Re-evaluating Criteria for Accelerated Approval

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Introduction

Accelerated approval is an expedited regulatory pathway that allows a drug to be approved by the US Food and Drug Administration (FDA) based on a surrogate endpoint (such as tumor shrinkage) that is considered reasonably likely to predict a clinical benefit (such as increased overall survival). Drugs granted accelerated approval must be further tested in post-marketing studies to verify the predicted clinical benefit and may be converted to "regular" approval if clinical benefit is confirmed or withdrawn from the market if it is not. Drugs or biologics eligible for accelerated approval must be intended to treat a serious or life-threatening disease, and should demonstrate the potential to address an unmet medical need—either by providing a therapy where none exists or by providing a meaningful therapeutic benefit over an existing therapy.

This pathway was designed as a response to the AIDS crisis in the 1980s and the resulting demand from HIV/AIDS patients for faster drug development. These patients, faced with a poor prognosis and no treatment options, were willing to accept the risk inherent with an expedited drug approval based on a surrogate endpoint. Since its implementation in January 1993, the accelerated approval pathway has mainly been used for the development of HIV/AIDS and oncology drugs and, more recently, for new influenza vaccines. According to a recent analysis, 35 oncology products had obtained accelerated approval for 47 indications as of July 1, 2010 (1). Of these 47 indications, 26 have been converted to regular approval with an average time to conversion from accelerated approval of 4.7 years. This represents significant time-savings in making potentially life-saving or life-prolonging medicines available for the sickest of patients.

In general, accelerated approval has been considered a success in oncology. However, in recent years, the process has come under increased scrutiny. While some have criticized the FDA as being lax in their oversight of post-marketing commitments, others have voiced concern that the FDA is making accelerated approval increasingly difficult to obtain (2-5). Two events in particular intensified this concern. The first occurred in 2010, when the FDA refused to file the application for trastuzumab emtansine (T-DM1), a novel approach to treating HER2-overexpressing metastatic breast cancer. The T-DM1 application was based on a single-arm phase II study that showed a 34% response rate in women with advanced HER2-overexpressing breast cancer who had received, on average, seven prior medicines including two HER2-targeted drugs (6). According to a Genentech press release, the FDA stated in its review that the T-DM1 trial did not meet the standard for accelerated approval because all available treatment choices approved for metastatic breast cancer, regardless of the HER2 status, had not been exhausted in the study population (7). The second event to raise concern occurred in February, 2011, when the Oncologic Drugs Advisory Committee (ODAC) was convened by the FDA to discuss whether

single-arm trials should continue to be used to support accelerated approval, as well as the requirements for confirmatory trials (8). There was consensus that single-arm trials should be reserved for exceptional circumstances where there are few patients and a significant treatment effect can be observed. Further, the majority agreed that, ideally, two controlled confirmatory trials should be conducted, and that these should be at least written and ideally underway at the time accelerated approval is granted. This meeting raised concern among many that the FDA would no longer accept single-arm trials for accelerated approval.

Despite these concerns, the FDA has continued to grant accelerated approval to promising new therapies tested in single-arm trials. In 2011, brentuximab vedotin obtained accelerated approval for Hodgkin lymphoma and anaplastic large cell lymphoma, and crizotinib received accelerated approval for ALK-positive non-small cell lung cancer. In July of this year, the FDA granted accelerated approval to carfilzomib for treatment of multiple myeloma. Each of these new agents was approved based on data from single arm trials. Further, while the proteasome inhibitor carfilzomib was studied in patients who had received at least two prior lines of therapy including bortezomib, which is also a proteasome inhibitor, some other available therapies for multiple myeloma were not exhausted in this patient population. Nonetheless, the availability of an increasing number of approved therapies in many cancer types has raised the bar that a new drug must meet to fill an "unmet need" and pushed drug developers to test new products in last-line disease settings, even though heavily pre-treated patients may be less likely to respond to or benefit from a new therapy. Other major barriers to utilization of the accelerated approval pathway include the lack of surrogate endpoints considered suitable for regulatory use, and the lack of confidence sponsors have early in development as to whether a product is best suited for accelerated approval or the standard development pathway. Possible solutions to these challenges will be proposed here.

Eligibility for the Accelerated Approval Pathway: What is "Unmet Need"?

At the time the accelerated approval pathway was designed, treatment options in oncology consisted primarily of surgery, radiotherapy, and cytotoxic chemotherapy. As the treatment paradigm in oncology has shifted to therapies targeted against specific oncogenic proteins or pathways, patients' lives have been improved and extended. Nonetheless, most of these newer treatments still are not curative, some improve survival by only weeks to months, and most cause significant toxicities. Therefore, despite the availability of new anti-cancer therapies, significant unmet need remains, especially in the setting of metastatic disease.

In oncology, sponsors usually pursue accelerated approval in one of two ways: single-arm trials utilizing historical controls in settings with no approved treatment options (such as in refractory disease), or comparator trials when approved therapies are available (such as in earlier disease settings). In the second situation, the investigational agent must demonstrate that it is potentially superior to the comparator in efficacy, tolerability, or practical benefit. This need to demonstrate superiority based on a surrogate endpoint when other approved therapies are available is a major barrier to companies pursuing accelerated approval with an investigational agent. Further, this paradigm may be overly restrictive in oncology because there is not only a need for better drugs, but also a need for mechanistic diversity. A new drug may have efficacy comparable to available agents but, by acting through a previously untargeted pathway, provide physicians with an additional therapeutic option from which to choose, depending on patient need. Post-approval studies will often identify unique benefits or safety issues that may change the consensus on which drug is superior or on how treatments should be optimally sequenced. Having an array of mechanistically diverse therapies available also fosters development of combination regimens that may overcome drug resistance and improve patient outcomes. The following proposal lays out a pathway for accelerated approval of new cancer drugs that recognizes this reality.

Unless a cancer is curable, it should be regarded as having an unmet medical need with any line of therapy. Novel investigational agents could be considered for accelerated approval if they demonstrate clear evidence of activity on a surrogate endpoint and have acceptable safety. Whether this should be assessed through single-arm trials using historical controls or through prospective randomized trials will depend on the end point being assessed, the clinical setting, the level of activity that would be clinically meaningful in that setting, and the appropriateness of historical controls. The current trend to pursue accelerated approval in more and more refractory populations could be curbed by better defining "available therapy" and the indication being sought, and by accepting that "unmet medical need" exists in any non-curative setting. If an investigational agent targets a specific mutation or pathway, and that information would be part of the labeled indication for patient selection, then the only drugs that should be considered "available therapy" for the purposes of accelerated approval are those that also target that same pathway. If a new drug targets a previously untargeted pathway, there is no "available therapy" in that setting. Regardless of the setting, new therapies should be shown to have at least comparable activity to existing treatments for the particular stage of disease. This pathway-based distinction recognizes our increasing understanding of cancer as a genetic disease: driver mutations not only represent druggable targets, they define unique diseases with unique biology, natural history and treatment requirements. Sponsors seeking accelerated approval need to engage in early discussions with the FDA to define the appropriate context for initial efficacy studies.

Novel Surrogate Endpoints to Support Accelerated Approval

The surrogate endpoints most commonly used for accelerated approval include progression-free survival (PFS) and objective response rate (ORR), (1, 9). In solid tumors, measurement of both RR and PFS relies on anatomical imaging using X-rays, CT scans, or MRIs, and is based on widely accepted standardized criteria (RECIST: Response Evaluation Criteria in Solid Tumors, (10)). Progression-free survival is defined as the time from randomization or treatment initiation until tumor progression or death. It usually allows a shorter follow-up period and smaller sample size than studies measuring overall survival (OS), and is not confounded by subsequent therapies. In some cases, PFS is accepted as an established surrogate for OS and can be used as the basis for full approval. Objective response rate is defined as the proportion of patients who experience tumor regression of a certain magnitude, and has the advantage over PFS that the treatment effect is directly attributable to drug activity and therefore can be assessed in single-arm trials. ORR has the disadvantage that it does not measure stable disease or minor regressions and does not measure the durability of a response. Both endpoints are limited by the subjectivity of radiologic measurements of tumor size.

Since the implementation of accelerated approval twenty years ago, the endpoints considered suitable for this pathway have changed little. Many have called for the FDA to accept new surrogate endpoints, such as novel imaging endpoints or biomarkers that can be measured earlier than RR or PFS, or can be used in settings where conventional RR and PFS cannot be readily or reproducibly assessed. In this section, we will discuss some novel biomarkers that are currently being studied and could potentially become "qualified" as surrogate endpoints for accelerated approval. The regulatory definition of qualification is provided in the draft Guidance, *Qualification Process for Drug Development Tools*, which provides a framework for interactions between the Agency and those wishing to develop tools such as surrogate endpoints (11). A biomarker that is accepted by the FDA as a surrogate endpoint is considered "qualified"- within a given context of use, analytically valid measurements of that biomarker can be expected to be relied upon to be "reasonably likely to predict clinical benefit." Qualification of a biomarker as a surrogate endpoint requires robust scientific and clinical evidence.

An example of a recently qualified surrogate endpoint is pathologic complete response (pCR) in localized breast cancer. In May, 2012, the FDA announced its acceptance of pCR as a surrogate endpoint in certain breast cancer settings (e.g., neoadjuvant) and published a draft Guidance, *Pathologic Complete Response*

in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval, to describe this endpoint and the basis for its qualification (12). In this Guidance, the FDA provided a formal regulatory definition of the proposed surrogate endpoint, pathologic complete response; explained the rationale for using this endpoint in the setting of neoadjuvant breast cancer therapy; summarized the evidence that supports the utility of pCR as a surrogate endpoint, and described the types of trials that would be appropriate for use of pCR to support accelerated approval. Importantly, the guidance noted that the analyses supporting use of pCR as a surrogate endpoint are currently limited to analyses of treatment response and stressed that future prospective studies are needed to fully understand the relationship of pCR to ultimate clinical benefit. Given the lack of alternative surrogate endpoints in early-stage breast cancer, pCR is acceptable despite this uncertainty in situations with significant unmet medical need (e.g., high-grade, triple negative breast cancer).

The pCR Guidance highlights several important criteria that contribute to the qualification of a novel surrogate endpoint, many of which have been reviewed elsewhere (13-15). First, the endpoint must have an accepted, standardized definition. Second, there should be data from multiple clinical studies demonstrating a strong correlation of the surrogate endpoint with clinical outcomes. Third, well-powered prospective studies are needed to validate that the surrogate endpoint is truly predictive of clinical benefit and to what extent (i.e., what degree of improvement in the surrogate is needed to predict a clinically meaningful improvement in patient outcome). Fourth, prospective studies are needed to determine if the surrogate endpoint can be generalized to other patient populations, other target organs, or drugs with other mechanisms (e.g., some measures useful only with cytotoxic drugs). The strength of evidence for the last three criteria will vary, depending on whether the surrogate is intended for use in "regular" approval or accelerated approval. For the latter, the evidence needs to support that the surrogate is "reasonably likely to predict clinical benefit". Evidentiary standards for meeting this threshold have not been established.

Using the above four criteria, we will briefly examine the utility of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging for early evaluation of drug activity in clinical trials. We have chosen to focus on FDG-PET in this document because there is a substantial body of literature regarding its use in the clinic that could soon lead to a consensus opinion on its appropriateness for use as a surrogate endpoint. FDG-PET is a functional imaging technique that has been used in routine clinical practice for assessment of many different types of cancer for over twenty years (15, 16). FDG-PET technology relies on the fact that cancers use glycolysis rather than aerobic respiration to adapt to low oxygen environments (the Warburg Effect), and it measures one consequence of this, which a major increase in the influx of labeled glucose into cancer cells. Thus, it provides a measure of tumor metabolism that can be used to assess drug activity and can be evaluated earlier than tumor regression when assessed using standard response criteria.

A semi-quantitative measurement of FDG uptake (standard uptake value, SUV) has been proposed as a biomarker of efficacy. SUV measurement could potentially be used to meet the first criterion described above by providing a standardized definition of what constitutes a response to therapy when assessed by FDG-PET. To meet the second criterion, multiple studies are needed to determine the analytical robustness of the measurement and whether a decrease in SUV following therapy correlates with improved patient outcome. There have been many retrospective and small prospective studies in a variety of cancer types that have demonstrated a promising correlation between SUV decrease and survival (14). To meet the third criterion, large prospective trials comparing a pre-defined change in SUV to clinical outcomes should be performed to assess the degree of correlation. At present, there are two ongoing multi-center trials prospectively designed to validate FDG-PET as a surrogate endpoint (lymphoma, CALGB-50303; NSCLC, RTOG-0235/ACRIN6668). The CALGB trial is a large, randomized phase III study in non-Hodgkin's lymphoma designed prospectively to collect FDG-PET imaging as well as event-free survival data. The RTOG trial is a phase III trial in locally advanced NSCLC in which the objective

is to evaluate the ability of the change in the standard FDG uptake value before and after treatment to predict overall survival.

Results of the trials discussed above could contribute to qualification of FDG-PET functional imaging as a surrogate endpoint in these diseases, if not in all cancer types. However, to meet the fourth criterion described above, prospective trials would be needed to determine the context-dependent utility of FDG-PET measurements. While FDG-PET is considered highly sensitive, in some contexts it may not be specific enough for use as a surrogate endpoint (16, 17). For example, in colorectal cancer, FDG accumulation occurs physiologically in the bowel wall and this accumulation is increased by inflammation. Also, FDG-PET measurements may not be appropriate for use with agents that affect glycolysis, such as AKT inhibitors. FDG-PET measurements may be more appropriate as surrogate endpoints in situations where more conventional endpoints are not feasible or practical. In these cases, quantitative longitudinal or serial changes in FDG activity during therapy that demonstrate persistent suppression of tumor metabolism may predict clinical outcomes earlier than standard anatomic measurements.

Besides pathologic complete response and FDG-PET measurements, there are a number of other potential surrogate endpoints being studied in a variety of disease settings. For example, the evaluation of circulating tumor cells (CTC) following treatment has been proposed as a surrogate for clinical outcome in multiple tumor types. Presently, however, there is no standard definition for CTC, and the many existing technologies for assaying CTCs may measure different markers or different cells. The only FDA cleared CTC enumeration methodology at this time is the Veridex CellSearch® CTC Kit, which has demonstrated prognostic significance in breast and prostate cancer and is currently being studied in a randomized phase III trial (AFFIRM; NCT00974311) to determine if CTC reduction is predictive of overall survival (18). Other potential surrogate endpoints that have been proposed include the measurement of gene rearrangements in acute lymphoblastic leukemia (ALL) to assess minimal residual disease (MRD; (19)), and the measurement of correlates of immunity in studies of idiotypic vaccine candidates for lymphoma (20). In the future, the availability of additional qualified surrogate endpoints will enable more efficient and expedited drug development.

Proposal for a Structured Accelerated Approval Process

Unlike fast-track designation and the recently designed "breakthrough therapy" designation, there is no formal process for designating a product for development through the accelerated approval pathway. Establishing a dialogue very early in the process (phase 1 or earlier) between the sponsor and the FDA would help sponsors devise an efficient development plan and may incentivize sponsors to establish novel surrogate markers more likely to predict clinical benefit and that would be of potential use for multiple therapeutic products. We propose a structured process where sponsors and FDA meet early and formally agree that either the drug will be developed using an "adaptive clinical development plan" with the possibility for accelerated approval if certain results are generated, or that the full approval process is necessary based on either existing data or new information that emerges during the drug development process. A decision to pursue accelerated approval should include the following: 1) an agreement between the FDA and sponsor that unmet need exists in the patient population being studied; 2) agreement on what surrogate endpoint will be assessed; 3) upfront agreement on what magnitude of benefit must be observed using the agreed-upon surrogate endpoint for accelerated approval to be granted; and 4) an agreement on post-marketing commitments. Whether a single-arm trial using historical data as a control or randomized trial with an active or placebo control is appropriate will depend on the situation as described above. In the case of a controlled randomized trial, the FDA and sponsor could agree on a pre-specified analysis plan in which an interim analysis is performed using a surrogate endpoint- if sufficient activity is observed at this point, accelerated approval could be granted and the original trial could then be completed using a traditional clinical endpoint for conversion to full approval. The challenge in this

situation is further enrollment after accelerated approval is granted. The decision of whether a drug should be developed using this adaptive clinical development plan should be made within a short period of time after review of relevant clinical and preclinical data (e.g. 60 days after submission by the sponsor of the data and protocol). This process and agreement documentation would be a key step in providing the predictability that is currently lacking. A more predictable path to approval would allow for better portfolio decisions within large sponsor organizations and facilitate critical funding for smaller organizations.

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