What does FDA do during review? How do we use the Patient Voice during review?

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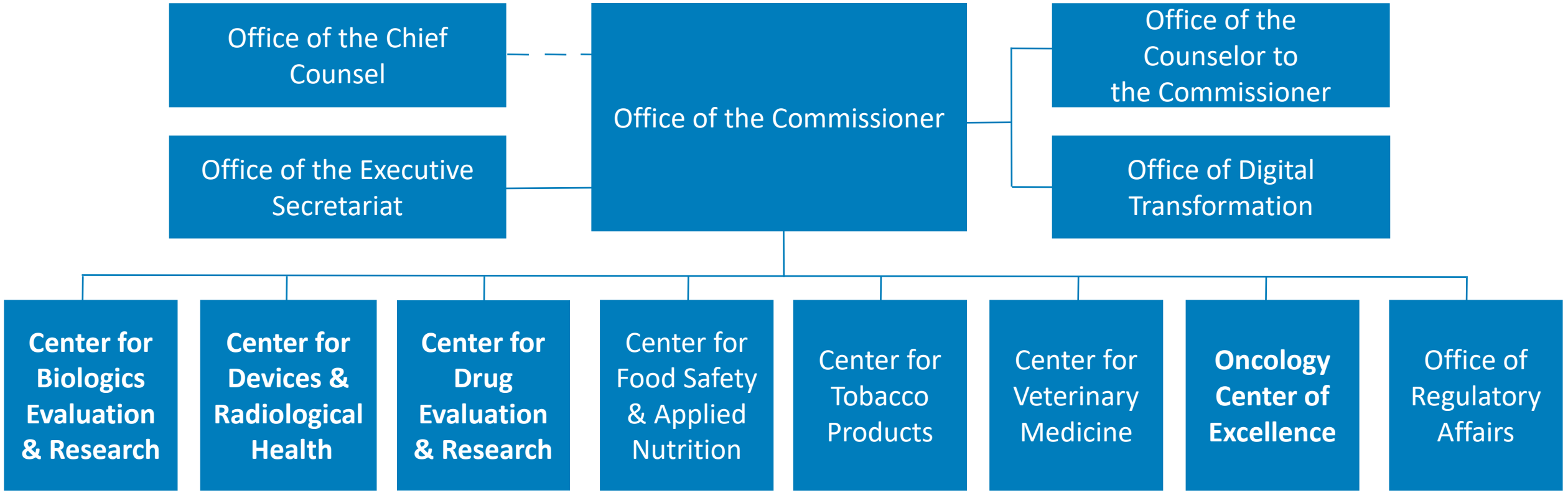
FDA Mission

"FDA is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation"

FDA Organization Structure



How did we get here? Prior to 1938

FDA was created in 1906, but could only respond to problems

- Companies had complete freedom to market
- No requirements for testing or approval
- No data of any kind had to be submitted
- Government could seek to remove dangerous or misbranded products

Commissioner Larrick explaining the Chamber of Horrors exhibit

https://www.fda.gov/about-fda/histories-product-regulation/american-chamber-horrors

Not surprisingly, there were some disasters

Notable disasters before 1938

- **Dinitrophenol** – weight loss drug, caused thousands of cataracts, enucleations in the 1930's; deaths related to hyperthermia

- **Elixir sulfanilamide** – sulfa drug killed over 100 people in 1937, many of them children
  - Diethylene glycol (anti-freeze) was the solvent
  - No animal testing – a chemist simply smelled and tasted the elixir

These events led to ➡

The Food, Drug and Cosmetic Act of 1938 (FD&C) – "Age of Safety"

Added key requirements:

- Pre-market notification

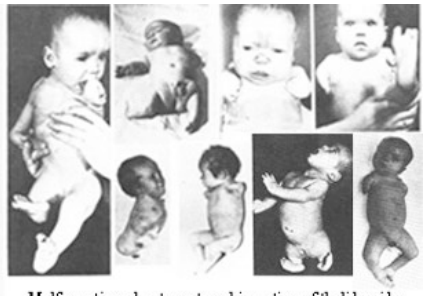
- Demonstration of safety, applications could be refused if:
  - Investigations do not include "all tests reasonably applicable to show whether drug is safe" when used under proposed labeling or found to be unsafe
  - Labeling is false or misleading

- Safety requirements have not notably changed – current application is that "safe" means that the benefits outweigh risks

The “Age of Effectiveness”: The 1962 Kefauver-Harris Amendments

Thalidomide disaster (a safety problem) led to a requirement for demonstrating *effectiveness* - the 1962 Act made at least 3 important changes:

- FDA had to give positive approval before a drug could be marketed
- A meaningful requirement to study drugs under an IND and an explicit requirement for informed consent (one year before the Declaration of Helsinki).
- *The effectiveness requirement*

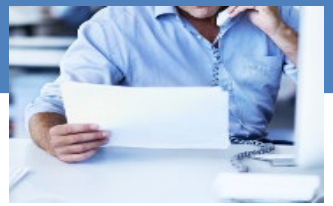


Malformations due to maternal ingestion of thalidomide (Schardein 1982 and Moore 1993).

Dr. Francis Kelsey received the President's Award for Distinguished Federal Civilian Service

When/Where does FDA Review occur prior to approval?

Premarket/Investigational Research



This stage involves the initial research and development of a new investigational product. FDA review occurs here before patients or subjects are exposed to the new product.

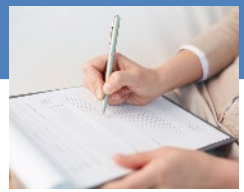
Sponsor submits an **Investigational New Drug (IND) Application**

Ongoing Studies during Development

This intermediate stage involves the ongoing review of study protocols and completed study reports to ensure patient safety and development progress.

Ongoing Sponsor submissions of trial **protocols, safety reports, annual reports, study reports**, etc

Premarket/Approval Decision



This final stage involves the FDA review to determine the safety and effectiveness of the product before it is available on the market.

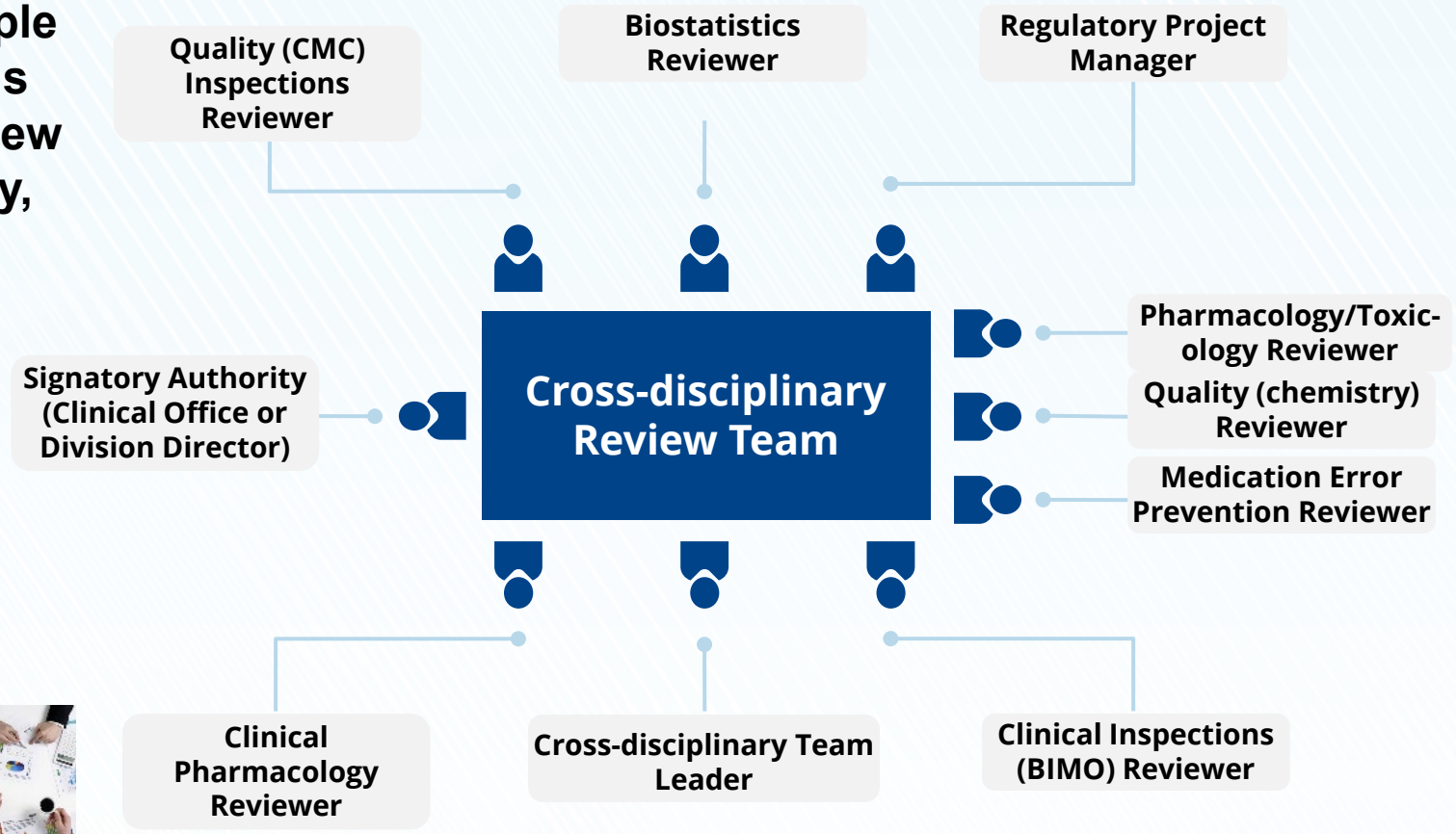
Sponsor submits **marketing (NDA or BLA) application**

More on FDA Cross-disciplinary Review Teams

There is no single discipline for the review of investigational or marketing applications!

FDA forms teams comprised of multiple disciplines to work together in various ways to create a cross-disciplinary view of safety issues, effectiveness, quality, etc.

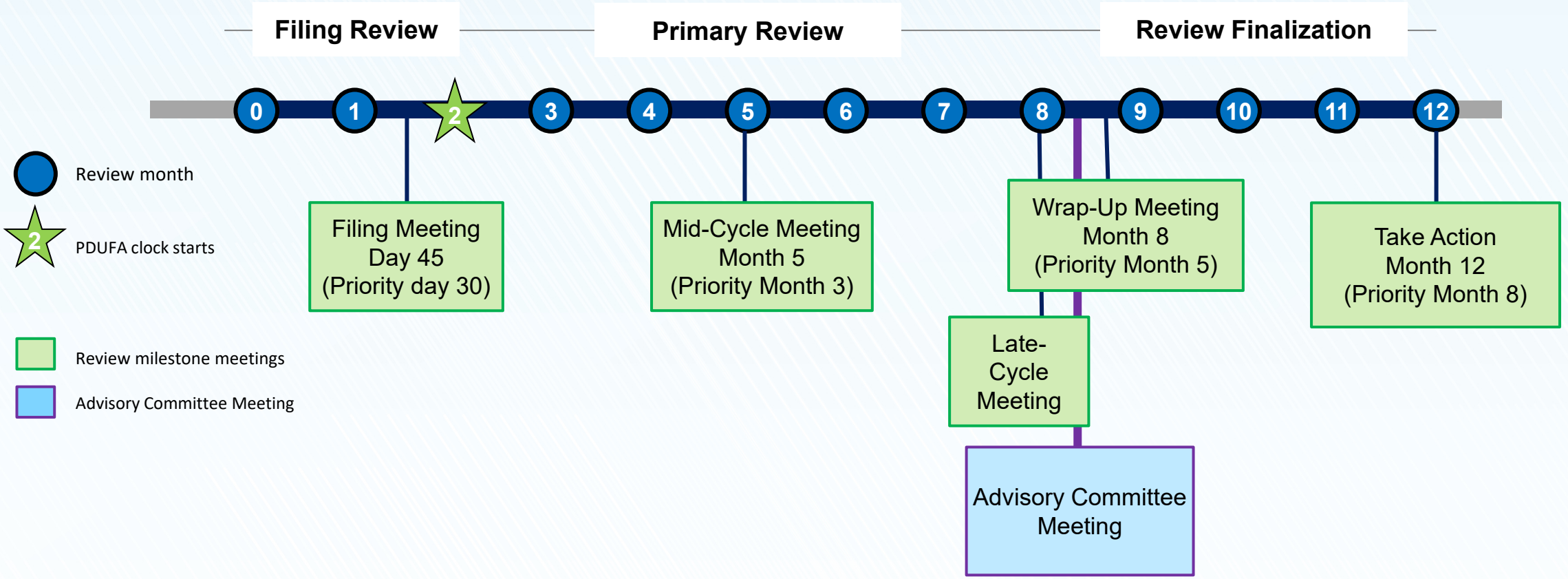
This is an example CDER New Drug Application Review Team:



Other Experts engaged via consultation processes to additional expertise to the team. Includes:

- **Legal Counsel**
- **Scientific Advisors (via AC or SGE process)**
- **Patient Experts (via AC or SGE process)**
- **Other center or FDA experts**

NDA/BLA Review Process – Basic Steps



- This is a sample timeline, which typically applies to novel drugs.
- FDA-Sponsor interactions can occur at any time throughout the review process
- Major Amendments, solicited or unsolicited, can extend the review clock (once) by 3 months

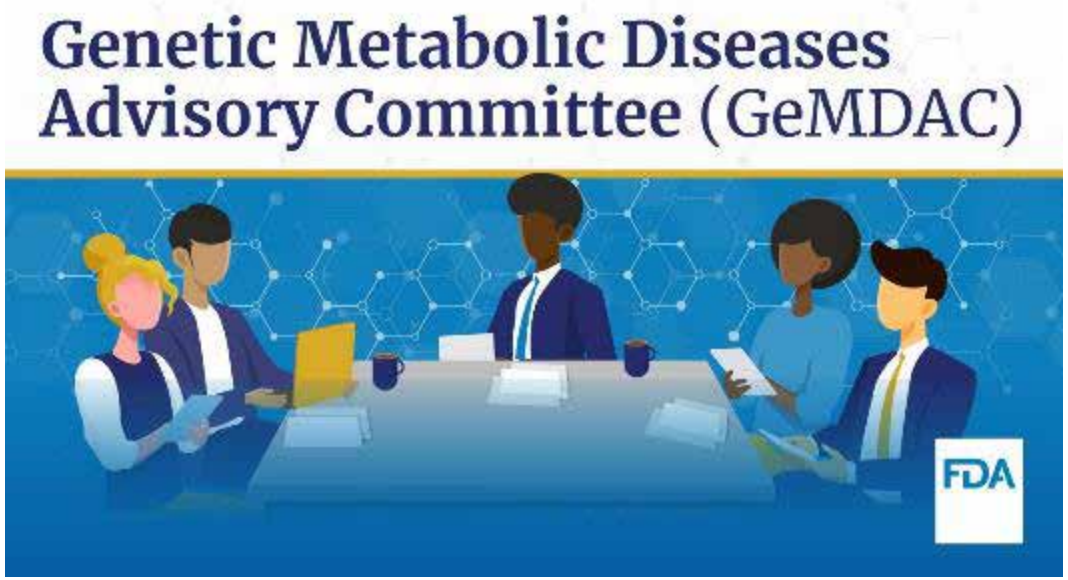
Role of Advisory Committees

The FDA uses committees and panels to obtain independent expert advice on scientific, technical, and policy matters.

The decision to hold an advisory committee is typically made during the filing review period. It is important to note that these committees do not make the regulatory decision, but rather inform it.

In December 2023, FDA announced it is creating a new advisory committee related to potential treatments for genetic metabolic diseases. The group will be comprised of experts in the areas of metabolic genetics, management of inborn errors of metabolism, small population trial design, translational science, pediatrics, epidemiology or statistics and related specialties.

https://www.fda.gov/advisory-committees/human-drug-advisory-committees/genetic-metabolic-diseases-advisory-committee



What occurs during the Primary Review phase?

Data Validation:

1. FDA examines both final summaries and raw data from nonclinical and clinical studies.
2. Validation of safety and effectiveness findings through thorough analysis.

In-Depth Analysis:

1. Recreation of analyses and, if necessary, conducting new ones to ensure robustness.
2. Scrutiny of trial and study designs for strength and reliability.

Comprehensive Review:

1. Reviewers evaluate the Sponsor's analyses and study conclusions critically.
2. Findings are compiled and discussed collaboratively among the entire FDA review team.

- Marketing applications contain data on a wide array of variables that require a diverse interdisciplinary team of scientific, clinical and technical expertise to evaluate
- No single discipline can decide if a medical product works
- We don't just look at the technical data; we also carefully consider the patient experiences with the new product

What about Patient Experience Data/Information?

1. **FDA-led Patient Engagement:**

   FDA gathers insights from patients through Patient Focused Drug Development (PFDD) meetings and Patient Listening Sessions.

2. **Informing Clinical Trials:**

   Information gained is used by FDA Reviewers to guide discussions with medical product developers on clinical trial designs and endpoint development. This includes patient-reported outcomes and patient preference information, or patient generated health data.

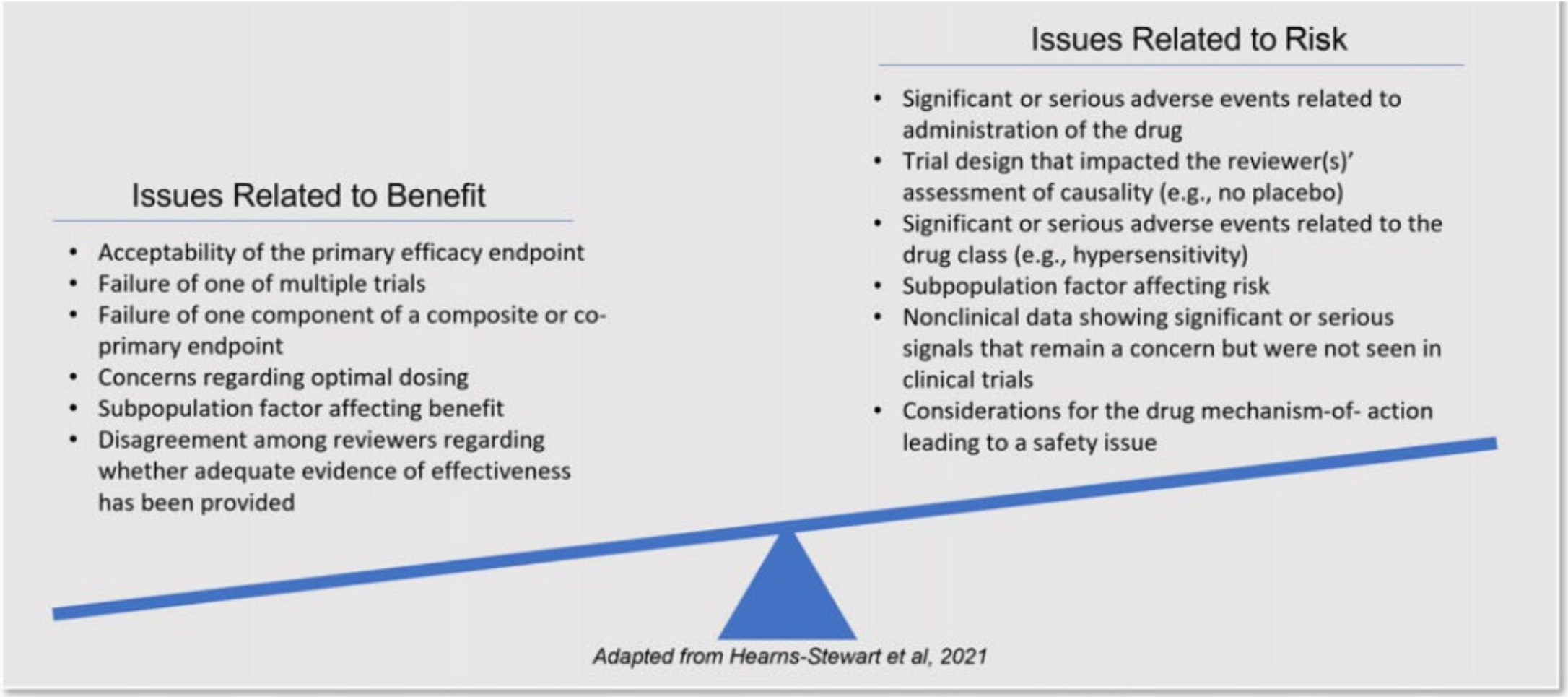
3. **Guidance for Data Collection:**

   Patients, Patient Groups, or Medical Product Sponsors follow a series of FDA Guidance for collecting and submitting patient experience data during development.
   https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

4. **Impact on Assessment:**
   - Patient-derived information informs the benefit-risk assessment, providing therapeutic context and understanding the condition's impact on daily lives.
   - Identifies symptoms that matter most to patients and captures their experiences with available treatments and ongoing unmet medical needs.
   - Patient insights on willingness to accept side effects and uncertainties play a crucial role in the review team's benefit-risk assessments.

Review Finalization: Making the Benefit-Risk Decision

- All drugs can have adverse effects – safety requires a showing that the benefits outweigh the risks.
- FDA required to implement a benefit-risk framework to balance consideration of the benefits and risks during review of an application
- Important that benefits and risks be well-characterized and that we identify uncertainties



Reminder: Official Action




	Traditional Approval	Accelerated Approval	Complete Response Letter	Withdrawn
Requirement	Clinical benefit has been established and the benefits outweigh the risks.	Earlier approval for some drugs for serious and life-threatening illnesses that fill an unmet need based on a surrogate endpoint.[1] Requires trial(s) to verify and describe the anticipated clinical benefit.	Issued if FDA concludes after its review that there are problems with the marketing application precluding approval. The letter includes FDA's justification for its decision and recommendations to address the deficiencies.	A drug application can be withdrawn voluntarily by the drug company at any time.
Information Shared with Public	Yes (Approvals are posted on fda.gov)	Yes (Approvals are posted on fda.gov)	No (Complete response letters are not publicly available unless shared by the company)	No

[1]A surrogate endpoint used for accelerated approval is a marker – a laboratory measurement, radiographic image, or other measure – that is considered reasonably likely to predict clinical benefit, but is not itself a direct measure of clinical benefit.

Resources Available

- FDA maintains robust website with helpful information for consumers, patients, caregivers, and healthcare providers
- We walk you through the step-by-step process in reviewing a marketing application – including a helpful infographic
- Check it out: https://www.fda.gov/drugs/information-consumers-and-patients-drugs/fdas-drug-review-process-continued