

CCR Perspectives in Drug Approval

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Developing Standards for Breakthrough Therapy Designation in OncologySandra J. Horning¹, Daniel A. Haber^{2,3}, Wendy K.D. Selig⁴, S. Percy Ivy⁶, Samantha A. Roberts⁵, Jeff D. Allen⁵, Ellen V. Sigal⁵, and Charles L. Sawyers^{3,7}**Abstract**

In July 2012, Congress passed the Food and Drug Administration Safety and Innovation Act (FDASIA). The Advancing Breakthrough Therapies for Patients Act was incorporated into a Title of FDASIA to expedite clinical development of new, potential "breakthrough" drugs or treatments that show dramatic responses in early-phase studies. Using this regulatory pathway, once a promising new drug candidate is designated as a "Breakthrough Therapy", the U.S. Food and Drug Administration (FDA) and sponsor would collaborate to determine the best path forward to abbreviate the traditional three-phase approach to drug development. The breakthrough legislation requires that an FDA guidance be drafted that details specific requirements of the bill to aid FDA in implementing requirements of the Act. In this article, we have proposed criteria to define a product as a Breakthrough Therapy, and discussed critical components of the development process that would require flexibility in order to enable expedited development of a Breakthrough Therapy. *Clin Cancer Res*; 19(16); 4297–304. ©2013 AACR.

Introduction

Advances in our understanding of the pathogenesis and the underlying molecular basis of many diseases have enabled the development of novel, effective, and greatly improved therapeutic agents. Particularly in oncology, the ability to target a driver oncogene or protective immune checkpoints has led to several therapeutic breakthroughs in diseases with few or no good systemic treatment options. These breakthroughs have established new classes of cancer therapeutics and represent quantum leaps in therapeutic progress. Unprecedented efficacy results in phase I trials for metastatic melanoma and non-small cell lung cancer (NSCLC) and grim diseases with short survival times led many to question the wisdom and ethics of continuing down the path of traditional drug development in situations where extraordinary efficacy and limited toxicity are observed in early studies (1, 2). In a 2011 report, the U.S. Food and Drug Administration (FDA) described the creation of an expedited drug development pathway for excep-

tional new drugs as a key priority for the agency (3). Important issues to be addressed in the creation of such a pathway include how to identify a potential breakthrough therapy and how to appropriately balance the need to provide patients suffering from serious or life-threatening diseases with expedited access to breakthroughs versus the need to protect patients from potentially ineffective or unsafe drugs.

The FDA currently uses several approaches to expedite the development of promising new medicines (Table 1). These include accelerated approval, fast-track, and priority review. Accelerated approval allows a drug to receive FDA approval based on a surrogate endpoint, such as objective response rate, considered reasonably, likely to predict a clinical benefit, such as prolonged survival. Accelerated approval is a critical pathway for expediting access to new therapies in disease settings in which the effect on the surrogate endpoint can be shown much sooner than an improvement in clinical benefit. This pathway is reserved for drugs/biologics that seek to treat a serious or life-threatening disease and that provide meaningful therapeutic benefit to patients over existing treatments. Accelerated approval is conditional, in that drugs approved via this pathway must undergo further clinical testing to confirm the predicted clinical benefit ("confirmatory trial"). If the confirmatory trial does not show that the drug provides clinical benefit for patients, FDA has the authority to remove the drug from the market or remove the indication from the drug's labeling in cases where the drug is approved for other uses. The fast-track program is a process designed to facilitate the development and expedite the review of drugs that treat serious diseases and address unmet medical needs. It entails early and frequent communication between the FDA and sponsor

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Table 1. FDA approaches to expedited drug development

	Accelerated approval	Fast-track designation	Priority review	Breakthrough Therapy designation
Eligibility	<ol style="list-style-type: none"> 1. Treat serious or life-threatening diseases 2. Provide meaningful therapeutic benefit over existing therapies 3. Surrogate endpoint reasonably likely to predict clinical benefit 	<ol style="list-style-type: none"> 1. Intent to treat broad range of serious diseases 2. Potential to fill an unmet medical need 	<ol style="list-style-type: none"> 1. Offer major advances in treatment over existing therapies 	<ol style="list-style-type: none"> 1. Treat serious or life-threatening diseases 2. Early clinical evidence of substantial improvement over existing therapies
Designation	No formal process	Can be requested by sponsor at any time; FDA has 60 days to respond	Requested by sponsor at time of NDA/BLA submission; FDA has 45 days to respond	Can be requested by sponsor at any time after IND submission; FDA has 60 days to respond
Clinical development	Conditional approval granted using surrogate endpoint from phase II trials or interim phase III data; controlled trials with hard clinical endpoints required to confirm clinical benefit	Earlier and more frequent communication	Not applicable	Abbreviated or condensed development; earlier and more frequent communication; delegation of senior reviewers and cross-disciplinary review team
Review process	NDA/BLA data submitted in one package; standard 10-month review	Option for Rolling NDA/BLA submission. Official review clock begins when last module is submitted	NDA/BLA data submitted in one package; review time shortened to 6 months	NDA/BLA data submitted as they are accumulated; review time shortened
Distinguishing features	<ul style="list-style-type: none"> • Conditional approval • Surrogate endpoint 	<ul style="list-style-type: none"> • Full approval • Rolling submission 	<ul style="list-style-type: none"> • Full approval • Review shortened to 6 months 	<ul style="list-style-type: none"> • Conditional or full approval • Expedited development • Rolling submission • Review shortened

NOTE: An investigational agent can be eligible for any combination of accelerated approval, priority review, or fast-track designation. A novel agent with breakthrough designation also automatically receives the conditions of fast-track and priority review, and receives the conditions of accelerated approval if applicable. Standard clinical development includes small phase I trials (typically <100 patients) to gain initial safety and pharmacologic data; slightly larger phase II trials (typically 100–200 patients) to evaluate appropriate dosing, gain a deeper understanding of safety, and obtain initial efficacy data; and large phase III trials (typically several hundred patients in oncology) to obtain efficacy data. Surrogate endpoints are those "considered reasonably likely to predict clinical benefit" and can include response rates (tumor shrinkage) or progression-free survival (time without disease worsening). Hard clinical endpoints are those that represent a direct benefit in the way a patient feels, functions, or survives and can include overall survival or symptom alleviation.

throughout development and review. Under this program, a sponsor may submit sections of a new drug application (NDA) or biologics license application (BLA), as they are ready ("rolling review"), rather than the standard requirement to submit the complete NDA or BLA application in one submission. Priority review is available to drugs that provide a significant improvement in the treatment, prevention, or diagnosis of a disease when compared with standard NDAs or BLAs. It shortens the goal review time from 10 months to 6 months from the 60-day filing date (or from 12 months to 8 months, respectively, from date of submission of the application).

These three approaches serve distinct, but complementary, roles in accelerating the pace of drug development and approval, and their use in oncology has contributed to the relative speed with which the FDA has reviewed new oncology medicines (4–6). With each of these approaches, however, investigational drugs typically go through the traditional three phases of clinical testing, including controlled phase III trials. Furthermore, none of these approaches specifically addresses how to expedite development of a potential breakthrough therapy in a way that shortens the time needed to conduct the major efficacy trial and minimizes the number of study participants placed on a comparatively ineffective control regimen.

In the 2011, Conference on Clinical Cancer Research cohosted by Friends of Cancer Research and the Engelberg Center for Health Care Reform at the Brookings Institution (Washington, DC), a panel was convened, Development Paths for New Drugs with Large Effects Seen Early, with the goal of developing consensus approaches to accelerate the development of drugs that show extraordinary activity early in development without compromising the FDA's rigorous standards for safety and efficacy (7). This panel proposed several pathways for earlier approval of a potential breakthrough therapy. These are described here briefly to give examples of possible expedited drug development programs and are not meant to represent the only ways a potential breakthrough could be developed. In one proposed pathway, a potential breakthrough product would move from phase I into a randomized "IIb" trial that could serve either as support for traditional approval, if effects were extraordinary, or as a screening trial into a phase III trial, if effects were moderate. This pathway would streamline the development of a true breakthrough product and reduce the number of patients required to achieve statistical significance when treatment effects are truly extraordinary. Other pathways proposed included phase I expansion cohorts. An example where a phase I expansion would support full approval of a drug could be the demonstration of a high percentage of durable complete responses. A second example could be an unprecedented overall response rate or clinical benefit rate that results in durable disease improvement or stabilization; this scenario might lead to accelerated approval. The exact pathway, a potential breakthrough therapy might take, would depend on several factors, including the disease setting and indication sought, and endpoint(s) used, as well as the magnitude and dura-

bility of the signal relative to the existing standard of care. Early communication between FDA and the sponsor would be essential in designing a successful and efficient development strategy.

In follow-up to the 2011 panel, The Advancing Breakthrough Therapies for Patients Act was introduced and included as a component of the 2012 reauthorization of the Prescription Drug User Fee Act [Food and Drug Administration Safety and Innovation Act (FDASIA)] to expedite development of potential "breakthrough" therapies. This legislation specifies that a drug may be designated as a Breakthrough Therapy if it is intended to treat a serious or life-threatening disease, and preliminary clinical evidence suggests that it provides a substantial improvement over existing therapies. Sponsors can request Breakthrough Therapy designation at the time of investigational new drug (IND) application, submission, or anytime after, and the FDA has 60 days to respond to this request. Upon designation, the FDA and sponsor would collaborate in a dynamic and cross-disciplinary process to determine the most efficient path forward. This legislation requires that an FDA Guidance be drafted that details the criteria for Breakthrough Therapy designation, as well as the processes FDA will take to make a designation and expedite the development, and review of a potential breakthrough therapy. These issues were discussed at the 2012 Conference on Clinical Cancer Research, and recommendations for designation and development of breakthrough therapies in oncology are provided here.

Breakthrough Therapy Designation

In this section, we propose criteria for Breakthrough Therapy designation, apply these criteria to different categories of potential breakthrough therapies, and discuss the process by which FDA will make a Breakthrough Therapy designation.

Criteria for Breakthrough Therapy designation

A profound therapeutic breakthrough was defined by Sharma and Schilsky, as one that "fundamentally alters the way oncologists think about a disease in terms of the prognosis, treatment options, and quality of life of our patients" (2). While future breakthroughs may be readily apparent to those familiar with the disease they aim to treat, they may be less apparent to others outside that particular field. Defining a threshold of evidence required to obtain Breakthrough Therapy designation is necessary to provide some degree of consistency and predictability to the process. Because it may be unrealistic and restrictive to define a breakthrough exclusively in quantitative terms based on early results such as response rates relative to existing therapies, we propose qualitative criteria to be met for Breakthrough Therapy designation. The qualitative criteria discussed below are contextual; ultimately, the designation of a new drug as a potential Breakthrough Therapy should be determined on a case-by-case basis by those with relevant expertise.

1. The diseases under study will be serious (either debilitating or life-threatening) and have no established standard of care, or the current accepted standard of care yields poor clinical outcomes (such as low response rates, lack of durability, limited survival, inadequate symptom control, severe acute or chronic effects, and reduced quality of life).
2. Breakthrough Therapy designation should be based on compelling early evidence suggesting major, clinically meaningful improvement over existing therapies in a defined disease setting.
 - a. The potential breakthrough therapy under consideration could be designated on the basis of early data suggesting substantial clinical efficacy (e.g., quality or rate of response and/or duration):
 - i. Early clinical studies should suggest a substantial, clinically meaningful improvement over a similarly defined concurrent or historical comparator.
 - ii. Acceptable safety in a reasonable number of treated patients (number of patients depends on incidence/prevalence of disease and an understanding of mechanism and expected toxicity).
 - b. The potential breakthrough therapy under consideration could be designated on the basis of early data suggesting a superior clinical therapeutic index compared with standard of care in a similarly defined population.
 - i. Should exceed or clearly maintain comparable efficacy.
 - ii. Superior safety or tolerability is the key consideration.
3. The potential breakthrough therapy under consideration will typically have a compelling scientific rationale and promising mechanism of action, such as targeting a molecular driver of a biologically characterized disease (e.g., ALK-positive subset of lung cancer).

Categories of breakthrough therapies

Next, we describe potential categories of breakthrough therapies together with the type of data that may be required at the time of the request for breakthrough designation. Note that combinations of new agents or new and existing agents could also be considered for Breakthrough Therapy designation; for example, a Breakthrough Therapy product could dramatically enhance the activity or tolerability of an existing regimen. The qualitative criteria described in the previous section are applied to these categories in Table 2. Selected examples of recent therapeutic breakthroughs are described in more detail in the Supplementary Material.

Categories.

1. Drugs that address conditions with poor outcomes, which may be defined by clinical or biologic subsets of disease, for which no established standard of care or available concurrent control exist.
 - a. Drugs that show unprecedented efficacy in previously untreatable diseases (e.g., vismodegib in advanced basal cell carcinoma, ivacaftor in G551D cystic fibrosis, multiple orphan diseases).
 - b. Drugs that show substantial efficacy in refractory populations (e.g., brentuximab vedotin in Hodgkin lymphoma after failure of autologous stem cell transplant or at least two previous therapies if not a transplant candidate).
2. Drugs that provide substantial therapeutic improvement over existing, established standard of care for conditions with poor outcomes, which may be defined by a clinical or biologic subset of disease.
 - a. Novel agents that act through a different mechanism than the existing standard of care (e.g., vemurafenib in BRAF-mutated metastatic melanoma, crizotinib in ALK-positive NSCLC).
 - i. If historical controls are used for comparison, they should be matched for clinical disease or subtype and context (i.e., stage/severity, previously treated), relevant demographics and prognostic factors. Any differences in management between the experimental group and controls other than administration of the investigational agent should be accounted for.
 - ii. In situations where the therapy is intended to treat a molecularly defined population, historical controls for new biologic subsets could be defined through retrospective analysis of biomarkers from tumor banks with well-annotated clinical datasets (e.g., cooperative group tissue banks).
 - iii. This category could include drugs with the shown efficacy in one tumor type (or other disease) driven by an identified mutation that subsequently show substantial clinical efficacy in a different tumor type sharing the driver mutation.
 - b. Second-generation targeted drugs that address unmet needs not addressed by first-generation compounds (i.e., limited response duration, poor tolerability).
 - i. Breakthrough Therapy designation could be granted if preliminary clinical evidence suggests that a second-generation drug is substantially

Table 2. Potential breakthrough categories, criteria, and development paths

Category	Qualitative criteria	Potential development path
1. Drug addresses serious condition with poor outcomes for which there is no standard of care	Unprecedented early activity in phase I: either CRR, ORR or CBR with acceptable safety	Phase IB expansion or single-arm pivotal trial could lead to full or accelerated approval in single-arm study
2. Drug provides substantial efficacy improvement over a well characterized standard of care for serious condition with poor outcomes	Exceptional early activity in phase I: based on response rates (CRR, ORR) and durability of response or disease control with acceptable safety	Randomized phase IIB trial could support full approval in modestly sized trial that achieves statistical significance. Such a trial could allow crossover. Randomized phase IIB may serve to screen for phase III if efficacy gain not considered exceptional. Under extraordinary circumstances, phase IB expansion or single-arm study could lead to full or, more likely accelerated approval
3. Drug provides substantial therapeutic index advantage over a well characterized standard of care for a serious condition with poor outcomes	Superior or clearly maintained efficacy combined with superior safety/tolerability	Randomized phase IIB trial used to screen for phase III trial most likely. Randomized phase IIB trial might support full approval in modestly sized trial if improvement in therapeutic index is exceptional.

Abbreviations: CRR = complete response rate, ORR = overall response rate, CBR = clinical benefit rate.

superior to its predecessor(s) and has a strong scientific rationale supported by preclinical or clinical evidence.

- ii. Clinical evidence could include biopsies of progressive disease after exposure to the first-generation drug that show the presence of an acquired mutation or alteration addressed by the second-generation drug.

- 3. Drugs that provide a substantial therapeutic index advantage over a standard of care with well-characterized efficacy and safety in a similarly defined population (e.g., a non-cardiotoxic anthracycline, antibody–drug conjugates).

Timing and content of designation request

The breakthrough therapies legislation states that the request for designation can be made at the time of IND application or any time thereafter. However, it also states that preliminary clinical evidence is required for designation. We propose that a sponsor may initiate discussion for consideration of a potential breakthrough designation at the time of IND submission or at any time thereafter, before receiving marketing approval of its BLA or NDA. The pre-IND meeting would be an opportunity to discuss and agree on the evidence needed to meet Breakthrough Therapy criteria and the con-

tents of a designation request, the potential timeline of a request based on an agreement about the preliminary clinical evidence needed, and the content of the IND. However, while the IND and potential for breakthrough designation may be discussed before an IND submission in a pre-IND meeting, a formal request for and decision on Breakthrough Therapy designation would still require and await the evaluation of preliminary clinical experience.

A request for Breakthrough Therapy designation should describe what category of Breakthrough Therapy the investigational agent would fit into by including a summary of the disease and setting the therapy aims to treat, expected outcomes for that patient population, and the existing (if applicable) therapies available to treat the disease. It should also describe how the investigational therapy meets the criteria for Breakthrough Therapy designation by describing its scientific rationale, mechanism of action, and the results of early-phase clinical studies. The request should outline a potential clinical development plan for confirming the early-phase studies as well as potential steps for streamlining manufacturing and development of a companion diagnostic (if necessary).

FDA response

The FDA has 60 days to respond to a request for Breakthrough Therapy designation. Requests for Breakthrough

Therapy designation will be reviewed by senior officials in the office of the Center Directors. We propose that the FDA should have the flexibility to consult external expertise, which may be particularly useful in rare diseases and in subpopulations identified by a biomarker. These experts could also be consulted for later discussions on the appropriate design of clinical studies, if necessary.

In the event of a negative decision, the FDA should issue a nondesignation letter that explains the FDA's rationale and provides recommendations of what criteria would need to be met in order for the product to be considered for Breakthrough Therapy designation.

Expedited Development Process

To facilitate development of a designated breakthrough therapy, FDASIA requires that the FDA include senior managers and experienced reviewers in a collaborative, multidisciplinary review. A cross-disciplinary project lead should be assigned to act as a liaison between the review team and the sponsor. Meetings between the sponsor and review team should be held frequently throughout the development program so that the FDA can provide timely advice to the sponsor and ensure the development program gathers the necessary nonclinical and clinical data as efficiently as possible and that the number of patients exposed to a potentially less efficacious treatment is minimized. In contrast to existing approval tracks, Breakthrough Therapy designation will provide an "all hands on deck" approach by the FDA as well as increased flexibility to hasten timelines for all components of the approval process. Figure 1 depicts

how the development timeline of a Breakthrough Therapy product may be amended, compared with the timeline of standard drug development.

We have proposed potential development paths for some of the different categories of Breakthrough Therapies in Table 2. Depending on the situation, we anticipate that single-arm trials or small randomized trials may be used to support approval of a breakthrough therapy. These smaller trials carry certain limitations. The data are unlikely to be as robust as that from a large controlled trial and the integrity of the data will be more vulnerable to any variances in measurements. Another limitation is that small trials have a smaller safety database, and single-arm trials introduce uncertainty in attribution of adverse events. Rare toxicities may go undetected before registration. Therefore, drugs receiving Breakthrough designation may require additional postmarket safety studies.

In addition to the clinical development plan, there are a number of issues that will require careful planning and collaboration between the sponsor and the multidisciplinary review team. For example, early discussion of what the sponsor would ultimately like to claim in the product label (i.e., the specific patient population expected to benefit) is an important step that can save time later in development. Other issues include, but are not limited to, the potential for long-term animal toxicology studies to delay development, the potential for existing manufacturing requirements to delay commercialization of Breakthrough Therapy products, and the potential for existing companion diagnostic review requirements to delay clinical development of

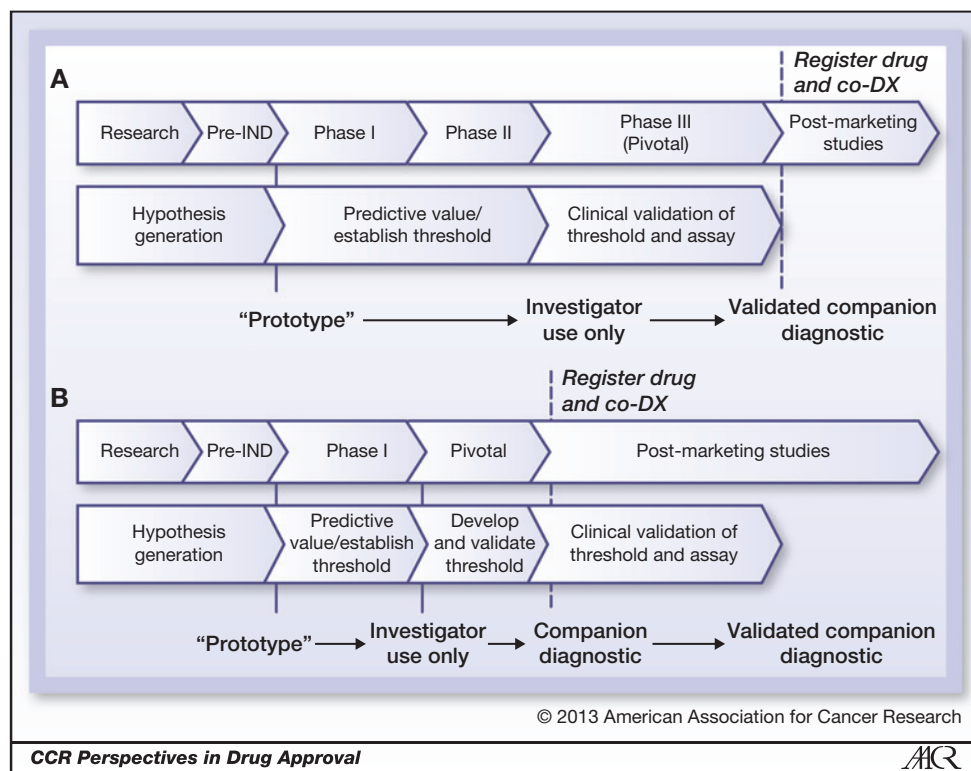


Figure 1. Development timelines for (A) standard drugs/biologics and (B) breakthrough therapies, and respective companion diagnostics (co-Dx). While standard investigational drugs typically go through the traditional three phases of clinical testing, breakthrough therapies will have a condensed or abbreviated development program. The type of pivotal trial for a Breakthrough Therapy will vary depending on its characteristics and those of the disease it aims to treat.

potential breakthrough therapies. These issues should not delay the development of a Breakthrough Therapy, but approval might be contingent on subsequent submission of relevant data by the sponsor. Below, we discuss some potential approaches for manufacturing and companion diagnostics to enable expedited development.

Chemistry, manufacturing, and controls

The key points to be considered in enabling acceleration of traditional chemistry, manufacturing, and controls (CMC) timelines are: (i) initial supply of product from clinical manufacturing process and/or clinical site for a predetermined time period; (ii) deferral until postapproval of process validation requirements that do not directly relate to safety (for instance, currently all process validation activities for biologics must be completed before submission); (iii) amount of real-time stability data for approval including acceptance of use of representative pilot scale data. For Breakthrough Therapy designation, the sponsor must be able to manufacture sufficient drug to supply a reasonable number of patients.

To facilitate expedited manufacturing of Breakthrough Therapy products, the regulatory acceptance of previous platform knowledge should be leveraged. Such knowledge will be applicable with respect to process (e.g., scale, validation), as well as products (e.g., formulation, characterization, validation of analytic methods, stability, and specifications). For example, the product specifications for monoclonal antibodies produced by an established production platform could be built on limits that are "generally regarded as safe," and limits for impurities like aggregates, Chinese Hamster Ovary Proteins (CHOP), leached protein A, fragments, sequence variants, oxidized variants, etc. could all be set at low and generally acceptable levels, independent of the clinical experience (e.g., <2% aggregates, <30 ppm CHOP, <20 ppm leached protein A). The use of comparability protocols should also be leveraged to enable the efficient execution of postapproval changes, technology transfer, and scale-up changes. In addition to ensuring good manufacturing practice compliance, postapproval inspections should be leveraged to bring technical experts to monitor the effects of postapproval changes and scale-up.

Companion diagnostics

Frequently, biomarkers, such as a specific mutation, translocation, or alteration leading to changes in gene or protein expression, may define the specific population that achieves benefit from a Breakthrough Therapy. This often necessitates the development of a companion diagnostic device to identify responsive populations. Current guidelines typically require contemporaneous approval of a biomarker-defined drug and its companion diagnostic device; however, the 2011 Draft Guidance, *In vitro* Companion Diagnostic Devices, does provide for flexibility when a new drug is intended to treat a serious and life-threatening disease (8). Because Breakthrough Therapy designation is likely to precede complete clinical validation

of the diagnostic hypothesis or establishment of thresholds for definition of the marker-positive population, expediting the development of a potential biomarker-defined Breakthrough Therapy might require development of a process for companion diagnostic device approval that enables selection of patients for pivotal clinical studies without the availability of prototype diagnostic assays (Fig. 1). This could lead to registration of a companion diagnostic device using a bridging study or to conditional approval of the companion diagnostic pending subsequent studies.

When dramatic clinical responses are observed in a subset of patients where the diagnostic hypothesis was generated in the context of an early study using an exploratory assay, modest development of the assay for the registration trial (e.g., analytic validation in a CLIA/CAP-certified lab or central reference laboratory) could be allowed to expedite clinical studies. Careful development of analytic performance criteria would be required to enable subsequent bridging studies. An accelerated or conditional process for premarket approval (PMA) of a companion diagnostic may be needed (e.g., rolling or modular PMA). This process may have to include those cases where drug approval in a marker-positive population occurs on a timeline inconsistent with completion of manufacturing processes to support prototype kit distribution. We propose the consideration of a network of central labs that run and participate in the ongoing process to clinically validate the diagnostic hypothesis after approval of the drug. Sponsors would generally be required to bank samples from early studies maintaining high ascertainment rates to enable continued companion diagnostic development after Breakthrough Therapy approval, where possible. For indications where tissue quantities are limited, a pathway that uses establishment of equivalency in a large sample set may be required for subsequent approval of the companion diagnostic through the PMA process (where no subsequent clinical studies in that indication are planned).

Conclusion

The Breakthrough Therapy designation is aimed at expediting development and approval of novel therapeutics that show substantial promise in early studies for indications where the condition is serious or life-threatening and the current treatment is inadequate. This designation also seeks to minimize the number of patients exposed to inadequate treatment in controlled clinical trials. Although formal FDA guidance has yet to be released, this designation is already being pursued and, at the time of this writing, has been granted to 3 investigational oncology drugs: ibuprofen for treatment of several B-cell malignancies, an ALK inhibitor for treatment of crizotinib-resistant NSCLC, and palbociclib for breast cancer, as well as to ivacaftor for additional cystic fibrosis indications. This level of activity shows the interest sponsors have in this new pathway; however, the FDA guidance on development of Breakthrough Therapies will be necessary to ensure consistency and predictability. We have discussed here major issues that the FDA will need to address in their guidance, with particular emphasis on

providing flexibility in current CMC and companion diagnostics guidelines so as not to delay approval once the necessary clinical evidence is gathered. However, some issues related to development of breakthrough therapies go beyond FDA guidance. One important issue is the need for harmonization with other regulatory agencies, in particular, the European Medicines Agency (EMA). Drug sponsors typically use the same global registration trials to support approval in both the United States and in the European Union. In the absence of an equivalent "Breakthrough Therapies" development pathway in the European Union, drugs that receive Breakthrough Therapy designation in the United States may still be required to go through the traditional drug development pathway for EMA approval. These differing requirements may make the Breakthrough Therapy pathway an unattractive option for drug sponsors. One existing initiative that may enable harmonization between the FDA and EMA about the development of breakthrough therapies is the Parallel Scientific Advice program between the 2 agencies. This program is applicable to oncology products, pediatric medicines, vaccines, and orphan disease products, and provides information for sharing between the FDA, EMA, and drug sponsor (9). While this program is intended to provide joint advice so that a new product can be developed as efficiently as possible while meeting requirements for both agencies, it does not ensure that those requirements will be the same. The EMA may be able to adapt its own expedited development pathways, such as the "exceptional circumstances" pro-

gram, which provides for limited clinical development in situations where comprehensive efficacy and safety data is not feasible, to be compatible with the FDA Breakthrough Therapy pathway. Moving forward beyond U.S. legislation and FDA guidance, efforts should be made to harmonize this designation on a global level at international forums.

Disclosure of Potential Conflicts of Interest

S.J. Horning has ownership interest (including patents) in Roche and Pharmacyclics. No potential conflicts of interest were disclosed by the other authors.

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