components of the combination as monotherapy only for short durations. In these circumstances, the study design typically employed to determine the contributions of the components to the combination — a four-arm factorial design comparing the combination to individual components and placebo or standard of care (SOC) therapy (AB v. A. v. B v. placebo or SOC) — will have limited utility. The following scenarios illustrate possible phase 2 study designs for combinations of two investigational drugs in different situations.

Scenario 1: The components of the combination cannot be administered individually

If in vivo or in vitro models, or phase 1 or other early clinical studies make clear that the components of the combination cannot be administered individually in clinical trials in the disease of interest (e.g., because such testing would involve administering treatment known to be ineffective as monotherapy), or can’t be administered as monotherapy for the duration needed to evaluate effectiveness (e.g., because of rapid development of resistance), proof-of-concept evidence for the combination ordinarily should come from a study directly comparing the combination (AB) to SOC. Alternatively, if SOC is known to be an effective therapy (not solely palliative), an add-on design could be used comparing the combination plus SOC to SOC alone.

In some resistance scenarios, it may be possible to administer the individual drugs in a combination as monotherapy for a short duration, but long enough to establish proof of concept in humans. For example, direct-acting antivirals (DAAs) to treat chronic hepatitis C virus infection can be administered as monotherapy for three days to establish antiviral activity and for initial dose exploration. For DAA studies of longer duration, the combination should be used or the individual components should be added to an active control.\(^5\)

\(^5\) See draft guidance for industry: Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment (section III. 4. b. – Phase 1b (proof-of-concept) trials) or consult the Division of Antiviral Drug Products in CDER for more specific recommendations.
Scenario 2: Each drug alone has activity and can be administered individually

If \textit{in vivo} or \textit{in vitro} models, or phase 1 or other early clinical studies indicate that each drug has some activity, but the combination appears to have greater than additive activity, and rapid development of resistance is not a concern, a four-arm, phase 2 trial comparing the combination to each drug alone and to placebo or SOC (AB v. A v. B v. SOC or \textit{placebo}) should be used to demonstrate the contribution of the components to the combination and proof of concept. As noted above, if SOC is a known effective therapy, a study design in which each of the arms is added to SOC could be used (AB + SOC v. A + SOC v. B + SOC v. placebo + SOC).

An adaptive trial design with the same four treatment arms might also be used where appropriate, initially using the treatment arms described above. The single-drug arms could be terminated early if it became clear that they had much less activity than the combination. These designs could demonstrate the activity of each component of (i.e., the contribution of each component to the combination) without exposing the large numbers of patients typically required for phase 3 trials to therapeutic products with inadequate activity. For these trials, it may not be necessary to use a clinical endpoint as a primary efficacy measurement. A credible pharmacodynamic or other biomarker, such as tumor response, may be adequate.

Scenario 3: One drug is active alone and one is inactive

If \textit{in vivo} or \textit{in vitro} models, or phase 1 or other early clinical studies suggest that one of the drugs is inactive or minimally active and one drug is modestly active, but the combination has substantial activity, the more active drug generally will require greater scrutiny and should ordinarily be studied as a single drug in a phase 2 study. The minimally active drug generally would not require study as a single drug beyond initial phase 1 safety studies. In this scenario, proof of concept and the contribution of each component could be demonstrated using a three-arm comparison of the active drug alone, SOC, and the combination (AB v. A v. SOC), or the combination and the individual drug added to SOC where SOC is a known effective therapy (AB + SOC v. A + SOC v. SOC).

If the inactive drug in a combination is a pharmacokinetic or metabolic enhancer that contributes to the activity of the combination only by increasing the therapeutic concentrations of the active drug, human pharmacokinetic data may provide adequate evidence to support the enhanced activity of the combination and demonstrate the contribution of the inactive drug. A confirmatory study of the combination would usually be needed to provide evidence of effectiveness for the combination (see section V.D).

\textbf{Dose Finding}

Dose-finding studies could be very important to refine the combination dose or doses and select doses for phase 3 trials. Depending on the role of each component, it may be

\footnote{Note that the placebo arm is intended to show the effect size compared to non-treatment, not to show the contribution of each component.}
useful to test multiple doses of both components to establish a best dose in terms of risks and benefits. If one component in a two-drug combination is more active than the other, it may be more important to study multiple doses of the more active drug (as part of the combination). For the same reason, it may be more important to study multiple doses of a drug that is significantly more toxic than the other component of the combination. Other study designs and types of studies also may be appropriate.

D. Confirmatory Studies (Phase 3)

If findings from in vivo or in vitro models and/or phase 2 trials adequately demonstrate the contribution of each component to the combination, phase 3 trials comparing the combination to SOC or placebo generally will be sufficient to establish effectiveness. If the contribution of the individual components is not clear and it is ethically feasible to use a component or components of the combination as monotherapy in a study arm, it may be necessary to demonstrate the contribution of the components in phase 3 studies (e.g., by use of a factorial design). For example, if phase 2 data do not provide sufficient evidence of the contribution of each component of a two drug combination, but provide strong evidence that the combination is superior to one of the components, a phase 3 trial comparing the combination to the more active component alone and SOC may be needed to demonstrate that the less active component contributes to the activity of the combination. In this and other situations, it will often be useful to study more than one dose of the more active drug in phase 3 studies.

Unexpected toxicity (e.g., serious adverse events observed at higher than expected rates) in phase 2 trials is a potential complication for development of a combination and progressing to phase 3 trials. If the toxicity can be attributed to one component of the combination, it may be possible to conduct phase 3 trials with the combination using a lower dose or doses of the more toxic component. If the toxicity cannot be attributed to an individual component of the combination, additional studies may be needed to identify the more toxic component and appropriate dosing for the combination before initiating phase 3 trials. The specifics of any phase 3 design should be discussed with the appropriate FDA review division at an End-of-Phase 2 meeting.

VI. REGULATORY PROCESS ISSUES IN CODEVELOPMENT

Sponsors should consider a number of regulatory issues when planning the codevelopment of two or more novel drugs for use in combination. Key issues are outlined below.

A. Early Interaction with FDA

Sponsors are encouraged to communicate as early as possible (e.g., pre-IND meeting) with the appropriate FDA review division when considering codevelopment of innovative combination therapy. Sponsors also are encouraged to consult FDA frequently throughout the development process. We believe such communication will help facilitate development of the combination therapy.
B. IND Submissions and Marketing Applications

Decisions about the type of IND submission(s) and marketing application(s) needed (e.g., individual component submissions, combination submission) will depend on the sponsor's overall codevelopment and marketing strategy. Until FDA has more experience with codevelopment, FDA recommends that these decisions be made on a case-by-case basis in consultation with the appropriate review division.

C. Labeling Issues

FDA also anticipates that the content of labeling for the combination and/or the components will be case specific, depending on the nature of the combination, the intended uses of the individual components, the marketing strategy, and other factors. Therefore, FDA does not believe it can provide generally applicable labeling guidance at this time. Again, we recommend consultation with the appropriate review division.

D. Pharmacovigilance

Applicants should develop a pharmacovigilance plan that takes into account the additional postmarket risks presented by initial marketing of two or more previously unapproved drugs for use in combination (compared to risks associated with marketing of a single drug). Risk will vary, depending on the nature of the combination and how the combination is marketed. The risk assessment should consider, among other things:

- Potential for use of each drug individually;
- Potential for use of any of the components of the combination in combinations with other drugs; and
- Drugs likely to be co-administered with the combination.

Applicants should discuss their pharmacovigilance plans with the appropriate review division and the Office of Surveillance and Epidemiology.
Draft Guidance for Industry and Food and Drug Administration Staff

In Vitro Companion Diagnostic Devices

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
Document issued on: July 14, 2011

You should submit comments and suggestions regarding this draft document within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this document that relate to CDRH contact Elizabeth Mansfield, at 301-796-4664, or elizabeth.mansfield@fda.hhs.gov; for questions for CBER contact Office of Communication, Outreach and Development (OCOD) at 301-827-1800 or 1-800-835-4709, or ocod@fda.hhs.gov; for questions for CDER, contact Christopher Leptak at 301-796-0017, or christopher.leptak@fda.hhs.gov.

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or by calling 1-800-835-4709 or 301-827-1800, or email ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

or

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Division of Drug Information
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Draft Guidance for Industry and Food and Drug Administration Staff

In Vitro Companion Diagnostic Devices

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

This guidance is intended to assist (1) sponsors who are planning to develop a therapeutic product¹ that depends on the use of an in vitro companion diagnostic device (or test) for its safe and effective use and (2) sponsors planning to develop an in vitro companion diagnostic device that is intended to be used with a corresponding therapeutic product.

Specifically, the guidance intends to accomplish the following:

- Define in vitro companion diagnostic device (hereafter referred to as an “IVD companion diagnostic device”)
- Explain the need for FDA oversight of IVD companion diagnostic devices
- Clarify that, in most circumstances, if use of an IVD companion diagnostic device is essential for the safe and effective use of a therapeutic product, the IVD companion diagnostic device and therapeutic product should be approved or cleared contemporaneously by FDA for the use indicated in the therapeutic product labeling
- Provide guidance for industry and FDA staff on possible premarket regulatory pathways and FDA’s regulatory enforcement policy

¹ As used in this guidance, therapeutic product includes therapeutic, preventive, and prophylactic drugs and biological products. Although this guidance does not expressly address therapeutic devices intended for use with in vitro diagnostics, the principles discussed in this guidance may also be relevant to premarket review of such devices.
• Describe certain statutory and regulatory approval requirements relevant to therapeutic product labeling that stipulates concomitant use of an IVD companion diagnostic device to ensure safety and effectiveness of the therapeutic product.

FDA encourages sponsors considering developing either the therapeutic or IVD companion diagnostic devices discussed in this guidance to request a meeting with both relevant device and therapeutic product review divisions to ensure that product development plans will produce sufficient data to establish the safety and effectiveness of the IVD companion diagnostic device/therapeutic product pair.

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.

II. Background

Diagnostic tests have been employed for many years to enhance the use of therapeutic products. Tests are also used during therapeutic product development to obtain the data FDA uses to make regulatory determinations. After a therapeutic product is commercially available for use, health care professionals may use a relevant diagnostic test, for example, to select the appropriate patient for a particular therapy or to optimize a dosing regimen.

Recently, the development of therapeutic products that depend on the use of a diagnostic test to meet their labeled safety and effectiveness claims has become more common. For example, such a test can identify appropriate subpopulations for treatment or identify populations who should not receive a particular treatment because of an increased risk of a serious side effect. One reason for increasing interest is the emergence of new technologies that can distinguish subsets of populations that respond differently to treatment. These technologies are making it increasingly possible to individualize, or personalize, medical therapy by identifying patients who are most likely to respond, or who are at lower or higher risk for a particular side effect.

When an appropriate scientific rationale supports such an approach, FDA encourages the development of therapeutic products that depend on the use of approved or cleared IVD companion diagnostic devices — several such IVD companion diagnostic devices for use with corresponding therapeutic products have already been approved or cleared.2

When results from a diagnostic device are a determining factor in patient treatment, health care professionals must be able to rely on those results. Inadequate performance of an IVD companion diagnostic device could have severe therapeutic consequences. Such a device might

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2 Examples of currently approved IVD companion diagnostic devices that illustrate the importance of established performance parameters for both the therapeutic product and the IVD companion diagnostic device include FDA approved HER-2 testing to determine whether Herceptin (trastuzumab) therapy is indicated for treatment of metastatic breast cancer and gastric cancer. Herceptin lacks effectiveness in the HER-2 marker negative population, and also has the possibility of causing severe adverse effects. Therefore it is important to use an IVD companion diagnostic device to identify only those patients who could benefit from the therapy.
fail analytically (e.g., by not accurately measuring the expression level of a protein of interest), or clinically (e.g., by not identifying those patients at increased risk for a serious adverse effect). Erroneous IVD companion diagnostic device results could lead to withholding appropriate therapy or to administering inappropriate therapy. Therefore, FDA believes that use of an IVD companion diagnostic device with a therapeutic product raises important concerns about the safety and effectiveness of both the IVD companion diagnostic device and the therapeutic product. Because an IVD companion diagnostic device with inadequate “performance characteristics”\(^3\) or other issues related to safety and effectiveness could expose a patient to preventable treatment risks, FDA will assess the safety and effectiveness of the IVD companion diagnostic device as used with the therapeutic when a therapeutic product depends on the IVD companion diagnostic device for its safe and effective use.

To facilitate the development and approval of therapeutic products that are intended for use with IVD companion diagnostic devices, as well as the development of the IVD companion diagnostic devices themselves, FDA is clarifying relevant policies related to these devices and products. FDA is also developing appropriate internal policies and procedures to ensure effective communication among the relevant centers and to promote consistent and efficient product review.\(^4\)

### III. Definition and Use of an IVD Companion Diagnostic Device

An *IVD companion diagnostic device* is an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product.\(^5\) The use of an IVD companion diagnostic device with a particular therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, as well as in the labeling of any generic equivalents of the therapeutic product.

An IVD companion diagnostic device could be essential for the safe and effective use of a corresponding therapeutic product to:

- Identify patients who are most likely to benefit from a particular therapeutic product\(^6\)

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\(^3\) See 21 CFR 809.10 (b)(12).

\(^4\) In some cases, an IVD companion diagnostic device intended for use with a therapeutic product and that therapeutic product may together constitute a “combination product.” See 21 CFR 3.2(e)(3) and (4). Whether an IVD companion diagnostic device and therapeutic product would together, in fact, constitute a combination product should be determined on a case-by-case basis. Also, combination product status could affect regulatory requirements beyond the scope of this guidance. For additional information, please contact the Office of Combination Products or refer to their webpage on the Agency’s website at [http://www.fda.gov/CombinationProducts/default.htm](http://www.fda.gov/CombinationProducts/default.htm).

\(^5\) Generally, this means that the use of the IVD companion diagnostic device with the therapeutic product allows the therapeutic product’s benefits to exceed its risks.

\(^6\) This may include identifying patients in a specific population for which the therapeutic is indicated because there is insufficient information about the safety and effectiveness of the therapeutic product in any other population. An example is a therapeutic that is indicated only for patients who by virtue of the presence of a marker in tumor cells are believed to be unlikely to respond to other therapies.
Contains Nonbinding Recommendations
Draft - Not for Implementation

- Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product
- Monitor response to treatment for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness

FDA does not include in this definition clinical laboratory tests intended to provide information that is useful to the physician regarding the use of a therapeutic product, but that are not a determining factor in the safe and effective use of the product. 7

Ideally, a therapeutic product and its corresponding IVD companion diagnostic device would be developed contemporaneously, with the clinical performance and clinical significance of the IVD companion diagnostic device established using data from the clinical development program of the corresponding therapeutic product — although FDA recognizes there may be cases when contemporaneous development may not be possible. An IVD companion diagnostic device that supports the safe and effective use of a particular therapeutic may be a novel IVD device (i.e., a new test for a new analyte), a new version of an existing device developed by a different manufacturer, or an existing device that has already been approved or cleared for another purpose.

The following section outlines FDA’s policy regarding approval of a therapeutic product for use with a corresponding IVD companion diagnostic device.

IV. Review and Approval of IVD Companion Diagnostic Devices and Therapeutic Products

Applications for an IVD companion diagnostic device and its corresponding therapeutic product will be reviewed and approved according to applicable regulatory requirements. The IVD companion diagnostic device application will be reviewed and approved or cleared under the device authorities of the Federal Food, Drug, and Cosmetic Act (Act) and relevant medical device regulations; the therapeutic product application will be reviewed and approved under section 505 of the Act (i.e., drug products) or section 351 of the Public Health Service Act (i.e., biological products) and relevant drug and biological product regulations. 8 FDA intends to review each IVD companion diagnostic device submission within the context of, or in

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7 Examples of such tests are commonly used and well understood biochemical assays (e.g., serum creatinine or transaminases) used to monitor organ function. Note, however, that circumstances may occur when use of such tests, in the context of the therapeutic product, rises to an IVD companion diagnostic device level and approval or clearance for such use will be necessary. Note also that a novel IVD device providing information that is useful in, but not a determining factor for the safe and effective use of a therapeutic product, would not be considered an IVD companion diagnostic device.

8 To the extent an IVD companion diagnostic device and a therapeutic product together meet the definition of a combination product, a single application for the combination product may be submitted in some cases, though where appropriate, and the Agency may require separate applications for the constituent parts of the combination product. See 21 CFR 3.4(c).
conjunction with, its corresponding therapeutic product, and FDA review of the test/therapeutic product pair will be carried out collaboratively among relevant FDA offices.

A. Novel Therapeutic Products

For a novel therapeutic product, an IVD companion diagnostic device should be developed and approved or cleared contemporaneously to support the therapeutic product's safe and effective use (e.g., co-development). The results of the IVD companion diagnostic device will be essential for the safe and effective use of the therapeutic product, and its use will be stipulated in the labeling of the therapeutic product (i.e., the therapeutic product is considered safe and effective only if used with the IVD companion diagnostic device). Before approving the therapeutic product, FDA will determine that the IVD companion diagnostic device is properly validated and meets the applicable standard for safety and effectiveness or for substantial equivalence for the use indicated in the therapeutic product’s labeling. Because the IVD companion diagnostic device is essential to the safe and effective use of the therapeutic, with some exceptions (see next section), FDA does not believe it may approve a novel therapeutic product or new therapeutic product indication for use with an IVD companion diagnostic device if the IVD companion diagnostic device is not approved or cleared for that indication. Approval or clearance of the IVD companion diagnostic device will ensure that the device has been adequately evaluated and has adequate performance characteristics in the intended population.

B. Approval of a Therapeutic Product without an Approved IVD Companion Diagnostic Device

FDA may decide that it is appropriate to approve a therapeutic product even though the IVD companion diagnostic device for which it is labeled for use is not being approved or cleared contemporaneously. Two such scenarios are discussed below. In general, if a therapeutic product is approved without approval or clearance of its IVD companion diagnostic device, FDA expects that an IVD companion diagnostic device that is intended for use with the therapeutic will be subsequently approved or cleared through an appropriate IVD device submission, and the therapeutic product label will be revised to include the IVD companion diagnostic device. In addition, FDA will consider whether additional protections are necessary to address the safety issues presented by the use of the therapeutic product without an approved or cleared IVD companion diagnostic device.9

1. New Therapeutic Products to Treat Serious or Life-Threatening Conditions

FDA may decide to approve a therapeutic product even if its IVD companion diagnostic device is not yet approved or cleared when the therapeutic product is intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists and the benefits from the use of the therapeutic product with an unapproved or uncleared IVD companion diagnostic device are so pronounced as to outweigh the risks from the lack of an approved or cleared IVD companion diagnostic device.

9 Safety measures might include a risk evaluation and mitigation strategy (REMS), or a postmarket requirement, if necessary,
2. *Already Approved Therapeutic Products*

FDA will generally not approve a supplement to an approved therapeutic product application to update the product’s labeling to stipulate the use of an IVD companion diagnostic device until the IVD companion diagnostic device is approved or cleared. Nevertheless, FDA recognizes that there may be occasions when the labeling for an already approved therapeutic product must be revised to address a serious safety issue and that the change made to address this issue may stipulate use of a diagnostic test that is not yet approved or cleared. Under these circumstances, if the benefits from the use of the therapeutic product with an unapproved or uncleared IVD companion diagnostic device are so pronounced as to outweigh the risks from the lack of an approved or cleared IVD companion diagnostic device, FDA does not intend to delay approval of changes to the labeling of the therapeutic product until the IVD companion diagnostic device is approved or cleared.

C. *General Policies*

If safe and effective use of a therapeutic product *depends on* the use of an IVD companion diagnostic device, an approved or cleared IVD companion diagnostic device should be available for use once the therapeutic product is approved. FDA expects that the therapeutic sponsor will address the need for an approved or cleared IVD companion diagnostic device in its therapeutic product development plan. The sponsor of the therapeutic product can decide to develop its own IVD companion diagnostic device; the sponsor can partner with a diagnostic device sponsor to develop the appropriate IVD companion diagnostic device; or the sponsor can explore modification of an existing IVD diagnostic device (its own or another sponsor’s) to accommodate the appropriate intended use. The following general policies apply whether a therapeutic product and its IVD companion diagnostic device are developed and manufactured by the same, or different, entities.

- FDA will apply a risk-based approach to determine the regulatory pathway for IVD companion diagnostic devices, as it does with all medical devices. This means that the regulatory pathway will depend on the level of risk to patients, based on the intended use of the IVD companion diagnostic device and the controls necessary to provide a reasonable assurance of safety and effectiveness. Thus, the level of risk together with available controls to mitigate risk will establish whether an IVD companion diagnostic device requires a premarket application (PMA) or, a 510(k),10 FDA advises sponsors to consult early with FDA on the likely regulatory pathway for the IVD companion diagnostic device. Premarket review by FDA will determine whether the IVD companion diagnostic device has adequate performance characteristics for its intended use.

- Except for the situations described in B, above, after completing review of the applications for a therapeutic product and an IVD companion diagnostic device and after determining that both products are ready for approval or clearance, FDA intends to issue approvals or approval and clearance for both products at the same time. FDA strongly

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10 Experience indicates that most IVD companion diagnostic devices will be Class III devices, although there may be cases when a class II classification with premarket notification (510(k)) or other type of submission is appropriate.
encourages sponsors to time their clinical developments and premarket submissions to facilitate concurrent approval.

- If an IVD diagnostic device is already legally marketed and the IVD diagnostic device manufacturer intends to market its device for a new use as an IVD companion diagnostic device for a novel therapeutic product, FDA would consider the new use of the IVD diagnostic device with the novel therapeutic product a major change in the intended use of the device, raising new or additional questions of safety and effectiveness (see 21 CFR 807.81(a)(3)(ii), 814.39(a)). Accordingly, an appropriate premarket submission (either PMA or 510(k)) for the new use must be approved or cleared for use with the novel therapeutic product.

- New IVD companion diagnostic devices intended to be used in the same manner as an existing approved or cleared IVD companion diagnostic device (e.g., different manufacturer, different technological characteristics) will be reviewed under a PMA or a traditional 510(k), as appropriate.

V. Labeling

A. Therapeutic Product Labeling

The Federal Food, Drug, and Cosmetic Act requires the labeling of prescription therapeutic and device products to include the information health care professionals need to use the products (21 U.S.C. 352(f), 21 CFR 201.100(c)(1), Part 801.109(c), (d)). The labeling often includes information about diagnostic tests that determine how, when, or whether a therapeutic product is used. The regulations for drug and biological product labeling expressly recognize the importance of diagnostic tests to the safe and effective use of these therapeutic products. According to the labeling regulations for drugs and biological products (21 CFR 201.56 and 57), product labeling must include information about (1) specific tests necessary for selection or monitoring of patients who need a drug; (2) dosage modifications in special patient populations (e.g., in groups defined by genetic characteristics); and (3) the identity of any laboratory test(s) helpful in following a patient’s response or in identifying possible adverse reactions. The labeling regulations identify labeling sections where such discussion is appropriate (e.g., Indications and Usage, Dosage and Administration, Contraindications, Warnings and Precautions, Use in Specific Populations). For example:

- If a drug or biological product has been shown to be safe and effective in only a certain patient population identified by a diagnostic test, the Indications and Usage section must clearly define the patient population in whom the drug is approved (21 CFR 201.57(c)(2)(i)(B) and (C)).

- If a diagnostic test is essential for monitoring either therapeutic or toxic effects, the type of test must be identified under Warnings and Precautions (21 CFR 201.57(c)(6)(iii)).

Because it is important that the approved labeling for an IVD companion diagnostic device and its corresponding therapeutic product be complete and consistent, FDA makes the following clarifications.
Ordinarily, information about the use of an IVD companion diagnostic device will be included in the labeling of its corresponding therapeutic product when the device meets the definition of an IVD companion diagnostic device (see Section III). As already clarified in Section IV.B, there may be situations when information about an unapproved or uncleared IVD diagnostic device is included in the labeling of a therapeutic product.

When appropriate, the therapeutic product labeling should identify a type of FDA approved or cleared IVD companion diagnostic device (i.e., the intended use of the device), rather than a specific manufacturer’s IVD companion diagnostic device. This will facilitate the development and use of more than one approved or cleared IVD companion diagnostic device of the type described in the labeling for the therapeutic product.

In cases, when an IVD companion diagnostic device is approved or cleared and is marketed after the therapeutic product is approved, the therapeutic product labeling should be updated to refer to the use of the IVD companion diagnostic device or type of IVD companion diagnostic device (21 CFR 201.56(a)(2)).

**B. IVD Companion Diagnostic Device Labeling**

The labeling for an in vitro diagnostic is required to specify the intended use of the diagnostic device (21 CFR 809.10(a)(2)). Therefore, an IVD companion diagnostic device that is intended for use with a therapeutic product must specify the therapeutic product(s) for which it has been approved or cleared for use. In some cases, if evidence is sufficient to conclude that the IVD companion diagnostic device is appropriate for use with a class of therapeutic products, the intended use/indications for use should name the therapeutic class, rather than each specific product within the class.

When an IVD companion diagnostic device has been approved or cleared for use with a therapeutic product in one disease or setting, the IVD companion diagnostic device labeling should be expanded through approval or clearance of a new premarket submission (PMA or 510(k) as appropriate) or PMA supplement if new or revised therapeutic product labeling becomes available that stipulates that the use of the IVD companion diagnostic device or type of IVD companion diagnostic device is essential for the safe and effective use of the therapeutic product in another disease or setting.

When an IVD companion diagnostic device has been approved or cleared for use with one therapeutic product and evidence becomes available that use of the same device is essential for the safe and effective use of a different therapeutic product, the IVD companion diagnostic device labeling should be expanded through approval or clearance of a different therapeutic product (PMA or 510(k) as appropriate) or PMA supplement (in accordance with Section IV, above) to include the new therapeutic product. Labeling of the therapeutic product should also be amended through submission of a supplement.
VI. Investigational Use

All diagnostic devices used to make treatment decisions in a clinical trial of a therapeutic product will be considered investigational devices, unless employed for an intended use for which the device is already approved or cleared. If used to make critical treatment decisions, such as patient selection, treatment assignment, or treatment arm, a diagnostic device generally will be considered a significant risk device under 21 CFR 812.3(m)(3) because it presents a potential for serious risk to the health, safety, or welfare of the subject, and the sponsor of the diagnostic device will be required to comply with the investigational device exemption (IDE) regulations that address significant risk devices. In such cases, FDA will expect the sponsor to conduct the trial under full IDE regulations.\(^\text{11}\)

If a diagnostic device and a therapeutic product are to be studied together to support their respective approvals (or clearance as appropriate for the diagnostic device), both products can be studied in the same investigational study, if the study is conducted in a manner that meets both the requirements of the IDE regulations and the investigational new drug (IND) regulations (21 CFR Part 312).

Information about the planned use of an IVD companion diagnostic device and its use in clinical trials should be included in an investigational submission. This information will help FDA understand and provide advice on how the IVD device will be used to enroll subjects into the trial(s) and how the test will be validated for use. For therapeutic product INDs, the therapeutic product review center (Center for Drug Evaluation and Research or Center for Biologics Evaluation and Research (CBER)) will engage appropriate expertise from the diagnostic product review center (Center for Devices and Radiological Health or CBER), and joint advice will be provided to the sponsor.

In addition, it will be helpful if both the IVD companion diagnostic device product sponsor and the therapeutic product sponsor submit information about the proposed IVD companion diagnostic device in a preIDE (a consultative submission designed to ensure that appropriate validation studies are planned and carried out) to the diagnostic review center. This will enable a more focused and in-depth discussion about the validation of the IVD companion diagnostic device and will aid in planning for a device PMA or 510(k) that is complete and timely. When appropriate, expertise from the relevant therapeutic review center will be included in the diagnostic review center meetings.

FDA strongly encourages sponsors considering developing either of the products discussed in this guidance to request a meeting with both relevant device and therapeutic product review divisions as early in development as possible.

\(^{11}\) Alternatively, if the IVD companion diagnostic device and therapeutic product are considered a combination product, FDA will expect the investigational device to be investigated under the IND for the therapeutic product