What Comes Next?
An overview of the role of data in FDA Approval Processes

Paul Schuette

Scientific Computing Coordinator

FDA/CDER/OTS/OB/IO/AIS

Paul.Schuette@fda.hhs.gov

Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

CDER Reviews

What happens after a submission package is delivered to the Center for Drug Evaluation and Research (CDER) in the US Food and Drug Administration (FDA)?

- Standard Review, 10-month clock
- Priority Review, 6-month clock

Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review

FDA

Fast Track

Fast track is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need.
Fast Track

Breakthrough Therapy

A process designed to expedite the development and review of drugs which may demonstrate substantial improvement over available therapy.
Breakthrough Therapy

Accelerated Approval

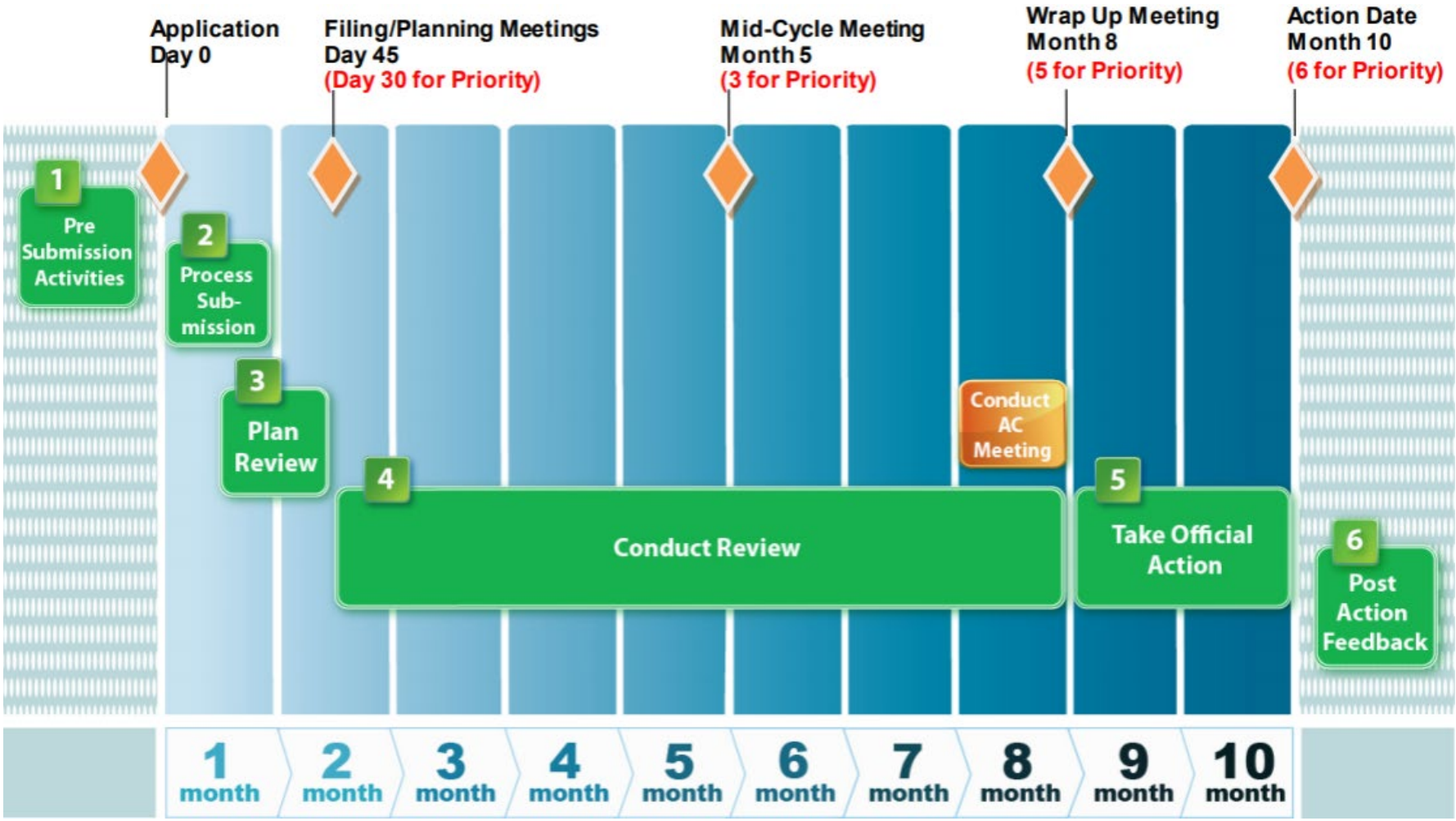
These regulations allowed drugs for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint.
Accelerated Approval

Priority Review

A Priority Review designation means FDA's goal is to take action on an application within 6 months.
Priority Review

Link

Major Steps
(21st Century Review)



Integrated Review Template

Three main components:

1. Executive Summary
2. Interdisciplinary Assessment
3. Discipline Specific Appendices

"New roles to support the review team and allow reviewers to focus on the science and regulatory aspects of the application- clinical data scientists will support clinical safety data verification and analyses, and medical editors will provide editing and formatting services" link

CDER Submissions

- Submissions to CDER and CBER for studies begun after December 17, 2016, are required to conform to CDISC standards (SDTM, ADaM).
- Other FDA Centers (CDRH, CTP, CVM and CFSAN) have different procedures and processes.
- The Study Data Technical Conformance Guide lays out technical expectations, in addition to adherence to CDISC standards.

Who uses NDA/BLA data?

- Office of Biostatistics (OB)
- Office of Clinical Pharmacology (OCP)
- Office of Pharmaceutical Quality (OPQ)
- Office of New Drugs (OND)
- Office of Scientific Investigations (OSI)
- Office of Computational Sciences (OCS)
- Office of Study Integrity and Surveillance (OSIS)

Data Checks and Fileablity

- OCS Jumpstart/DataFit: Pinnacle 21 software used to evaluate CDISC compliance
- CluePoints Cooperative Research and Development Agreement (CRADA): data anomaly detection, data quality assessment
- Reviewer/Analyst applied tests
  - Format, completeness
  - Missing Data
  - Outliers
- Identify sites for inspection

Filing Meeting

"Each discipline makes a recommendation on fileability of the application at the filing meeting that is held by day 45 of the review (day 30 for priority reviews). If the application is found fileable a planning meeting is held to further discuss timelines, high-level labeling revisions and review activities."

CDER 21st Century Review Process Desk Reference Guide

Refuse to File

"Complex significant deficiencies that cannot be corrected before filing and that may result in a refusal to file pursuant to § 314.101(d)(3) and other authorities. Examples of such deficiencies include, but are not limited to: …

Required content is not submitted electronically where the FDA has specified the format of such submissions in guidance pursuant to section 745A of the FD&C Act or required content is not submitted in an electronic format that the FDA can review, process, and archive, where such electronic submissions are required by an applicable regulation. Electronic submission issues that CDER considers to be filing issues include particular organization, file format, coding, or formatting problems that are specified in applicable guidances issued pursuant to section 745A(a) of the FD&C Act."

Refuse to File:NDA and BLA Submissions to CDER, Guidance for Industry, 2017

Analyses

- Can the sponsor's results be independently replicated based on the stated protocol and statistical analysis plan?
- Sponsor's code can help navigating the "garden of diverging paths"
- Other analyses
  - Sensitivity Analyses
  - Safety

Study Data Technical Conformance Guide

4.1.2.10 Software Programs

Sponsors should provide the software programs used to create all ADaM datasets and generate tables and figures associated with primary and secondary efficacy analyses. Furthermore, sponsors should submit software programs used to generate additional information included in Section 14 CLINICAL STUDIES of the Prescribing Information, if applicable. The specific software utilized should be specified in the ADRG. Refer to FDA Statistical Software Clarifying Statement for more information. The main purpose of requesting the submission of these programs is to understand the process by which the variables for the respective analyses were created and to confirm the analysis algorithms and results. Sponsors should submit software programs in ASCII text format. Executable file extensions should not be used. Link

Statistical Software Clarifying Statement

"FDA does not require use of any specific software for statistical analyses, and statistical software is not explicitly discussed in Title 21 of the Code of Federal Regulations [e.g., in 21CFR part 11]. However, the software package(s) used for statistical analyses should be fully documented in the submission, including version and build identification."

Statistical Software Clarifying Statement, cont

"As noted in the FDA guidance, E9 Statistical Principles for Clinical Trials …`The computer software used for data management and statistical analysis should be reliable, and documentation of appropriate software testing procedures should be available.' Sponsors are encouraged to consult with FDA review teams and especially with FDA statisticians regarding the choice and suitability of statistical software packages at an early stage in the product development process."

Link

Information Requests (IR)

"An IR letter is a letter sent to an applicant during an application review to request further information or clarification that is needed or would be helpful to allow completion of the discipline review. FDA does not consider IR letters to be action letters because they do not represent a complete review of the submission and therefore do not stop the user fee review clock."

Guidance for Industry Information Request and Discipline Review Letters Under the Prescription Drug User Fee Act

Internal Meetings

- Joint Assessment Meetings (JAM)
  - Established as part o the Integrated Review Process
  - Includes disciplines working on review
  - Identifies review issues/deficiencies
  - JAM meetings are scheduled throughout the review process
  - Labelling Meeting(s)
- Midcycle Meeting

Midcycle Meetings

"Objectives of the meeting are to:

- Present status and key findings of all reviews, consults, and inspections.
- Confirm the decision that was made regarding the need for an Advisory Committee meeting.
- Identify any issues that could preclude an approval action.
- Begin high-level discussion of labeling (e.g., are major claims supported) and need for PMRs and/or PMCs.
- Determine if a REMS is needed (if not already determined) and, if so, the goals and the elements of the REMS.
- Revise the review plan and interim timelines, if needed."

CDER 21st Century Review Process Desk Reference Guide

Advisory Committees

"Advisory committees provide independent advice and recommendations to the Food and Drug Administration (FDA) on scientific and technical matters related to the development and evaluation of products regulated by the Agency. Through the advisory committee system, FDA is able to secure independent professional expertise in accomplishing its mission and maintaining the public trust. CDER and CBER request advice from advisory committees on a variety of matters, including various aspects of clinical investigations and applications for marketing approval of drug products. Although the committees provide recommendations to the Agency, final decisions are made by FDA."

Guidance for Industry Advisory Committees: Implementing Section 120 of the Food and Drug Administration Modernization Act of 1997

Complete Response

21CFR part 314

"Complete response letter. FDA will send the applicant a complete response letter if the agency determines that we will not approve the application or abbreviated application in its present form for one or more of the reasons given in § 314.125 or § 314.127, respectively.

(1) Description of specific deficiencies. A complete response letter will describe all of the specific deficiencies that the agency has identified in an application or abbreviated application, except as stated in paragraph (a)(3) of this section.

(2) Complete review of data. A complete response letter reflects FDA's complete review of the data submitted in an original application or abbreviated application (or, where appropriate, a resubmission) and any amendments that the agency has reviewed. The complete response letter will identify any amendments that the agency has not yet reviewed.

(3) Inadequate data. If FDA determines, after an application is filed or an abbreviated application is received, that the data submitted are inadequate to support approval, the agency might issue a complete response letter without first conducting required inspections and/or reviewing proposed product labeling."

Emergency Use Authorization (EUA)

"During a public health emergency, the FDA can use its Emergency Use Authorization (EUA) authority to allow the use of unapproved medical products, or unapproved uses of approved medical products, to diagnose, treat, or prevent serious or life-threatening diseases when certain criteria are met, including that there are no adequate, approved, and available alternatives.

Before the FDA can issue an EUA, the Secretary of Health and Human Services must make a declaration of emergency or threat justifying authorization of emergency use for a product."

FAQs on Emergency Use Authorizations (EUAs) for Medical Devices During the COVID-19 Pandemic

Also see Emergency Use Authorization of Medical Products and Related Authorities Guidance for Industry and Other Stakeholders

COVID-19

COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders

COVID-19 Lessons Learned:

- Utility of Master Protocols/Platform trials
- Value of large pragmatic trials
- Value of decentralized clinical trials

Questions and Comments?


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Open Source

Open-source: denoting software for which the original source code is made freely available and may be redistributed and modified. (Oxford)

Some open-source software:

- R
- Python
- Linux