The New Drug Approval Process: NDA Submission and Review

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Orientation

- Overview for this session

- What to expect*

*Any figures, tables and other snapshots used to illustrate aspects of today's discussion come from review memoranda, guidance, or documents made publicly available by FDA. Therefore, they are merely representations of what you might see in an NDA submission and not the actual contents of a submission to FDA unless excerpted directly by the Agency.

Orientation

- Polling Question 1 (please leave a comment in the chat)
  - (Part A) How many of you are –
    - a) FDA staff, reviewers, etc.
    - b) Attorneys or legal professionals
    - c) Regulatory affairs professionals
    - d) Something else
  - (Part B) Have you ever read an NDA or any section of an NDA?

Key Sources in Practice

- Legal
  - Statute (Federal Food, Drug, and Cosmetic Act [FDCA], Section 505 = 21 U.S.C. Section 355)*
  - Regulations (21 CFR Part 314)**
  - PDUFA reauthorizations (read the Agency's PDUFA commitment letters)
- Agency Resources
  - Guidance
  - CDER 21st Century Review Process – Desk Reference Guide
  - CDER Manual of Policies and Procedures (MAPPs)

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Purpose of the NDA

- According to FDA regulations (21 CFR 314.2):
  - The NDA serves to "establish **an efficient and thorough drug review process** in order to: (a) Facilitate the **approval of drugs shown to be safe and effective**; and (b) **ensure the disapproval of drugs not shown to be safe and effective**. These regulations are also intended to establish an effective system for FDA's surveillance of marketed drugs."

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Purpose of the NDA: Translation

- Provide FDA with a sufficiently thorough document to evaluate:
  - The drug's benefits and risks
  - Whether the drug meets the statutory standard for drug approval
  - The methods, processes, facilities and packaging are sufficient to ensure the drug's identity, strength, quality, and purity
  - The appropriateness, accuracy, and adequacy of the drug's proposed labeling
  - The basis for the claims of a safe and effective product

Overview: Contents of an NDA

- Cover Letter
  - *Best practice but not a requirement
- Application forms and index
- Summary of the NDA
  - Provides overview of the application and proposed labeling (prescribing information, “PI”)
- Technical sections

The NDA Summary

- Overview of the entire application
- Factual summary of key clinical and non-clinical data supporting conclusions about safety and effectiveness
- Provide objective discussion of benefit – risk profile
- Purpose is to provide anyone picking up an individual section of the NDA a good general understanding of drug

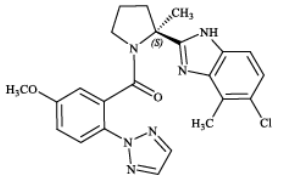
Technical Sections of an NDA

- Chemistry, Manufacturing and Controls
  - Composition, manufacture and specifications for the drug substance and drug product

Buffer	Concentration of daridorexant after 24 hours (mg/mL)		Concentration of daridorexant after 26 hours (mg/mL)	
pH=1.2 (n = 3)	0.188	Mean: 0.188	0.188	Mean: 0.188
	0.188		0.188	
	0.189		0.188	
pH=4.5 (n = 3)	0.002	Mean: 0.002	0.002	Mean: 0.002
	0.001		0.002	
	0.002		0.002	
pH=6.8 (n = 3)	0.001	Mean: 0.001	0.001	Mean: 0.001
	0.001		0.001	
	0.001		0.001	

- Nonclinical pharmacology and toxicology
  - *In vitro* and *in vivo* non-human animal studies of the drug

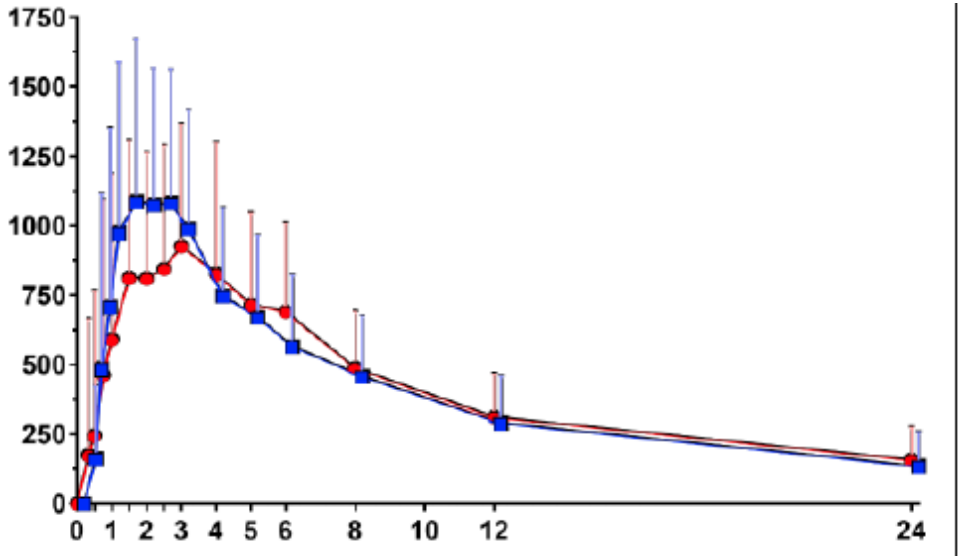
QUVIVIQ contains daridorexant hydrochloride, an orexin receptor antagonist. The chemical name of daridorexant hydrochloride is (S)-(2-(5-chloro-4-methyl-1*H*-benzo[*d*]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride. The molecular formula is $C_{23}H_{23}N_6O_2Cl$ * HCl. The molecular weight is 487.38 g/mol.
The structural formula is:



FDA, Product Quality Review Quviviq (Jan. 7, 2022) https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/214985Orig1s000ChemR.pdf (last accessed April 25, 2022)

Technical Sections of an NDA

- Human Pharmacokinetic and Bioavailability
  - Studies of “what happens” to the drug in the body
- Microbiology data
  - For anti-infectives only



FDA, Integrated Review Quviviq (Jan. 7, 2022) https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/214985Orig1s000IntegratedR.pdf (last accessed April 25, 2022)

Technical Sections of an NDA

- Clinical Data
  - Description and analysis of studies supporting the drug's use including "any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant"
  - Summaries of the data – ISS and ISE
  - Discussion of benefit – risk
  - Updates to safety during NDA review

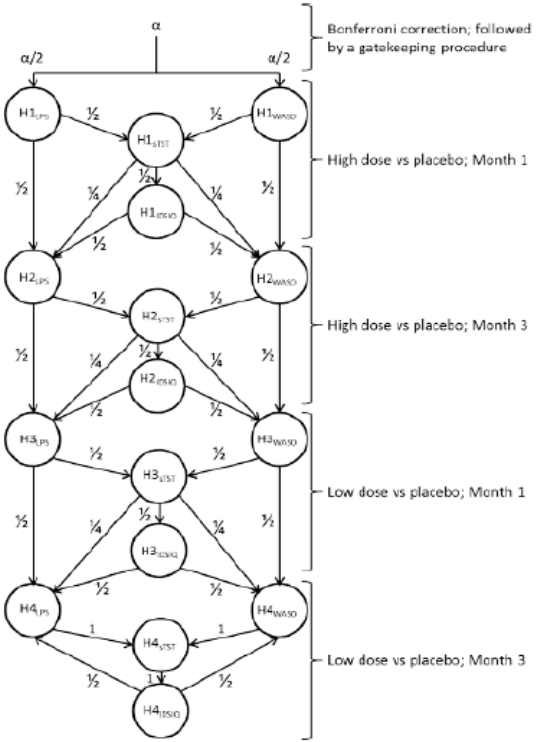
Table 4 Primary and Secondary Efficacy Results for Change from Baseline in Sleep Onset, Sleep Maintenance, and Subjective Total Sleep Time at Month 1 and Month 3 in Patients with Insomnia (Study 1)

Treatment group/ dose (N)	Baseline	Month 1			Month 3		
	mean (SD)	mean (SD)	Change from baseline LSM (95%CL)	Difference to placebo LSM (95%CL)	mean (SD)	Change from baseline LSM (95%CL)	Difference to placebo LSM (95%CL)
WASO (wake after sleep onset, min): sleep maintenance, assessed by PSG							
50 mg (310)	95 (38)	65 (35)	-29 [-33, -25]	-23* [-28, -18]	65 (39)	-29 [-33, -25]	-18* [-24, -13]
25 mg (310)	98 (39)	77 (42)	-18 [-22, -15]	-12* [-17, -7]	73 (40)	-23 [-27, -19]	-12* [-17, -6]
placebo (310)	103 (41)	92 (42)	-6 [-10, -2]		87 (43)	-11 [-15, -7]	
LPS (latency to persistent sleep, min): sleep onset, assessed by PSG							
50 mg (310)	64 (37)	34 (27)	-31 [-35, -28]	-11* [-16, -7]	30 (23)	-35 [-38, -31]	-12* [-16, -7]
25 mg (310)	67 (39)	38 (32)	-28 [-32, -25]	-8* [-13, -4]	36 (34)	-31 [-34, -27]	-8* [-12, -3]
placebo (310)	67 (40)	46 (36)	-20 [-23, -17]		43 (34)	-23 [-26, -20]	
sTST (subjective total sleep time, min): patient-reported							
50 mg (310)	313 (58)	358 (74)	44 [38, 49]	22* [14, 30]	372 (79)	58 [51, 64]	20* [11, 29]
25 mg (310)	310 (60)	345 (66)	34 [29, 40]	13* [5, 20]	358 (72)	48 [41, 54]	10* [1, 19]
placebo (310)	316 (53)	338 (65)	22 [16, 27]		354 (73)	38 [31, 44]	

FDA, Printed Labeling Quviviq (Jan. 7, 2022) https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/214985Orig1s000lbl.pdf (last accessed April 25, 2022)

Technical Sections of an NDA

- Statistical Analysis
  - Documentation of the analyses used to evaluate both efficacy and safety data



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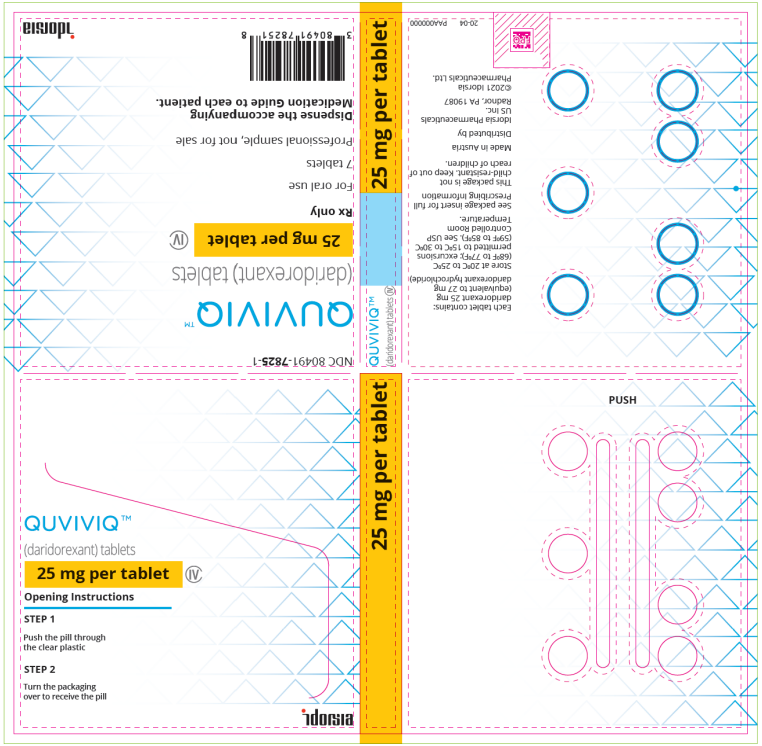
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/214985Orig1s000IntegratedR.pdf
(last accessed April 25, 2022)

Technical Sections of an NDA

- Pediatric Use
  - Studies evaluating use in pediatric populations (unless waived or deferred) to enable benefit-risk determination in pediatric subpopulations
  - Children are not just small adults!

- Samples and Labeling
  - Representative samples of drug for FDA validation of analytical procedures
  - Finished market packaging (e.g., container/closure plus labeling and associated components)
  - Label and all labeling including the package insert



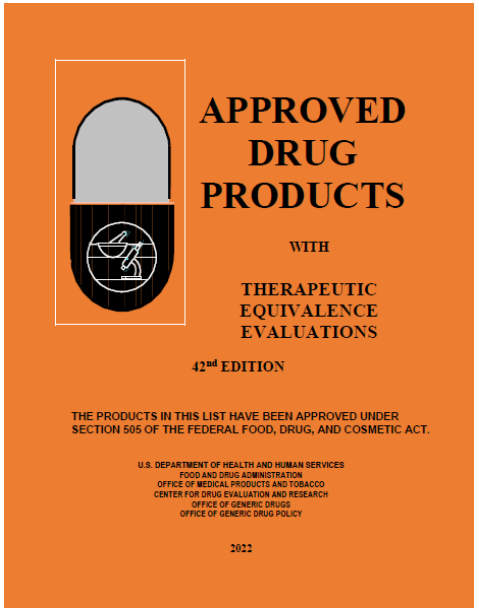
FDA, Printed Labeling Quviviq (Jan. 7, 2022) https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/214985Orig1s000lbl.pdf (last accessed April 21, 2022)

Technical Sections of an NDA

- Case Report Forms and Tabulations
  - Tabulations of clinical data from AWCs, clinical pharmacology studies and other safety data
  - Case reports for deaths and adverse events

- Patent Information and Certification*
  - 21 C.F.R. 314.50 (h)-(i)
  - 21 C.F.R. 314.53
  - The “Orange Book”
    https://www.fda.gov/media/71474/download

- Disclosure and Certifications
  - Claimed exclusivities
  - Financial disclosures by investigators

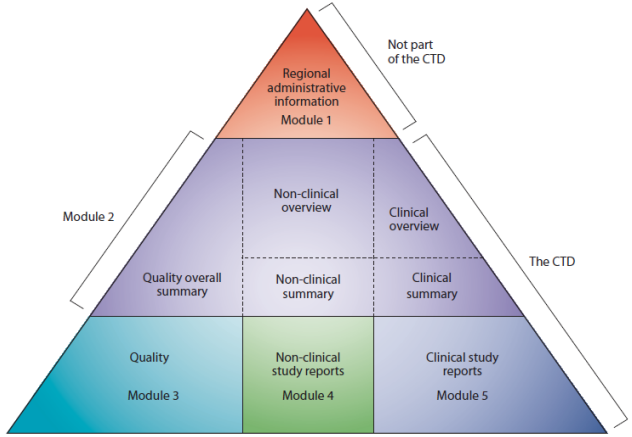


Technical Sections of an NDA

- Incorporation by reference and Drug Master Files (DMFs)
  - Applicant may incorporate information from another application or DMF that is already on file
  - Allows applicant to reuse information already submitted as well as for another party (e.g., a development partner) to use information without disclosing their contents.
  - Need to obtain right of reference from the owner of the information
- DMFs
  - Drug substance
  - Packaging materials
  - Excipients, colorants, flavors, essences, or materials used in their preparation
  - FDA-accepted reference information

Common Technical Document (CTD)

- Standardized approach for the organization and presentation of common sections of regulatory submissions across jurisdictions
- Electronic CTD (eCTD) became standard requirement for NDAs in 2017
- 5 Modules – 4 common and 1 unique
  - Module 1 – Administrative Information (unique)
  - Module 2 – TOC, Overviews and Summaries
  - Module 3 – Quality
  - Module 4 – Nonclinical Study Reports
  - Module 5 – Clinical Study Reports



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

The Review Process

User Fees

- Beginning with PDUFA I in 1992, FDA was granted authority to charge and collect certain fees associated with drug review
- Reauthorized every 5 years
- Currently PDUFA VI in effect
  - *PDUFA VII currently under consideration in Congress
- Fees for applications (NDA) and program fees

PDUFA Goals

- Impact (or tradeoff) for collecting user fees – FDA agreed to numerous goals and timelines
- Apply to applications (NDAs), meeting requests, etc.
- Improved predictability of NDA review process re: procedural steps, communication with applicants, timing of FDA “actions”

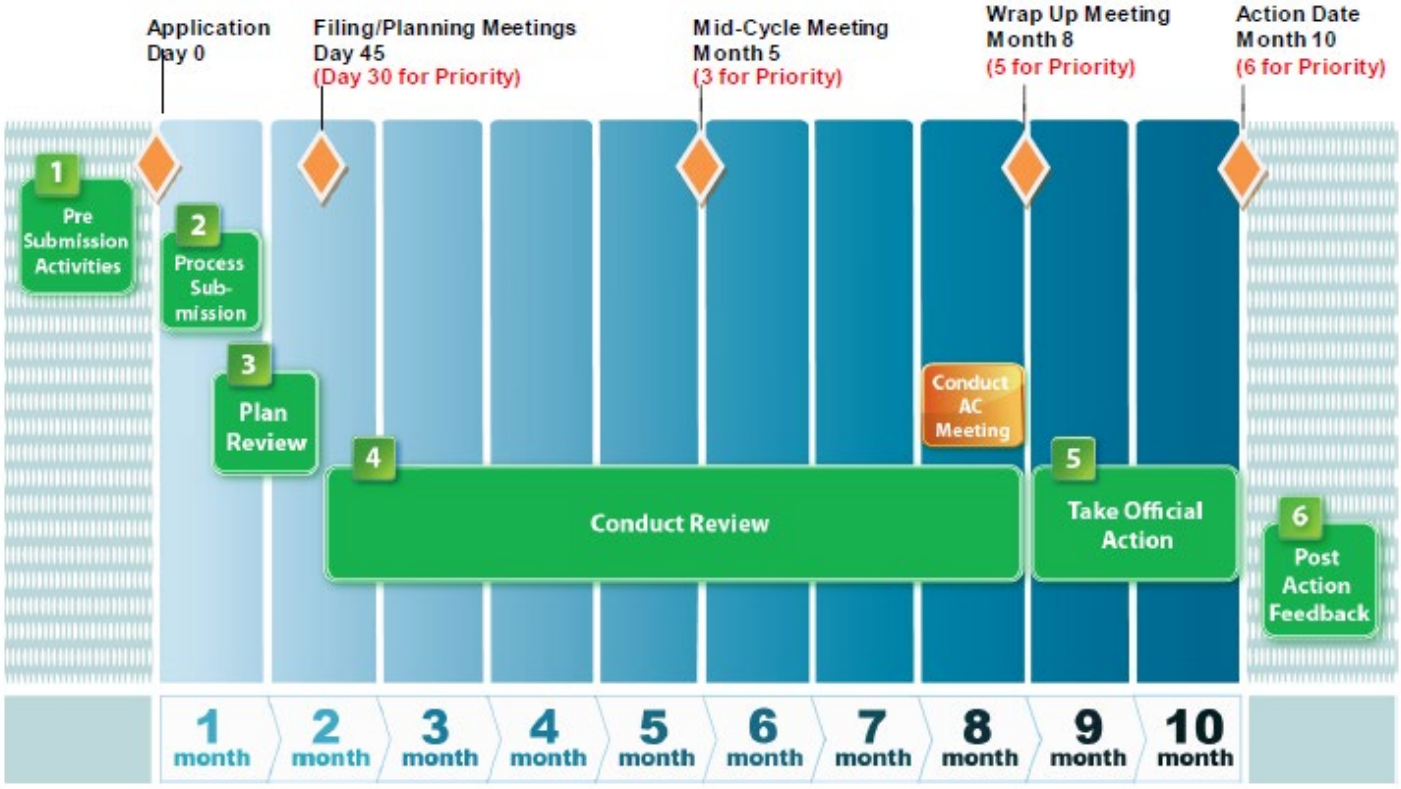
PDUFA FEES FY2022

	2022	2021
Application Fee – Clinical Data Required	$3,117,218	$2,875,842
Application Fee – No Clinical Data Required	$1,558,609	$1,437,921
Program Fee	$369,413	$336,432

Fee Exemptions and Waivers

- Waivers, exemptions and reductions are available under certain circumstances
- Most useful
  - For small business submitting its first human drug application for review
  - For drugs with orphan designation
  - For resubmissions

Overview of the Review Process



PDUFA Key Terms

- New Molecular Entity (NME) – an active ingredient that contains no active moiety that has been previously approved by FDA or previously marketed as a drug in the US

- Standard Review v. Priority Review
  - Under PDUFA, FDA agreed to review every application to determine if it was eligible for expedited review
  - 10 months v. 6 months to take action
  - Affects the timelines throughout NDA review process

Overview of PDUFA Goals

Table 1: Original and Resubmitted Applications and Supplements:

SUBMISSION COHORT	STANDARD	PRIORITY
NME NDAs and original BLAs	90% in 10 months of the 60 day filing date	90% in 6 months of the 60 day filing date
Non NME NDAs	90% in 10 months of the receipt date	90% in 6 months of the receipt date
Class 1 Resubmissions	90% in 2 months of the receipt date	90% in 2 months of the receipt date
Class 2 Resubmissions	90% in 6 months of the receipt date	90% in 6 months of the receipt date
Original Efficacy Supplements	90% in 10 months of the receipt date	90% in 6 months of the receipt date
Class 1 Resubmitted Efficacy Supplements	90% in 2 months of the receipt date	90% in 2 months of the receipt date
Class 2 Resubmitted Efficacy Supplements	90% in 6 months of the receipt date	90% in 6 months of the receipt date

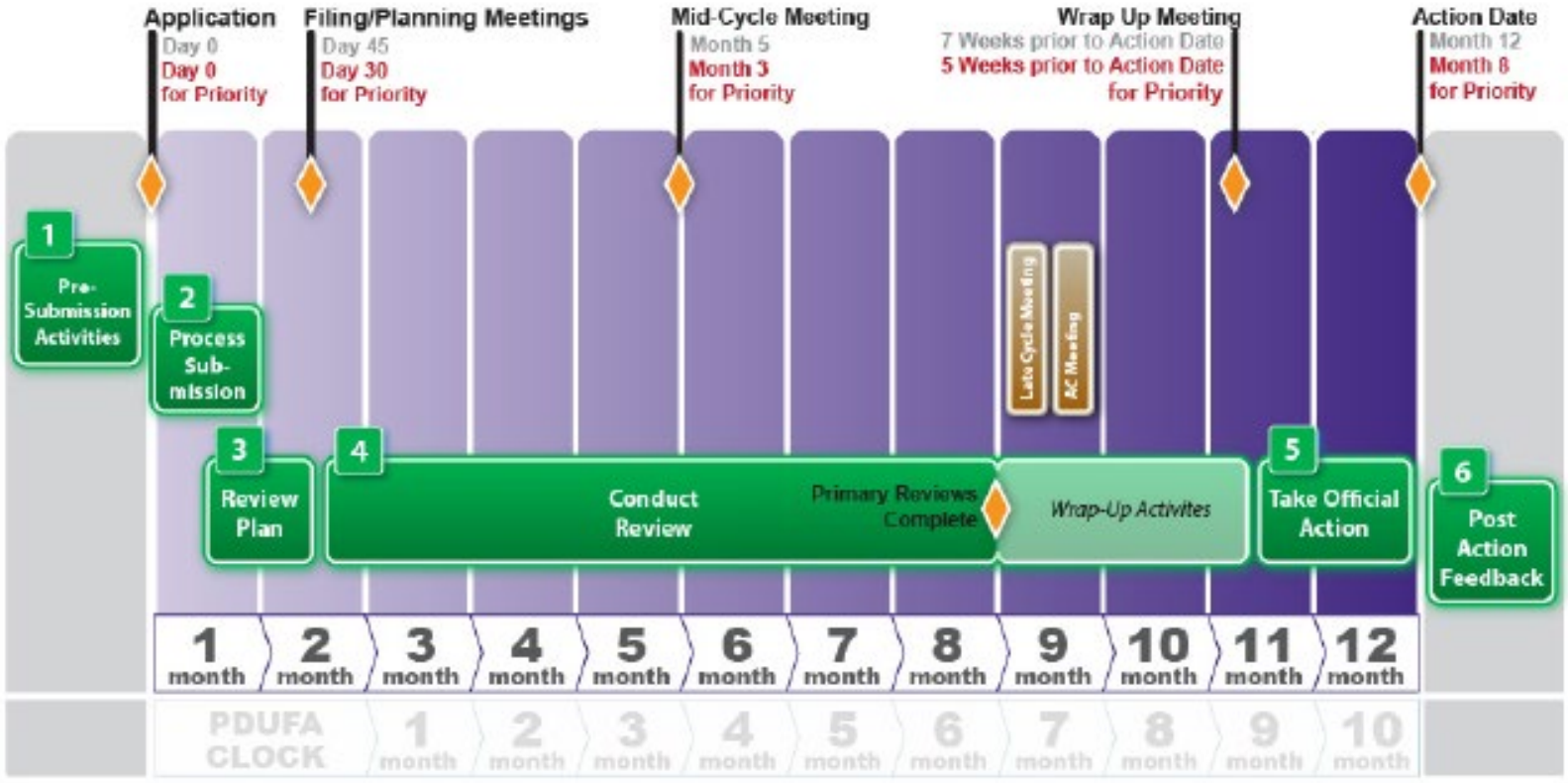
Table 2:

	PRIOR APPROVAL	ALL OTHER
Manufacturing Supplements	90% in 4 months of the receipt date	90% in 6 months of the receipt date

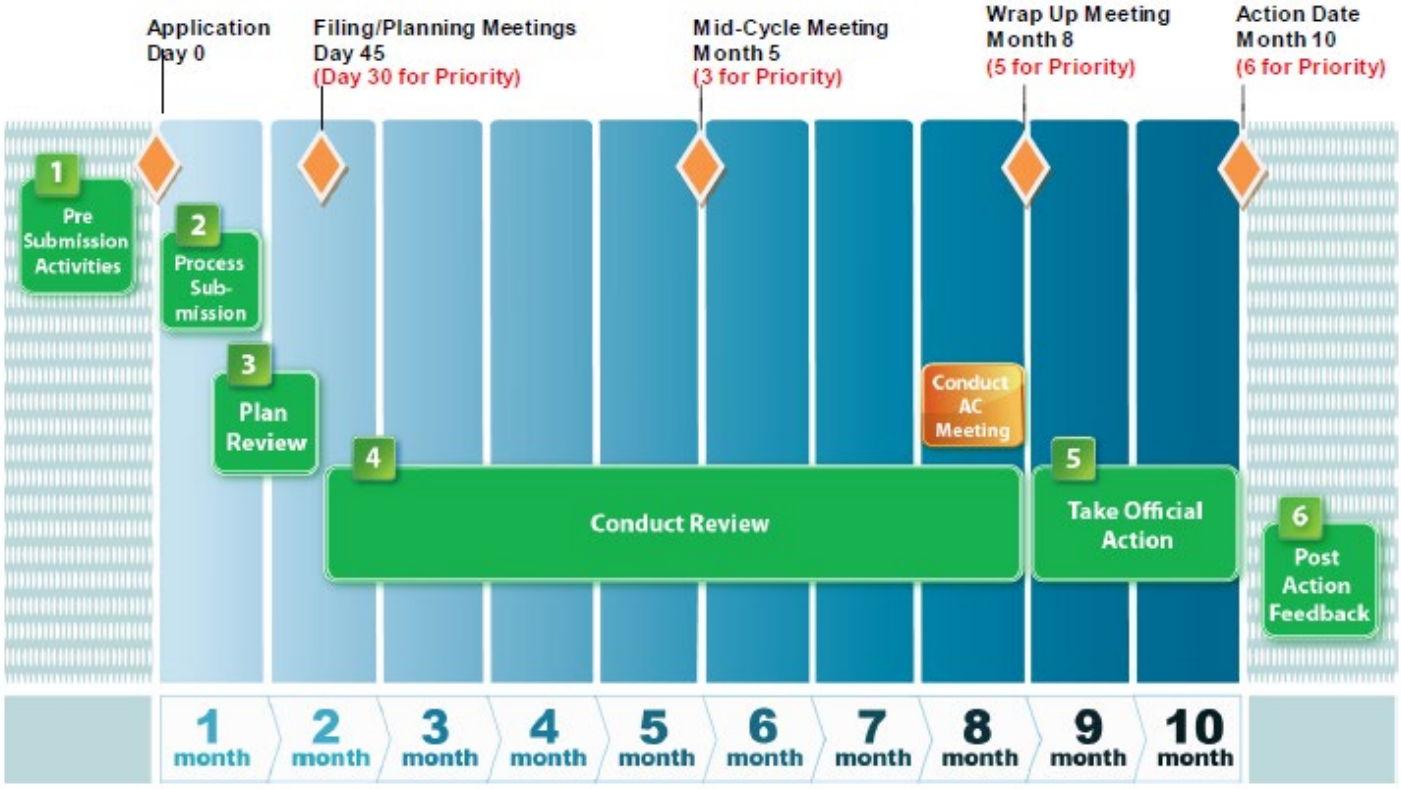
More PDUFA Terms

- Review timeline
  - All applications - begins on day of receipt
- PDUFA time clock
  - "The Program"
    - Applies to NME NDAs (and original BLAs)
    - Begins on day 60, if filed
  - All other applications
    - Begins on day of receipt
- Action date v. PDUFA goal date
- Signatory authority

Applications in “The Program”



Applications NOT in “The Program”



Key Takeaways

- 6 Step Process
- More interactions and opportunity for feedback from FDA for PDUFA V/VI program ("The Program") applications
- Several different timelines to understand based on application type

Filing Review

- Within 60 days FDA determines if the NDA is fileable (not a review for approval) and notifies sponsor.
- If accepted for filing, FDA provides a 74-day letter, which confirms PDUFA goal date, confirms standard versus priority review, and communicates any filing review issues identified by FDA (or lack thereof).
- An application may be considered incomplete based on deficiencies that on their face render an application incomplete, applications that are unreviewable or inconsistent with statutory or regulatory requirements.
- If incomplete or deficient, FDA may refuse-to-file (RTF)

Response to Refuse-to-File (RTF)

- Within 30 days of the date of the RTF notification, the applicant may request in writing an informal conference with the FDA to discuss whether the FDA should file the application.
- Applicant may request that FDA file over protest (after informal meeting)
- If an NDA is filed over protest, the filing date will be 60 days after the receipt date of the informal conference meeting request and does not receive benefit of certain meetings and other interactions with FDA during the review
- Notes –
  - Filing over protest removes application from many program goals
  - Not aware of any NDA filed over protest being approved on the first round
  - Key filing regulations - 21 CFR 314.101

Review Phase

- During filing review, FDA plans out its approach to the “substantive” review

- If filed, the NDA is reviewed by various FDA disciplines
  - Medical
  - Pharmacology
  - Chemistry
  - Biopharmaceutical
  - Statistical
  - Microbiology

- Internally FDA discusses the application at several timepoints and disciplines draft individual review memos

Possible Interactions/Feedback

- Information Requests (IRs) (sent to Applicant by FDA)
- Amendments (submitted to FDA by Applicant)
- Feedback from the Mid-Cycle Meeting*
- Discipline Review Letters*
- Advisory Committee Meetings
- Labeling Review and Discussion of Risk Evaluation and Mitigation Strategies (REMS), Post-marketing requirement / Post-Marketing Commitment (PMR/PMC)
- “Deficiencies Preclude Labeling Discussion”
- Late-Cycle Meeting*

*Only applies to applications in The Program

Advisory Committee Meetings

- Standing committee of external experts from select areas of science/medicine
- Depending on the nature of the questions before the committee, FDA and the applicant will present detailed overviews of key clinical data, trial designs, statistical analyses, as well as quality information and product characterization details
- Committee then discusses and votes on questions posed by FDA
- FDA has discretion to take an application to an Advisory Committee
- These meetings are used sparingly because of the massive investment of effort, time and resources
- Committee's decision is merely advisory
- Numerous provisions of FDCA invoke authority (or even mandate) use of an Advisory Committee
  - Key provision in the context of NDA review – 21 USC Section 355(s)

Advisory Committee Meetings

- March 30, 2022 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee
  - Video of live meeting - https://www.youtube.com/watch?v=AVVZMMvDOUg
  - Meeting Information, Agenda, Materials, etc. - https://www.fda.gov/advisory-committees/peripheral-and-central-nervous-system-drugs-advisory-committee/updated-meeting-time-and-open-public-hearing-time-march-30-2022-meeting-peripheral-and-central

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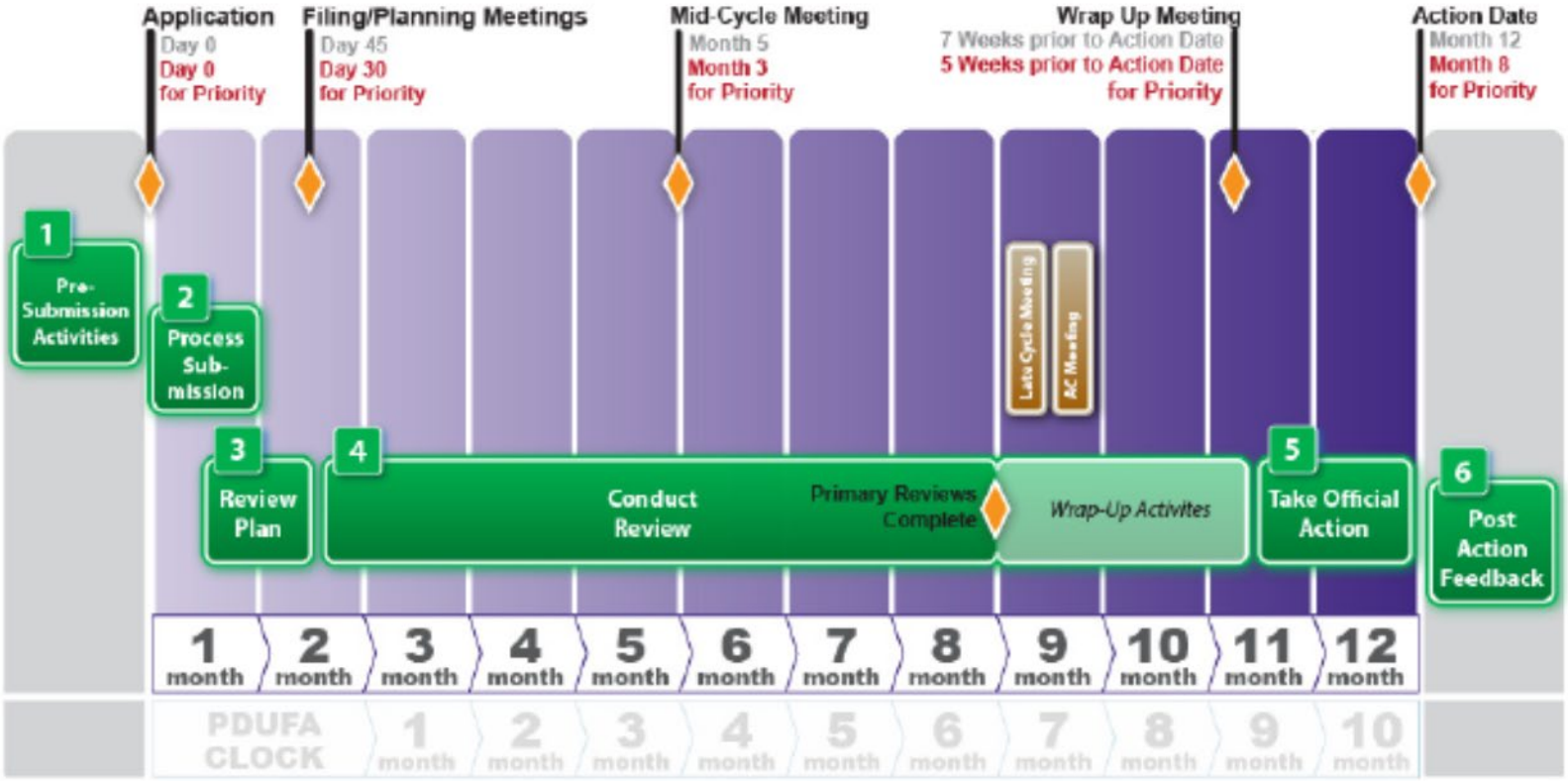
Pre-Approval Inspections (PAIs)

- Inspections cover both product manufacturing and quality issues as well as data integrity issues
  - May include manufacturing sites, clinical trial sites, data monitors, IRBs, and contract research organizations
  - Establishment inspections: GMPs
  - Bioresearch Monitoring (BIMO) site inspections/audits: GLPs, GCPs
- Proposed manufacturing sites that have not been previously inspected are priorities
- Negative inspection findings may be grounds for a CRL

Revisiting the Review Process



FDA Action on NDA – Option 1

- Approval letter
  - Approval of drug for indication and other conditions set forth in the approved PI
  - FDA will post approval letter, approved labeling and summary basis of approval (SBA) on-line
    - Trade secret info is redacted
    - SBA includes reviews from the various disciplines and the decision maker (Division or Office Director)
  - Approval may include PMR/PMCs to conduct studies or be subject to REMS

Applicant Options to Respond: During the Review

- Submit Amendments
  - Adding or clarifying information in the application
  - Could extend the review clock (i.e., if deemed a major amendment)
- Dispute resolution options
  - Procedural/Administrative issues – consumer safety officer or ombudsman
  - Scientific/Medical Disputes – request a formal meeting
    - Request an advisory committee (FDA has complete discretion)
- Withdraw the application
  - Must be done before the action date
  - Despite the negative outcome of CRL, there are disadvantages to withdrawing the NDA

FDA Action on NDA – Option 2

- Complete response letter (CRL)
  - i.e., a DENIAL
  - Sets forth the deficiencies which prevent approval of the application in its current form
  - Reasons for denial can range from inadequate data for safety or efficacy to inadequate manufacturing processes to compliance issues to failure to submit a necessary NDA component
    - RTF intended to weed out inadequate applications
    - In practice, findings regarding safety and efficacy drive CRLs
  - Within 30 days, applicant can request Type A meeting for further clarification

Applicant Options to Respond: After the CRL

- End-of-Review Meeting
  - Type A meeting – 3 month deadline
  - After 3 months becomes Type B
  - Never pass up this opportunity
- Formal Dispute Resolution Request (FDRR)
  - Appeal decision to the next highest office level above the signatory authority
  - Used sparingly
  - Must have End-of-Review meeting
  - Have the option of serial appeal (i.e., appeal again to the next highest office level)

Applicant Options to Respond: After the CRL

- Resubmission of NDA
  - Address each of the CRL identified deficiencies
  - Shorter review clock (2 or 6 months depending on Class 1 v. Class 2)
  - Class 1 – minor changes (labeling, reanalysis of existing data, postmarketing study commitments, etc.)
  - Class 2 – anything that is not Class 1
- Withdrawal of NDA
- Administrative Hearings, Judicial Review of CRL (or Approval of Competitor's Application)
  - Know they exist but they are uncommon to rare

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Polling Question

- True or False?
  - “The Program” includes all NMEs and Priority review designated applications.

Related Topics:
Formal Meetings
Expedited Programs

Formal Meetings under PDUFA

- Sponsor or Applicant may request meetings with relevant FDA review divisions
- Goals of such meetings
  - Obtain feedback or alignment on development plans, study designs, planned submissions, etc.
  - Resolve a dispute directly with review division
  - Discuss and understand Agency identified deficiencies
- In practice
  - More frequently used during development than during NDA review
  - Most important meetings for a development program in relation to the ultimate goals of NDA submission and approval:
    - pre-IND, EOP, pre-NDA, EOR

Formal Meetings under PDUFA

- Process
  - Draft and submit meeting request and background materials (i.e., the briefing package)
  - FDA either denies or grants meeting as an interactive meeting or Written Response Only (WRO)
  - FDA provides preliminary responses
  - Sponsor/applicant may respond to preliminary responses (no new information)
  - Meeting held and FDA issues either final WROs or Meeting Minutes
- Meeting Types
  - Type A: FDRR, clinical holds, SPA disagreement, EOR (w/n 3 mo.), RTF (w/n 30 days)
  - Type B: pre-IND, pre-NDA, pre-BLA, pre-EUA, EOR (after 3 mo.), REMS/PMRs, BTD Dev.
  - Type B (EOP): end-of-phase 1 (limited), end-of-phase 2
  - Type C: catch all (or biomarker as a new surrogate endpoint)

Formal Meetings under PDUFA

Table A: Meeting Management Procedural Goals

Meeting Type	FDA Response to Request	FDA Receipt of Meeting Package	FDA Preliminary Responses to Requester (if applicable†)	Requester Response to FDA Preliminary Responses (if applicable†)	FDA Scheduled Meeting Date (days from receipt of request)	FDA Meeting Minutes to Requester (if applicable†)
A	14 days	With meeting request	No later than 2 days before meeting	--	Within 30 days	30 days after meeting
B	21 days	No later than 30 days before meeting	No later than 2 days before meeting	--	Within 60 days	30 days after meeting
B (EOP)*	14 days	No later than 50 days before meeting**	No later than 5 days before meeting	No later than 3 days after receipt of preliminary responses	Within 70 days	30 days after meeting
C	21 days	No later than 47 days before meeting***	No later than 5 days before meeting	No later than 3 days after receipt of preliminary responses	Within 75 days	30 days after meeting

FDA, Draft Guidance: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products (Dec. 2017) https://www.fda.gov/media/109951/download (last accessed April 25, 2022)

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H&M

Polling Question

- True or False?
  - (1) Pre-NDA meetings are Type A meetings.
  - (2) A pre-NDA meeting and an End-of-review meeting may both be classified as the same type.

Expedited Programs for Serious Conditions

- History
  - Outgrowth of the “Subpart E” regulations (21 CFR 312 Subpart E)
  - Arose in response to HIV/AIDS Epidemic in late 1980s
  - FDA recognized the need to expedite therapies for those suffering from serious conditions with no available therapy
  - Subpart E regulations articulated the Agency’s recognition of the need for “flexibility,” patient and provider willingness to accept greater risk in the face of “life-threatening and severely debilitating illnesses.
  - Benefit-risk determinations should take into account severity of disease and lack of available therapy

Expedited Programs for Serious Conditions

- The programs:
  - Fast Track Designation
  - Breakthrough Therapy Designation
  - Accelerated Approval
  - Priority Review
- Goal
  - Expedite therapeutic development for serious conditions with an unmet medical need

Expedited Programs: Key Factors

- Serious condition –
  - Disease or condition must have a substantial impact on day-to-day functioning (i.e., morbidity)
    - Clinical judgement factors into determining whether a disease is “serious”
  - Drug must be intended to treat or affect a serious condition or a serious aspect of a condition
- Available therapy v. unmet medical need
  - Available therapy considers both approved/licensed products and standard of care (SOC)
  - If there is no available therapy -> clear case of unmet medical need
  - If there is therapy available -> depends (Improvement over available therapy? Available therapy approved under accelerated approval?)

Expedited Programs

	Fast Track	Breakthrough Therapy	Accelerated Approval	Priority Review
Nature of Program	Designation	Designation	Approval Pathway	Designation
Reference	Section 506(b) of the FD&C Act	Section 506(a) of the FD&C Act	21 CFR part 314, subpart H 21 CFR part 601, subpart E Section 506(c) of the FD&C Act	Prescription Drug User Fee Act of 1992
Qualifying Criteria **(All must be drug intended to treat a serious condition)**	**Nonclinical or clinical data** demonstrate the potential to address unmet medical need **OR** QIDP	**Preliminary clinical evidence** indicates that the drug may demonstrate **substantial improvement on a clinically significant endpoint(s) over available therapies**	Generally provides a **meaningful advantage over available therapies** **AND** demonstrates an effect on a **surrogate endpoint or intermediate clinical endpoint**	An application (original or efficacy supplement), if approved, would provide a **significant improvement in safety or effectiveness** **OR** Pediatric study labeling change, QIDP, priority review voucher

FDA, Guidance: Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014) https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf (last accessed April 25, 2022)

Expedited Programs

	Fast Track	Breakthrough Therapy	Accelerated Approval	Priority Review
When to submit request	With IND or after Ideally, no later than the pre-BLA or pre- NDA meeting	With IND or after Ideally, no later than the end-of-phase 2 meeting	Discussions during development, supporting, for example, the use of the planned endpoint Confirmatory trials should usually be already underway at the time of approval	With original BLA, NDA, or efficacy supplement
Timelines for FDA response	Within 60 calendar days of receipt of the request	Within 60 calendar days of receipt of the request	Not specified	Within 60 calendar days of receipt of original BLA, NDA, or efficacy supplement
Features	Actions to expedite development and review Rolling review	Intensive guidance on efficient drug development Organizational commitment Rolling review Other actions to expedite review	Approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit	Shorter clock for review of marketing application

FDA, Guidance: Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014) https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf (last accessed April 25, 2022)

Expedited Programs

- A few more thoughts on accelerated approval
  - Advantage over available therapies – what's the difference between other expedited programs?
  - Endpoints
    - Surrogate that is reasonably likely to predict clinical benefit
      - Biomarkers, laboratory results, histological markers, etc.
      - Contrast with validated surrogate
      - FDA examples – HIV viral load, tumor shrinkage
    - Intermediate is an endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM
      - Short-term clinical benefit in setting of chronic disease
      - FDA examples – in MS, relapse rate over 13 months v. durability over 2 years
  - Accelerated approval does not change the statutory standard for safety and effectiveness

FDLI

Thank you!

Follow-up questions, clarifications, or otherwise –

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