Factors to Consider in Assessing the Accelerated Approval Pathway

Mark Thornton, MD, MPH, PhD
President, Sarcoma Foundation of America
Sr. Clinical Consultant,
Biologics Consulting Group, Inc.
Factors to Consider in Accelerated Approval for Rare Diseases

- Extremely high unmet medical need
- Extreme rarity
- Absence of any prior clinical study of formally collected clinical data
- Slow disease progression with significant irreversible symptoms
- Significant delay between the onset of irreversible disease and clinical diagnosis
- Lack of readily measurable, recognized clinical endpoints due to unusual clinical disease manifestations
Historical Perspective

How we got here –
The rare cancer perspective
“Exceptional” Approval Could Replace “Accelerated” For Rare Cancer Drugs

An “exceptional” approval process should be carved out of the accelerated approval program for products targeting rare cancers where there is little likelihood of completing confirmatory trials, members of FDA’s Oncologic Drugs Advisory Committee recommended.

One way to deal with products targeting rare cancers may be to develop “an exceptional approval strategy for exceptional diseases,” committee consultant Gail Eckhardt (University of Colorado Health Sciences Center) said during the Nov. 8 meeting, convened to review incomplete accelerated approval commitments (“The Pink Sheet” Sept. 26, 2005, p. 27).

[Editor’s Note: To watch a webcast or order a video/DVD of this meeting, visit FADAAdvisoryCommittee.com.]

During the meeting, FDA, sponsors and committee members identified the lack of patients for rare cancers as one of several barriers to the completion of accelerated approval confirmatory studies (see preceding story).

“One way to proceed towards approval of” agents targeting limited patient populations “would be to not have them necessarily on [the accelerated approval] track because I think we’re finding that some of the randomized trial designs, placebo control and accrual is so slow we never get there,” Eckhardt said.

Instituting an exceptional approval program would allow products to avoid being in a “fugue state of approval for years and years and years with never meeting commitments,” she said.

Eckhardt suggested that a “body of data” requirement could be established to provide a standard for full approval of such agents based on limited trial data. “That could be a constellation of data that doesn’t necessarily have to be randomized, but needs to be done in a high quality manner,” she explained.

difficult since the agency does not have jurisdiction over physician prescribing of off-label uses.

In suggesting an exceptional approval process, committee members drew upon the European Medicines Agency’s recent restructuring of its accelerated approval program, which was presented at the meeting.

In an effort to ensure that sponsors complete confirmatory trials for products targeting diseases where standard Phase III trials are feasible, the European agency carved a “conditional” approval program out of the agency’s “exceptional circumstances” pathway.

The exceptional circumstances pathway is intended to review products for which “comprehensive data cannot be provided (because of specific circumstances: rarity, medical ethics, state of scientific knowledge),” the European Agency said.

EMEA recognizes exceptional circumstances products will likely never have the same level of data as products approved under the standard pathway.

For those drugs for which substantial data can be collected but still warrant accelerated approval, EMEA will grant a conditional marketing authorization if the products show a positive risk/benefit ratio “based on preliminary evidence.”

Following conditional approval, sponsors are expected to produce the same quality of data as standard approval products. To ensure completion of confirmatory trials, the authorization expires after one year, although sponsors can apply for renewal.

In another nod to the EMEA system, committee members recommended that the U.S. accelerated approval program be renamed “conditional approval” to better convey the nature of the approval pathway.

“Accelerated approval is no longer an acceptable term.
BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Citizen Petition to Request a Guidance Document to Improve the Accelerated Approval Process for Drugs and Biologics Intended to Treat Patients with Rare Cancers

To whom it may concern:

On behalf of The Alliance Against Alveolar Soft Part Sarcoma (“TAAASPS”) and the Sarcoma Foundation of America (“SFA”), the undersigned submit this petition under 21 C.F.R. § 10.30 to request the Commissioner of Food and Drugs to issue a guidance document to provide specific guidelines under the Food and Drug Administration’s (“FDA” or “the agency”) accelerated approval process for drugs that are intended to treat rare cancers, including alveolar soft part sarcoma (ASPS). Specifically, we request guidelines for approval of any drug or biological product intended to treat a rare cancer that might not yet have an established surrogate endpoint, or that has an established surrogate endpoint but is unable to achieve final approval based upon adequate and well-controlled clinical studies, due to the rarity of the cancer and/or ethical constraints in conducting such studies.

Sarcomas are a rare and diverse group of malignant tumors that develop from fat, muscle, nerves, joints, blood vessels, bones, or other connective or supportive tissues. They constitute about one percent of all adult malignancies, and are more prevalent in children, constituting...
To modernize cancer research, increase access to preventative cancer services, provide cancer treatment and survivorship initiatives, and for other purposes.

IN THE SENATE OF THE UNITED STATES

Mr. KENNEDY (for himself and Mrs. HUTCHISON) introduced the following bill, which was read twice and referred to the Committee on

A BILL

To modernize cancer research, increase access to preventative cancer services, provide cancer treatment and survivorship initiatives, and for other purposes.

1 Be it enacted by the Senate and House of Representa-tives of the United States of America in Congress assembled,

3 SECTION 1. SHORT TITLE.

4 This Act may be cited as the “21st Century Cancer ALERT (Access to Life-Saving Early detection, Research and Treatment) Act”.
1 SEC. 13. ACTIVITIES OF THE FOOD AND DRUG ADMINISTRATION.

2 It is the sense of the Senate that the Food and Drug Administration should—

3 (1) integrate policies and structures to facilitate the concurrent development of drugs and diagnostics for cancer diagnosis, prevention, and therapy;

4 (2) consider alternatives or surrogates to traditional clinical trial endpoints (for example, other than survival) that are acceptable for regulatory approval as evidence of clinical benefit to patients; and

5 (3) modernize the Office of Oncology Drug Products by examining and addressing internal barriers that exist within the current organizational structure.
THE WALL STREET JOURNAL

OPINION      | May 29, 2008
Grassley's War on Cancer Patients
By MARK THORNTON
May 29, 2008: Page A17

The news did not make it to the front pages, but on Feb. 28 a powerful member of the U.S. Senate launched an attack on the Food and Drug Administration, the drug companies and the desperate cancer patients they treat.

Charles Grassley (R., Iowa), ranking member of the Senate Finance Committee, requested that the Government Accountability Office launch an inquiry into whether the FDA behaved appropriately in granting the "accelerated approval" of Avastin, a drug for treating women with metastatic breast cancer. Mr. Grassley's action will have a catastrophic effect on America's ability to develop new drugs.

At issue is the concept of "surrogate endpoints" and the FDA's "accelerated approval" regulations. In the 1980s, at the height of the AIDS epidemic, AIDS activists were livid at the slow pace of development of new drugs to fight HIV. They lobbied heavily for changes in the law to allow an expedited pathway for the approval of new drugs for any disease deemed serious or life-threatening. The historic results were new laws and regulations that created an accelerated approval mechanism by which a drug could be allowed on the market if it showed early evidence of an effect on a surrogate endpoint. For cancer, examples of surrogate endpoints are tumor shrinkage or a delay in the disease's progression.

THE WALL STREET JOURNAL

OPINION      | MAY 7, 2010
The FDA vs. Bone Cancer Patients
The EU has approved a revolutionary treatment, but Americans wait.

Mark Thornton: The FDA vs. Bone Cancer Patients - WSJ.com http://online.wsj.com/article/SB1000142405274870386670457525224...
COMMENTARY

Peter Pitts and Dr. Mark Thornton

U.S. needs breakthrough ‘progressive’ medicines

A recent global cancer conference was abuzz with discussions of a potential breakthrough therapy in the treatment of alveolar soft part sarcoma, a rare form of cancer affecting only about 100 patients per year in the U.S.

If ASPP is not eliminated through surgery, it is always fatal. A new therapy for ASPP, called codrinil, was found in early testing to melt away the tumors in up to 70 percent of treated patients.

Yet there is no development pathway for FDA approval for such small populations of patients, so the world’s next Gleevac lies on a shelf, with fingers crossed that years from now, a far larger, longer clinical trials in higher-prevalence cancers are performed with codrinil. ASPP patients might get access through indirect means.

Simply put, at the Food and Drug Administration, there is no official process for the approval of a product developed to attack a condition affecting just 100 patients. A Grand Canyon exists between reality and hopes for our new age of personalized medicine.

Enter Sen. Kay Hagan, D.N.C. As a member of the Senate Health, Education, Labor and Pensions Committee, she has proposed legislation known as the TREAT Act, which calls for FDA reform that would fast-track drugs that show promising early data in treating deadly diseases.

This bill is an acknowledgement of the failings of the 1990s’ accelerated approval regulations, which rely on “surrogate endpoints” for a clinical trial to represent and reflect the endpoint that is usually used for a drug’s approval.

The result is an arcane amalgamation of our nation’s No. 1 killer, and completely amayse medicine choices for many rare cancer types. The TREAT Act reforms the accelerated approval pathway to allow state-of-the-art clinical endpoints that are “reasonably likely to predict clinical benefit” as the basis for approval for life-threatening diseases.

For cancer, this change could allow a return to the notion of simple, universal measures such as significant tumor death, or delay in disease progression, as the basis for rapid release of new products to desperately ill patients. Additional data following confirmatory studies would then allow progression to full approval.

Safeguards are included in the bill to remove the product from the market should it not live up to its initial promise. Also, as a humanitarian gesture for micro-populations with deadly disease, there is the creation of an “Exceptional Approval” pathway.

This would authorize approvals when the usual data “cannot ethically, feasibly or practically be generated.” This pathway would be a game changer for U.S. rare-disease populations of extraordinarily small numbers.

Thanks to Hagan, there can be a new way forward for development of therapies not just for rare cancers, but for thousands of life-threatening rare diseases where there are no realistic opportunities for drug-development. Such reforms go beyond helping only the forgotten orphans.

By fostering innovations in new areas of drug development, jobs are created and businesses prosper, and innovation accelerates the boundaries of medical knowledge and patient possibilities.

Now is the time to embrace a 21st century FDA — and progressive approvals is a good place to start.

Peter Pitts, a former FDA associate commissioner, is president of the Cancer for Medics for the Public Interest. Dr. Mark Thornton, a former FDA medical officer, is president of the National Organization Against Rare Cancers and is employed to the biotechnology industry.
FOR IMMEDIATE RELEASE

Obama Signs FDA User Fee Legislation Bringing Hope to Rare Disease Patients

EveryLife Foundation for Rare Diseases Applauds Congress for Including Provision to Empower the FDA to Accelerate Approval of Lifesaving Treatments

July 10, 2012, Washington, DC – Yesterday President Obama signed into law The Food and Drug Administration Safety and Innovation Act (FDASIA), S. 3187, bipartisan legislation that will spur the development of lifesaving treatments for 30 million Americans suffering from rare diseases.

“We are thrilled the language to improve access to the FDA’s Accelerated Approval pathway for rare diseases has been included in FDASIA,” said Emil Kakkis, MD, President, EveryLife Foundation for Rare Diseases. “We wish to thank Representatives Cliff Stears (R-FL) and Ed Towns (D-NY) for being champions for the rare disease community.”

Stearns and Towns first introduced Unlocking Lifesaving Treatments for Rare Diseases Act (ULTRA) to empower FDA to use all the science available for allowing surrogate endpoints in clinical trials for rare diseases to determine whether a drug is working, significantly decreasing the development time and cost. Stears and Towns later introduced Faster Access to Specialized Treatments (FAST) Act that improved Accelerated Approval for life-threatening diseases while maintaining high safety and efficacy standards.

FDAs Accelerated Approval has been successful in getting treatments approved for cancer and AIDS patients, but has been essentially unavailable for rare disease treatments. There are currently fewer than 400 FDA-approved treatments for nearly 7000 rare diseases. Investment and interest in development will surge for rare diseases if there is access to the Accelerated Approval pathway.

“We would not have been successful if it were not for the great work of Energy and Commerce Chairman Fred Upton (R-MI), Biotechnology Industry Organization (BIO), and more than 300 patient organizations that advocated for improving the FDA’s regulatory process,” added Kakkis.

FDASIA is the culmination of more than a year of negotiations between industry and FDA and includes the reauthorization of the drug and device user fees.

The Foundation will host its fourth Rare Disease Workshop on “Developing Guidance and Policy Recommendations for Accelerated Approval in Rare Diseases” on November 15th in Washington, D.C. FDA, NIH, industry and academic scientists are invited to participate.

The EveryLife Foundation for Rare Diseases is dedicated to accelerating biotech innovation for rare disease treatments through science-driven public policy. We can do more with the science we already have and bring life saving treatments to millions of people suffering from rare diseases.
Factors to Consider

Guidance for Special Flexibility for Ultra-Rare Diseases Under FDASIA
Special Flexibility for the Ultra-Rare

• Extremely high unmet medical need
  – Feedback from groups representing ultra-rare, life threatening diseases indicate acceptance of greater safety risks and lessened assurance of the efficacy of the product
    • Leveling the playing field; not lowering standards

• Extreme rarity
  – The EU has bravely tried to carve out a definition of ultra-rare (< 1:50,000, or approx. 6000 U.S.) versus Orphan, in opposition to the forces who are motivated to maintain the status quo.
  – Industry has found ways to make sizable profits from populations of 200,000 down to 6,000 range. Much harder to hope for any ROI in much smaller populations, especially if regulatory uncertainty exists.
Special Flexibility for the Ultra-Rare

• Absence of any prior clinical study of formally collected clinical data
  – Disconnect between disease-focused clinical assessment for many rare diseases and the regulatory precedents set for endpoints used in more common diseases makes determining how to evaluate a disease or treatment effect difficult.

• Slow disease progression with significant irreversible symptoms
  – If the clinical manifestations of the disease are not reversible and the goal of therapy is disease stabilization, achieving sufficient power to detect the difference between placebo and treated patients is extremely difficult (e.g., Fabry disease and loss of renal function)
Special Flexibility for the Ultra-Rare

- Significant delay between the onset of irreversible disease and clinical diagnosis
  - Slow and inconsistent changes early in progression difficult to study using clinical endpoints
  - Common in rare neurological disorders, leading to late, rapid decline (e.g., Adrenoleukodystrophy and Batten’s disease)

- Lack of readily measurable, recognized clinical endpoints due to unusual clinical disease manifestations
  - For example, autosomal recessive dystrophic epidermolysis bullosa, where the disease process is not measured using any reasonable intermediate clinical endpoints, short of major clinical events easily confounded by supportive symptomatic care
Regulatory Creep and the Need for Advocacy

Decelerated Approval and A Cautionary Tale
A History of Accelerated Approval:
Overcoming the FDA’s Bureaucratic Barriers in order to
Expedite Desperately Needed Drugs to Critically Ill Patients
(Jacob W. Stahl, Class of 2005
Harvard Law School)

V. President Clinton’s “Reinventing the Regulation of Cancer Drugs”

A. Political Pressure on the President to Apply Accelerated Approval to Cancer

Although the FDA indicated in 1992 that it would grant accelerated approval for cancer
drugs, by 1996 it had only done so in one instance. By comparison, eleven AIDS drugs had been
granted accelerated approval.¹ Meanwhile, the FDA was under pressure from Congressional
Republicans who were proposing a dramatic overhaul of the entire drug approval process.² At
many of these hearings, representatives of cancer patient groups pleaded for accelerated approval
for oncology drugs.

One of the themes highlighted at these hearings was that the FDA was unfairly favoring AIDS
patients at the expense of cancer patients. Eugene Schonfeld, Ph.D., President of the National
Kidney Cancer Association, a management expert, and himself suffering from an advanced stage
of cancer, testified that because the FDA approves AIDS drugs more rapidly than it does cancer
drugs, it makes AIDS drugs relatively more profitable. Consequently, pharmaceutical companies
were likely to shift resources towards AIDS drugs.

¹ “FDA puts new cancer drugs on front burner.” 32 Medical Post, April 23, 1996 at 7.
² See “Reinvention Thwarts Change.” Pharmaceutical Executive, December 1, 1996. These hearings ultimately
culminated in the FADMA the next year.
A History of Accelerated Approval: 
Overcoming the FDA’s Bureaucratic Barriers in order to Expedite Desperately Needed Drugs to Critically Ill Patients 
(Jacob W. Stahl, Class of 2005 Harvard Law School) - Continued

Moreover, Dr. Schonfeld testified that Dr. Kessler told him that the reason AIDS drugs were being approved more quickly was that AIDS activists “are screaming louder” than advocates for patients of other diseases.¹ Likewise, Ellen Stovall, Executive Director of the National Coalition For Cancer Survivorship lamented, “Perhaps the cancer community has been too reticent or willing to accept the agency’s procedures,” an obvious reference to AIDS activists who had put extreme pressure on the FDA for years.²

A second theme highlighted at the hearings was that cancer patients were every bit as willing to take risks as were AIDS patients. Dr. Schonfeld related that in one conversation with Dr. Kessler, the Commissioner told him that that AIDS patients were willing to take risks whereas cancer patients would not. Dr. Schonfeld retorted, “[W]hy do so many cancer patients go to Mexico and the Bahamas for treatment?”³ Ellen Stovall similarly remarked that cancer patients were willing to risk taking chemotherapy despite its dreary side-effects, emphasizing that, “[O]ur very survival depends on accepting the risks of this nature.”⁴

¹ Hearing of the Health and Environmental Subcommittee of the House Commerce Committee, “The Need for FDA Reform,” Chaired by Representative Thomas Bliley, February 27, 1996.
² Statement of Ellen L. Stovall, Executive Director for Cancer Survivorship on Reform of the Food and Drug Administration before the Senate Labor and Human Resources Committee, February 21, 1996.
³ Testimony at the Health and Environmental Subcommittee, supra note 192.
⁴ Testimony before the Senate Labor and Human Resources Committee, supra note 193.
How AA begat AAv2.0

- AIDS patient, and to a lesser extent cancer patient, advocacy resulted in fundamental change in regulatory behavior in the 1990’s
- Over 20 years vigilance, sense of urgency dimmed from advocates
- Regulators caution, conservatism and avoiding sins of commission shifted the pendulum
  - The spirit of AA has been stifled in proportion to strict or flexible adherence of Prentice criteria for surrogate endpoints
  - “The surrogate is not validated” remark has killed many programs, and is a sin of omission difficult to quantify
  - Especially painful in the ultra-rare setting
- Setting reasonable standards for qualification of biomarkers in the ultra-rare setting is the main intent of the advocacy behind FDASIA
  - Less regulatory uncertainty = Greater industry risk-taking in ultra-rares
A Cautionary Tale

• Rare HIV subgroup product
  – Product X and Company A (late 2012, post-FDASIA)
    • Indication is a severe/fatal neurologic disease due to an opportunistic non-HIV virus (U.S. incidence of 2000)
    • AA requested based on surrogate (decline in the responsible non-HIV virus); pivotal trial needing 60 patients (a survival trial would require 250 patients)
    • Given patient participation rates in clinical trials of 1-2%, only 20-40 patients might be available per year
    • FDA found surrogate unacceptable ("The surrogate is not validated"), and required a survival trial; EMEA gave the OK for the surrogate, with post-marketing confirmation of the surrogate
  • Hope dimming that company will continue development
• The lesson is that even with HIV, AA can be an elusive goal if the indication is too rare, and intent of laws can be easily diluted.
• Is this the tip of the iceberg?
Solutions?

Where to from here?
Food for Thought – Advocating for Compliance and Accountability to the Law

• Institute a Rare Disease Oversight Committee at FDA akin to the Clinical Hold Oversight Committee of the mid-1990’s
  – Congressional accountability provisions of the first PDUFA altered clinical hold behavior profoundly (at first)
• Establish a patient volunteer/SGE Rare Disease Ombudsman position (possibly within OOP or OSHI?)
  – Companies trying to develop products for ultra-rare settings could have a safe harbor to voice possible actions counter to the intent of FDASIA
  – FDA Division would have opportunity to explain reasons for denial of surrogate before being reported to Congress