Accelerated Approval – Separating Fact and Fiction

Jacqueline Corrigan-Curay
Principal Deputy Center Director
Center for Drug Evaluation and Research
FDA
January 30, 2023

Overview

- Accelerated approval - Evidence standards
- Overuse / Underuse or Just right?
- Confirmatory Trials
- Once on the market – always on the market?
- Coming attractions

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FD&C Act section 505(d) (21 U.S.C. § 355(d)); draft Guidance for Industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019).

Food and Drug Administration Safety Innovations Act (FDASIA)

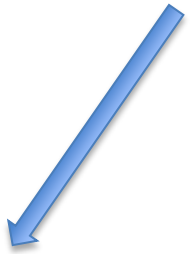
"The Secretary may approve an application for approval of a product for a **serious or life-threatening disease or condition**…upon a determination that the product has **an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit**, or on a **clinical endpoint that can be 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))

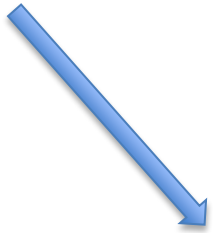
Meeting Patient's Needs by Streamlining Development

- 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



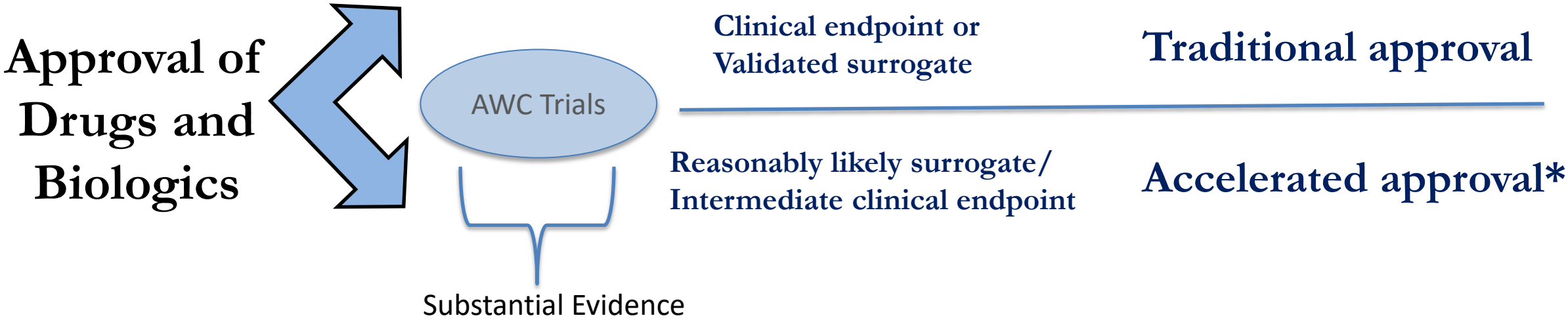
Validated Surrogate - marker that is *known to predict clinical benefit*, e.g., blood pressure and stroke, forced expiratory volume (FEV1) in certain pulmonary diseases



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

https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

U.S. Drug and Biological Product Approval Pathways



AWC – Adequate and Well Controlled Trials
21 CFR 312.126

* 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)

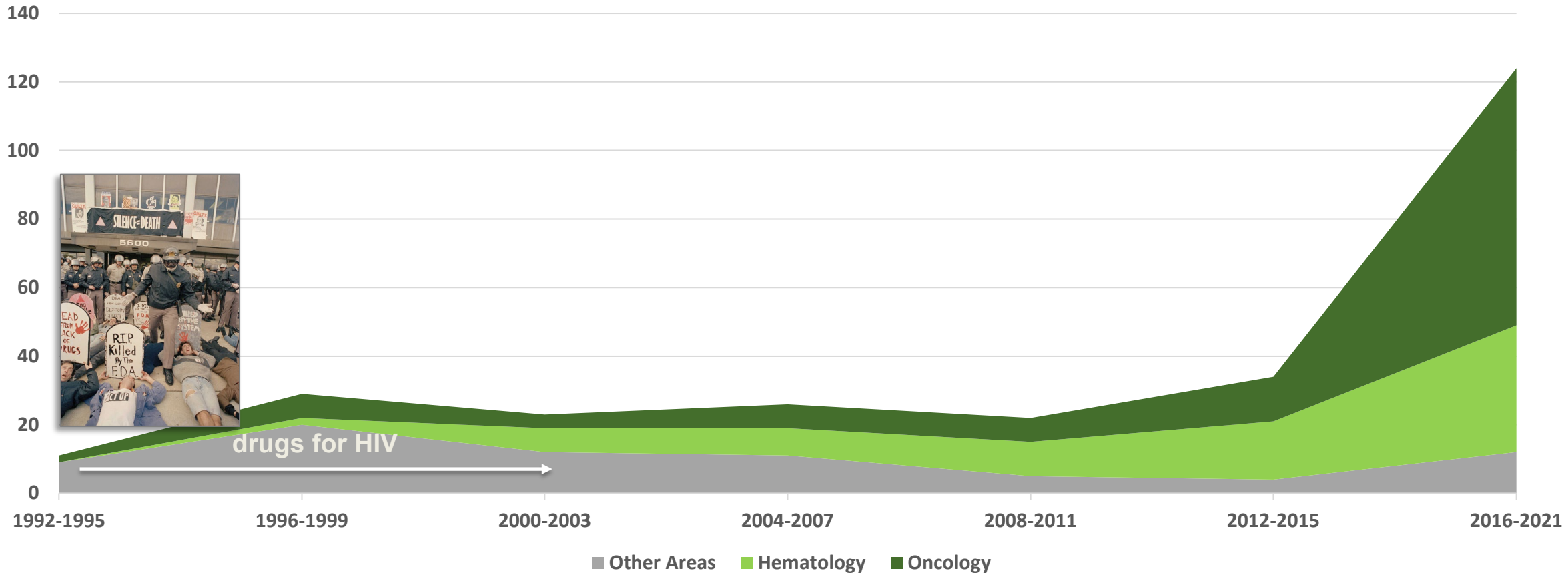
Meeting Patient's Needs by Streamlining Development

- 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
- There is a tradeoff between smaller, faster drug development to meet an unmet medical need for serious, life-threatening disease and the greater uncertainty as to whether the reasonably likely surrogate does indeed predict clinical benefit

Challenges with Accelerated Approval

- Main challenge is identification of a surrogate for which we have sufficient evidence that it is reasonably likely to predict clinical benefit
- Identification of a surrogate endpoints requires sufficient understanding of disease pathogenesis
- 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
- Epidemiologic data may demonstrate a relationship between a surrogate and disease outcome but need evidence that the change in the surrogate correlates with a change in clinical benefits

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.

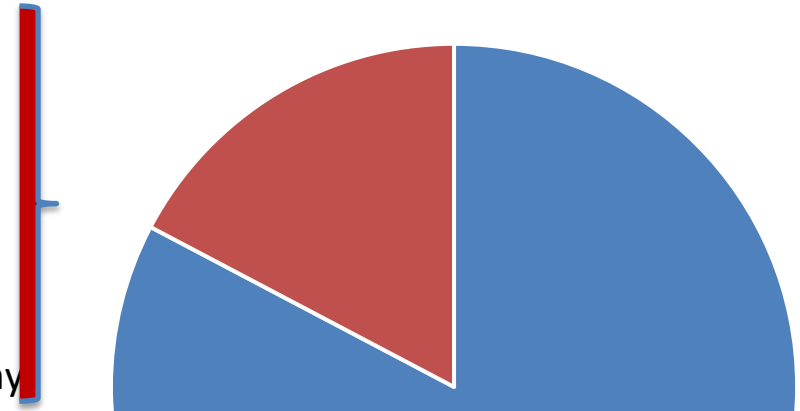
2 Other Areas is a combination of the eight other therapeutic areas (Anti-Infective, Anti-Viral, Bone/Reproductive/Urology, Inborn Errors, Cardio/Renal, Metab/Endo, Neurology, Pulmonary/Allergy/Rheumatology) where CDER had 5 or fewer accelerated approvals since 2000.

* Through June 2021

Accelerated Approvals Oncology vs Non-Oncology Jan 2019 – December 2022

Non-Oncology

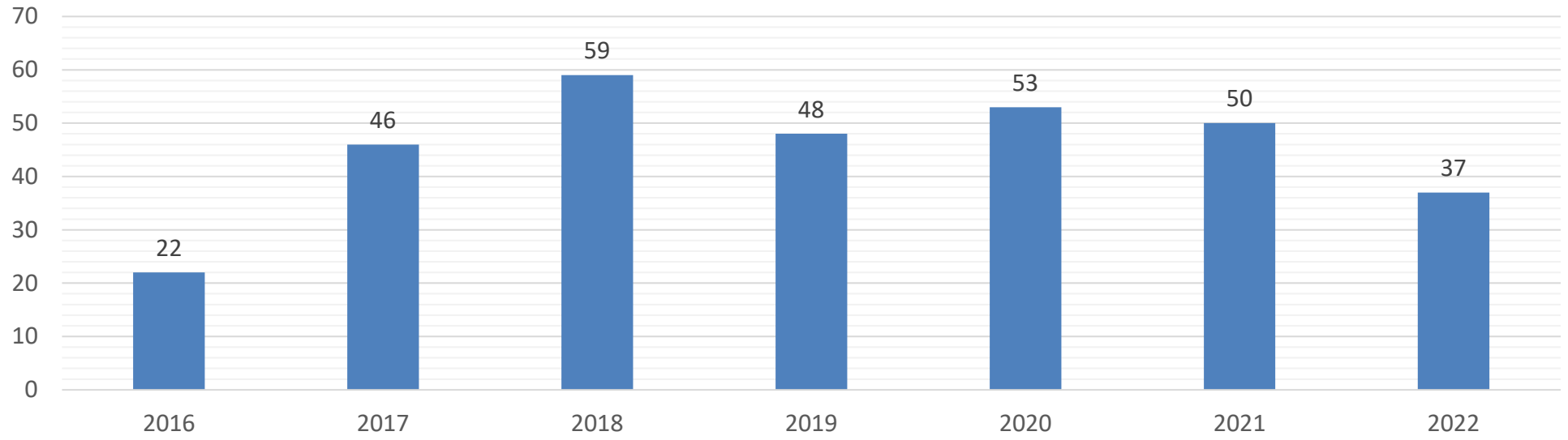
Achondroplasia
Alzheimer's Disease
Chagas Disease
Duchenne Muscular Dystrophy
Multi-Drug Resistant Tuberculosis
Myelofibrosis*
Primary Immunoglobulin A Nephropathy
Sickle Cell Disease



* Intermediate or high risk primary or secondary (post polycythemia vera or post essential thrombocytemia) myelofibrosis with platelet count below $50x10^9$

Multiple supplements for alternate dosing for Keytruda for different indications counted as 1

CDER NOVEL DRUG APPROVALS



2016	2017	2018	2019	2020	2021	2022
27%	13%	7%	19%	23%	28%	16%

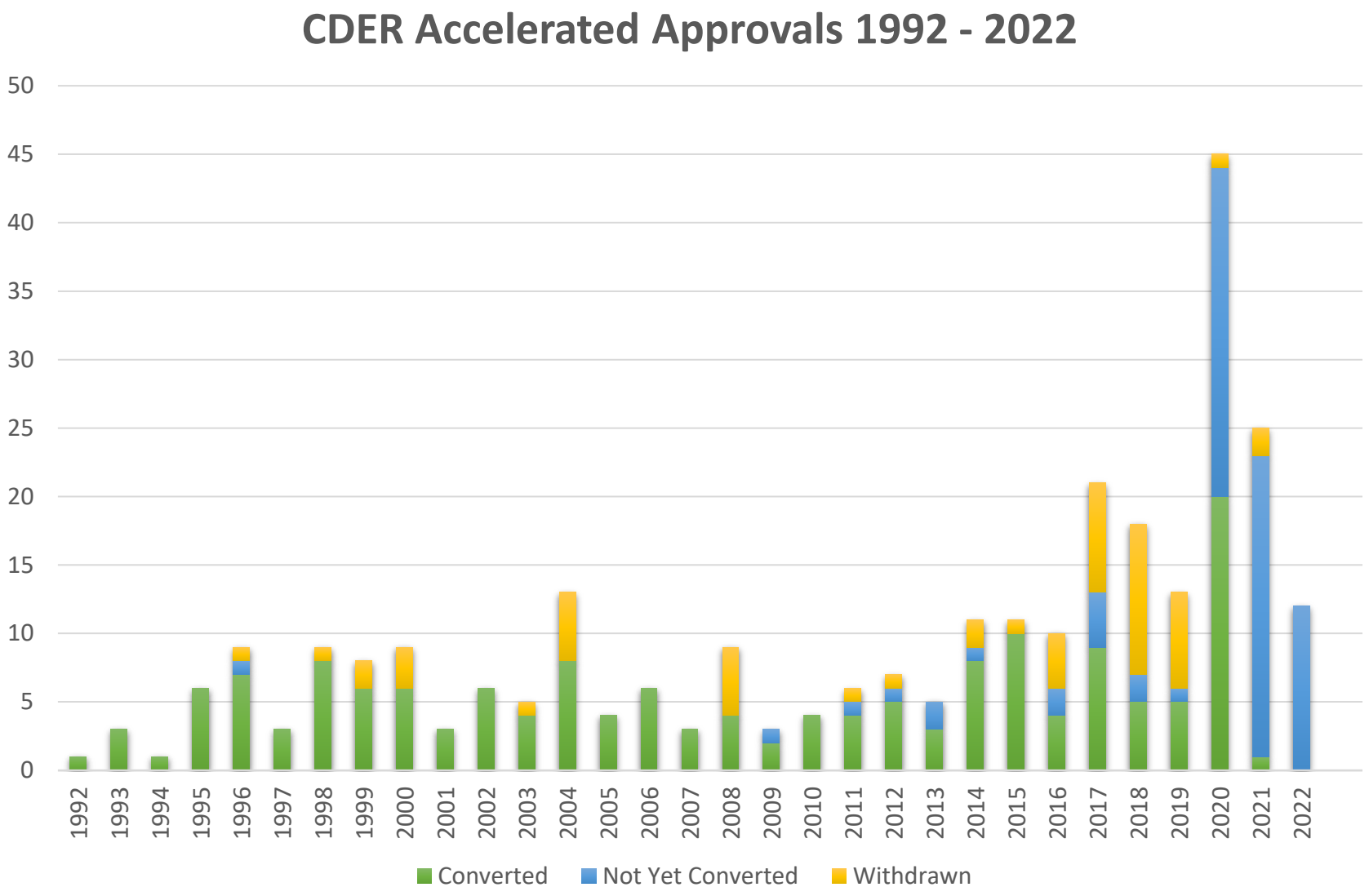
% approved under Accelerated Approval

2016	2017	2018	2019	2020	2021	2022
67%	83%	75%	78%	83%	79%	83%

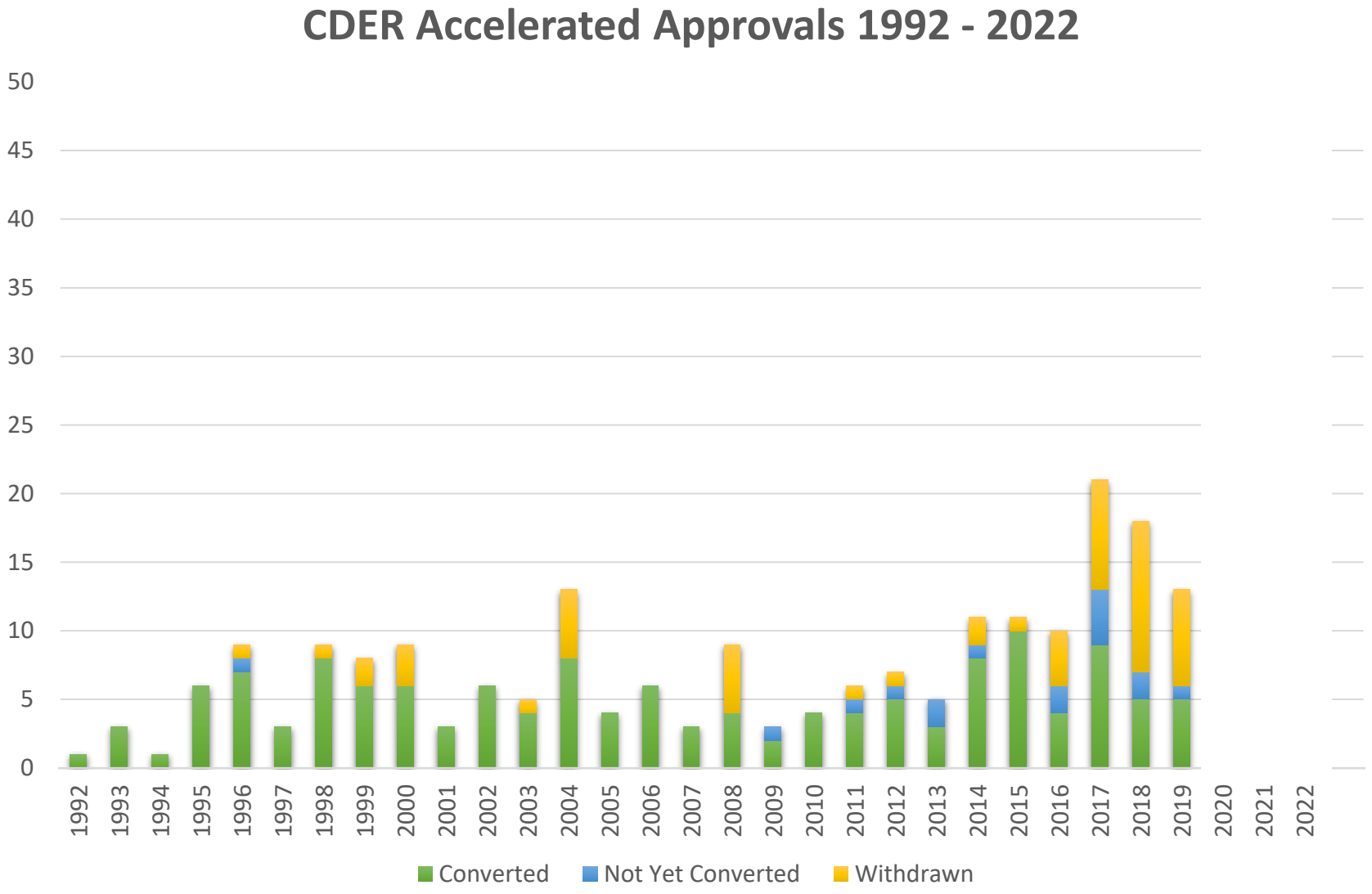
% Oncology Accelerated Approval

Confirmatory Trials

- Post-marketing trials are routinely be required to verify and describe the drug's clinical benefit.
- 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
- 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



Status of CDER accelerated approvals as of 12/31/2022 by year of accelerated approval



Status of CDER accelerated approvals as of 12/31/2022 by year of accelerated approval

Accelerated Approval Program

Infectious Disease Indications Accelerated Approvals

- Ongoing (excluding vaccines)
- Verified Clinical Benefit (excluding vaccines)
- Ongoing (vaccines)
- Verified Clinical Benefit (vaccines)
- Withdrawn

Non-malignant Hematological, Neurological, and Other Disorder Indications Accelerated Approvals

- Ongoing
- Verified Clinical Benefit

Cancer Accelerated Approvals

- Ongoing
- Verified Clinical Benefit
- Withdrawn
- Other

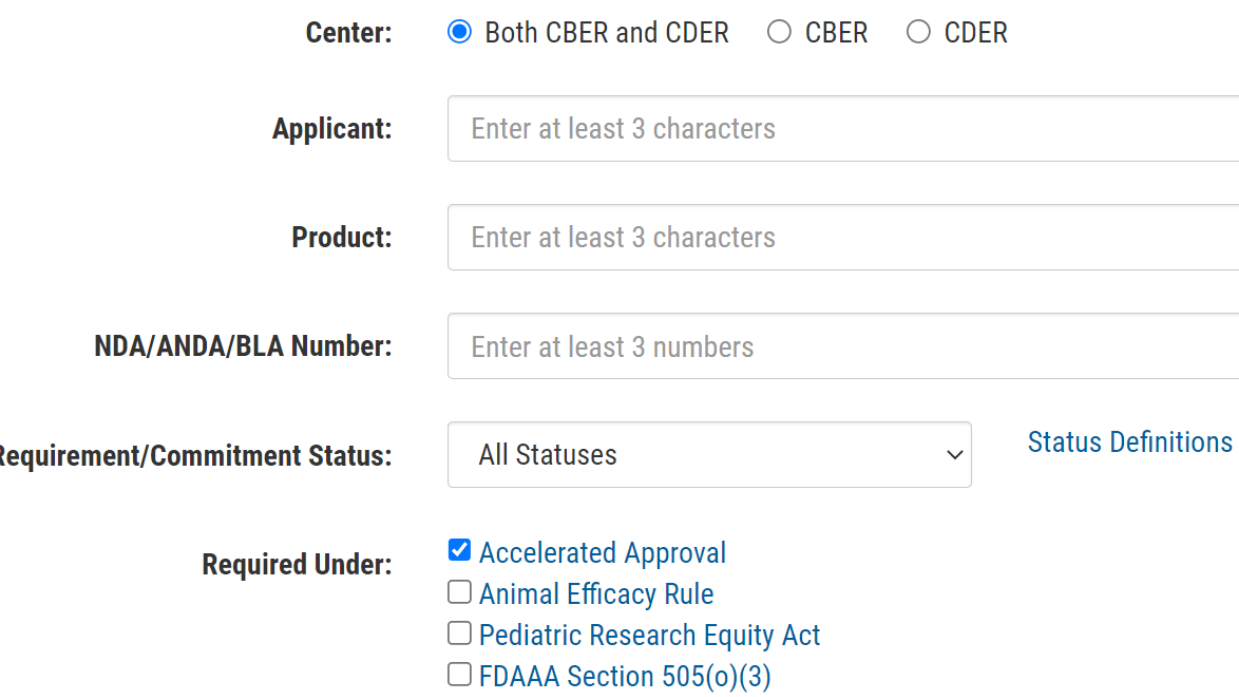
https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program

Search:

Export Excel Show 10 entries

Drug Name	Accelerated Approval Indication	Accelerated Approval Date	AA PMR	Original Projected Completion Date [2]
Lampit (nifurtimox)	For the treatment of chagas disease in pediatric patients birth to less than 18 years of age and weighing at least 2.5 kg	8/6/2020	**PMR 3868-1**: Complete the CHICO SECURE part of Study 16027 to determine the seroconversion rate in subjects treated with nifurtimox at the 4-year timepoint. Obtain antibody titers by serial dilution for all available serum samples measured by the F29-ELISA, Recombinant-ELISA and Lysate-ELISA in addition to IHA.	2/28/2022
Sirturo (bedaquiline)	For the treatment of pulmonary multi-drug resistant tuberculosis as part of combination therapy, in adult and pediatric patients (12 to less than 18 years of age and weighing at least 30 kg) to include patients ≥ 5 to <12 years of age and weighing at least 15 kg	5/27/2020	**PMR 1988-1**: Conduct a confirmatory randomized double blind placebo controlled multicenter Phase 3 trial in subjects with sputum smear-positive pulmonary multidrug resistant tuberculosis (MDR-TB). This trial should assess long term outcomes of failure or relapse or death at least 6 months after all MDR-TB treatment is completed.	3/31/2022

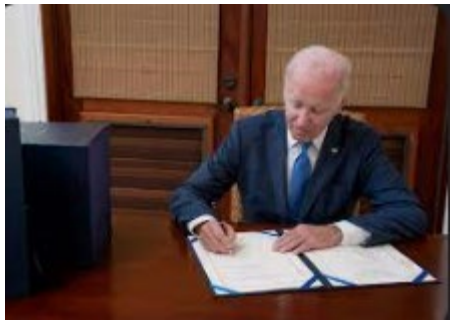
Postmarket Requirements and Commitments



The data on the PMR and PMC public website are updated quarterly.

Annual report published in Federal Register on the performance of postmarket studies and clinical trials that FDA requires, or has requested, of manufacturers

https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm



Looking Forward

Consolidated Appropriations Act, 2023
Section 3210 Modernizing Accelerated approval

"(D) STUDIES BEGUN BEFORE APPROVAL.—The Secretary may require, as appropriate, a study or studies to be underway prior to approval, or within a specified time period after the date of approval, of the applicable product."

- Oncology review of 93 AA indications for 64 products between December 31, 1992 and May 31, 2017
- 51 satisfied their postmarketing requirement(s) and verified benefit, the median time from AA to **verification of benefit was 3.4 years** (range, 0.5-12.6 years)
- For those that had **ongoing confirmatory trials at the time of AA, the median time to verification of benefit was 3.1**
- For the 9 indications **without ongoing trials**, the **median time to verification of benefit was 5.5 years**.

Beaver, J., et al, A 25-Year Experience of US Food and Drug Administration Accelerated Approval of Malignant Hematology and Oncology Drugs and Biologics *JAMA Oncol*. doi:10.1001/jamaoncol.2017.5618

Looking Forward

Consolidated Appropriations Act, 2023

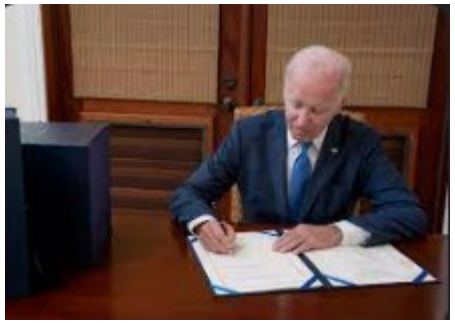
Section 3210 Modernizing Accelerated approval

Expedited procedures for Withdrawal

- Providing the sponsor with **due notice and an explanation for the proposed withdrawal;**
- (III) An opportunity for a **meeting with the Commissioner or the Commissioner's designee**; and
- an opportunity for **written appeal to—**
- **"(aa) the Commissioner; or (bb) a designee of the Commissioner** who has not participated in the proposed withdrawal of approval (other than a meeting pursuant to subclause (III) and is not subordinate of an individual (other than the Commissioner) who participated in such proposed withdrawal;
- Providing an **opportunity for public comment on the proposal to withdraw** approval;
- The **publication of a summary of the public comments received**, and the Secretary's response to such comments, on the website of the Food and Drug Administration; and
- Convening and consulting an **advisory committee** on issues related to the proposed withdrawal, if requested by the sponsor and if no such advisory committee has previously advised the Secretary on such issues with respect to the withdrawal of the product prior to the sponsor's request.''.

Makena Timeline for Possible Withdrawal

- **February 2011** – CDER approved Makena under AA based on data from Trial 002
- **2019** – Sponsor submitted results/analysis of Trial 003 (confirmatory trial) to FDA
- **October 2019** – Advisory Committee meeting
  - 16-0: Trial 003 did not verify clinical benefit
  - 13-3: data from Trial 002 and 003 do not show SEE in reducing the risk of recurrent PTB
  - 9-7: recommending withdrawing Makena from market
- **October 2020** – Notice of opportunity for a hearing sent to sponsor
- **October 2020** – Sponsor requested a hearing
- **December 2020** – Sponsor submitted data and information in support of hearing request
- **August 2021** – FDA's Chief Scientist granted sponsor's hearing request
- **October 2022** – Hearing held
- **January 2022** – Presiding Officer's Report Issued
- *Process Remains On-going*

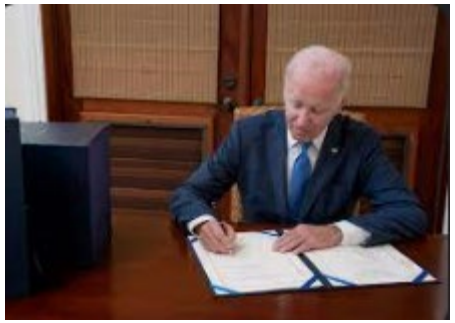


Looking Forward

Consolidated Appropriations Act, 2023

Section 3210 Modernizing Accelerated approval

- **Specify conditions for post approval study(ies)**, which may include enrollment targets, study protocol and milestones, including data of study completion
- **Sponsor reporting on progress of post approval study**, including toward enrollment targets, milestones and other information **not later than 180 days after the approval of such drug** and not less frequently than every 180 days thereafter until the study is completed or terminated
  - Information available on FDA website in easily searchable format
- **Guidance** on:
- How sponsor questions related to the identification of novel surrogate or intermediate clinical endpoints may be addressed in early-stage development meetings with the Food and Drug Administration;
- Use of novel clinical trial designs that may be used to conduct appropriate post approval studies
- Expedited withdrawal procedures
- Considerations related to use of surrogate or intermediate clinical endpoints, including evaluating evidence related to such endpoints



Looking Forward

Consolidated Appropriations Act, 2023

Section 3210 Modernizing Accelerated approval

ACCELERATED APPROVAL COUNCIL

- Minimal Membership specified and includes leadership CDER, CBER and Oncology Center of Excellence
- The Council shall convene not fewer than 3 times per calendar year to discuss issues related to accelerated approval, including any relevant cross-disciplinary approaches related to product review with respect to accelerated approval.
- **POLICY DEVELOPMENT**.—The Council shall directly engage with product review teams to support the consistent and appropriate use of accelerated approval across the Food and Drug Administration. Such engagement may include—
  - (i) developing guidance for FDA staff and best practices for, and across, product review teams, including with respect to communication between sponsors and the FDA and the review of products under accelerated approval;
  - (ii) providing training for product review teams; and
  - (iii) advising review divisions on best practices with respect to product-specific development, review, and withdrawal of products under accelerated approval.

Looking Forward

- Accelerated approval will continue 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
- With greater uncertainty comes greater risk of failed therapies – striking the right balance is key
- 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/public health
- We look forward to implementing the new provisions of the statute

Acknowledgments

- Julia Beaver
- Khair Elzarrad
- Kevin Fain
- Maarika Kimbrell
- Diane Maloney
- Gautam Mehta
- Sarah Walinsky


FDA
U.S. FOOD & DRUG
ADMINISTRATION