Accelerated Approval Program

30 Years On - Insights and Experiences

March 11, 2022

Virtual Public Meeting

REAGAN-UDALL FOUNDATION FOR THE FDA

REAGAN-UDALL FOUNDATION FOR THE FDA

Welcome & Opening Remarks

Susan C. Winckler, RPH, Esq.

CEO, Reagan-Udall Foundation for the FDA

Meeting Moderator

Thank you for joining

Please keep your cameras off and microphones muted throughout the meeting because of the number of attendees.

This workshop is being recorded.

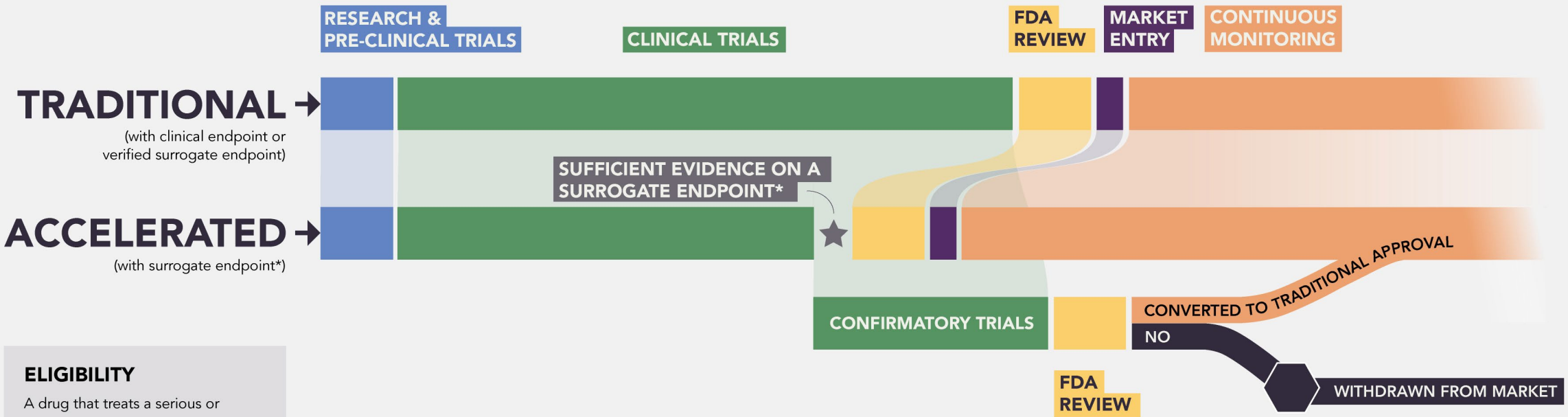
The recording, along with the slide deck and transcript, will be available on www.ReaganUdall.org early next week.

Agenda

REAGAN-UDALL FOUNDATION FOR THE FDA

1:00 PM	Welcome & Opening Remarks
1:05 PM	FDA Panel Presentations: Accelerated Approval 1992 – 2022
2:05 PM	Patient Perspective Panel
3:00 PM	Fireside Chat Sharing Patient Advocacy, Provider, Industry, and Payor Perspectives
3:55 PM	Closing Remarks/Adjourn

Approval Pathways for Drugs & Biologics



ELIGIBILITY

A drug that treats a serious or life-threatening disease, taking into account unmet medical need. The drug is studied using a **surrogate endpoint,*** which in this case, is a marker (such as tumor shrinkage) that is considered reasonably likely to predict a clinical benefit (such as increased overall survival).

REAGAN-UDALL FOUNDATION for the Food and Drug Administration

Accelerated Approval 1992 - 2022

REAGAN-UDALL FOUNDATION for the Food and Drug Administration

- *Accelerated Approval 30 Years On: Lessons and Next Steps*
  Jacqueline Corrigan-Curay, JD, MD
  Principal Deputy Center Director, Center for Drug Evaluation and Research, FDA

- *Failure or Success, Results are Essential*
  Kevin Fain, JD, MPH, DrPH
  Senior Policy Advisor, Office of New Drug Policy, Center for Drug Evaluation and Research, FDA

- *Accelerated Approval in Oncology: 1992-2022*
  Gautam Mehta, MD
  Clinical Reviewer and Medical Officer, Office of New Drugs, Center for Drug Evaluation and Research, FDA

Accelerated Approval – Meeting Patients' Needs

Jacqueline Corrigan-Curay
Principal Deputy Center Director
Center for Drug Evaluation and Research
FDA

Reagan-Udall Accelerated Approval Program
March 11, 2022

Overview

- Drug Approval Standards and Endpoints
- Accelerated Approval
  - What is it?
  - Why do we have it?
  - What are the tradeoffs?
  - Success and challenges

What is the standard for a drug or biological product to be approved

- Approval of a drug requires:
  - Substantial evidence of effectiveness
  - Demonstration that the benefit of the drug outweighs the risk for the intended use

- Substantial evidence of effectiveness is defined as:

  "evidence consisting of ***adequate and well-controlled investigations****, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved,* ***on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling*** *or proposed labeling thereof."*

FD&C Act section 505(d) (21 U.S.C. § 355(d)); draft Guidance for Industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019).

Clinical endpoints are used to measure effectiveness

- **Most straightforward:**
  - Improved survival
  - Reduced occurrence of outcomes that decrease survival (e.g., acute, severe events such as hospitalizations for serious disease-related complications; organ failure)
- **More challenging:**
  - Endpoints intended to reflect how a patient feels or functions
  - Developed using a detailed, stepwise, data-driven approach to ensure, for example, that the endpoint:
    - Measures aspects of the disease that are important to patients
    - Are sensitive to change with an intervention
    - Provides an accurate and reliable assessment across populations of patients with the disease (e.g., early vs. late-stage patients)

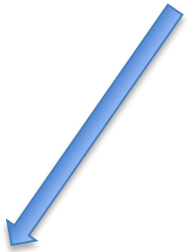
Meeting Patient's Needs by Streamlining Development

- For **serious and life-threatening diseases without adequate therapies**, there is an urgency to get effective and safe therapeutics to patients
- In certain cases, we may have sufficient understanding of the disease to identify a **surrogate endpoint or intermediate clinical endpoint** that occurs earlier in the course of the disease and is predictive of a clinically meaningful outcome/endpoint
  - Creates an opportunity for a more streamlined development program by enabling trials that may be shorter and in certain cases smaller
  - Greater access as confirm the benefit

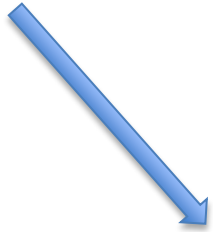
Meeting Patient's Needs by Streamlining Development

- A surrogate endpoint is often a laboratory measurement, radiographic image, physical sign, or other measure, that is not itself a direct measurement of clinical benefit, is expected to predict clinical benefit (or lack of benefit or harm)
  - Data supporting a conclusion that a surrogate endpoints is indeed able to predict a clinical endpoint may be based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence

Strength of Evidence Distinguishes Surrogates



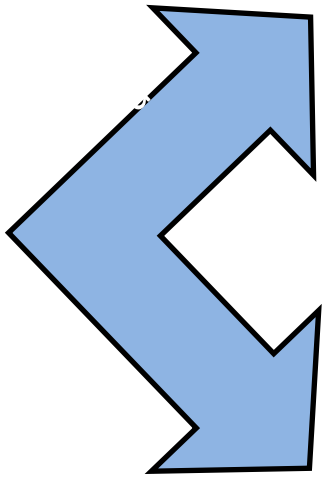
Validated Surrogate - marker that is *known to predict clinical benefit*, e.g., blood pressure and stroke, Forced expiratory volume (FEV1) in certain pulmonary diseases



Reasonably Likely Surrogate - marker that is *reasonably likely to predict clinical benefit*, e.g., total kidney volume in polycystic kidney disease, clearance of amyloid plaque in Alzheimer's disease

U.S. Drug and Biological Product Approval Pathways

Approval of Drugs and Biologics



Traditional approval

Clinical endpoint or
Validated surrogate

Accelerated approval*

Reasonably likely surrogate or
Intermediate clinical endpoint

* 21 CFR Part 314, Subpart H (for drugs)
21 CFR Part 601, Subpart E (for biologics)
Food and Drug Administration Safety and Innovation Act 506(c)

Food and Drug Administration Safety Innovations Act (FDASIA)

"The Secretary may approve an application for approval of a product for a serious or life-threatening disease or condition…upon a determination that the product has **an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit**, or on a **clinical endpoint that can be measured earlier than irreversible morbidity or mortality**, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, **taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments**."

Section 506 (c) of the Food Drug and Cosmetic Act (21 U.S.C. 356(c))

Food and Drug Administration Safety Innovations Act (FDASIA)

(2) LIMITATION.—Approval of a product under this subsection may be subject to 1 or both of the following requirements:

(A) That the sponsor conduct appropriate postapproval studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit.

(B) That the sponsor submit copies of all promotional materials related to the product during the preapproval review period and, following approval and for such period thereafter as the Secretary determines to be appropriate, at least 30 days prior to dissemination of the materials.

Accelerated Approval Framework

- Allows FDA to approve a drug:
  - for a serious or life-threatening disease for which there are not adequate therapies
  - based on adequate and well controlled clinical trials that demonstrate that the drug has a significant effect on either
    - a surrogate endpoint that is reasonably likely to predict clinical benefit or
    - an intermediate clinical endpoint that can be measured earlier than irreversible morbidity or mortality
- Uncertainty regarding whether the drug will impact a clinical outcome remains at time of approval
  - Such uncertainty is resolved with a post-approval study that is conducted after approval
  - Uncertainty by definition means that not every study will confirm benefit
- Failure to confirm benefit can result in withdrawal of the drug

Why do we subject those with serious and life-threatening diseases to this uncertainty?

Accelerated Approval

the beginning

- **1987** AZT approved based on a single placebo controlled clinical trial of patients with AIDS who had recovered from their first episode of P. carinii (P. jirovecii) pneumonia and patients with AIDS-related complex who had multiple clinical symptoms*
- **1992** FDA issued accelerated approval regulations
- **1992** Accelerated Approval- zalcitabine approved in combination with zidovudine for the treatment of adults with advanced HIV infection (CD4 < 300 cells/mm3) and significant clinical or immunologic deterioration
- As of **December 2021**, 307 accelerated approvals

*Brook, *Approval of Zidovudine (AZT) for Acquired Immunodeficiency Syndrome: A Challenge to Medical and Pharmaceutical Communities*, JAMA (1987)

The early 1990s were in many ways the most terrible of those first years of the AIDS epidemic in America. Research on the disease was in high gear, but drug after drug failed to stop H.I.V. Funerals for friends and family in their 20s, 30s, 40s and 50s continued unabated, and many of us at risk for getting sick had given up hope of a normal life. My friends and I, most of us just a few years out of college, lived in the moment because we weren't sure of how much time we had left.

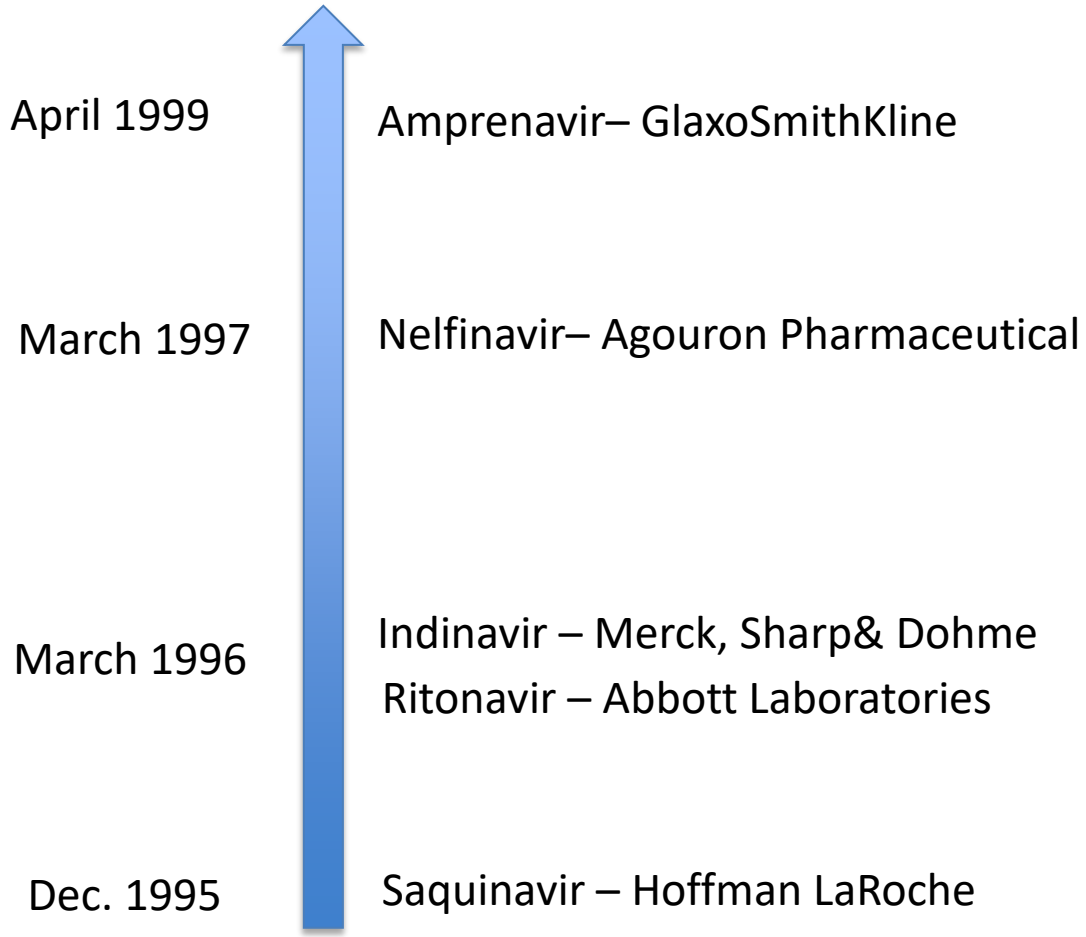
My cousin Carl died from AIDS-related lymphoma in July 1995. That was also the year I found out that I, too, was H.I.V. positive. I wondered if Carl's fate might be my own soon enough.

But then we got lucky. In 1996 a new generation of treatments called protease inhibitors emerged that were able to control H.I.V. Doctors talked about the Lazarus effect: watching their patients go from near death to health. I enrolled in a clinical trial and started taking the drugs that year. I am alive because of them.

OPINION | The Moral Danger of Declaring the Pandemic Over Too Soon

By Gregg Gonsalves
Dr. Gonsalves is an associate professor of epidemiology at the Yale School of Public Health, a longtime AIDS activist and a 2018 MacArthur fellow.

The New York Times

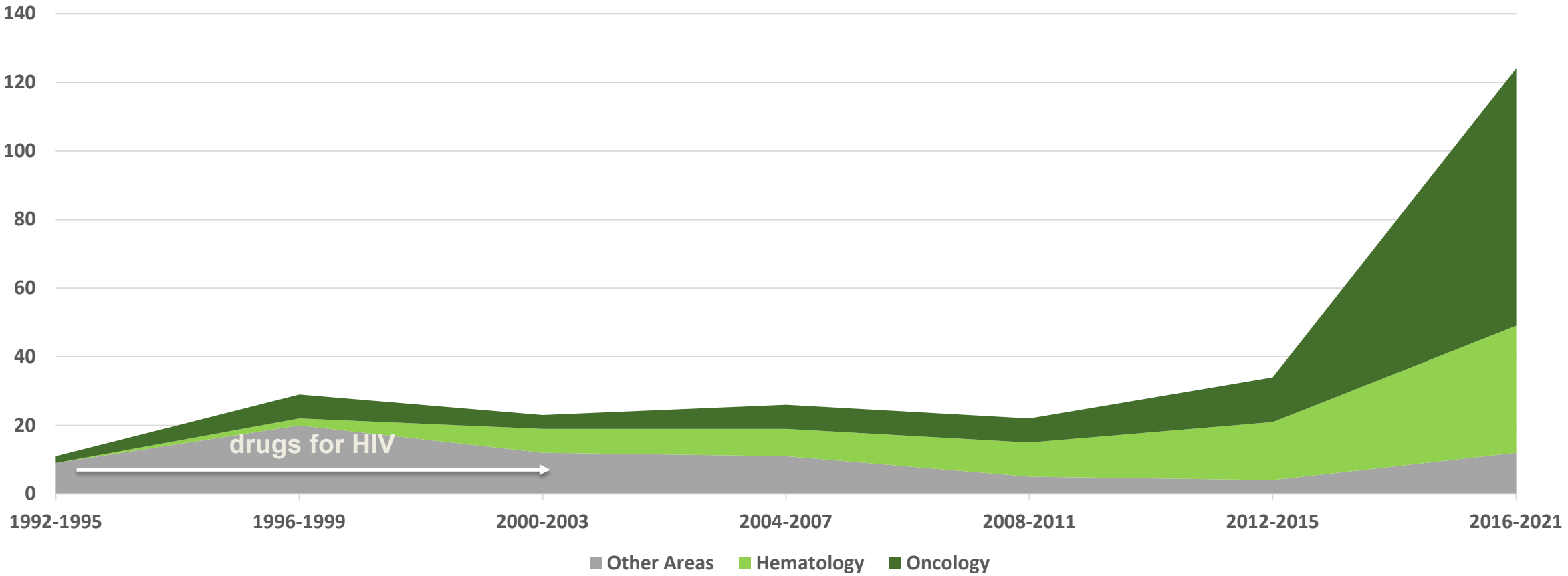


Accelerated Approvals of Protease Inhibitors in the Mid- 1990s

Requirements for Accelerated Approval

- **Reasonably likely surrogate:**
  - Requires a robust dataset to support that the surrogate predicts a clinical benefit of interest but allows for more uncertainty than would be expected for a validated surrogate endpoint
- **Post-marketing confirmatory trials** to verify and describe the anticipated clinical benefit
- **Indication statement in labeling discloses that approval based on surrogate** and clinical benefit to be confirmed
- **Special review for promotional materials**
- **Approval may be withdrawn** if trials fail to verify clinical benefit

Most of FDA's recent accelerated approvals are in oncology



1 Accelerated approvals classified as Hematology can also be considered oncologic. 7 of 37 hematology accelerated approvals are for non-oncologic indications, such as sickle cell, transfusional hemosiderosis, and thalassemia. The others are for oncologic indications.

2 Other Areas is a combination of the eight other therapeutic areas (Anti-Infective, Anti-Viral, Bone/Reproductive/Urology, Inborn Errors, Cardio/Renal, Metab/Endo, Neurology, Pulmonary/Allergy/Rheumatology) where CDER had 5 or fewer accelerated approvals since 2000.

* Through June 2021

Accelerated Approval in Oncology

- Key driver was scientific advancement in understanding of genetic, molecular, and immunomodulatory drivers of cancer in 1990s and early 2000s leading to:
  - Discovery of molecular mechanisms of disease and subsequent targeted therapeutics
  - Identification of biomarkers to support decision-making in early drug development
  - Establishment of surrogate endpoints to support approval decisions
- Many drugs were transformative:

Years of access prior to conversion

  - Pembrolizumab (Keytruda) for **non-small cell lung cancer** ---------- **1.1**
  - Imatinib mesylate (Gleevac) for **chronic myelogenous leukemia** ------ **2.6**
  - Nivolumab (Opdivo) **Melanoma** ---------- **4.3**

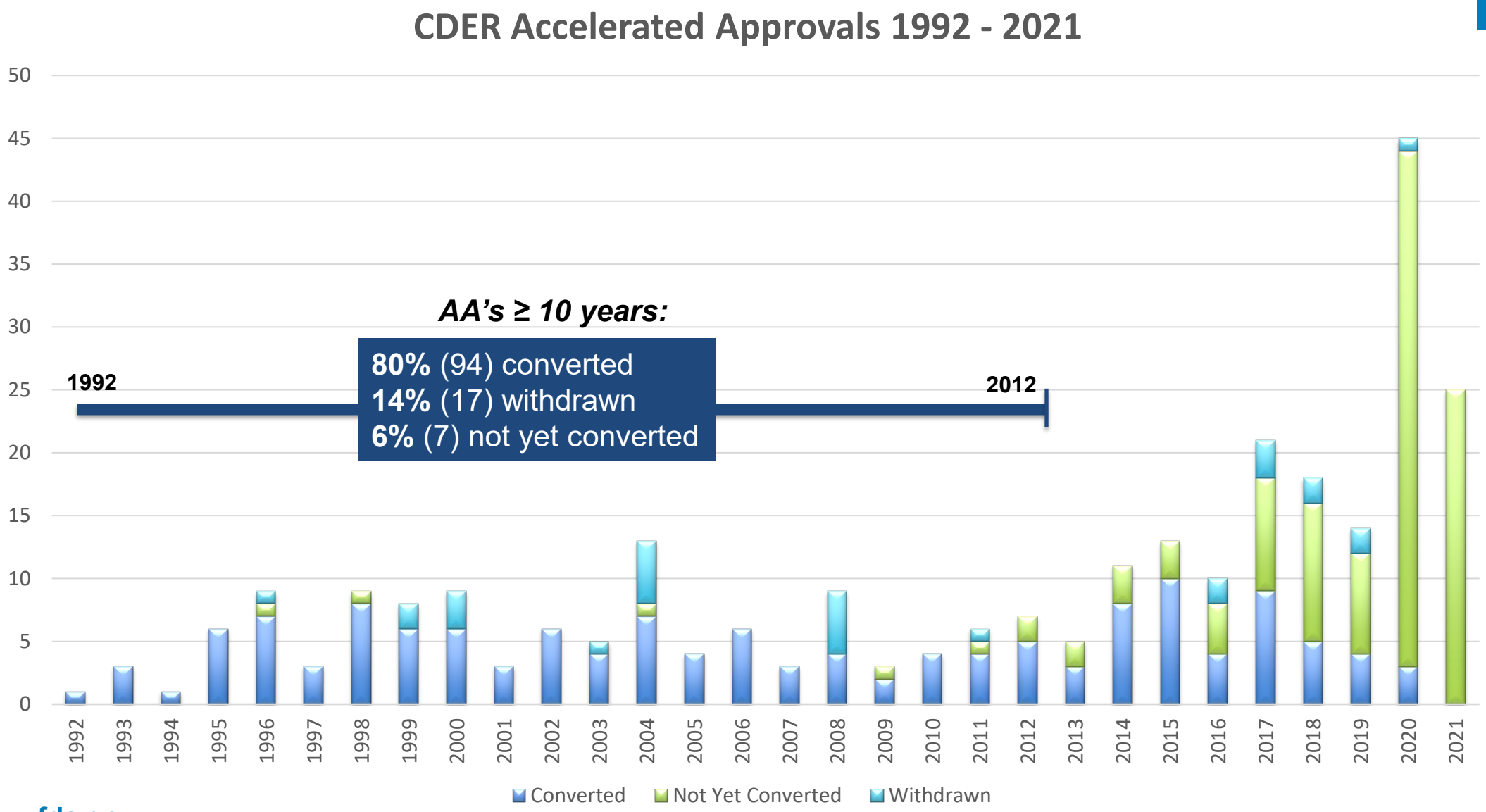
Challenges with Accelerated Approval

- Surrogate endpoints can improve feasibility, but the challenge in many diseases, is that there is very limited understanding of the pathogenesis that leads to disease complications and progression
- Data to support a relationship between the surrogate endpoint and clinical benefits of interest are often limited, as well as information critical to establishing a biomarker as a surrogate endpoint
- Many animal models of diseases do not fully recapitulate key aspects of the human disease and are not "translational"—meaning that apparent drug "benefit" observed in such models fails to predict drug benefit in clinical studies

Challenges with Accelerated Approval (2)

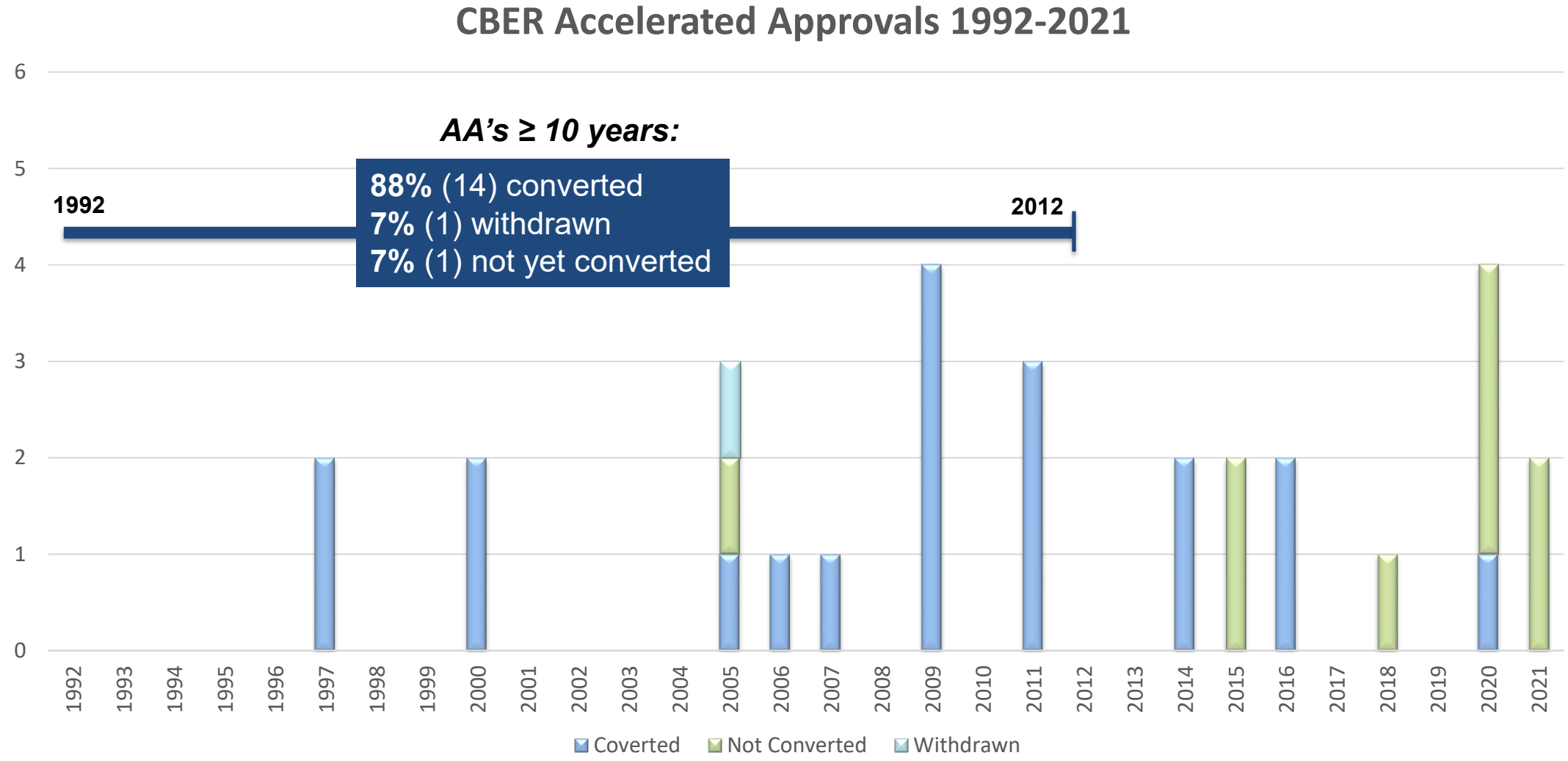
- Once a drug is on the market, if confirmatory trials are not ongoing at the time of approval there can be challenges in conducting the trials needed to confirm clinical benefit
- The framework is built around providing greater access with more uncertainty and therefore can expect some failures
  - But for diseases with few or no alternative therapies, many patients may feel they are personally benefiting even when well designed trials demonstrate no clinical benefit and there can be toxicity
- The withdrawal procedure, described in the statute is as follows --*The Secretary may withdraw approval of a product approved under accelerated approval using expedited procedures (as prescribed by the Secretary in regulations which shall include an opportunity for an informal hearing)* – in practice is not expedited

A snapshot: where do we stand?



Status of CDER accelerated approvals as of 12/31/2021 by year of accelerated approval.

A snapshot: where do we stand?



Status of CBER accelerated approvals as of 12/31/2021 by year of accelerated approval.

Looking Forward

- Accelerated approval continues to be an important pathway for serious and life-threatening diseases with inadequate therapeutic options when:
  - We have identified appropriate surrogates that are reasonably likely to predict clinical benefit, as we have seen in oncology and certain other diseases but
    - Remains a challenge in many diseases with unmet needs because the underlying pathology is not well understood and models to identify surrogates are lacking
- With greater uncertainty comes greater risk of failed therapies – where should that line be drawn?
  - In the face of unmet medical need removing a therapy is challenging
- A failed study can occur for reasons that do not negate that the surrogate is reasonably likely
- Providing access and completing confirmatory trials expeditiously serves patients

Acknowledgments

- Julia Beaver
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- Diane Maloney
- Gautam Mehta
- Sarah Walinsky


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Failure or Success, Results are Essential

Kevin M. Fain
Senior Policy Advisor, Office of New Drug Policy
Center for Drug Evaluation and Research
FDA

Reagan-Udall Accelerated Approval Program
March 11, 2022

Outline

- Regulatory Framework for Confirmatory Trials
- Confirmatory Trials: Plan and Progress
  - Confirmatory Trial Approval and Timeframes
  - Reporting of Confirmatory Trial Status
  - Reasons for Confirmatory Trial Delays
- Confirmatory Trials: Regulatory Options Based on Results
  - Involuntary Withdrawal
  - Voluntary Withdrawal

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Regulatory Framework for Confirmatory Trials

Accelerated Approval Regulatory Framework

Approval Requirements of Section 505 of the FDC Act Still Apply

- Accelerated Approval of a drug under section 506(c) still requires (among other things):
  - Substantial evidence based on adequate and well-controlled clinical investigations of the drug's effect, and the benefits of the drug outweigh its risks
- But the effect can be shown on a surrogate endpoint that is reasonably likely (not known) to predict benefit in how patients feel, function, or survive.
- So there is still some "uncertainty as to the relation of the surrogate endpoint to clinical benefit" (21 CFR 314.510)

Confirmatory Trials

- Post-marketing trials can be required to verify and describe the drug's clinical benefit.
  - Such trials would "usually be studies already underway at time of approval" (21 CFR 314.510)
  - Must also be adequate and well-controlled (21 CFR 314.510)
- By assessing the drug's clinical benefit, the goal of the confirmatory trial is to address the remaining uncertainty of the surrogate endpoint's relation to clinical benefit
- Expectation is that some trials will not confirm clinical benefit
- Completion of confirmatory trials and submission of results to FDA is critical for the agency's determination of the drug's benefit

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Confirmatory Trials: Plan and Progress

Confirmatory Trials: Approval and Timeframes

- Approval of a drug under the accelerated approval pathway will establish the required confirmatory trial and specific milestones
  - For initiation, enrollment targets, completion, and final report submission to FDA
- Sample excerpt from approval letter

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated November 22, 2019. This requirement, along with required completion dates, is listed below.

Source: Approval letter publicly available on Drugs@FDA (Accessed on 3/4/2022)

Confirmatory Trials: Approval and Timeframes

3746-1 Complete Study GBT440-032: the ongoing Phase 3, randomized, double-blind, placebo-controlled trial in pediatric patients (age 2 years to < 15 years) with Sickle Cell Disease (HOPE Kids 2). Expected enrollment of approximately 224 patients (age 2 years to < 15 years) with at least 15 patients from age 2 years to < 4 years of age. Include patients with baseline hemoglobin of less than 6 g/dL. The primary endpoint is change from baseline at 24 weeks in time averaged maximum of mean velocity (TAMMV) arterial cerebral blood flow as measured by transcranial doppler (TCD). The secondary endpoint is change from baseline in TCD flow velocity at Week 48 and Week 96.

Interim Report Submission (based on primary analysis):	07/2025
Study/Trial Completion:	03/2026
Final Report Submission:	09/2026

Source: Approval letter publicly available on Drugs@FDA (Accessed on 3/4/2022)

Confirmatory Trials: Reporting of Status

- **Annual Report**
  - FDA regulations (21 CFR 314.540) require sponsors of drugs approved under the accelerated approval pathway to submit annual reports required by 21 CFR 314.81
  - These annual reports must include status information about the confirmatory trials (21 CFR 314.81(b)(2)(vii)).
- **Status Information**
  - Accrual rate (number of subjects enrolled to date and total planned enrollment)
  - Study status category (pending, ongoing, delayed, terminated, submitted)
  - Completion date and final study report submission date (if applicable)
  - Revised schedule, and reasons for revision, if schedule has changed

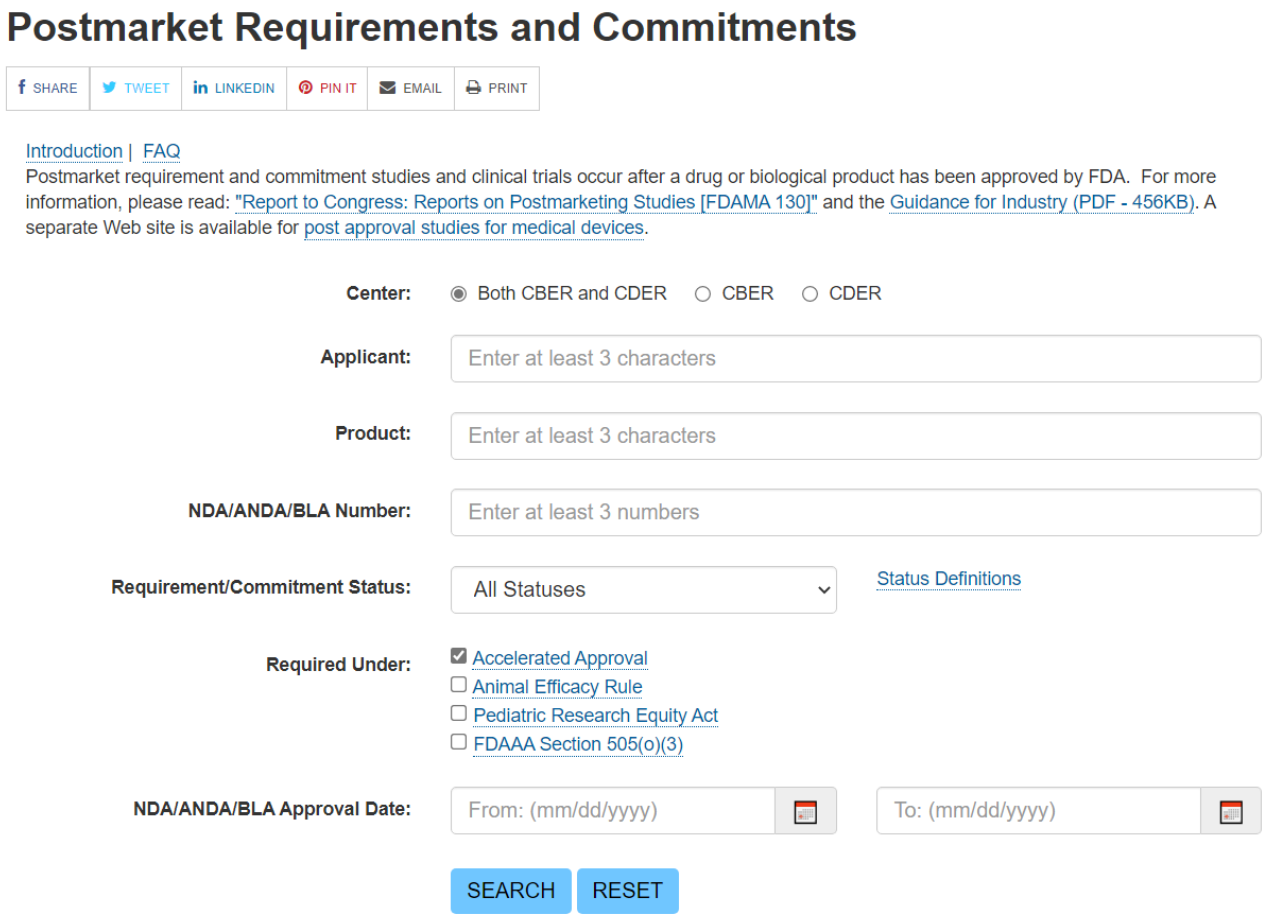
Status Categories

Defined by Annual Report regulation (21 CFR 314.81(b)(2)(vii)(8))

- Pending = study has not been initiated, but is not considered delayed
- Ongoing = study is proceeding according to or ahead of the original schedule
- Delayed = study is behind the original schedule
- Terminated = study was ended before completion and a final study report has not been submitted to FDA
- Submitted = study has been completed or terminated and a final study report has been submitted to FDA

Confirmatory Trials: Tracking of Status

Confirmatory Trial Status: Publicly Available Information (FDA's Website)



Postmarket Requirements and Commitments

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Introduction | FAQ

Postmarket requirement and commitment studies and clinical trials occur after a drug or biological product has been approved by FDA. For more information, please read: "Report to Congress: Reports on Postmarketing Studies [FDAMA 130]" and the Guidance for Industry (PDF - 456KB). A separate Web site is available for post approval studies for medical devices.

Center: ◉ Both CBER and CDER ○ CBER ○ CDER

Applicant: Enter at least 3 characters

Product: Enter at least 3 characters

NDA/ANDA/BLA Number: Enter at least 3 numbers

Requirement/Commitment Status: All Statuses — Status Definitions

Required Under:
- ☑ Accelerated Approval
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA Section 505(o)(3)

NDA/ANDA/BLA Approval Date: From: (mm/dd/yyyy) — To: (mm/dd/yyyy)

SEARCH RESET

Confirmatory Trials: Reasons for Delay

Sample Reasons - Trial Completion and Final Report Submission

- "The trial completion milestone was missed because there have been **fewer PFS events** than originally predicted. Revised trial completion and final report submission milestone due dates were acknowledged in a letter dated February 21, 2020."
- "The applicant requested revised milestones because all patients with treatment-naïve NSCLC enrolled in the proposed LIBRETTO-001 study have **not reached a response** and the trial has not reached completion. Revised milestones were acknowledged in a letter dated 09/01/2021."
- "The final report submission milestone was missed because the final overall survival analysis **has not yet been reached**."

Source: Postmarket Requirements and Commitments (fda.gov) (Accessed on 3/4/2022)

Confirmatory Trials: Reasons for Delay

Sample Reasons – Protocol

- "The final protocol milestone was missed because the onset of this trial is **based on the results from another study**. Revised milestones were acknowledged in a letter issued in March 2017."
- "Final protocol milestone was missed. Additional time needed to **incorporate feedback** from the agency."

Sample Reasons - Enrollment

- "The applicant requested revised Trial Completion and Final Report Submission milestone due dates because of **difficulty in enrollment**. Revised milestones were acknowledged in a letter dated 10/01/2019."
- The trial is underway but is **behind the original schedule**. Enrollment has been completed with a total of 763 patients enrolled.

Source: Postmarket Requirements and Commitments (fda.gov) (Accessed on 3/4/2022)

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Confirmatory Trials: Regulatory Options Based on Results

Involuntary Withdrawal of Accelerated Approval: Informal Hearing

Avastin Example

- FDA withdrawal of breast cancer indication that had been approved through accelerated approval pathway
  - Confirmatory trial results submitted (November 2009)
  - NOOH issued by CDER (December 2010)
  - Genentech requested hearing (December 2010)
  - FDA granted hearing request and published notice of hearing (May 2011)
  - Hearing (June 2011)
  - FDA Commissioner issued final decision withdrawing approval of the indication (November 2011)

Example of Confirmatory Trial Status

Applicant:	GENENTECH INC
Product:	GAVRETO (pralsetinib)
NDA/BLA Number:	213721
NDA/BLA Approval Date:	09/04/2020
Annual Report Due Date: (must be submitted within 60 days of this date)	09/04/2022
Annual Report Received:	11/02/2021

Requirement/Commitment Number: 1

Required Under:	Accelerated Approval
Original Projected Completion Date:	10/31/2022
Description:	Submit the final report, including datasets, from an ongoing clinical trial to verify and further characterize the clinical benefit of pralsetinib for the treatment of patients with 1) treatment-naïve RET fusion-positive NSCLC and with 2) RET fusion-positive NSCLC who have previously received platinum chemotherapy to provide a more precise estimation of the BICRassessed overall response rate and duration of response after all responders in the population of patients with treatment-naïve NSCLC (approximately 120 patients) have been followed for at least 12 months from the date of initial response (or until disease progression, whichever comes first) and after all responders in the population of patients with NSCLC previously treated with platinum therapy (87 patients) have been followed for at least 6 months.
Current Status:	Ongoing

Source: Postmarket Requirements and Commitments (fda.gov) (Accessed on 3/4/2022)

Confirmatory Trial Fails to Verify Clinical Benefit: Important Considerations

- In certain situations, results from clinical trials that fail to verify clinical benefit might be attributable to other factors (i.e., not related to the drug's true effect), such as
  - Selection of the primary end point
  - Trial design
  - Inability to select the patients most likely to have a response
  - Statistical issues (e.g., power calculation, hierarchical statistical testing procedures)
- If there are clear reasons why a trial may not have achieved its primary end point, no evidence that the surrogate marker is not reasonably likely to predict clinical benefit and an unmet medical need still exists,
  - Then FDA may work with the sponsor to identify subsequent clinical trials that could satisfy the accelerated approval requirement.

Involuntary Withdrawal of Accelerated Approval: Based on Confirmatory Trial

- **Withdrawal** is an option, pursuant to Section 506(c)(3), that may apply in certain circumstances for reasons related to the confirmatory trial ("involuntary withdrawal").
  - For example, based on results of confirmatory trial or failure to complete trial
- FDA may withdraw approval using expedited procedures, which shall include opportunity for an informal hearing, if
  - Sponsor fails to conduct any required post-approval study of the drug with **due diligence**;
  - A required post-approval study fails to **verify and describe the clinical benefit**;
  - Other evidence demonstrates that the product is **not safe or effective** under the conditions of use; or
  - Sponsor disseminates **false or misleading** promotional materials with respect to the product.

Involuntary Withdrawal of Accelerated Approval: Informal Hearing

- Informal Hearing Procedures
  - FDA regulations for withdrawal (21 CFR 314.530) incorporate hearing procedures in 21 CFR Part 15, including presiding officer.
  - The regulations also provide for convening an Advisory Committee as part of the hearing.
- Important Features for an Informal Hearing
  - The relevant center (CDER/CBER) must first issue a notice of opportunity for a hearing (NOOH) for the proposed withdrawal.
  - Then, the sponsor must specifically request a hearing and submit data and information upon which the sponsor intends to rely at the hearing.
  - Many steps are involved for the hearing, such as document production, required submissions, advisory committee planning, and other procedural issues.

Voluntary Withdrawal of Accelerated Approval: Based on Confirmatory Trial

- If FDA determines there are grounds for withdrawal, the Agency may ask the applicant to request withdrawal of approval under 21 CFR 314.150(d). (Noted in Expedited Programs for Serious Conditions – Drugs and Biologics Guidance, May 2014)

§ 314.150 Withdrawal of approval of an application or abbreviated application.

*****

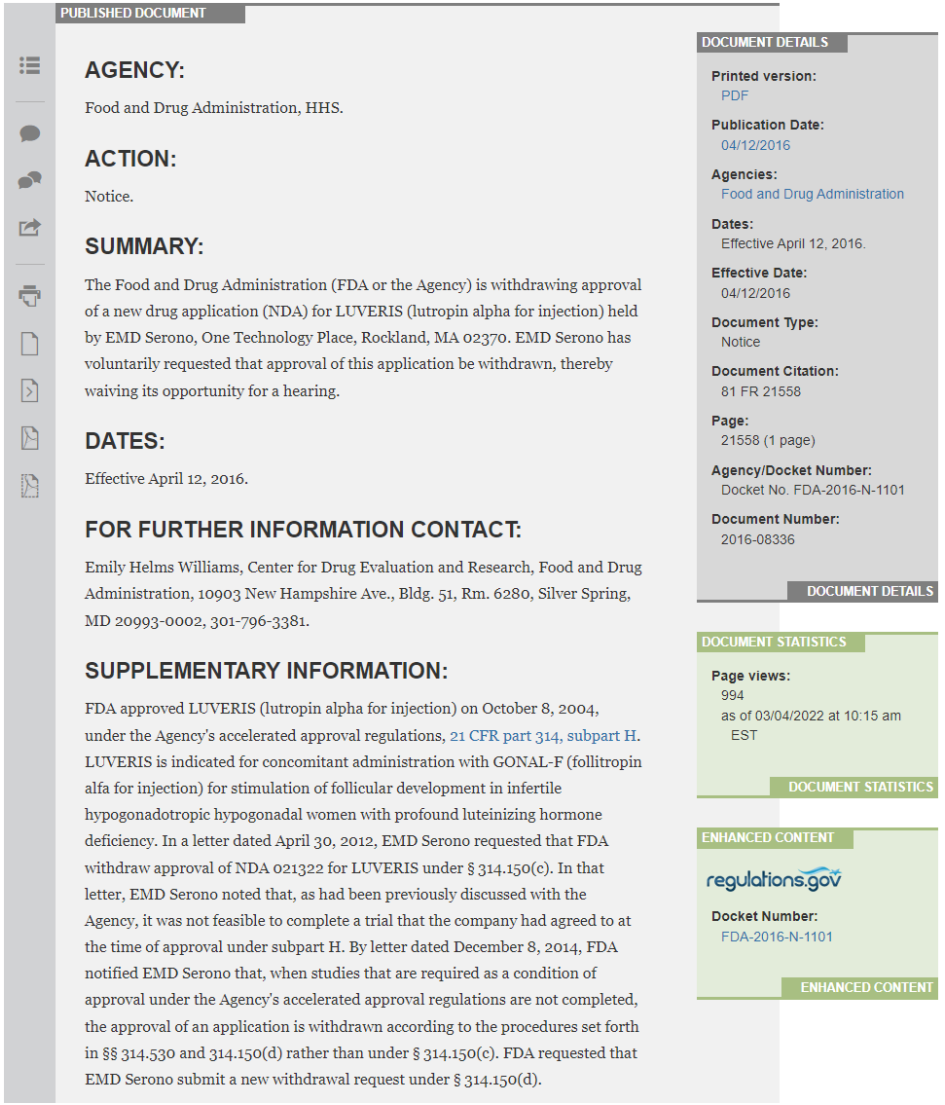
(d) FDA may notify an applicant that it believes a potential problem associated with a drug is sufficiently serious that the drug should be removed from the market and may ask the applicant to waive the opportunity for hearing otherwise provided for under this section, to permit FDA to withdraw approval of the application or abbreviated application for the product, and to remove voluntarily the product from the market. If the applicant agrees, the agency will not make a finding under paragraph (b) of this section, but will withdraw approval of the application or abbreviated application in a notice published in the FEDERAL REGISTER that contains a brief summary of the agency's and the applicant's views of the reasons for withdrawal.

[57 FR 17993, Apr. 28, 1992, as amended at 58 FR 25927, Apr. 28, 1993; 64 FR 402, Jan. 5, 1999]

Voluntary Withdrawal of Accelerated Approval: Based on Confirmatory Trial

Example of Voluntary Withdrawal:

Failure to Complete Confirmatory Trial



PUBLISHED DOCUMENT

AGENCY:

Food and Drug Administration, HHS.

ACTION:

Notice.

SUMMARY:

The Food and Drug Administration (FDA or the Agency) is withdrawing approval of a new drug application (NDA) for LUVERIS (lutropin alpha for injection) held by EMD Serono, One Technology Place, Rockland, MA 02370. EMD Serono has voluntarily requested that approval of this application be withdrawn, thereby waiving its opportunity for a hearing.

DATES:

Effective April 12, 2016.

FOR FURTHER INFORMATION CONTACT:

Emily Helms Williams, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6280, Silver Spring, MD 20993-0002, 301-796-3381.

SUPPLEMENTARY INFORMATION:

FDA approved LUVERIS (lutropin alpha for injection) on October 8, 2004, under the Agency's accelerated approval regulations, 21 CFR part 314, subpart H. LUVERIS is indicated for concomitant administration with GONAL-F (follitropin alfa for injection) for stimulation of follicular development in infertile hypogonadotropic hypogonadal women with profound luteinizing hormone deficiency. In a letter dated April 30, 2012, EMD Serono requested that FDA withdraw approval of NDA 021322 for LUVERIS under § 314.150(c). In that letter, EMD Serono noted that, as had been previously discussed with the Agency, it was not feasible to complete a trial that the company had agreed to at the time of approval under subpart H. By letter dated December 8, 2014, FDA notified EMD Serono that, when studies that are required as a condition of approval under the Agency's accelerated approval regulations are not completed, the approval of an application is withdrawn according to the procedures set forth in §§ 314.530 and 314.150(d) rather than under § 314.150(c). FDA requested that EMD Serono submit a new withdrawal request under § 314.150(d).

DOCUMENT DETAILS

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DOCUMENT STATISTICS

ENHANCED CONTENT

regulations.gov

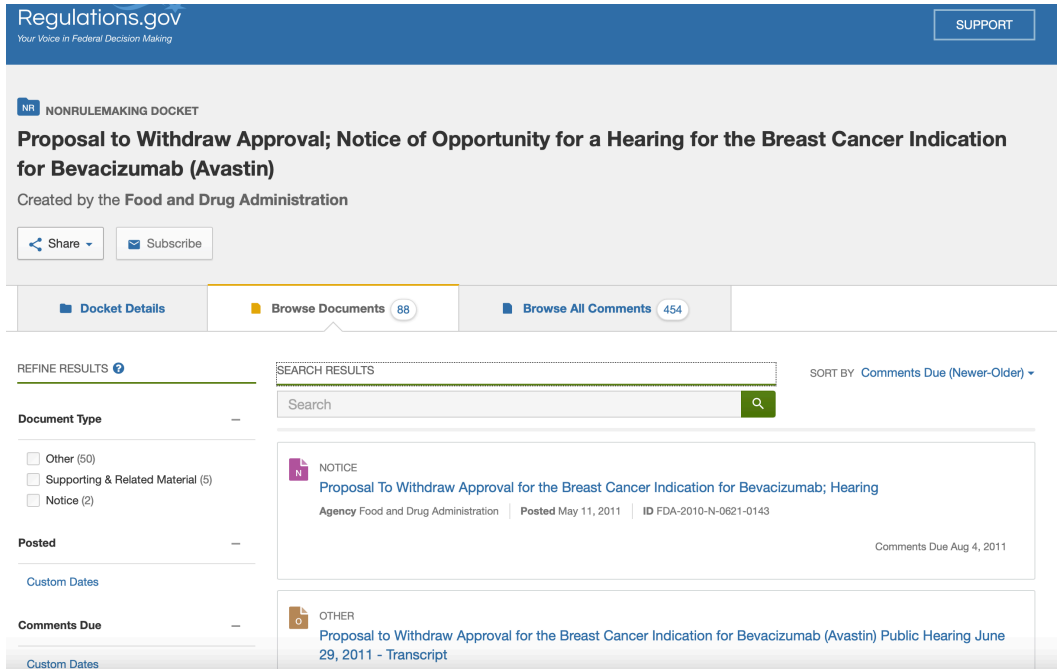
Docket Number: FDA-2016-N-1101

ENHANCED CONTENT

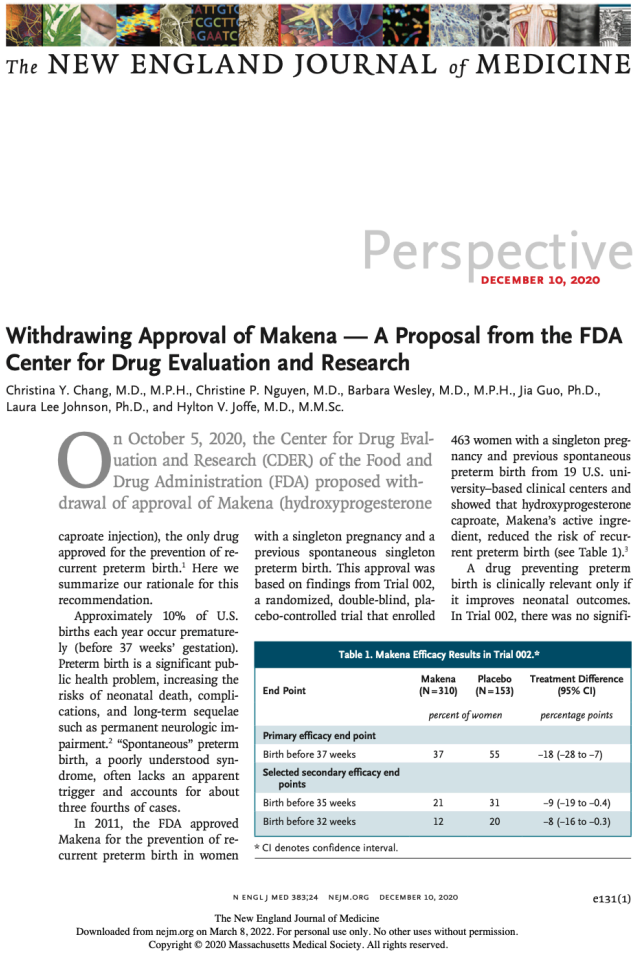
Source: EMD Serono; Withdrawal of Approval of a New Drug Application for LUVERIS. 81 Federal Register 21558 (4/12/2016) (Accessed on 3/4/2022)

Involuntary Withdrawal of Accelerated Approval: Informal Hearing

Publicly Available Information



Public Docket for Hearing. Avastin.
FDA-2010-N-0621


The NEW ENGLAND JOURNAL of MEDICINE

Perspective
DECEMBER 10, 2020

Withdrawing Approval of Makena — A Proposal from the FDA Center for Drug Evaluation and Research

Christina Y. Chang, M.D., M.P.H., Christine P. Nguyen, M.D., Barbara Wesley, M.D., M.P.H., Jia Guo, Ph.D., Laura Lee Johnson, Ph.D., and Hylton V. Joffe, M.D., M.M.Sc.

On October 5, 2020, the Center for Drug Evaluation and Research (CDER) of the Food and Drug Administration (FDA) proposed withdrawal of approval of Makena (hydroxyprogesterone caproate injection), the only drug approved for the prevention of recurrent preterm birth.[1] Here we summarize our rationale for this recommendation.

Approximately 10% of U.S. births each year occur prematurely (before 37 weeks' gestation). Preterm birth is a significant public health problem, increasing the risks of neonatal death, complications, and long-term sequelae such as permanent neurologic impairment.[2] "Spontaneous" preterm birth, a poorly understood syndrome, often lacks an apparent trigger and accounts for about three fourths of cases.

In 2011, the FDA approved Makena for the prevention of recurrent preterm birth in women with a singleton pregnancy and a previous spontaneous singleton preterm birth. This approval was based on findings from Trial 002, a randomized, double-blind, placebo-controlled trial that enrolled 463 women with a singleton pregnancy and previous spontaneous preterm birth from 19 U.S. university–based clinical centers and showed that hydroxyprogesterone caproate, Makena's active ingredient, reduced the risk of recurrent preterm birth (see Table 1).[3]

A drug preventing preterm birth is clinically relevant only if it improves neonatal outcomes. In Trial 002, there was no signifi-

Table 1. Makena Efficacy Results in Trial 002.*

End Point	Makena (N=310)	Placebo (N=153)	Treatment Difference (95% CI)
	percent of women		*percentage points*
Primary efficacy end point			
Birth before 37 weeks	37	55	−18 (−28 to −7)
Selected secondary efficacy end points			
Birth before 35 weeks	21	31	−9 (−19 to −0.4)
Birth before 32 weeks	12	20	−8 (−16 to −0.3)

* CI denotes confidence interval.

Proposed Withdrawal of Makena.
CDER Perspective Piece

Voluntary Withdrawal of Accelerated Approval: Based on Confirmatory Trial

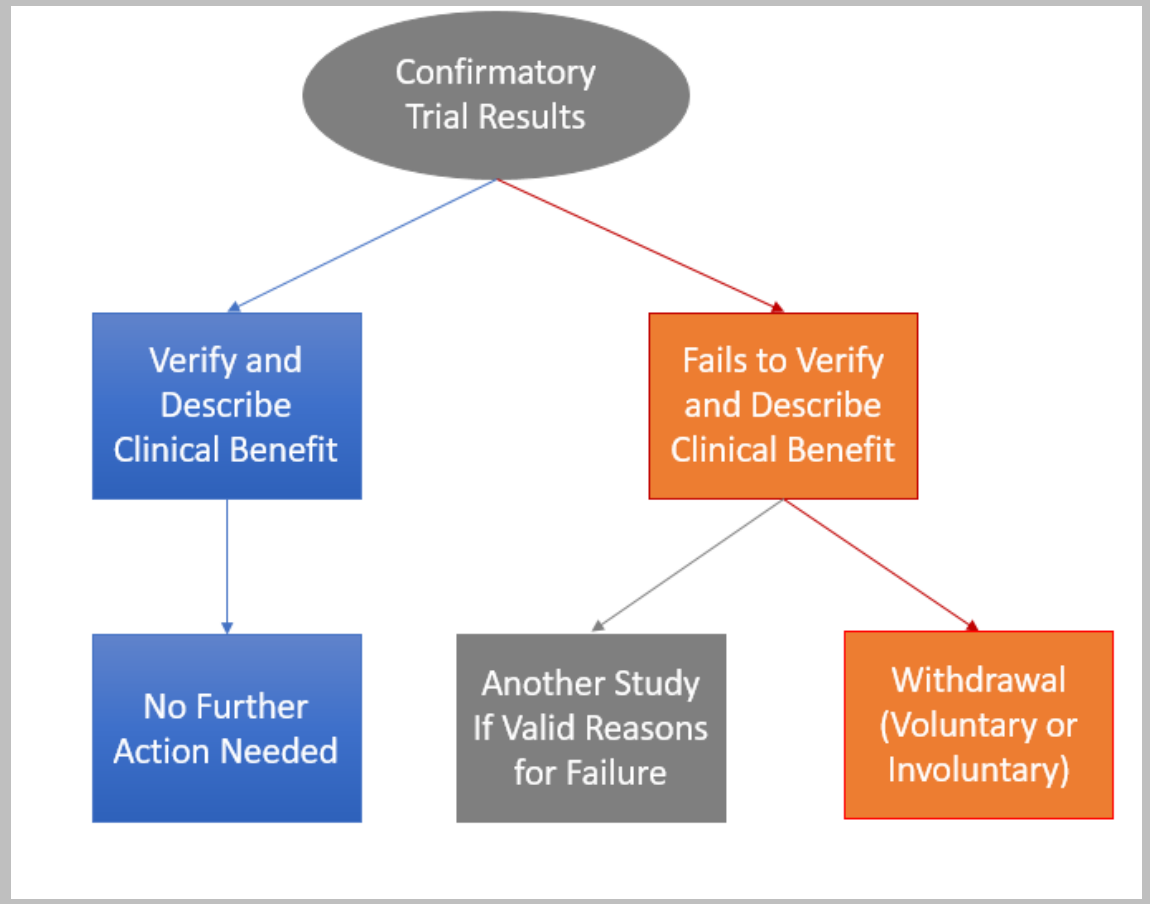
SUPPLEMENTARY INFORMATION:

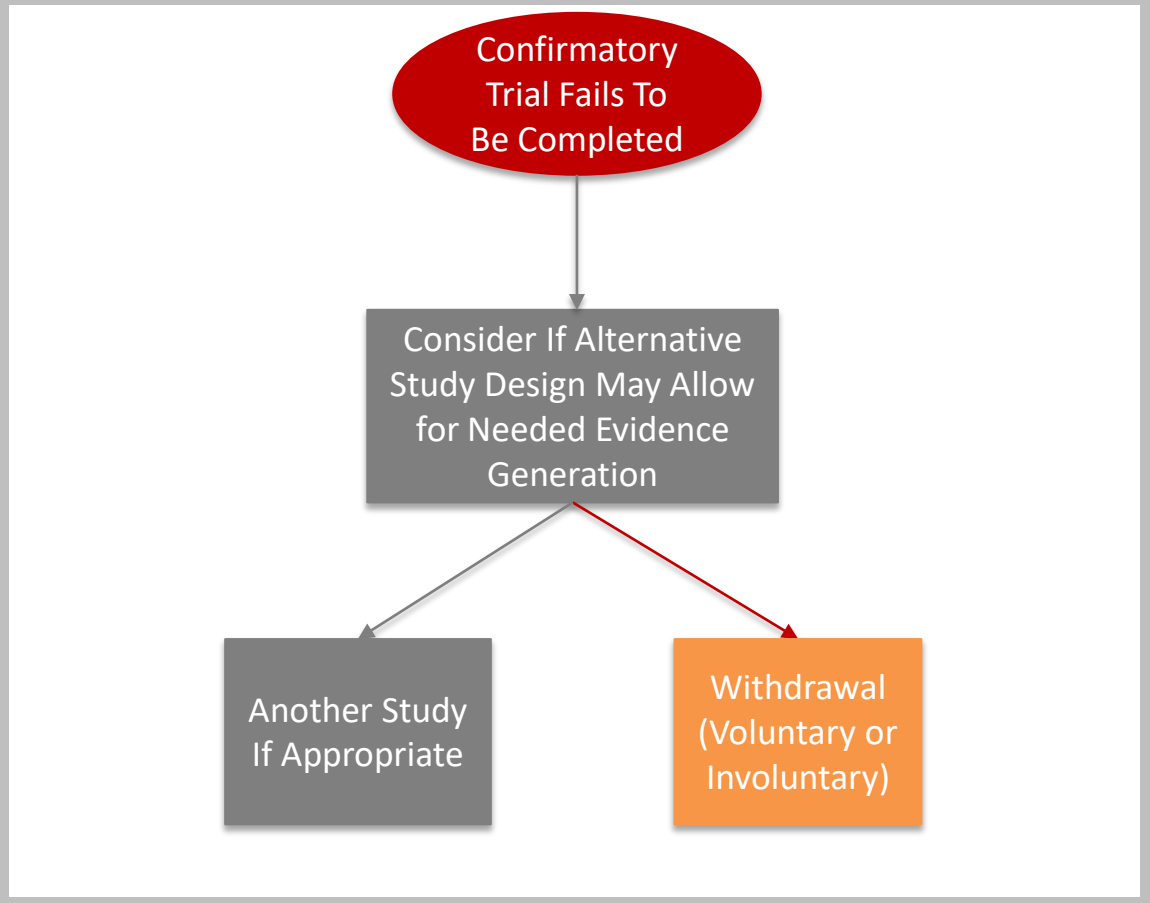
Following additional correspondence, by letter dated July 23, 2015, EMD Serono requested that FDA withdraw approval of NDA 021322 for LUVERIS under § 314.150(d) because a postmarketing study that was required as a condition of approval under subpart H was not completed. Because that study was required to verify and describe the clinical benefit of the drug product, the clinical benefit of LUVERIS has not been confirmed, and it has not been established to be safe and effective. In its July 23, 2015, letter, EMD Serono waived any opportunity for a hearing otherwise provided under §§ 314.150 and 314.530. FDA responded by letter dated September 2, 2015, acknowledging EMD Serono's request that FDA withdraw approval of LUVERIS under § 314.150(d). FDA also acknowledged that EMD Serono waived its opportunity for a hearing.

Therefore, under section 505(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(e)) and § 314.150(d), and under authority delegated by the Commissioner to the Director, Center for Drug Evaluation and Research, approval of NDA 021322, and all amendments and supplements thereto, is withdrawn (see DATES). Distribution of this product in interstate commerce without an approved application is illegal and subject to regulatory action (see sections 505(a) and 301(d) of the FD&C Act (21 U.S.C. 355(a) and 331(d)).

Source: EMD Serono; Withdrawal of Approval of a New Drug Application for LUVERIS. 81 Federal Register 21558 (4/12/2016) (Accessed on 3/4/2022)

Confirmatory Trials: Summary of Options






FDA
U.S. FOOD & DRUG
ADMINISTRATION

Accelerated Approval in Oncology: 1992-2022

Gautam Mehta, MD
Division of Oncology 2
Center for Drug Evaluation and Research
US Food and Drug Administration
03/11/2022

Disclosures

- I have no disclosures
- I will not discuss off-label use

Outline

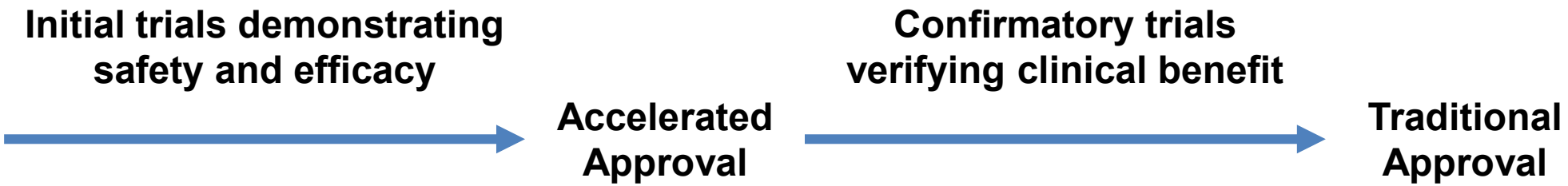
- Review Accelerated Approval in Oncology
  - Experience in Oncology to date
  - Endpoints used to support approval
  - What happens after Accelerated Approval

- Introduce Project Confirm

Accelerated Approval in Oncology

- Cancer is the 2nd leading cause of death in the US*

- Majority of FDA's Accelerated Approvals have been granted in Oncology
  - Balances **early access** to anti-cancer products with **uncertainty**



*Mortality in the United States, CDC, 2020

Accelerated vs. Traditional Approval in Oncology

Approval Year	2020 Approvals	2021 Approvals
Accelerated Approval	24 (36%)	19 (33%)
Traditional Approval	42 (64%)	39 (67%)

Oncology Accelerated Approval Endpoints

- Response Rate – Do tumors shrink with treatment?
  - Allows for single-arm trials
  - Earlier measurement of effect

- Progression-Free Survival
- Disease-Free Survival/Recurrence-Free Survival

Oncology Traditional Approval Endpoints

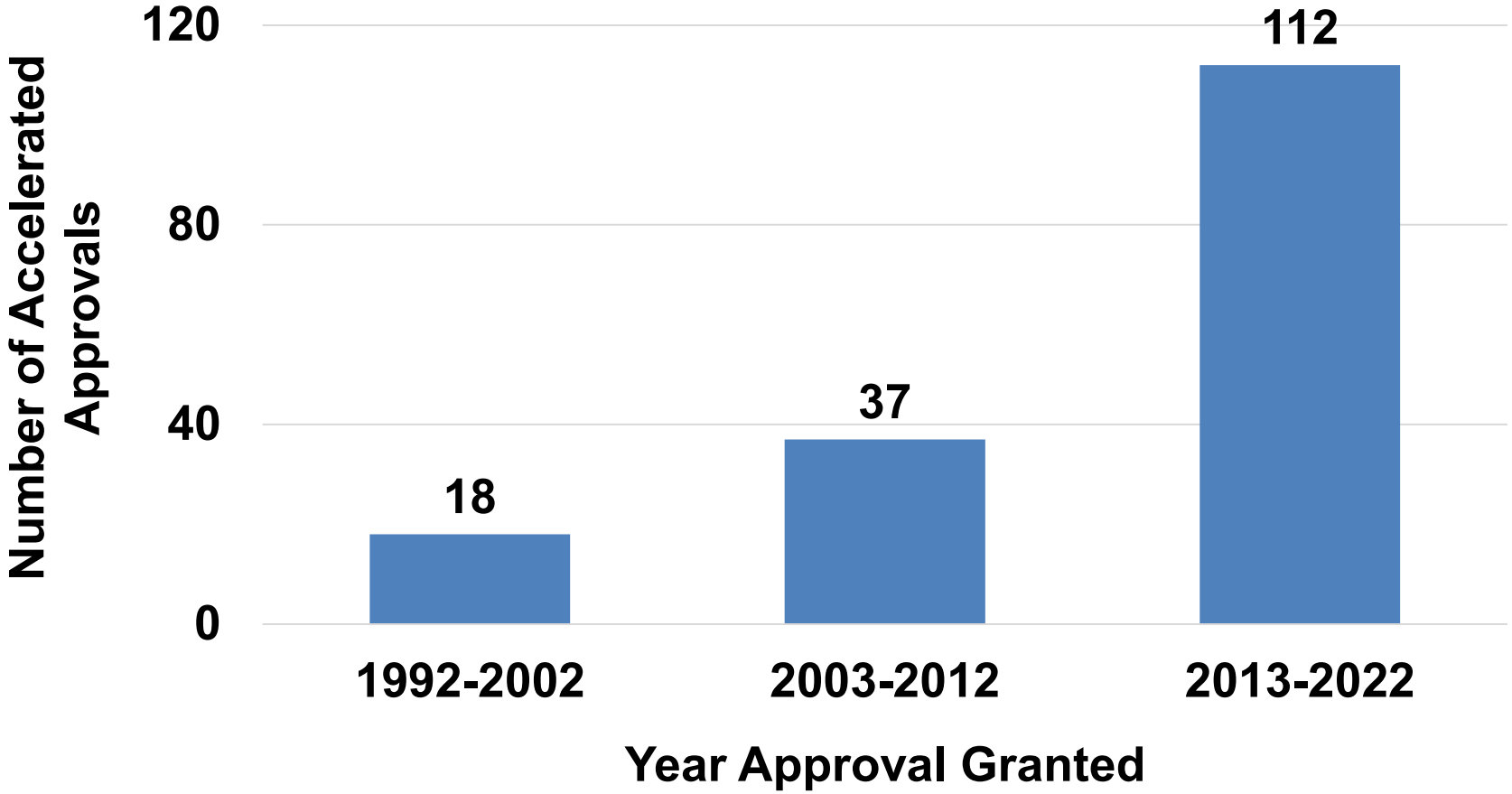
- Response Rate
  - Rare cancers
  - Long natural history
  - Tumor response is the clinical benefit
  - Randomized controlled trial lack equipoise

- Progression-Free Survival
- Disease-Free Survival/Recurrence-Free Survival

- Overall Survival

Accelerated Approval through the Decades

- 167 Accelerated Approvals have been granted in Oncology



Early Access through Accelerated Approval

Drug	Indication	Time to Verification of Benefit (years)
Capecitabine	Metastatic Breast Cancer	3.4
Imatinib	CML, GIST	2.6, 6.7
Oxaliplatin	Colorectal Cancer	1.4
Bortezomib	Multiple Myeloma	1.9
Trametinib/Dabrafenib	BRAF Melanoma	1.9
Pembrolizumab	NSCLC	1.1
Nivolumab	Melanoma	4.3
Crizotinib	ALK+ NSCLC	2.2
Enfortumab	Bladder Cancer	1.5
Olaparib	BRCA+ Ovarian Cancer	2.7
Pembro/Lenvatinib	Endometrial Cancer	1.8
Palbociclib	Breast Cancer	2.1

Beaver *et al*., JAMA Oncology 2018; Drugs@FDA; https://www.fda.gov/media/151146/download

Verification of Benefit

- *Approval…subject to…the following requirements:*
  - *That the sponsor conduct appropriate **postapproval studies** to **verify** and describe the predicted **effect on irreversible morbidity or mortality or other clinical benefit**.*

-Section 506(c) of the FDC Act

- Confirmatory trial may be in a different line of therapy
- Results in Traditional Approval being granted
- Median time to verification of benefit: 3.1 years

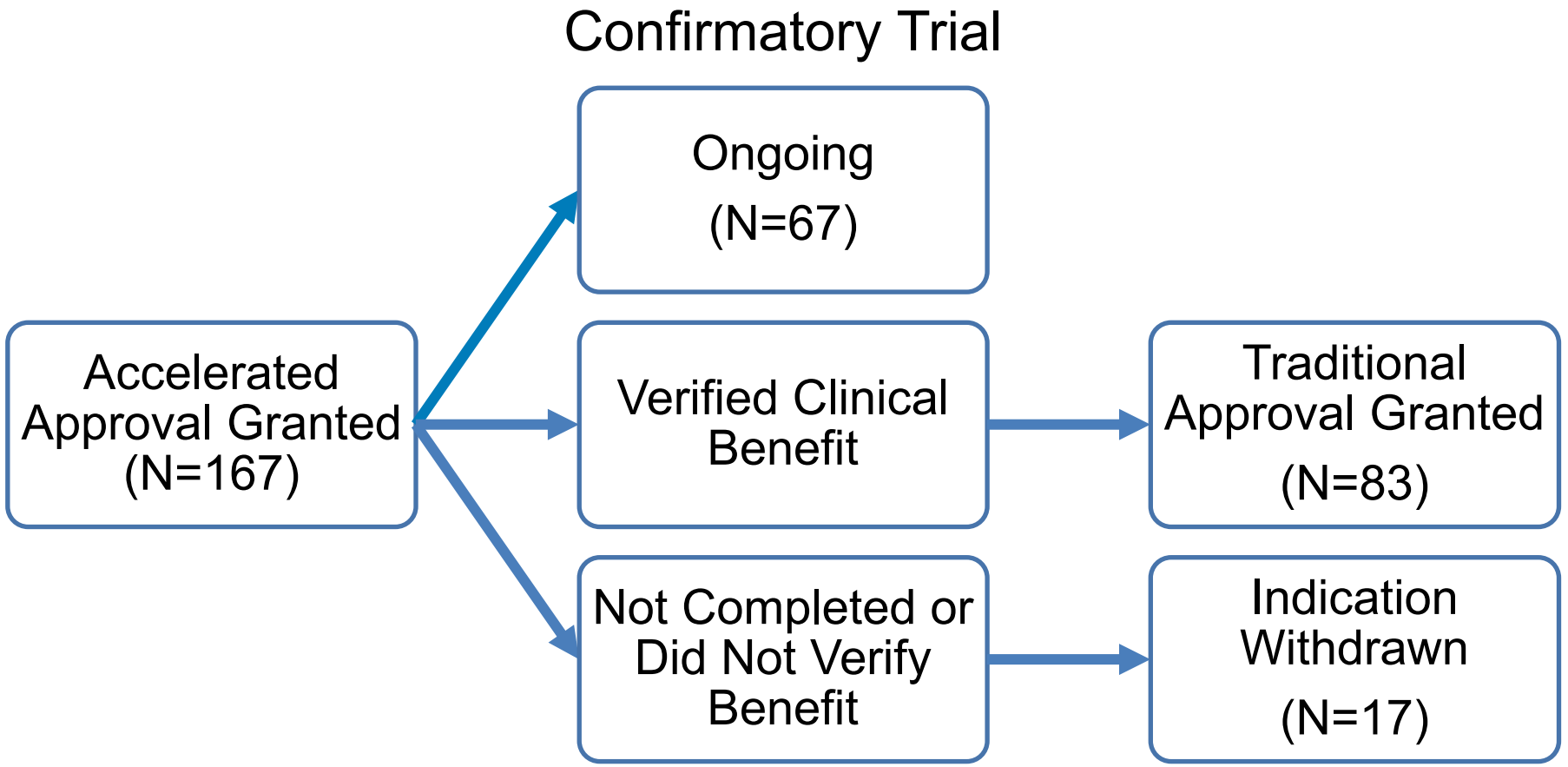
Withdrawal

- *The Secretary may withdraw approval [if]…*
  - *The sponsor **fails to conduct any required postapproval study** of the drug with due diligence*
  - *A **study required** to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit of the product **fails to verify and describe such effect or benefit***

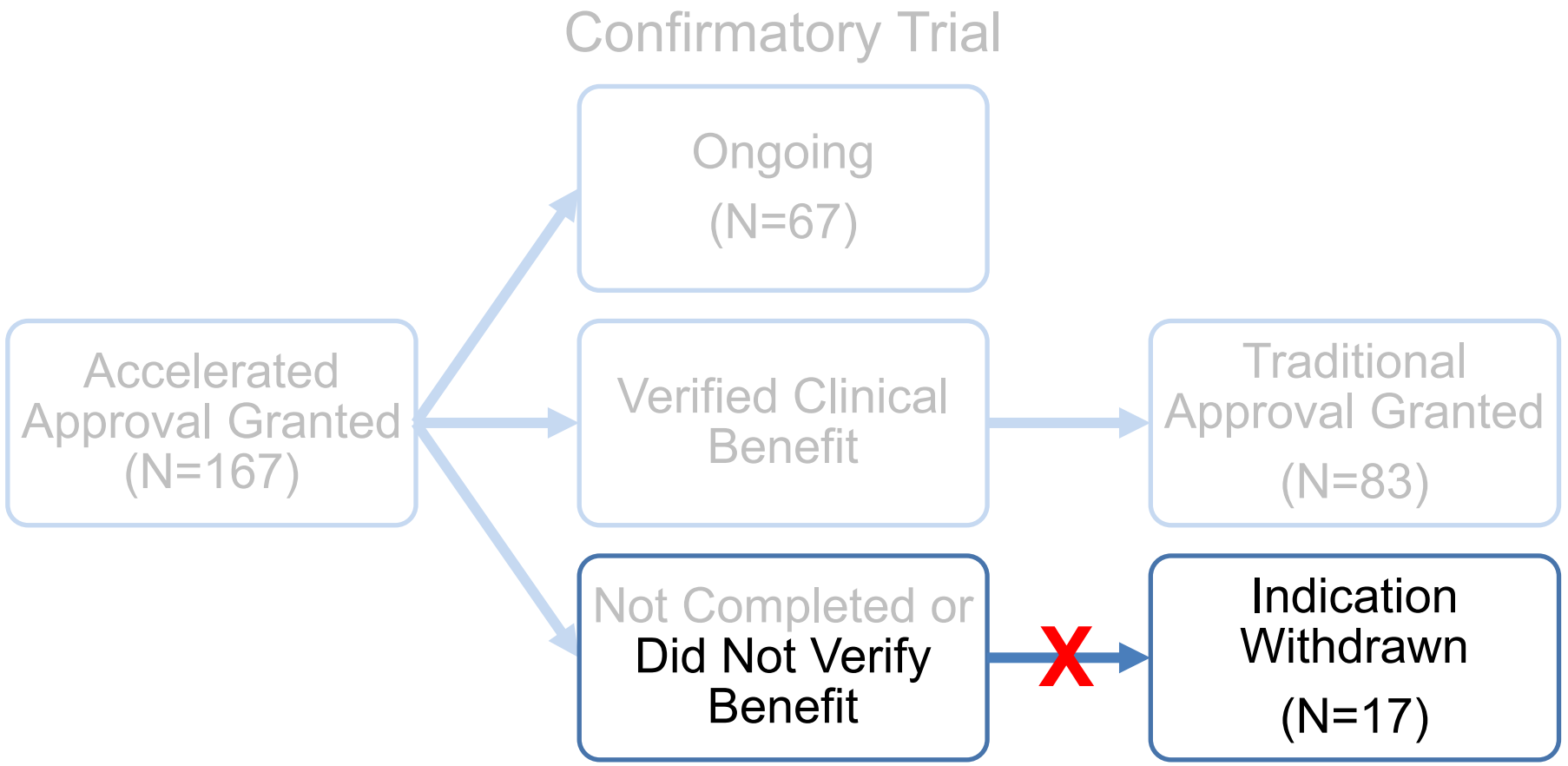
-Section 506(c) of the FDC Act

- May be withdrawn
  - Voluntarily by sponsor
  - By FDA after a public hearing

Accelerated Approvals in Oncology



“Dangling” Accelerated Approvals



“Dangling” Accelerated Approvals

Perspective

MAY 6, 2021

“Dangling” Accelerated Approvals in Oncology

Julia A. Beaver, M.D., and Richard Pazdur, M.D.

N ENGL J MED 384;18 NEJM.ORG MAY 6, 2021

ADVISORY COMMITTEE MEETING

April 27-29, 2021: Meeting of the Oncologic Drugs Advisory Committee Meeting Announcement

APRIL 27 - 29, 2021

Anti-PD(L)1 Accelerated Approvals

- 91 indications approved for anti-PD-(L)1 antibodies
- 38 Accelerated Approval indications
- 10 “Dangling” Accelerated Approval indications

Atezolizumab
TNBC- 1L
Urothelial – 2L
Urothelial cis-ineligible

Durvalumab
Urothelial- 2L

Pembrolizumab
Urothelial cis-ineligible
Gastric/GEJ
Hepatocellular
Small cell-lung

Nivolumab
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Beaver, *et al.,* N Engl J Med, 2022

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Beaver, *et al.,* N Engl J Med, 2022

Summary

- The majority of Accelerated Approvals have been granted in Oncology
  - Has allowed for early access to potentially life-saving therapies for patients with cancer

- The majority of confirmatory trials verify clinical benefit
  - Minority lead to withdrawal of the indication

PROJECT CONFIRM ☑

Promoting the transparency of Accelerated Approvals for oncology indications

1. Oncology Center of Excellence Initiative

2. Public, searchable database of Accelerated Approvals
   - Updated in real-time

3. Public education on Accelerated Approval
   - Address frequently asked questions
   - Describe processes for verification of benefit and for withdrawal

https://www.fda.gov/about-fda/oncology-center-excellence/project-confirm

Contact: OCE-Confirm@fda.hhs.gov

Acknowledgements

- Fatima Rizvi
- Kirsten Goldberg
- Tamy Kim
- Angelo de Claro
- Martha Donoghue
- Harpreet Singh
- Julia Beaver
- Richard Pazdur

Contact Us:

OCE-Confirm@fda.hhs.gov

Project Confirm:

https://www.fda.gov/about-fda/oncology-center-excellence/project-confirm

Patient Perspective Panel

- Alberto Rubio, MBA
  - patient with HIV
- Navdeep Singh, PhD
  - patient with beta-thalassemia
- Teonna Woolford
  - patient with sickle cell disease
- Katherine Couvillon
  - patient with metastatic breast cancer

Fireside Chat

- Provider: **Julie R. Gralow, MD, FACP, FASCO**
  Chief Medical Officer, American Society of Clinical Oncology
- Patient Advocate: **Kay Holcombe, MS**
  Board Chair, National Organization for Rare Disorders
- Industry: **Michelle McMurry-Heath, MD, PhD**
  President & CEO, BIO
- Payor: **Michael Sherman, MD, MBA**
  Chief Medical Officer, Point32 Health

Closing Remarks

Jacqueline Corrigan-Curay, JD, MD
Principal Deputy Center Director, Center for Drug Evaluation and Research, FDA

REAGAN-UDALL
FOUNDATION
FOR THE FDA