Assessment of the Program

for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs in PDUFA V

Interim Report

May 20, 2015

Contract HHSF223201110018B, Order HHSF22312003

ERG

Presentation Outline

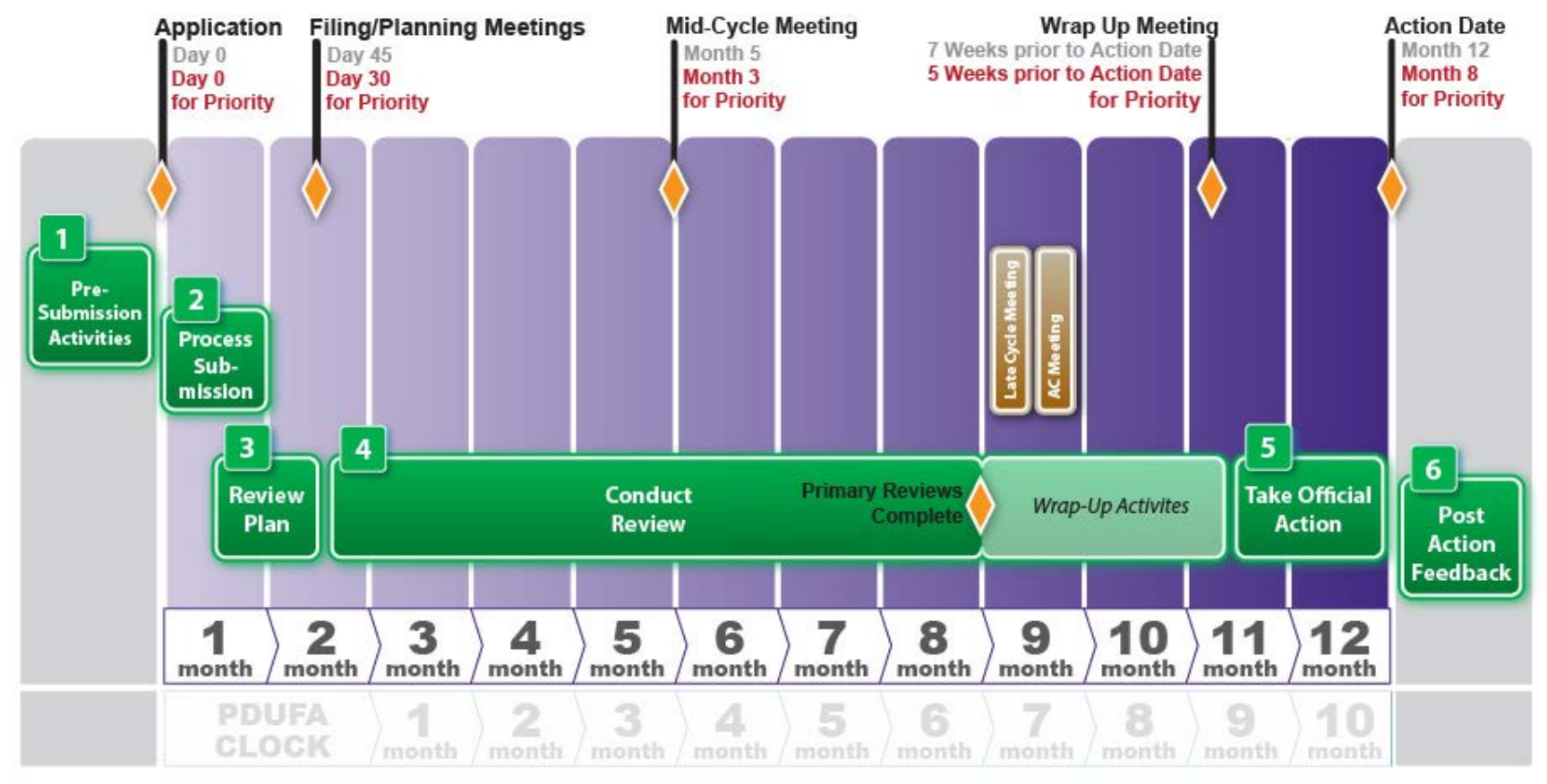
- Introduction
- Results highlights
- Findings and recommendations
- Next steps

Introduction

The Program

- Scope
  - NME NDAs and original BLAs with first-cycle reviews in PDUFA V
- Major attributes
  - Mid-cycle communication
  - Late-cycle meeting
  - Review clock begins on 60-day filing date
- Goals
  - Improve communication between applicants and FDA review teams
  - Improve transparency of reviews
  - Improve efficiency and effectiveness of reviews

Review Timeline



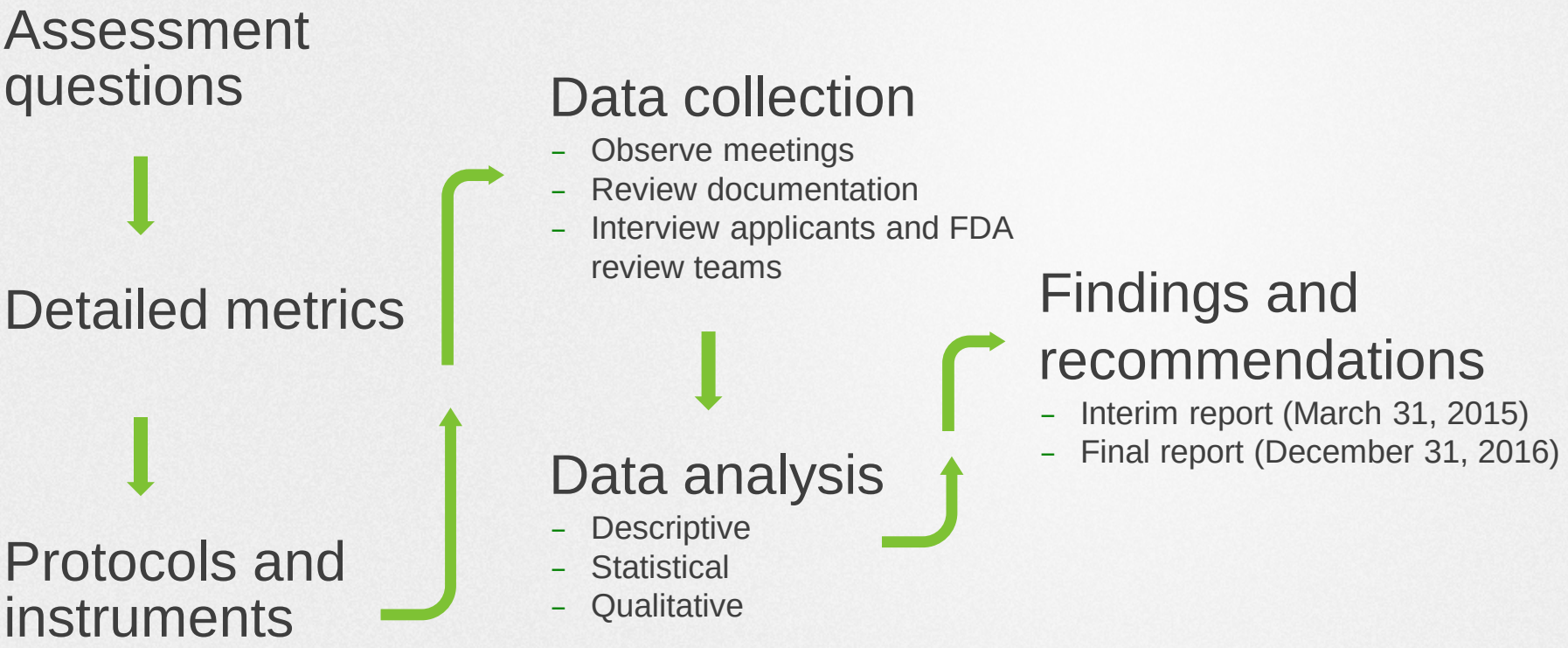
Program Evaluation

- Commitment under PDUFA V
- Identify relationships between

Program attributes	and	First-cycle regulatory outcomes
Review process attributes		Time to first-cycle regulatory outcomes
Application attributes		

- Understand how applicants and FDA staff characterize communication and application reviews in the Program

Evaluation Methods



Interim Report

- Executive Summary
- Introduction
- Methods
- Results
  - Overall
  - Pre-submission Meetings
  - Filing Letters
  - Mid-Cycle Communications
  - Discipline Review Letters
  - Late-Cycle Meetings
  - Inspections
  - Review Process and Application Attributes
- Assessment Questions and Answers
- Findings and Recommendations
- Appendices

Available on FDA website

http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm327030.htm

Results Highlights

Program and Baseline Cohorts

Applications		Baseline (FYs 2008-2012)	Program (FYs 2013-2014)
Filed and acted upon	NME NDA	147	42
	Original BLA	72	22
	Total	219	64
First-cycle actions	Approval (AP)	120	46
	Complete Response (CR)	92	14
	Withdrawal after Filing (WD)	7	4
	Total	219	64
Percent of filed applications approved in first cycle		54.8%	71.9%

Data encompass NME NDAs and original BLAs received during FYs 2008-2012 and acted on by September 30, 2014 (baseline) or received and acted on during FYs 2013-2014 (Program).

First-Cycle Approvals

First-cycle approval rate higher in Program than in baseline

Review Priority	First-Cycle Approval Rate		p-Value
	Baseline	Program	
All	54.8% (n = 219)	71.9% (n = 64)	0.015
Priority	71.8% (n = 78)	92.6% (n = 27)	0.027
Standard	45.4% (n = 141)	56.8% (n = 37)	0.218

Data encompass NME NDAs and original BLAs received during FYs 2008-2012 and acted on by September 30, 2014 (baseline) or received and acted on during FYs 2013-2014 (Program).

Complete Response Letters

Top three issues in Complete Response (CR) letters

Issue Cited in CR Letter*	Standard Applications		Priority Applications	
	Baseline (FYs 2008-2012) (n=71)	Program (FYs 2013-2014) (n=12)	Baseline (FYs 2008-2012) (n=21)	Program (FYs 2013-2014) (n=2)
Efficacy	40.9%	58.3%	81.0%	50.0%
Product quality	50.7%	50.0%	76.2%	100.0%
Safety	71.8%	58.3%	54.1%	0.0%

Data encompass NME NDAs and original BLAs received during FYs 2008-2012 and acted on by September 30, 2014 (baseline) or received and acted on during FYs 2013-2014 (Program).

**Note that CR letters can include more than one issue with the application. This is why these percentages do not sum to 100%.*

Time to First-Cycle Action

Median time to first-cycle action longer in Program

Cohort	Median Time from Receipt to First-Cycle Action (Months)							
	Approval		Complete Response		Withdrawal		Overall	
	Standard	Priority	Standard	Priority	Standard	Priority	Standard	Priority
Baseline (FYs 2008-2012)	10.0	6.0	10.0	6.0	6.4	3.9	10.0	6.0
Program (FYs 2013-2014)	12.0	7.9	12.0	7.9	8.3	N/A	12.0	7.9

Data encompass NME NDAs and original BLAs received during FYs 2008-2012 and acted on by September 30, 2014 (baseline) or received and acted on during FYs 2013-2014 (Program).

Longer time to first-cycle action in Program expected due to two-month difference in review clock compared to baseline.

Goal Extensions

Goal extensions due to major amendments less frequent in Program, more often associated with approval

Cohort	Percent of Applications that Received a Goal Extension	Percent of Applications With a Goal Extension that Received First-Cycle Approval	Time After Original Submission When Goal Extension Was Issued
Baseline (FYs 2008-2012)	26.0% *(57 / 219)*	59.7% *(34 / 57)*	Standard: 6.2 to 9.9 months Priority: 3.2 to 5.9 months
Program (FYs 2013-2014)	18.8% *(12 / 64)*	91.7% *(11 / 12)*	Standard: 5.9 to 11.0 months Priority: 1.4 to 5.9 months

NME NDAs and original BLAs received during FYs 2008-2012 and acted on by September 30, 2014 (baseline) or received and acted on during FYs 2013-2014 (Program).

First-Cycle Approval Trends

Applications aimed at unmet medical needs tend to have higher first-cycle approval rates

Applications with *Higher* Approval Rate*	**Applications with *Lower* Approval Rate***
Priority review	Longer-than-average primary review time
Major amendment / goal extension	One or more significant issues identified at mid-cycle communication

*On average, compared to Program cohort as a whole.

Time to Approval Trends

Unexpected issues or submissions late in review can impact a timely review

Applications with *Longer* Time to Approval*	**Applications with *Shorter* Time to Approval***
Longer-than-average primary review time	Priority review
Major amendment / goal extension	Inspections completed within Program timelines
Presented to Advisory Committee	
One or more major deficiencies identified at late-cycle meeting	
Applicant informs FDA of intent to submit additional data at time of LCM	

*On average, compared to Program cohort as a whole.

Information Exchange

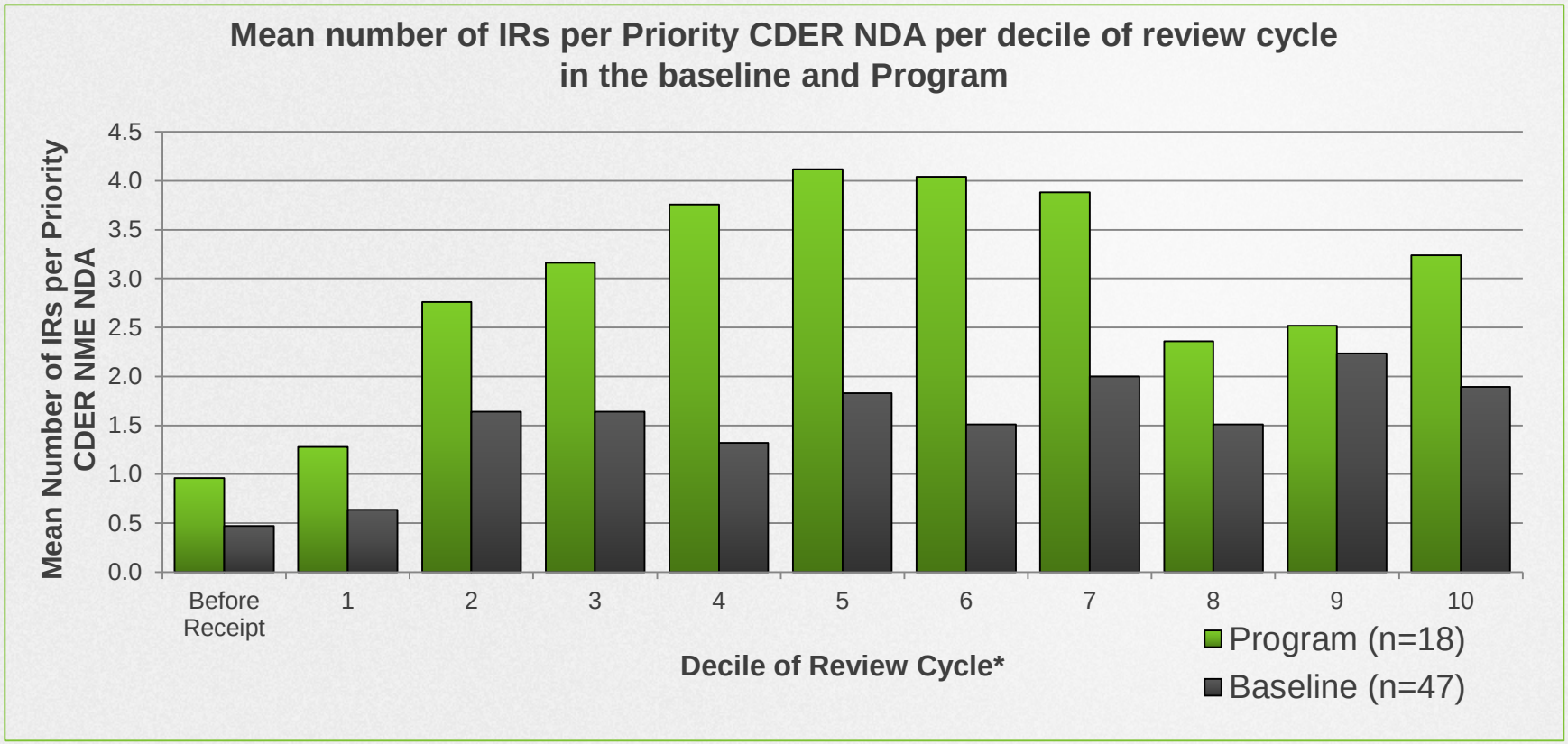
As measured by number of IRs, information exchange greater in Program, especially in Priority reviews

		Baseline	Program
Mean number of IRs per application		14.7	20.7
	Priority	16.4	29.2
	Standard	14.1	15.2
Mean number of requested items per application*		45.6	61.8
	Priority	49.9	74.9
	Standard	43.6	53.4

Data encompass CDER NDAs and CBER BLAs received in FYs 2008-2012 and acted on by September 30, 2014 (baseline) or received and acted on in FYs 2013-2014 (Program). Data does not include CDER BLAs due to limitations in data.

**An "item" is a single dataset/analysis/submission requested in an IR; an IR often includes multiple items. Mean number of items is the sum of all items requested in IRs during application reviews.*

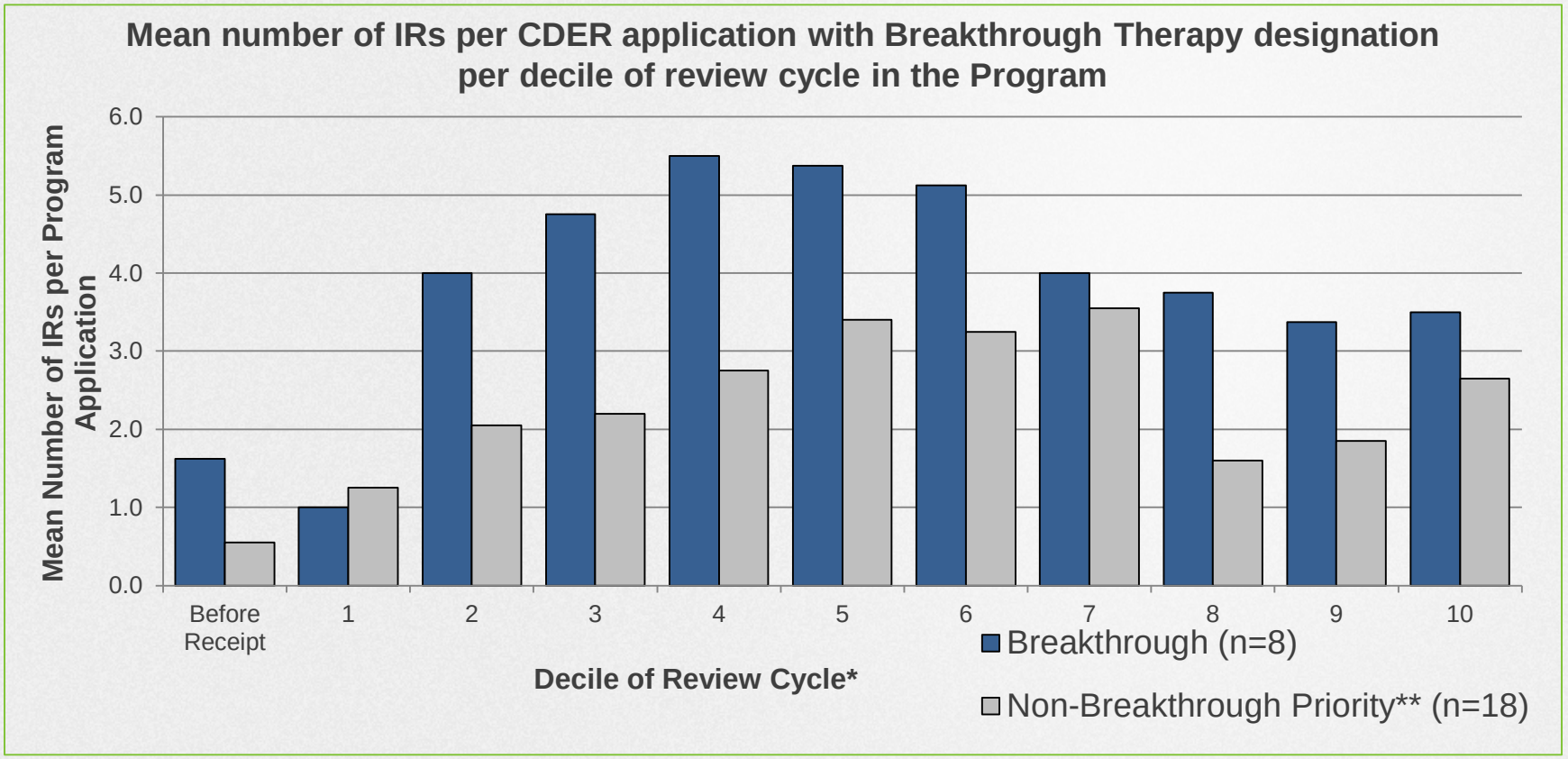
Program Priority v. Baseline Priority



Data encompass CDER NME NDAs received in FYs 2008-2012 and acted on by September 30, 2014 (baseline) or received and acted on in FYs 2013-2014 (Program). Due to data limitations, ERG did not include BLAs in this dataset.

**ERG calculated mean values by decile of review to account for differences in review times for PDUFA IV versus PDUFA V applications, Standard versus Priority applications, and applications with/without goal extensions.*

Breakthrough v. Non-Breakthrough



Data encompass CDER Program applications received and acted on in FYs 2013-2014, including NDAs and BLAs.

**ERG calculated mean values by decile of review to account for differences in review times for PDUFA IV versus PDUFA V applications, Standard versus Priority applications, and applications with/without goal extensions.*

***Priority applications that did not receive a Breakthrough Therapy designation.*

Special Designations

Relatively high first-cycle approval rates and relatively short times to first-cycle approval

Category	Group of Program Applications*			
	Breakthrough Therapy (n=8)	Fast Track (n=20)	Orphan Drug (n=24)	All Program (n=64)
First-cycle approval rate	87.5%	85.0%	83.3%	71.9%
Median time to first-cycle approval	6.3 months	7.9 months	8.0 months	11.0 months
Mean number of IRs per application	42.0	29.6	28.2	22.3
Mean number of IR items per application	103.5	91.4	106.8	79.5
Received Priority review	87.5%	85.0%	70.8%	42.2%

Data encompass NME NDAs and original BLAs received and acted on during FYs 2013-2014.

**Designations are not mutually exclusive; any given application can have one or more of these designations.*

Pre-Submission Meetings

- Most applicants requested a meeting
- Applicants want to discuss:
  - Chemistry, Manufacturing and Controls (CMC)
  - Top-line results and data
  - Format/content
- Applicants cite value of open communication during IND stage

Mid-Cycle Communications (MCCs)

- Valued by applicants
- Some FDA reviewers considered redundant to already existing communication channels
- FDA attendees ranged from two staff to the entire review team
- Majority of issues discussed pertained to Clinical (25.0%) or Product Quality (24.1%)

Late-Cycle Meetings (LCMs)

- Most helpful with significant issues that could be resolved in review cycle
- Sometimes used to discuss labeling and postmarketing commitments/requirements
- Some FDA reviewers suggested opt-out option if no significant issues to discuss

Advisory Committees (ACs)

- FDA review teams and applicants agree that it eases burdens and time pressures to provide:
  - Early notification and confirmation (e.g., in filing letter and MCC)
  - Ample time between the LCM and AC (when possible)
- Less common in first two years of Program (23%) than baseline (39%)

Inspections

- Challenging for FDA reviewers and applicants to know status of inspections
- Completion targets met for 42.4% of applications
- Late inspections have potential to affect timeliness of first-cycle actions

Findings and Recommendations

Enhanced Review Transparency

Overall, the Program has been successful in enhancing review transparency and communication.

Recommendation

No action needed.

Enhanced Predictability

Overall, new Program milestone communications (mid-cycle communications and late-cycle meetings) have enhanced the predictability of reviews by:

- Serving as “anchor points” for applicant and FDA planning and work.
- Providing a forum for holistic, multi-disciplinary discussion of application status and paths forward to resolve approvability issues promptly, if possible.

Recommendation

No action needed.

Enhanced Ability to Resolve Substantive Issues

By providing more opportunity to identify, discuss, and resolve substantive issues during the review, the Program has created conditions that enhance the ability of applicants and FDA reviewers to work toward application approval in the first review cycle where possible. This is especially true for applications with substantive but resolvable issues where the full review clock is needed.

Recommendation

No action needed.

Increased Burden for FDA

Program implementation has not been resource-neutral.

- Implementation has increased burden on FDA's primary reviewers, diverting effort from review work to meeting preparation and sometimes resulting in a need for additional primary review addenda.
- FDA review teams have been able to manage burden, but have noted that additional new burdens might in some cases introduce a risk of missed deadlines, compromise thoroughness of reviews, and impact other non-Program work.

Recommendation

If/when new review process requirements are added, analyze the associated burden to determine whether additional staff or other resources will be needed to maintain the timeliness and thoroughness of reviews.

Early Approval Efforts

In some cases, implementation of Program milestone communications might hamper FDA's ability to approve Priority applications as early as desired.

Recommendation

As part of ERG's ongoing Program assessment, assess the extent to which FDA's refined Program implementation guidelines for expedited reviews* is mitigating this challenge.

FDA Action Taken

CDER issued refined Program implementation guidelines for expedited reviews.

(September 2014)

Pre-NDA/BLA Advice

Regardless of sponsor size and experience, many sponsors need more guidance on the format and structure of an application to meet FDA expectations by review division/team and indication/therapeutic area.

- Sponsors sometimes request additional Type C meeting many months before data-oriented pre-submission meeting.
- Some FDA review teams believe that existing guidance should be sufficient and holding an earlier meeting without data is premature.

Recommendation

Evaluate efficient options for when and how to communicate information about the format and structure of applications by therapeutic area or division. Options could include but are not limited to internal reviewer aids and increased use of Type C written responses.

Application Orientation Meetings

In certain CDER review divisions with Priority applications where early action is expected / desired, holding an Application Orientation Meeting within a month or so of submission has helped:

- Acquaint FDA disciplines with application datasets.
- Establish early communication between applicants and FDA about review expectations and perspectives.

Recommendation

Consider the value of providing information about Application Orientation Meetings to FDA review teams, along with the option to conduct such meetings at the review team's discretion (e.g., for certain Priority / Breakthrough Therapy / expedited review applications).

Information Requests

Given the high volume of information requests:

- Providing target dates for responses is a good practice.
- Applicants would also benefit from receiving confirmation that their responses are complete.

Recommendation

First, adopt inclusion of target dates for information request responses as a good practice.

Second, develop a simple optional approach for tracking information requests and amendments that can be shared between review teams and applicants.

Signatory Authority Involvement

Early involvement of the signatory authority can:

- Help ensure that all parties at FDA are knowledgeable about the application.
- Foster early agreement.

Thereby facilitating timely labeling decisions and avoiding last-minute surprises if the Office identifies concerns that the division did not.

Recommendation

Reiterate the importance of the presence and involvement of the signatory authority throughout the review as specified by Program guidelines.

MCC Format

MCCs have generally been most productive when FDA reviewers:

- Provided applicants with an informal (telephone, email) “heads up” about meeting topics.
- Permitted two-way communication to clarify questions.

Recommendation

Establish these as good practices for the conduct of MCCs.

FDA Action Taken

CDER implemented as good practices.

(September 2014)

MCC Attendance

MCCs have generally been most efficient and least burdensome to review teams when attendees are selected based on anticipated need rather than including the entire team.

Recommendation

Provide internal guidelines on how to select review team members to participate in MCC, focusing on core team members and disciplines with issues.

FDA Action Taken

Implemented this practice.

(September 2014)

Label Change Practices

Providing explanations/rationales for proposed label changes is a good practice for applicants and FDA review teams. This practice has helped both parties understand the others' reasoning, enabling them to respond effectively – which then reduces the amount of back-and-forth required and the time required to complete negotiations.

Recommendation

Include explanations/rationales for proposed label changes (either in written form or by telephone) as a good practice.

Inspection Information

Inconsistent availability/communication of information about the status and results of inspections has hindered review transparency and predictability, both internally at FDA and between FDA and applicants.

Recommendation

Conduct a process analysis examining inspection information flows and communication channels, with the aim of identifying improvements.

Next Steps

Next Steps

- Ongoing data collection and analysis
- Analysis of FDA Program refinements
- Analysis of regulatory outcomes overall (across review cycles)
- Final assessment on December 31, 2016