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Developing Standards for Breakthrough Therapy Designation

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A. 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 novel agent against a driver oncogene or protective immune checkpoint 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), 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 US Food and Drug Administration (FDA) described the creation of an expedited drug development pathway for exceptional 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 sick patients with expedited access to breakthroughs versus the need to protect patients through rigorous trials from potentially ineffective or unsafe drugs.

The FDA currently uses several approaches to expedite the development of promising new medicines. These include: 1) Accelerated Approval; 2) Fast-Track; and 3) Priority Review; these approaches are described in more detail in Table 1.

1. 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 (or an intermediate clinical endpoint that predicts the drug's clinical benefit) can be shown much sooner than the effect on the standard endpoint that demonstrates 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 will generally seek 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.

2. 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 throughout the development and review process. 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.
3. Priority Review is available to drugs that provide a significant improvement in the treatment, prevention, or diagnosis of a disease when compared to 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. Further, 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 co-hosted by Friends of Cancer Research and the Engelberg Center for Health Care Reform at the Brookings Institution, 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 and approval of drugs that demonstrate 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 by this working group 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 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, endpoint(s) used, as well as the magnitude and durability of the signal relative to the existing standard of care (SoC). Early communication between FDA and the sponsor would be essential to 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 re-authorization of the Prescription Drug User Fee Act (Food and Drug Administration Safety and Innovation Act; FDASIA) to expedite development of new, potential "breakthrough" therapies. This legislation specifies that a new 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 designation at the time of investigational new drug application (IND) submission or anytime after, and the FDA has sixty 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. In this report, we will address these issues as they pertain to the oncology field.

B. Breakthrough Designation

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

B.1 Criteria for Breakthrough 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. This pathway should not be viewed as a default pathway for all oncology drugs. Defining a threshold of evidence required to obtain Breakthrough 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 have proposed qualitative criteria to be met for Breakthrough 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 no established SoC exists or the current accepted SoC yields poor clinical outcomes (such as low response rates, lack of durability, limited survival, inadequate symptom control, severe acute or chronic effects, reduced quality of life).

2. Breakthrough 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 calibrated to incidence/prevalence of disease, depends on 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 to SoC in a similarly defined population.
        i. Should exceed or clearly maintain comparable efficacy
        ii. Superior safety or tolerability advantage 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).

B.2 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 could also be considered for Breakthrough designation. The qualitative criteria described in the previous section are applied to some of these categories in Table 2. Selected examples of recent therapeutic breakthroughs are described in more detail in the Appendix. For each of these categories, it is possible that a Breakthrough Therapy may target a molecularly defined subset of disease, necessitating the use of a companion diagnostic (co-Dx). It is important to note that in this situation, Breakthrough designation may precede complete clinical validation of the diagnostic (Dx) hypothesis or establishment of thresholds for definition of the marker-positive population (see section C); therefore, flexibility in the review of the co-Dx will be needed.

<u>Categories</u>

1. Drugs that address conditions with poor outcomes, which may be defined by clinical or biologic subsets of disease, for which no established SoC or available concurrent control exist.
    a. Drugs that demonstrate efficacy in previously untreatable diseases (e.g., vismodegib in advanced basal cell carcinoma, ivacaftor in G551D cystic fibrosis, multiple orphan diseases).
    b. Drugs that demonstrate efficacy in refractory populations (e.g., brentuximab vedotin in Hodgkin's disease after failure of autologous stem cell transplant or at least two prior therapies if not a transplant candidate).

2. Drugs that provide substantial therapeutic improvement over existing, established SoC 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 SoC (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 biological subsets could be defined through retrospective analysis of biomarkers from tumor banks with well annotated clinical datasets (e.g. cooperative group tissue banks).
    b. Second-generation targeted drugs that address unmet needs not addressed by first-generation compounds (i.e., limited response duration, poor tolerability).
        i. Breakthrough designation could be granted if preliminary clinical evidence suggests that a second-generation drug is substantially 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 demonstrate 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 SoC with well characterized efficacy and safety in a similarly defined population (e.g., a non-cardiotoxic anthracycline, antibody-drug conjugates).

4. Drugs that dramatically enhance the activity or tolerability of an existing regimen (e.g., boceprevir and teleprevir treatments for Hepatitis C).

5. Drugs that have previously demonstrated efficacy in a tumor type driven by an identified mutation/pathway alteration could be considered eligible for Breakthrough designation in a different tumor type with the same mutation/alteration based on substantial clinical efficacy in the additional tumor type (e.g., crizotinib for treatment of ALK+ pediatric ALCL).

B.3 Designation Process – Timing and Content of Request

The Breakthrough Therapies language 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 prior to receiving marketing approval of its biologics license application (BLA) or new drug application (NDA). The pre-IND meeting would be an opportunity to discuss and agree on the evidence needed to meet Breakthrough Therapy criteria and the contents 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 prior to an IND submission in a pre-IND meeting, a formal request for and decision on Breakthrough designation would still require and await the evaluation of preliminary clinical experience.

A request for Breakthrough designation should describe what category of Breakthrough therapy the investigational agent would fit into by including a summary of the disease 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 it meets the criteria for Breakthrough designation by describing the scientific rationale and mechanism of action of the investigational agent, and describing the early phase clinical studies and results of those 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).

B.4 Designation Process – FDA Response

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

C. Expedited Development Process

To facilitate the development of a designated Breakthrough Therapy, FDASIA requires that the FDA include senior managers and experienced reviewers in a collaborative, multi-disciplinary 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 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.

We have proposed potential development paths for some of the different categories of Breakthrough Therapies in Table 2. 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 multi-disciplinary review team. For example, discussing target labeling early 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 products; and the potential for existing co-Dx review requirements to delay clinical development of 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 have proposed considerations for manufacturing and companion diagnostics to enable expedited development. We have also proposed timeframes and FDA-sponsor interactions to facilitate this process. We have provided these proposals primarily to stimulate discussion; they are not intended to advocate for the adoption of rigid standards for Breakthrough Therapy development.

C.1 Considerations for Chemistry, Manufacturing, and Controls (CMC)

The key points to be considered in enabling acceleration of traditional CMC timelines are:

1. Initial supply of product from clinical manufacturing process and/or clinical site for a pre-determined period of time.
2. Deferral until post-approval (or prior to commercialization) of certain process validation requirements that do not directly relate to safety. For instance, for biologics, all process validation activities have to be completed prior to submission.
3. Amount of real time stability data for approval including acceptance of use of representative pilot scale data.

Considerations

* The regulatory acceptance of prior platform knowledge should be leveraged to allow for significant acceleration on the CMC side. Such knowledge will be applicable in respect to process (e.g., scale, validation), as well as products (e.g., formulation, characterization, validation of analytical methods, stability, 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, < 30ppm CHOP, < 20ppm Leached ProA).

* The use of comparability protocols should be leveraged to make this program as feasible as possible for industry. This will enable the efficient execution of post-approval changes, technology transfer, and scale up changes that will be required under such a program.

* In addition to ensuring Good Manufacturing Practice compliance, post-approval inspections should be leveraged to bring technical experts to monitor the effects of post-approval changes and scale up. This program actually existed in PDUFA I and II to go back and monitor successful implementation of validation in the small molecule realm.

* The sponsor needs to be able to manufacture sufficient drug to supply a reasonable number of patients. The ability to reliably manufacture "reasonable" quantity should be a pre-requisite for approval.

C.2 Considerations for 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. Expediting development of a potential biomarker-defined Breakthrough Therapy might require

development of a process for co-Dx approval that enables selection of patients for pivotal clinical studies without the availability of prototype Dx assays. This could lead to registration of a co-Dx using a bridging study or to conditional approval of the companion diagnostic pending subsequent studies. Such a process may be required to avoid delays in clinical study execution where a compelling diagnostic hypothesis is generated from early studies using exploratory assays that are validated at the laboratory level (e.g., laboratory developed tests; LDTs), that will undergo additional validation in the future to meet regulatory rigor. Consultation with the Center for Devices and Radiological Health (CDRH) will be required to enable development of this accelerated process.

One scenario might be dramatic clinical responses observed in a subset of patients where the diagnostic hypothesis was generated in the context of an early study using an assay that is not a prototype diagnostic. Significant time would be required to develop an assay for the initiation of subsequent studies that would require patient selection/enrichment and/or randomization based upon marker status. Although current guidelines typically require contemporaneous approval of a targeted therapy and its co-Dx, the 2011 draft Guidance on co-development of companion diagnostics does provide for flexibility when a new drug is intended to treat a serious and life-threatening disease (8). This flexibility could be utilized to enable approval of the Breakthrough drug without concurrent approval of the co-Dx. This may enable minimal development of the assay for the registration trial (e.g., allowing transfer to a CLIA/CAP-certified lab or central reference laboratories as an LDT) in order to support expedited clinical studies for Breakthrough drugs. Process considerations for this scenario are described:

i. Careful development of adequate analytical performance criteria would be required in this case to enable subsequent bridging studies.
ii. 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 that is not consistent 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.
iii. Some precedence can be derived from K-ras and ALK immunohistochemistry assays, and sponsors will generally be required to bank samples from early studies maintaining high (>90%) ascertainment rates to enable continued companion diagnostic development post Breakthrough approval where possible. For indications where tissue quantities are limited, such as lung tumors, a pathway that employs 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).

C.3 Proposed Timeline for FDA-Sponsor Interactions

We envision greater direction from FDA in general and a closer working relationship between the FDA and sponsor throughout development. We recommend a combination of meeting types, but, at a minimum, type A meetings would be held once a product is designated as a Breakthrough. We also propose a new category of meeting to be at the sponsor's disposal. These would be arranged between the single points of contact representing the FDA and the sponsor, and essentially create a "hotline" to one another to enable findings from studies to be shared in real-time. This construct would enable FDA to participate in the decision making process in a real-time fashion. It would also enable periodic assessments of the approval status based on rolling information (non-clinical, CMC, etc.).

<u>Proposed Timeline</u>

During Phase I

- At the time Breakthrough Therapy designation is granted, an FDA Breakthrough Therapy team and single point of contact is provided to the sponsor along with a communication plan.
- Meeting/teleconference in mid phase I:

1. Review interim clinical data.
2. Agree if phase I extension is sufficient given Breakthrough designation or agree on phase II/III protocol synopsis.
3. Streamline manufacturing qualification/validation plan based on one lot (for both development and market).
4. Review quality control, stability plan.
5. Agree on streamlined development of companion diagnostic, including a statistical analysis plan (SAP) for prospective/retrospective analysis of phase I data if appropriate.

End of Phase I /Phase I Extension Meeting
Raw but audited Phase I data are submitted. Determination of adequacy of phase I extension as appropriate versus proceeding to phase II. Randomized phase II protocol as appropriate is submitted and phase II/III starts immediately, timing for mid phase II/III meeting is proposed.

Mid phase II/III meeting
FDA and sponsor team review, discuss and agree on:
1. End of study analyses
2. Any changes in plans and available data for manufacturing and controls and companion diagnostic
3. Draft label components for indication, warnings and precautions, administration
4. SAP for prospective/retrospective analysis of phase I data if appropriate for Dx hypothesis.

Between mid phase II/III and end of phase II/III - pre-BLA/NDA meeting
- FDA and sponsor teams communicate via e-mail re: details/revisions based on mid phase II/III discussions; a pre-BLA/NDA meeting would be conducted if needed to review Table of Contents of application and post-application coordination. FDA sets date for inspections.
- Discussions with CDRH and CDER regarding streamlined path for companion diagnostic, possibly including plan to make the investigational use of the IVD available prior to the approval of the regulated device.

BLA/NDA submission
BLA/NDA submission with full data sets and analyses (as agreed), full bioanalytical reports (potentially unaudited), audited non-clinical data, audited manufacturing and controls data along with stability and controls plans, module 2 summaries, labeling, BUT only summary clinical, clinical pharmacology and non-clinical study reports, and only integrated safety and efficacy when justified (in most cases this would not be applicable). Sponsor submits inspection info separately but concurrently to field office(s) and/or inspection office.

BLA/NDA review cycle
Weekly teleconferences for FDA and sponsor teams to review each section of application, design phase IV study and phase IV manufacturing plans/commitments, advisory committee preparations (if needed), agree on final label, and additional studies to enable companion diagnostic if needed. We propose that the review period be limited to 3 months.

Advisory committee (if needed)

Approval/start of phase IV
Approval of application (includes agreed phase IV plan), phase IV start (clinical, manufacturing), FDA review and approval of promotional material, sponsor and FDA review and agree on revised label components upon phase IV completion.

Phase IV completion
Phase IV data submitted, label revised.

D. Conclusion

The Breakthrough Therapy designation is aimed at accelerating development and approval of novel therapeutics that show substantial promise in early studies for indications where the current treatment is inadequate. This designation also seeks to minimize the number of patients tested in controlled clinical trials. We have discussed here major issues that the FDA will need to address in its Guidance on development of Breakthrough Therapies, with particular emphasis on providing flexibility in current CMC and companion diagnostics guidelines so as not to delay approval once the 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 often 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 EU, drugs that receive Breakthrough designation in the US may still be required to go through the traditional drug development pathway for EMA approval. These differing requirements may make the Breakthrough pathway an unattractive option for drug sponsors. One existing initiative that may enable harmonization between the FDA and EMA regarding development of Breakthrough Therapies is the Parallel Scientific Advice program between the two agencies. This program is applicable to oncology products, pediatric medicines, vaccines, and orphan disease products, and provides for information 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 adapt its own expedited development pathways, such as the "exceptional circumstances" program, 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 US legislation and FDA guidance, efforts should be made to harmonize this designation on a global level at international forums.

E. Tables

Table 1: FDA Approaches to Expedited Drug Development

	Accelerated Approval	**Fast-track Designation**	**Priority Review**	**Breakthrough Designation**
Eligibility	1. Treat serious or life-threatening diseases 2. Provide meaningful therapeutic benefit over existing therapies 3. Surrogate endpoint reasonably likely to predict clinical benefit	1. Intent to treat broad range of serious diseases 2. Potential to fill an unmet medical need	1. Offer major advances in treatment over existing therapies	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

Notes: 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. NDA: New drug application; BLA: Biologics license application; IND: Investigational new drug.

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 SoC[+]	Unprecedented early activity in Phase I: either CRR*, ORR* or CBR* with acceptable safety	Phase I B 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 SoC 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 SoC 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.

+SoC = Standard of Care
*CRR= Complete Response Rate, ORR=Overall Response Rate, CBR=Clinical Benefit Rate

F. Glossary of Abbreviations

ALK	Anaplastic lymphoma receptor tyrosine kinase
BLA	Biologic License Application
BRAF	v-raf murine sarcoma viral oncogene homolog B1
CAP	College of American Pathologists
CBER	Center for Biologics Evaluation
CBR	Clinical benefit rate
CDER	Center for Drug Evaluation
CDRH	Center for Devices and Radiologic Health
CFTR	Cystic fibrosis transmembrane conductance regulator
CHOP	Chinese Hamster Ovary Protein
CLIA	Clinical Laboratory Improvement Amendments
CMC	Chemistry, Manufacturing, and Controls
Co-Dx	Companion Diagnostic
CRR	Complete response rate
Dx	Diagnostic
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
IND	Investigational New Drug
K-ras	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LDT	Laboratory developed test
NDA	New Drug Application
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
PDUFA	Prescription Drug User Fee Act
PMA	Premarket Approval
ProA	Protein A
SAP	Statistical analysis plan
SoC	Standard of Care

G. Appendix- Case Studies of Recent Therapeutic Breakthroughs

Vemurafenib

Vemurafenib (Zelboraf) is a targeted therapy which selectively inhibits the kinase activity of $BRAF^{V600E}$. The V600E mutation is present in 50-60% of melanomas and drives proliferation of these malignant cells [reviewed in (10)]. Phase I results demonstrated response rates that substantially exceeded responses achieved by the current SoC for this deadly disease: twenty-six of 32 patients (81%) positive for the $BRAF^{V600E}$ mutation had an unconfirmed objective response to treatment (11). In contrast, the standard therapies approved for treatment of metastatic melanoma, high-dose interleukin 2 and dacarbazine, have response rates between 10-20% and do not improve overall survival (12, 13). A phase II trial in 132 patients with metastatic melanoma with the $BRAF^{V600E}$ mutation was also conducted and confirmed a best overall response rate of 52%.

At the time phase II results were obtained, the sponsor was also conducting a randomized, controlled, multicenter phase III trial of vemurafenib vs. dacarbazine in patients with previously untreated unresectable or metastatic melanoma with the $BRAF^{V600E}$ mutation. The phase III trial was originally designed with 680 patients with a primary efficacy endpoint of overall survival, based on discussion with the Agency. However, given the impressive phase I and phase II results, the Agency requested the applicant modify the statistical analysis plan of the phase III trial to add progression-free survival as a co-primary endpoint. Following the positive phase III analysis, active patients on the control arm were given the opportunity to cross-over to the experimental arm. Full approval was granted to vemurafenib and its companion diagnostic, the COBAS 4800 BRAF V600 Mutation Test, in August, 2011 based on the phase III and phase II trials.

Because the phase III trial was ongoing prior to the phase II trial result, development of vemurafenib was completed relatively quickly. However, had an interactive process of communication been in place between the FDA and sponsor, an alternate development plan may have conserved patients, resources and time. A smaller, randomized IIb study could have been sufficiently powered to demonstrate clinical benefit (7), allowing for full approval.

Crizotinib

Crizotinib (Xalkori) is an inhibitor of anaplastic lymphoma kinase (ALK), a gene rearrangement present in approximately 5% of patients with non-small cell lung cancer (NSCLC) (14). Phase I results demonstrated a 57% response rate in 82 ALK-positive NSCLC patients, again far exceeding response rates of 10% given by treatment options available at the time (15, 16). Crizotinib went on to receive accelerated approval in August, 2011 based on the results of two single arm trials in which a total of 255 patients with ALK-positive NSCLC demonstrated a median response rate between 50-60% with a median duration of 42 weeks. Its companion diagnostic, the Vysis ALK Break Apart FISH Probe Kit, was also approved at this time. Randomized confirmatory trials are ongoing patients with ALK+ NSCLC and patients with ALK+ non-squamous carcinoma of the lung. Although receiving accelerated approval allowed crizotinib to reach the market quickly, controlled trials in ALK+ patients are still required in the post-marketing setting.

Vismodegib

Vismodegib (Erivedge) is an inhibitor of the Hedgehog pathway. Aberrant hedgehog signaling is a major driver of basal cell carcinoma pathogenesis (17). Vismodegib was tested in a single-arm phase II trial in which 33 patients had confirmed metastatic basal cell carcinoma (mBCC) and 63 had locally advanced basal cell carcinoma (laBCC), and the majority of patients in this trial were previously treated. The primary efficacy endpoint in this trial was overall response rate, which was 30% in mBCC patients and 43% in laBCC patients. These responses were durable, with a median duration of 7.6 months. Although basal cell carcinoma is very common, and is usually managed with surgical excision, there is no established effective treatment for mBCC or laBCC, which are rare disorders. Given the absence of

therapeutic options in an uncommon condition and the impressive efficacy seen in the phase II trial, vismodegib was granted full FDA approval on January 30, 2012 after only a three month review. Further, although vismodegib is a targeted agent, because the vast majority of basal cell carcinomas express the target, no companion diagnostic was necessary for development.

Ivacaftor

Ivacaftor (Kalydeco) targets a defective form of the cystic fibrosis transmembrane regulator (CFTR) protein. This form is a result of the specific G551D mutation in the CFTR gene, and is present in approximately 4% of cystic fibrosis patients, with a total of approximately 1200 cystic fibrosis patients in the United States harboring the G551D mutation. Two placebo-controlled phase II trials involving 213 patients determined that ivacaftor resulting in significant and sustained improvements in lung function. Ivacaftor received full approval on January 31, 2012 following a three month review. CDRH was consulted to help address the adequacy of available tests for identification of specific CF gene mutation identification. CDRH noted that there are several FDA-cleared diagnostic tests available that can detect the G551D mutation. Furthermore, identification of specific CFTR genotypes in patients with CF is now almost a standard of care of CF patients (18).

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