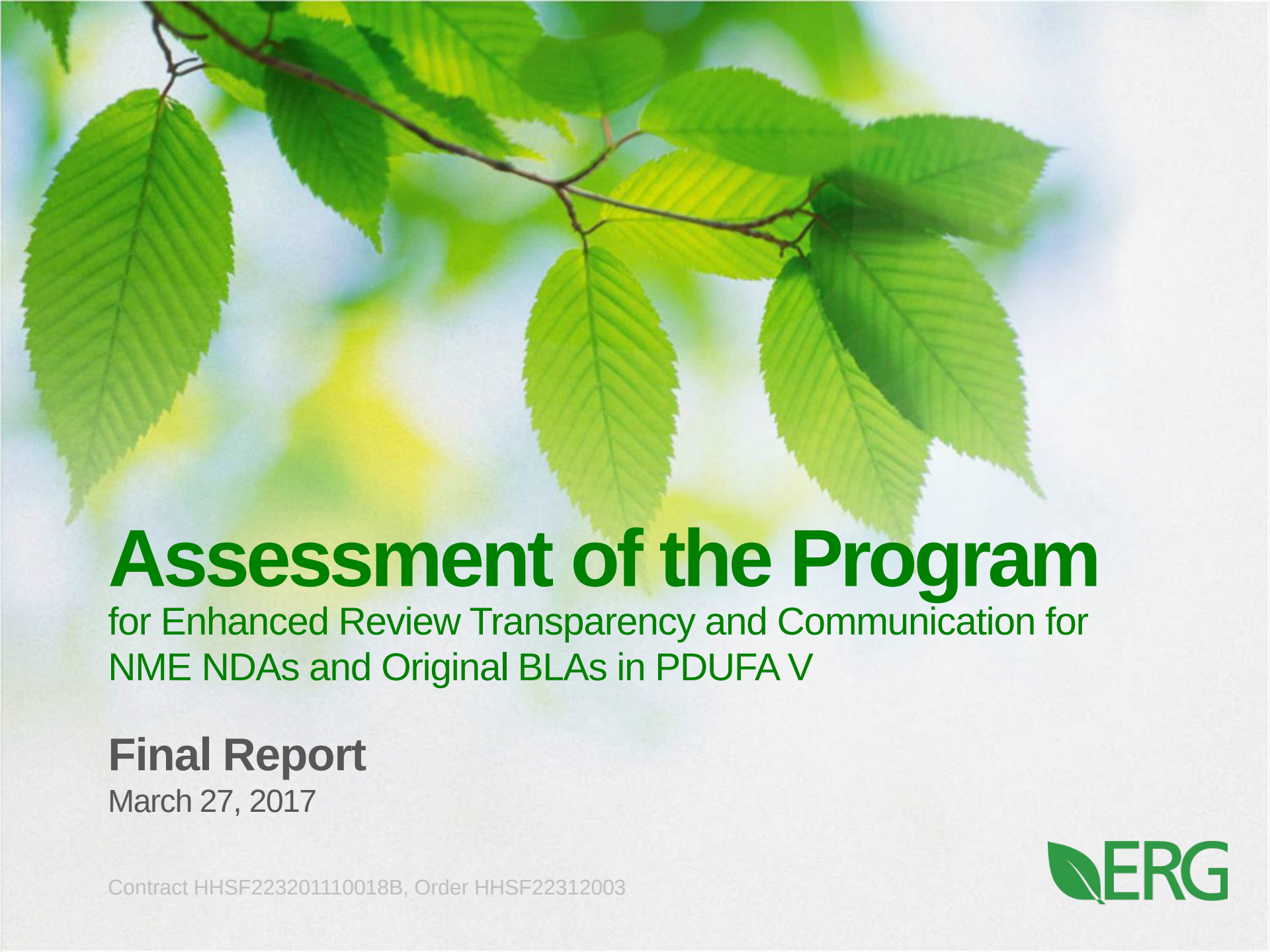


Assessment of the Program

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

Final Report

March 27, 2017

Contract HHSF223201110018B, Order HHSF22312003

ERG

Presentation Outline

- Introduction
- Results highlights
- Answers to assessment questions
- Findings and recommendations

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

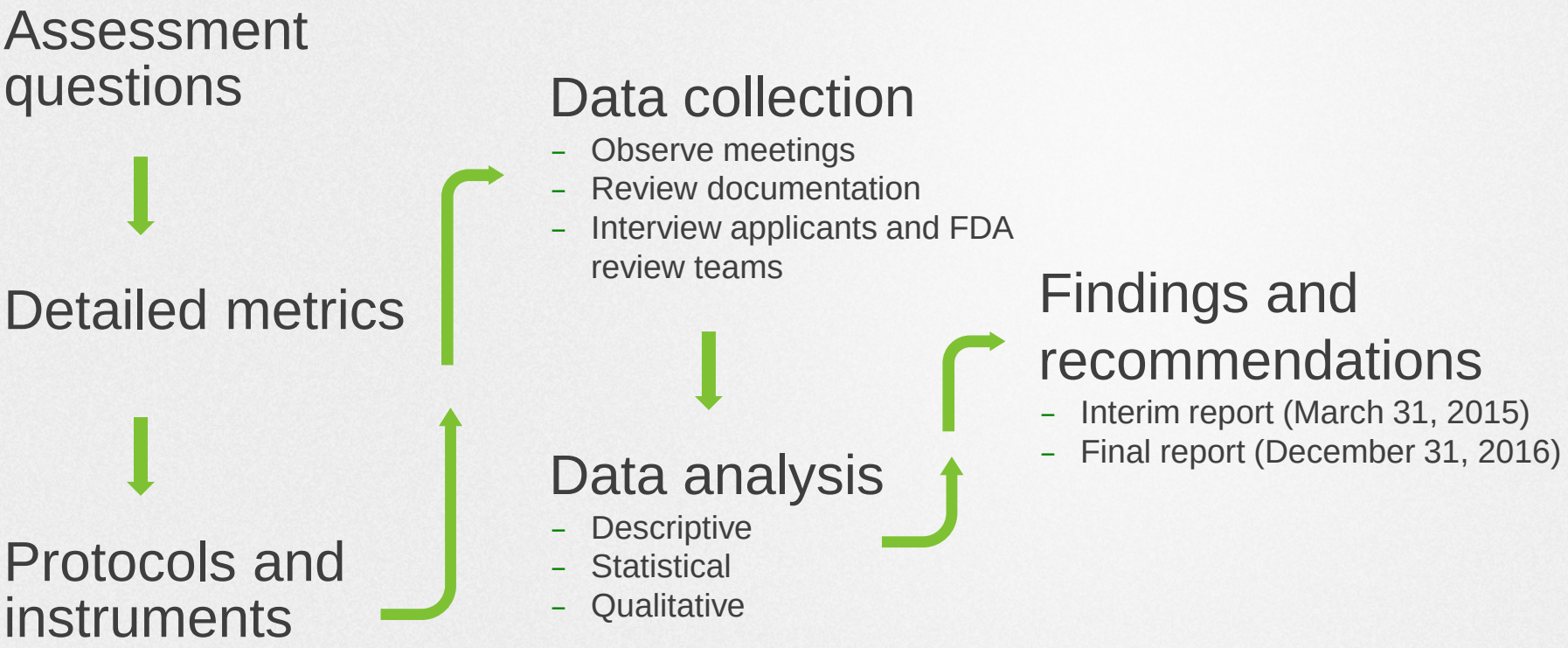
Program Evaluation

- 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



Final 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

Results Highlights

Program and Baseline Cohorts

Applications		Baseline	Program
Filed and acted upon	NME NDA	147	109
	Original BLA	72	62
	Total	219	171
First-cycle actions	Approval (AP)	120	136
	Complete Response (CR)	92	29
	Withdrawal after Filing (WD)	7	6
	Total	219	171
Percent of filed applications approved in first cycle		54.8%	79.5%

Data encompass NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program).

Milestone Communications

Milestone Communication	Topics Most Frequently Discussed	Perceived Value of Communication
Pre-submission meeting	• Product Quality • Topline results and data • Format/content of submission	• Open and early communication • Assessment of readiness to submit • Shared understanding of expectations for submission (transparency)
Mid-cycle communication	• Clinical • Product Quality • Labeling, PMR/PMC, LCM, safety, pediatrics, REMS, AC	• Open communication • Shared understanding of progress and potential issues to permit work toward resolution (transparency)
Late-cycle meeting	• Review issues • Labeling, PMR/PMC	• Open communication • Shared understanding of progress (transparency) • Opportunity to understand issues and work toward resolution

First-Cycle Approval Rates

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)	79.5% (n = 171)	< 0.001
Priority	71.8% (n = 78)	90.1% (n = 81)	0.003
Standard	45.4% (n = 141)	70.0% (n = 90)	< 0.001*

Data encompass NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program).

**N was too small to achieve statistical significance at the time of the interim assessment (when cohort was applications received and acted on in FYs 2013-2014). N is now large enough to achieve statistical significance.*

First-Cycle Approval Rate Patterns

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
	One or more major deficiencies identified at late-cycle meeting

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

Time to First-Cycle Action

As expected, 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	10.0	6.0	10.0	6.0	6.4	3.9	10.0	6.0
Program	12.0	7.9	12.0	7.9	8.7	6.2	12.0	7.9

Data encompass NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program).

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

Time to Approval Patterns

Unexpected issues or submissions late in review can impact time to approval

Applications with *Shorter* Time to Approval*	**Applications with *Longer* Time to Approval***
Breakthrough Therapy designation	Major amendment / goal extension
Late-cycle meeting scheduled within Program timelines	Longer-than-average primary review time
Inspections completed within Program timelines	One or more major deficiencies identified at late-cycle meeting
Early action	
Priority review	
Accelerated Approval	

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

Special Designations

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

Category	Group of Program Applications*			
	Breakthrough Therapy (n=34)	Fast Track (n=49)	Orphan Drug (n=64)	All Program (n=171)
First-cycle approval rate	85.3%	87.8%	85.9%	79.5%
Median time to first-cycle approval	6.3 months	8.0 months	8.0 months	11.0 months
Received Priority review	97.1%	83.7%	70.8%	47.4%

Data encompass NME NDAs and original BLAs received and acted on from October 1, 2012 to June 30, 2016.

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

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	26.0% *(57 / 219)*	59.7% *(34 / 57)*	Standard: 6.2 to 9.9 months (median 8.1) Priority: 3.2 to 5.9 months (median 4.1)
Program (Interim)	18.8% *(12 / 64)*	91.7% *(11 / 12)*	Standard: 5.9 to 11.0 months (median 8.8) Priority: 1.4 to 5.9 months (median 2.9)
Program (Final)	22.8% *(39 / 171)*	89.7% *(35 / 39)*	Standard: 3.4 to 12.0 months (median 9.2) Priority: 2.0 to 8.0 months (median 5.6)

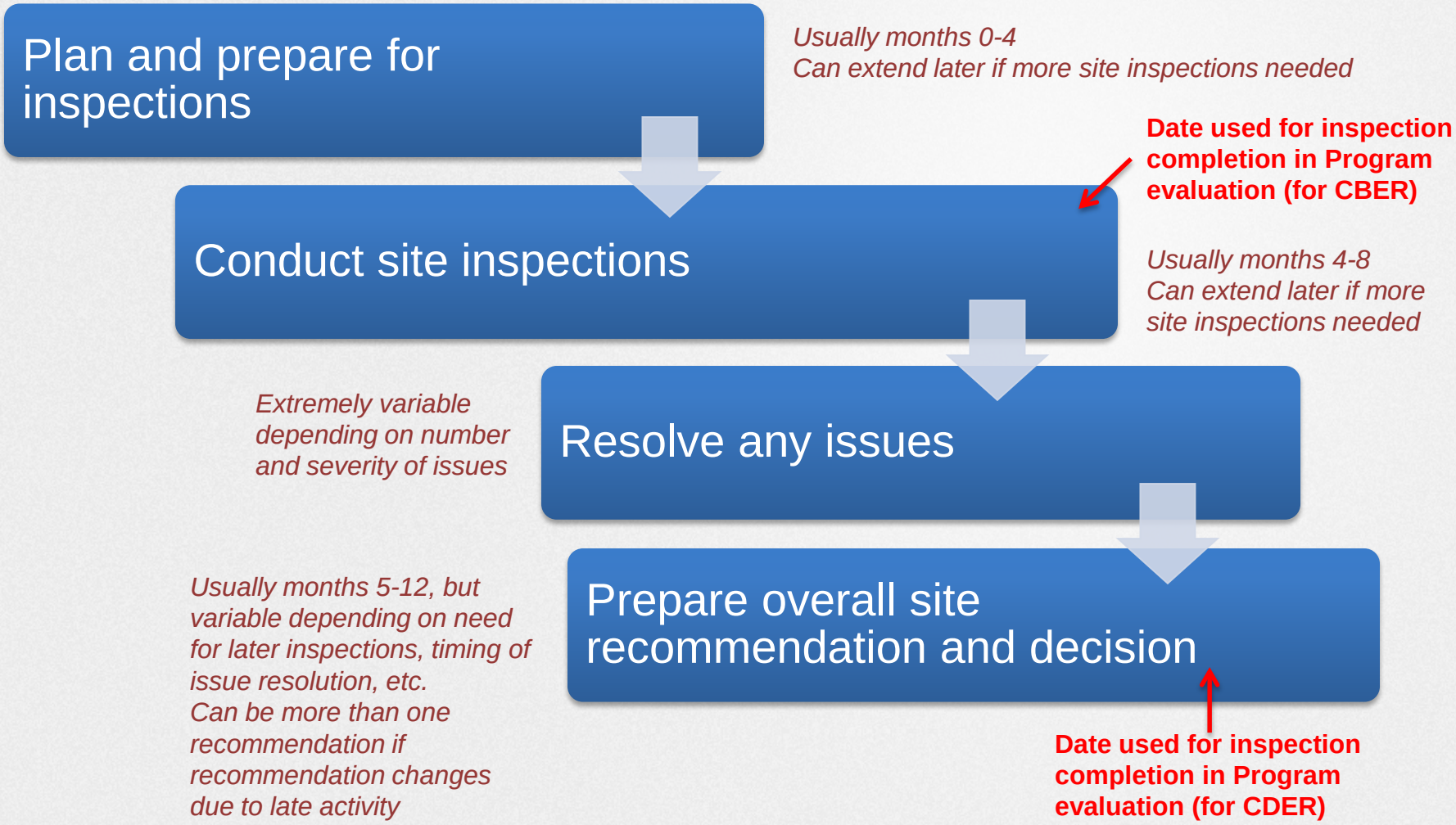
NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program).

Inspections

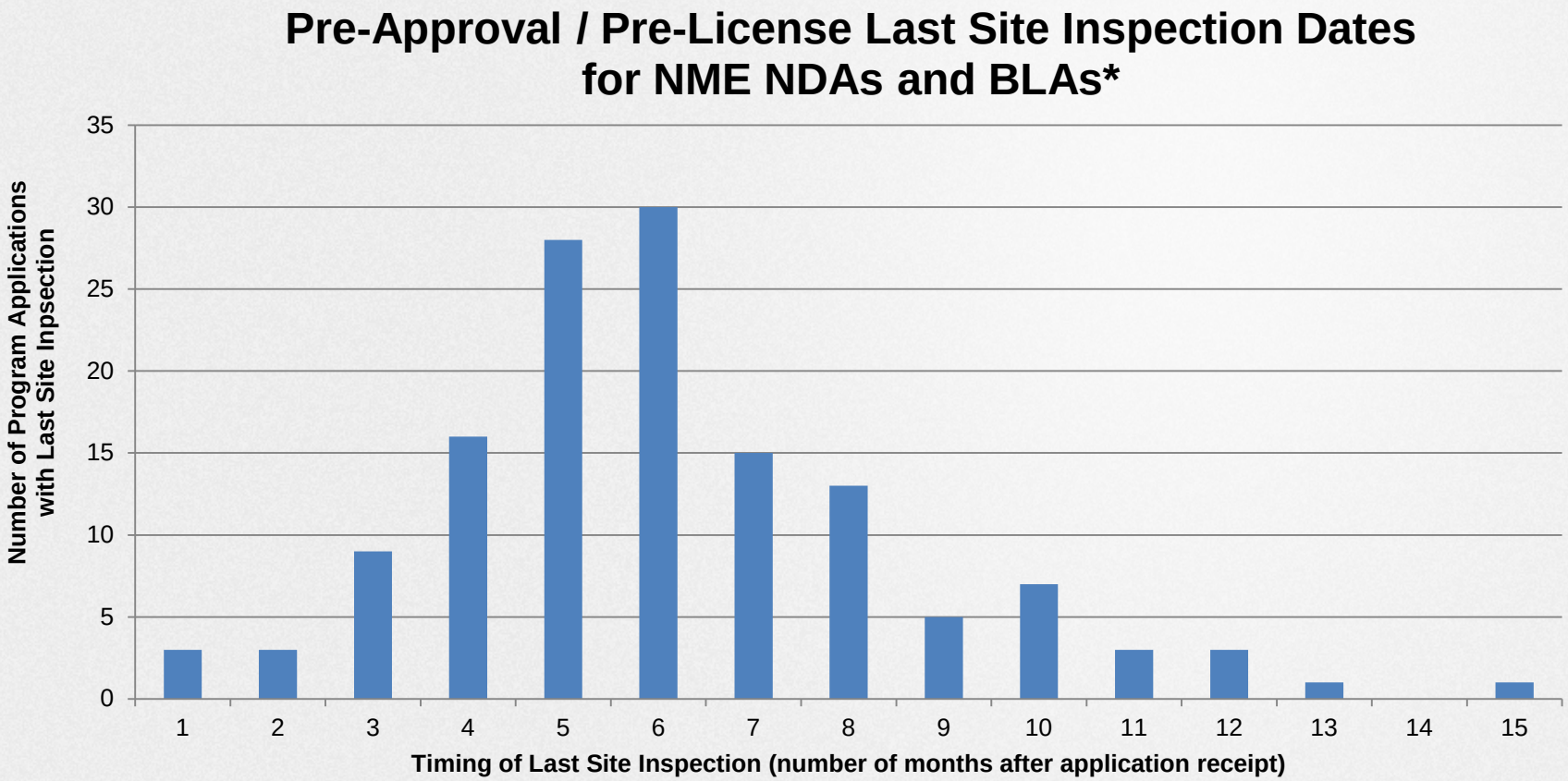
- PDUFA V expectation is to complete inspections:
  - Priority: within 6 months of receipt
  - Standard: within 10 months of receipt
- For purpose of this Program evaluation, inspection completion defined as:
  - CDER: Last overall site acceptability recommendation date
  - CBER: Latest GMP or GCP site inspection date*

**GMP = Good Manufacturing Practice, GCP = Good Clinical Practice*

Inspections (GMP)

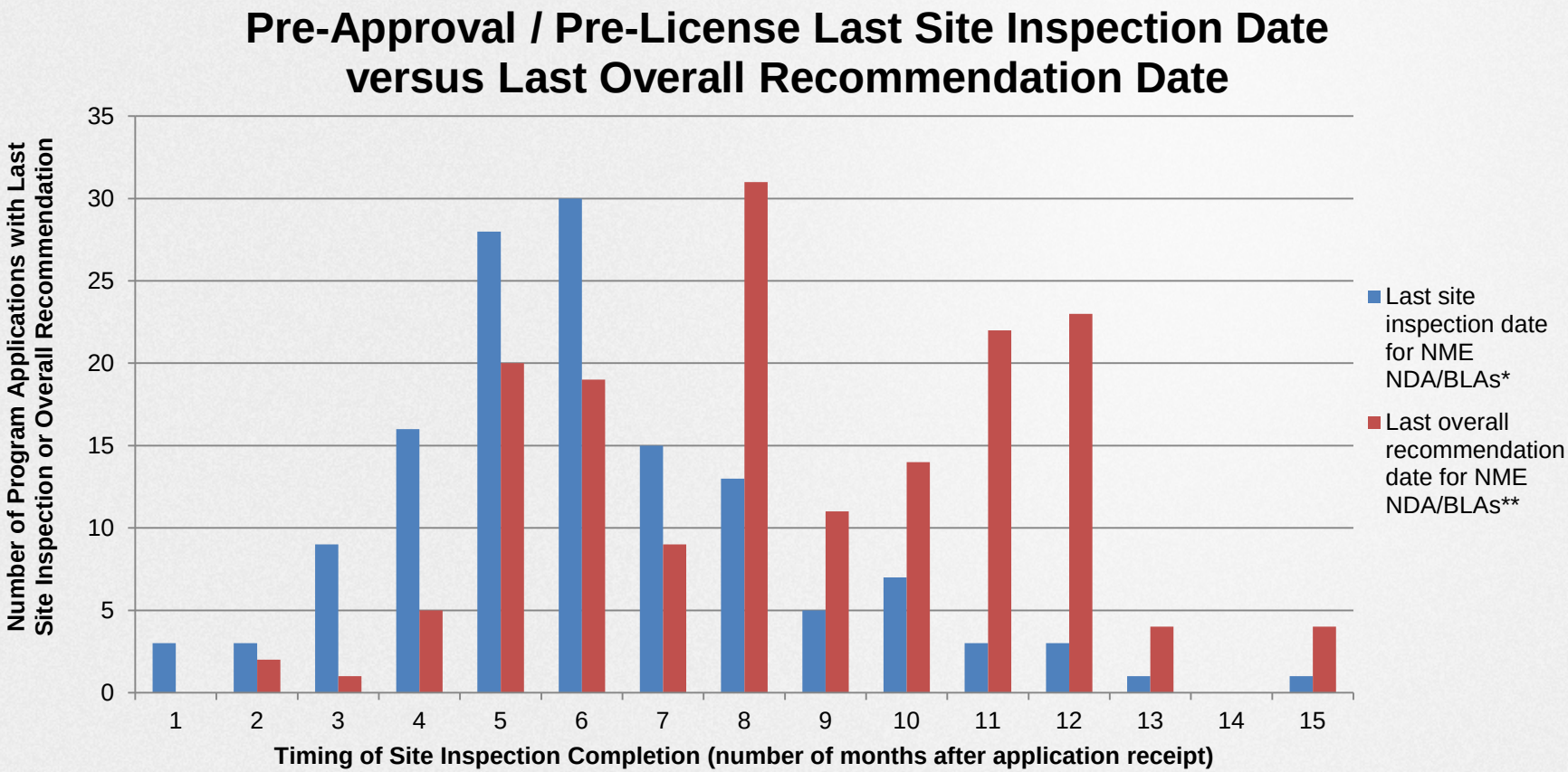


Inspections (GMP)



**NME NDAs and original BLAs received and acted on from October 1, 2012 to June 30, 2016.*
Excluded: 33 applications without inspection date, 1 application with inspection date outside review cycle.

Inspections (GMP)



**NME NDAs and original BLAs received and acted on from October 1, 2012 to June 30, 2016. 33 applications without a PAI/PLI inspection date are excluded as well as 1 application with a PAI/PLI inspection date outside of the review cycle.*
***NME NDAs and original BLAs received and acted on from October 1, 2012 to June 30, 2016.*

Inspections (GMP)

- Between interim and final Program evaluation reports, management of CDER's pre-approval inspection process responsibilities consolidated under Office of Pharmaceutical Quality (OPQ)
- ORA leads and conducts most pre-approval inspections performed for NME NDAs
- OPQ performs initial facility evaluation, participates in some pre-approval inspections, and makes final facility recommendation

Inspections (GMP)

- Historically, challenging for FDA reviewers and applicants to know status of inspections

  Number of applications after transition period insufficient to verify improvement in communication

- Program evaluation completion targets met for 46.1% of applications

  Many reasons: number and severity of issues to be resolved, need for more inspections late in process, attempt to achieve acceptability in time for approval, etc.

Complete Response Letters

Top three issues in Complete Response (CR) letters

Issue Cited in CR Letter*	Standard Applications		Priority Applications	
	Baseline (n=71)	Program (n=22)	Baseline (n=21)	Program (n=7)
Efficacy	40.9%	50.0%	81.0%	85.7%
Product quality	50.7%	45.5%	76.2%	71.4%
Safety	71.8%	45.5%	54.1%	42.9%

Data encompass NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (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 Resubmission

- Sample size too small for statistical analysis
- 11 Program applications resubmitted compared to 65 baseline applications resubmitted
  - Few Program applications received CR and were eligible for resubmission
  - Not enough time elapsed for significant number of resubmissions of Program applications

Assessment Questions and Answers

Program-Related Outcomes

What is the relationship between Program attributes and NME NDA/original BLA first-cycle regulatory outcomes?	First-cycle approval rate higher in Program than in baseline (statistically significant)
What is the relationship between Program attributes and time to NME NDA/original BLA first-cycle regulatory outcomes?	First-cycle reviews longer in Program than in baseline (statistically significant). Applicants still viewed Program as having value in enhancing review: • Transparency • Communication • Predictability • Efficiency

Review Process-Related Outcomes

What is the relationship between review process attributes and NME NDA/original BLA first-cycle regulatory outcomes?	Two attributes associated with higher first-cycle approval rates: • Priority review (statistically significant) • Major amendment / goal extension (expected due to purpose of goal extensions) One attribute associated with lower first-cycle approval rate: • Longer time to primary review completion
What is the relationship between review process attributes and time to NME NDA/original BLA first-cycle regulatory outcomes?	Two attributes associated with longer mean time to first-cycle approval: • Longer time to primary review completion • Major amendment / goal extension (as expected)

Application-Related Outcomes

What is the relationship between application attributes and NME NDA/original BLA first-cycle regulatory outcomes?	Higher first-cycle approval rates with applications that address unmet medical need: • Priority review (statistically significant)
What is the relationship between application attributes and time to NME NDA/original BLA first-cycle regulatory outcomes?	Shorter time to first-cycle approval with applications that address unmet medical need: • Priority review (statistically significant)

Applicant and FDA Perceptions

How do applicants and FDA review staff characterize enhanced communication under the Program?	Characterizations of Program communications largely positive: • Communication excellent and constructive • Milestone communications facilitate: ✓ More holistic discussion of application ✓ Broader FDA input ✓ Greater understanding of each party's perspectives ✓ More efficient resolution of questions and issues • Review staff responsive, constructive, and flexible Improved transparency still needed for status and results of inspections

Applicant and FDA Perceptions

How do applicants and FDA review staff characterize application reviews under the Program?	Characterizations of Program reviews largely positive: • Very transparent • Very predictable • Very efficient • Especially beneficial for applications that require substantive discussion and issue resolution throughout review Program milestones add to review staff burden, but additional burden is manageable

Findings and Recommendations

Changes from Interim Report

Due to effective FDA actions, ERG removed three recommendations made in interim report:

- Mid-Cycle Communication (MCC) procedures

  Good practices have become nearly universal in the Program.

- Early involvement of signatory authority

  Practice has been consistent with Program expectations.

- Flexibility for expedited reviews

  FDA provided refined guidelines for expedited reviews in September 2014.

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.

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.

Note: This is already a part of FDA consideration of new process requirements.

Pre-NDA/BLA Information

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).

Note: FDA is proposing this option for PDUFA VI.

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.

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.

Note: FDA is not legally permitted to disclose inspection results to applicants when sites are owned by contractors.

Recommendation

Examine inspection information flows and communication channels, with the aim of identifying improvements.

Note: FDA is performing such an examination.