U.S. FOOD & DRUG ADMINISTRATION

Keynote:
Generic Drug Program Update

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CDER/FDA

SBIA Generic Drug Forum
April 11, 2018

- ***Caution:*** variable cut off dates used in slides.

  For example, some data reflect fiscal year (FY) and others reflect calendar year (CY).

- FY2017 data represent preliminary data that are being further reviewed and validated for official reporting purposes. October 1, 2017 used as cut-off.

OUTLINE

1. Review of Generic Drug Program and Roles
2. Success under GDUFA
3. Impact of GDUFA Regulatory Science
4. GDUFA II Overview
5. Reminders to Industry
6. Closing Comments

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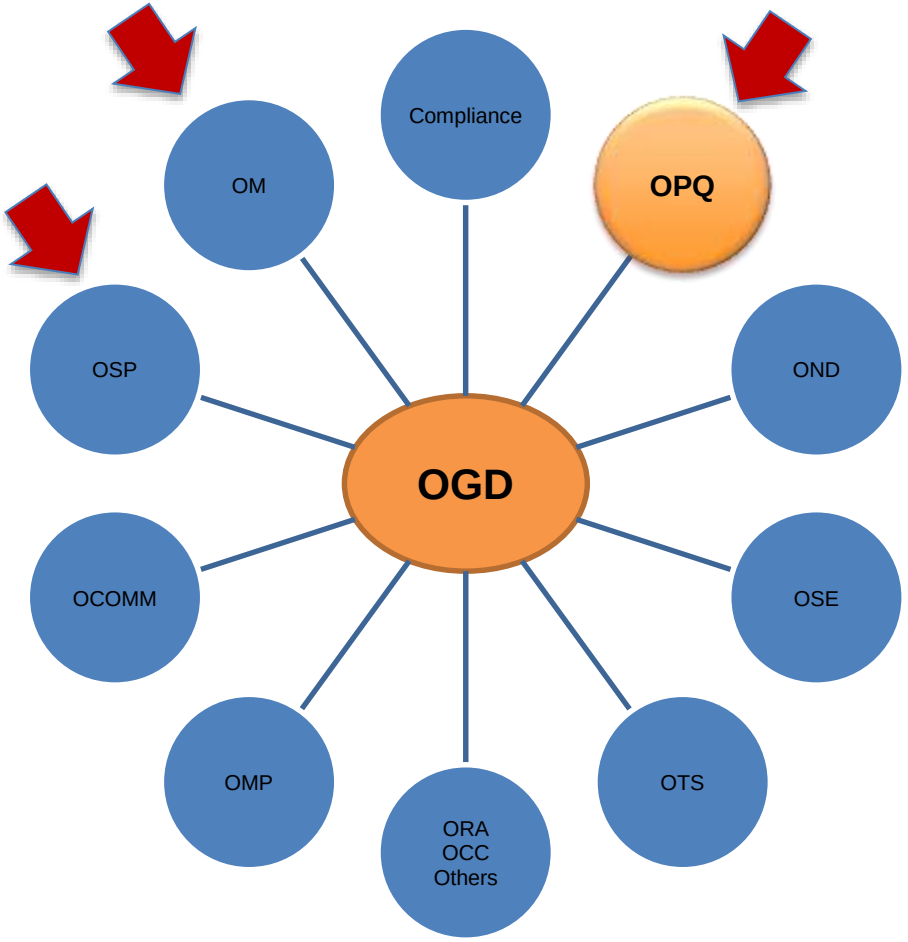
FDA's Generic Drug Program

- FDA's work related to ANDA review/assessment and approval encompasses complex scientific, regulatory and legal issues unique to the generic/Hatch-Waxman space
- Necessitates broad Interactions across **Multiple Offices** in CDER and FDA

FDA's Generic Drug Program

- OGD interfaces with applicants to coordinate the review of ANDAs
- **OPQ and OGD** collaborate to evaluate Pharmaceutical Quality, Bioequivalence, and Labeling
- OGD issues regulatory action on ANDAs

- The PROGRAM involves all of CDER
- Other FDA units:
  - ORA
  - Office of the Commissioner, esp. Office of Chief Counsel (OCC)
  - CBER, CDRH

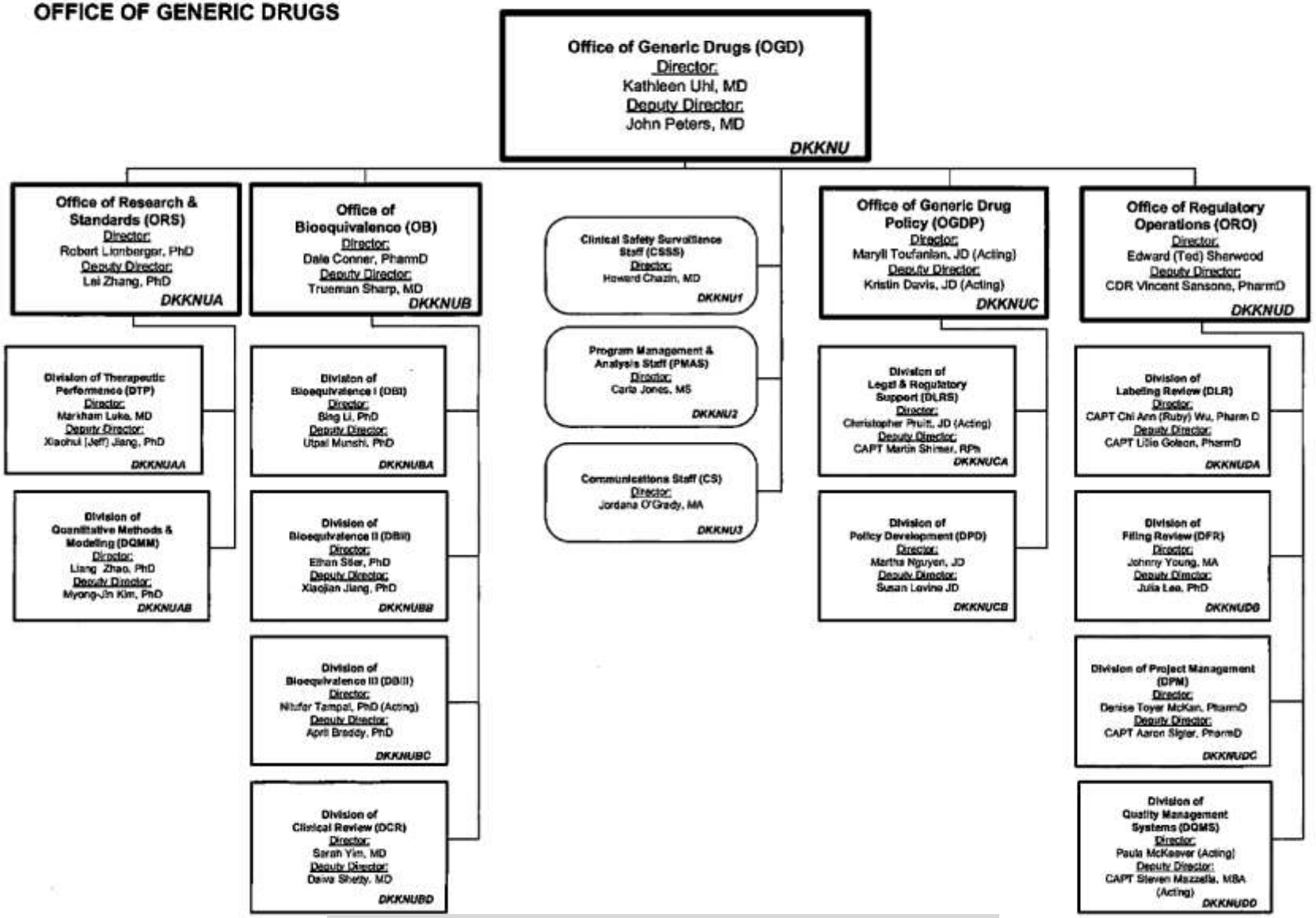


OFFICE OF MEDICAL PRODUCTS AND TOBACCO

CENTER FOR DRUG EVALUATION AND RESEARCH

OFFICE OF GENERIC DRUGS

February 1, 2018



Current OGD Organizational Chart

Current State: FDA Generic Drug Program

- GDUFA I implementation:
  - Successfully orchestrated major organizational changes – created OGD and OPQ super offices
  - Built and implemented new IT infrastructure to manage ANDAs and provide data for official reports
  - Improved program efficiencies and output
- FDA is meeting or exceeding GDUFA goals
- Standing up and implementing GDUFA II and FDARA (the re-authorizing legislation), while closing out all GDUFA I goal dates

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Original ANDAs

- GDUFA goal: increasing % meeting shorter review goals over Years 3, 4, and 5*

- As of October 1, 2017, FDA acted on:
  - **Cohort Year 3 - 97%**

    GOAL – 60% within 15 months of submission
  - **Cohort Year 4 - 100%**

    GOAL – 75% within 15 months of submission**
  - **Cohort Year 5 - 99%**

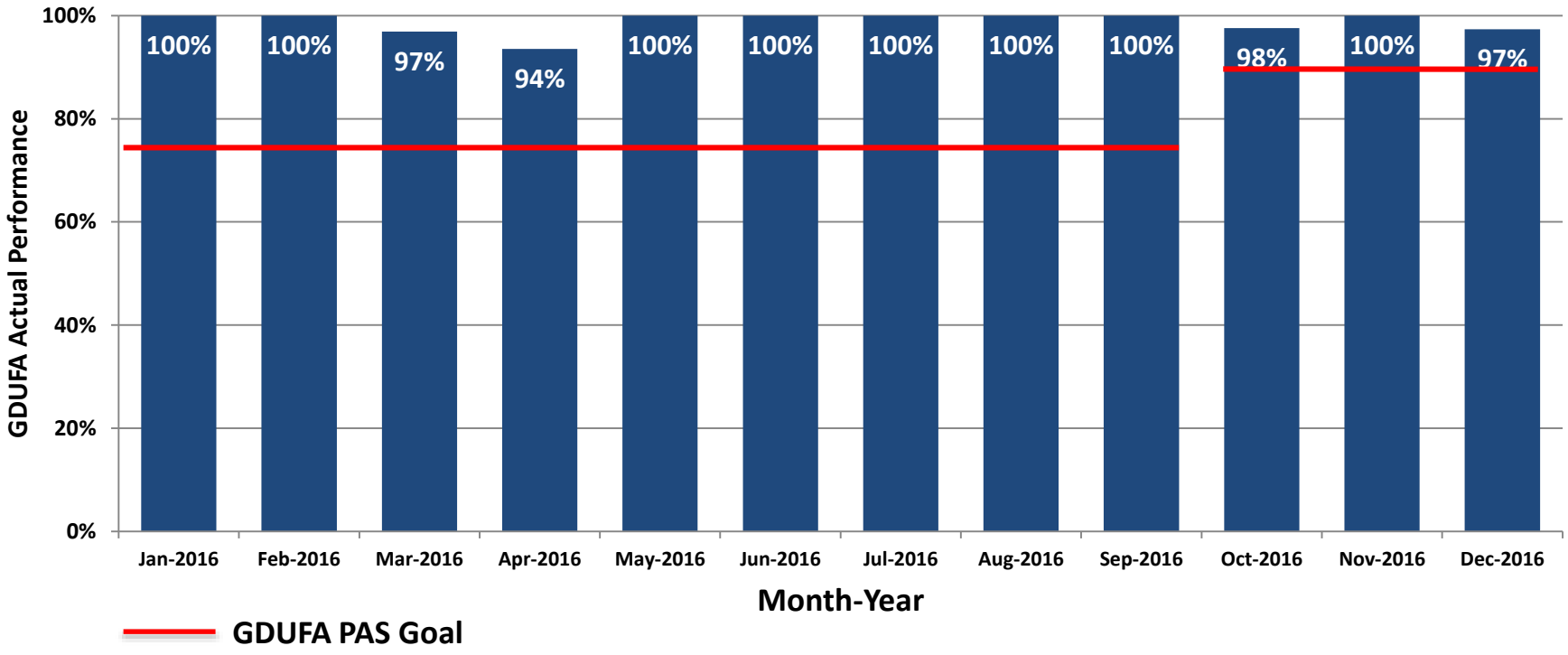
    GOAL – 90% within 10 months of submission**

Data from Years 4 & 5 may change b/c some ANDAs were under review and within goal at cut-off date.

*Updated 10/1/2017. Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.
Cohort Year 4 (FY2016) – Some are still under review and within goal; all mature by December 31, 2017. This number may change.
Cohort Year 5 (FY2017) – Many are still under review and within goal; all mature by July 31, 2018. This number may change.
**Percent represents the current percentage of regulatory actions FDA completed within the review-time goal. Final performance will depend on the outcome of pending submissions.

GDUFA Goal: PAS

(data reflect month of submission & PASs with goal dates that came to maturity as of 10/1/2017)

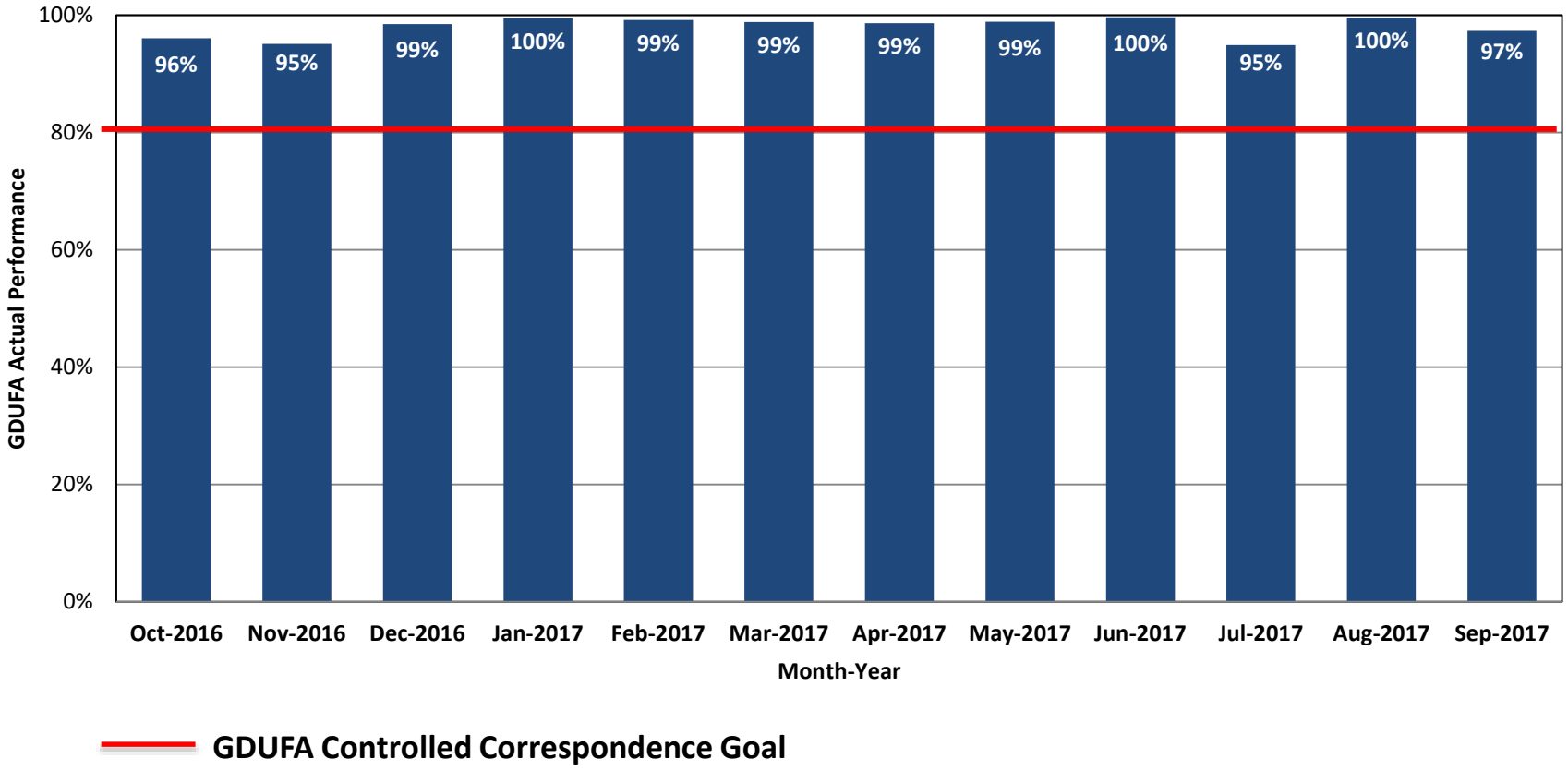


Goal dates provided on submissions received through December 2016, as those are the goal dates that have actually accrued.
The cohort data is not mature enough to report on whole fiscal year data.
Updated 10/1/2017. Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.

GDUFA Goal: Controlled Correspondence

(data reflect month of submission)

Controlled Correspondence
FY 16 GDUFA Performance by FDA Receipt Date – All Disciplines



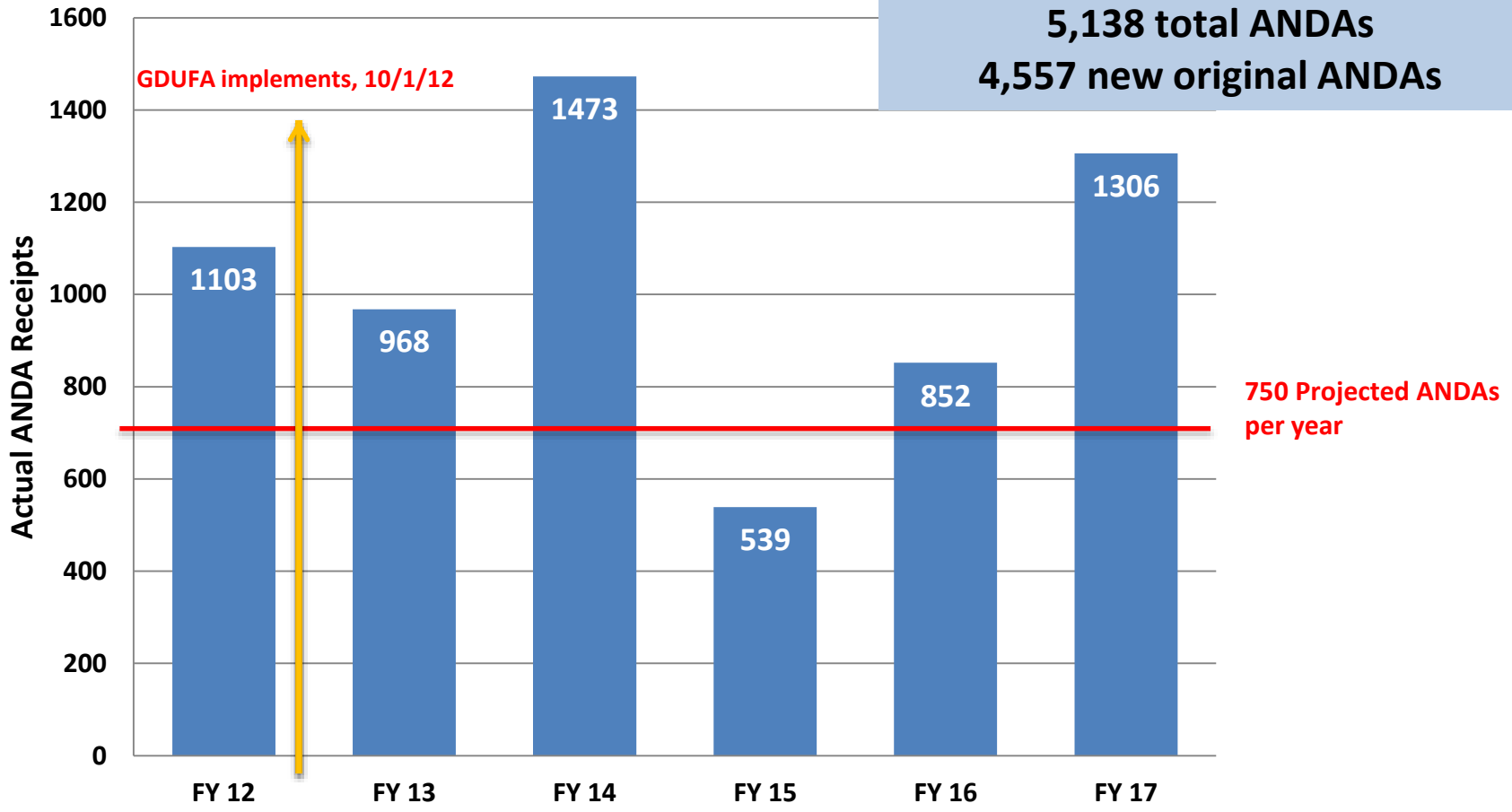
Goal dates provided on submissions received in FY 2016 and 2017.
Updated 10//12017. Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.
Activities Report of the Generic Drug Program, found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm375079.htm

GDUFA I WORKLOAD EXCEEDED ESTIMATES

- Number of original applications greater than projected numbers during GDUFA negotiations
- Throughout GDUFA I, we saw increases in:
  - Number of applications
  - Number of amendments
  - Number of controls
  - Number of companies
  - Number of facilities

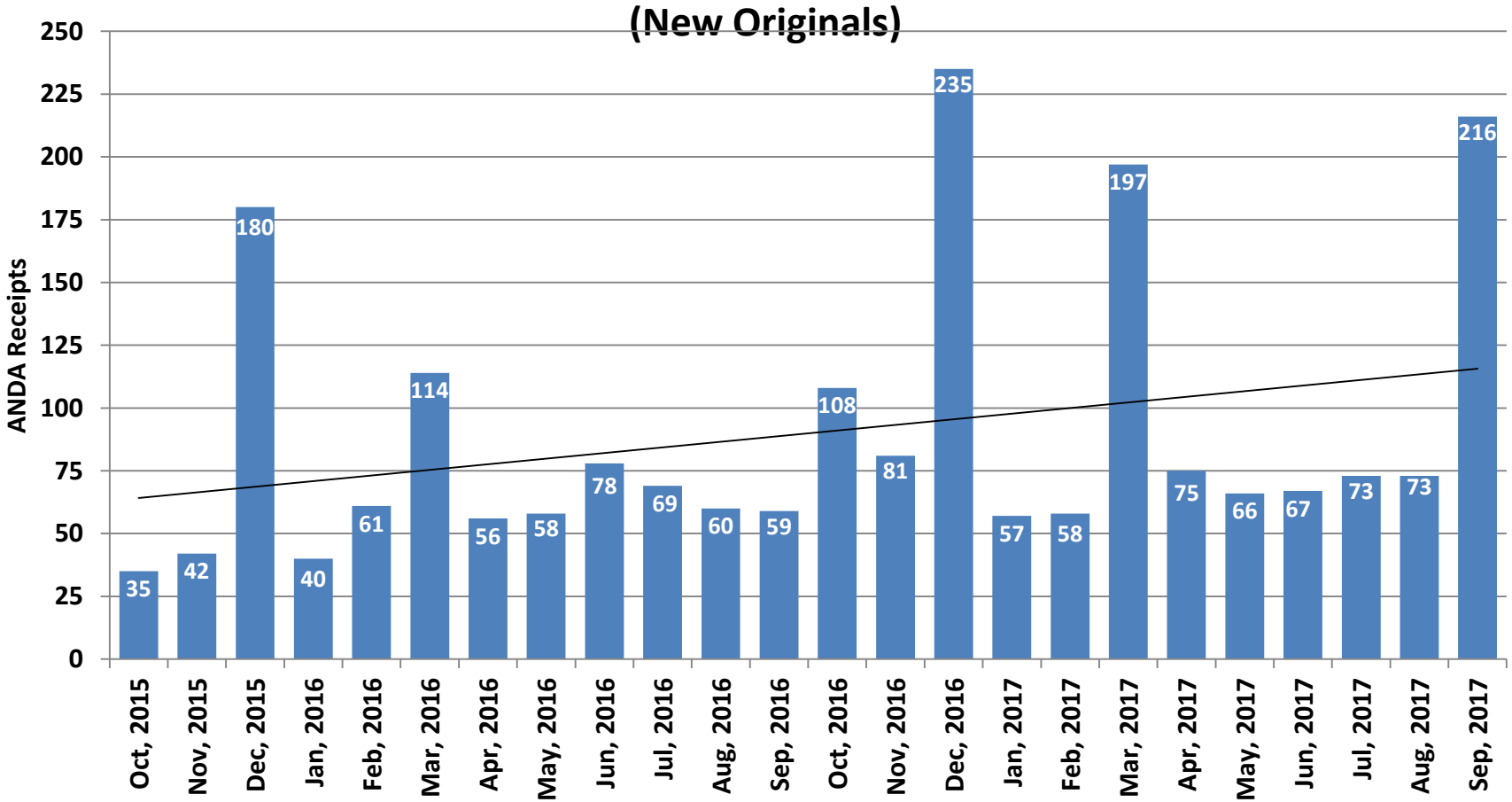
Projected vs Actual* ANDA Receipts

GDUFA I =
5,138 total ANDAs
4,557 new original ANDAs



*Updated 10/1/2017. Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.

Highly Variable Month to Month ANDA Submissions



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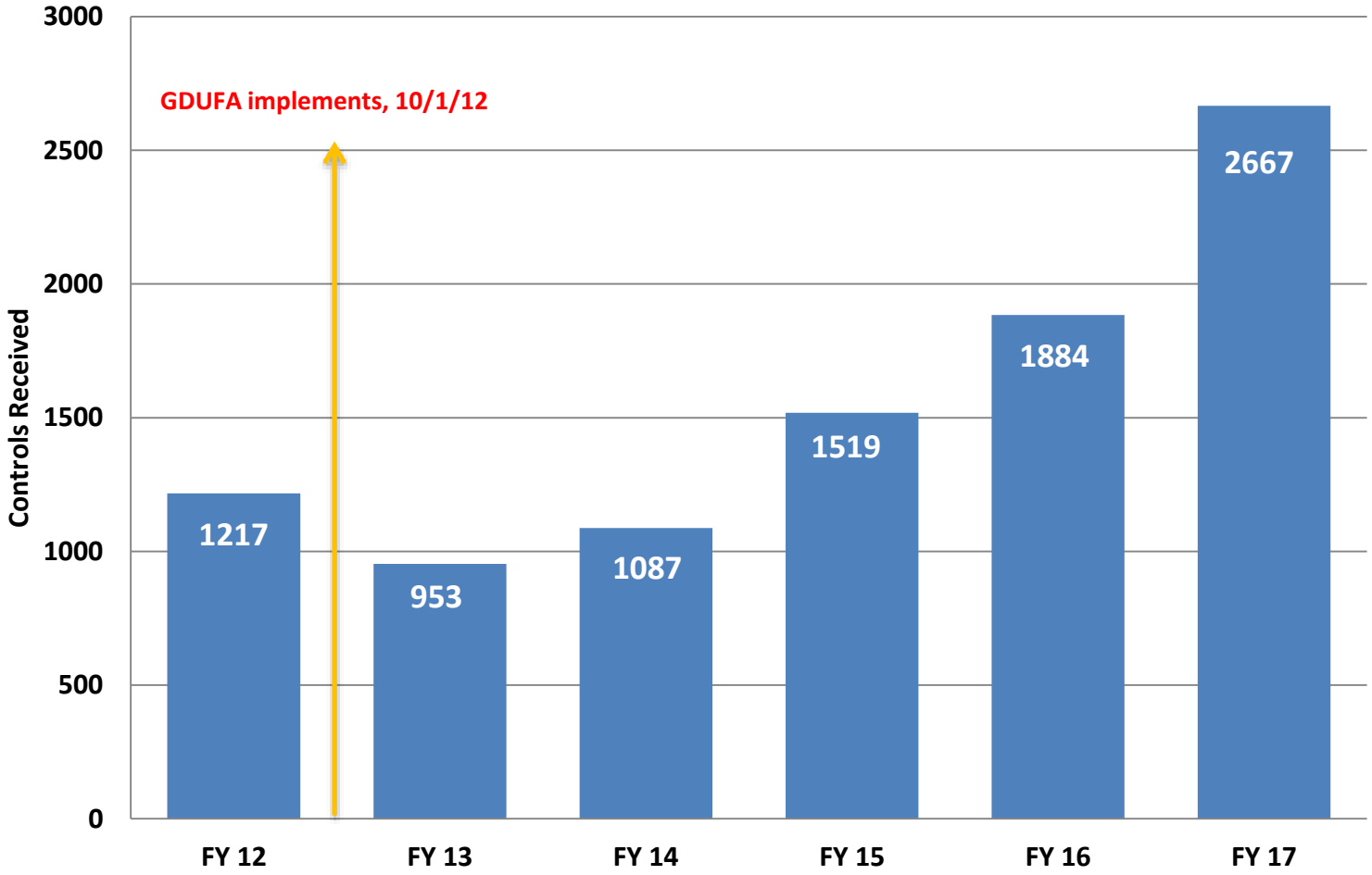
“Controls” Received

Generic drug product development questions



* Updated 10/1/2017. Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes. Numbers reflect controls submitted that are accepted for review, as per Controls Guidance for Industry.

CONTROLS

- Increasing number of “controls” submissions
  - **>8,000 submitted** in GDUFA I
- Seeing increasing complexity of controls
- ~20% controls do not follow FDA guidance
- PLEASE READ and FOLLOW “Controls” GUIDANCE – https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM583436.pdf

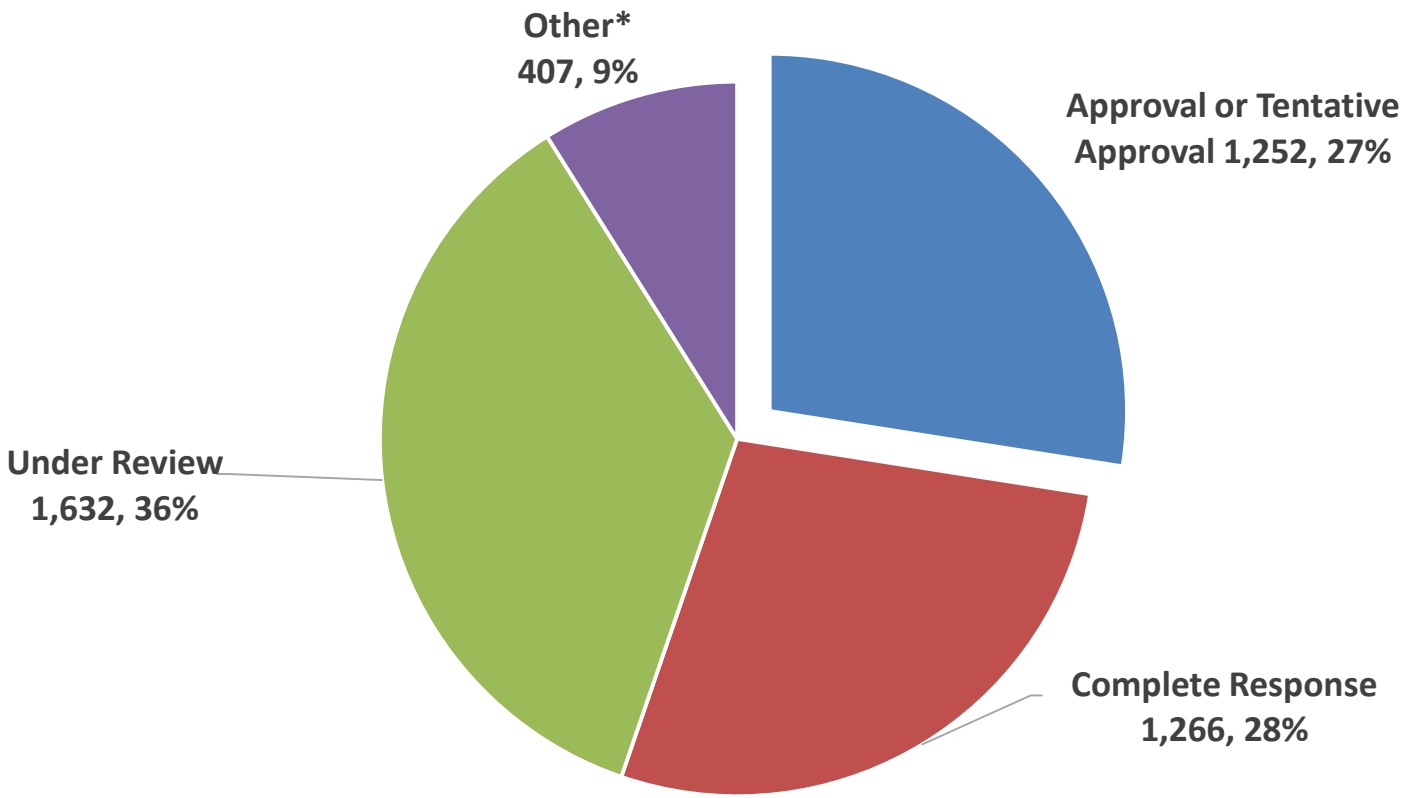
REGULATORY ACTIONS

GDUFA requires a Regulatory Action by the Goal date:

1. Approval (AP)
2. Tentative Approval (TA)
3. Complete Response Letter (CR or CRL)
4. Refuse to Receive (RTR)

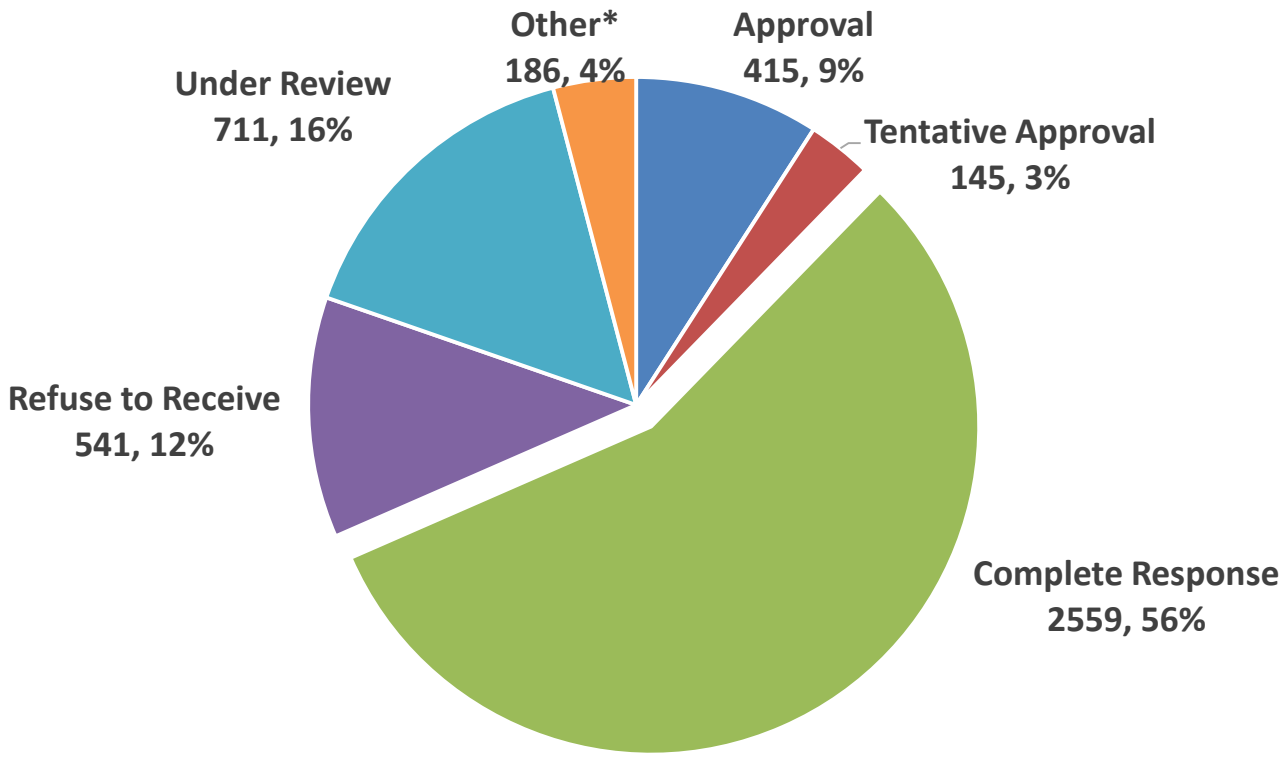
Regulatory action stops the review clock.

Current Application Status for GDUFA I original ANDAs (n=4,557)



Data as of 12/22/2017, Data Source: ANDAs originally submitted during GDUFA I, internal FDA database.
Data generated by CDER/OTS/OB, Jingyu (Julia) Luan, PhD, Jing Han, PhD, and Stella Grosser, PhD.
*Other includes: 'Withdrawn', 'Refuse to Receive', 'Unacceptable - User Fees Not Paid', 'Cancelled'.

GDUFA I
First Regulatory Action on Original ANDAs



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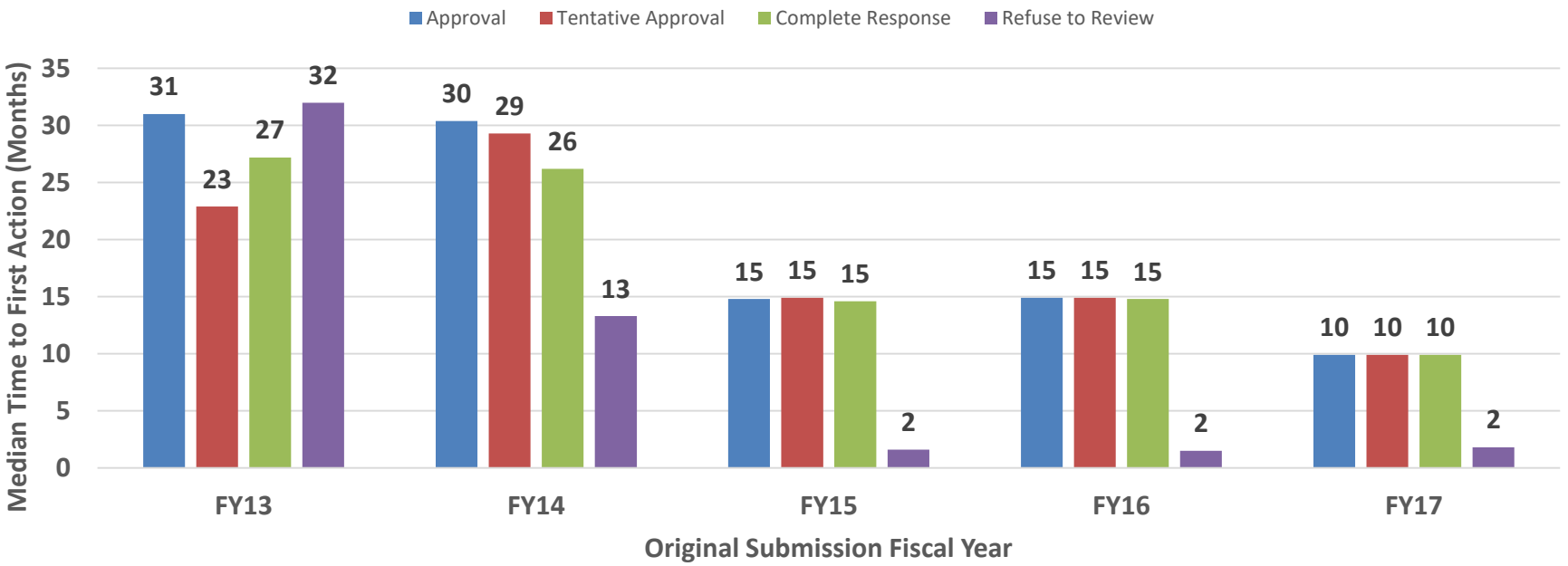
Data generated by CDER/OTS/OB, Jingyu (Julia) Luan, PhD, Jing Han, PhD, and Stella Grosser, PhD.
*Other includes: 'Withdrawn', 'Rescind-RTR', 'Unacceptable - User Fees Not Paid', 'Void Action - Decisional Correction', 'Canceled', 'N/A', 'Presubmission', 'Rescind - Unacceptable – User Fees Not Paid'.

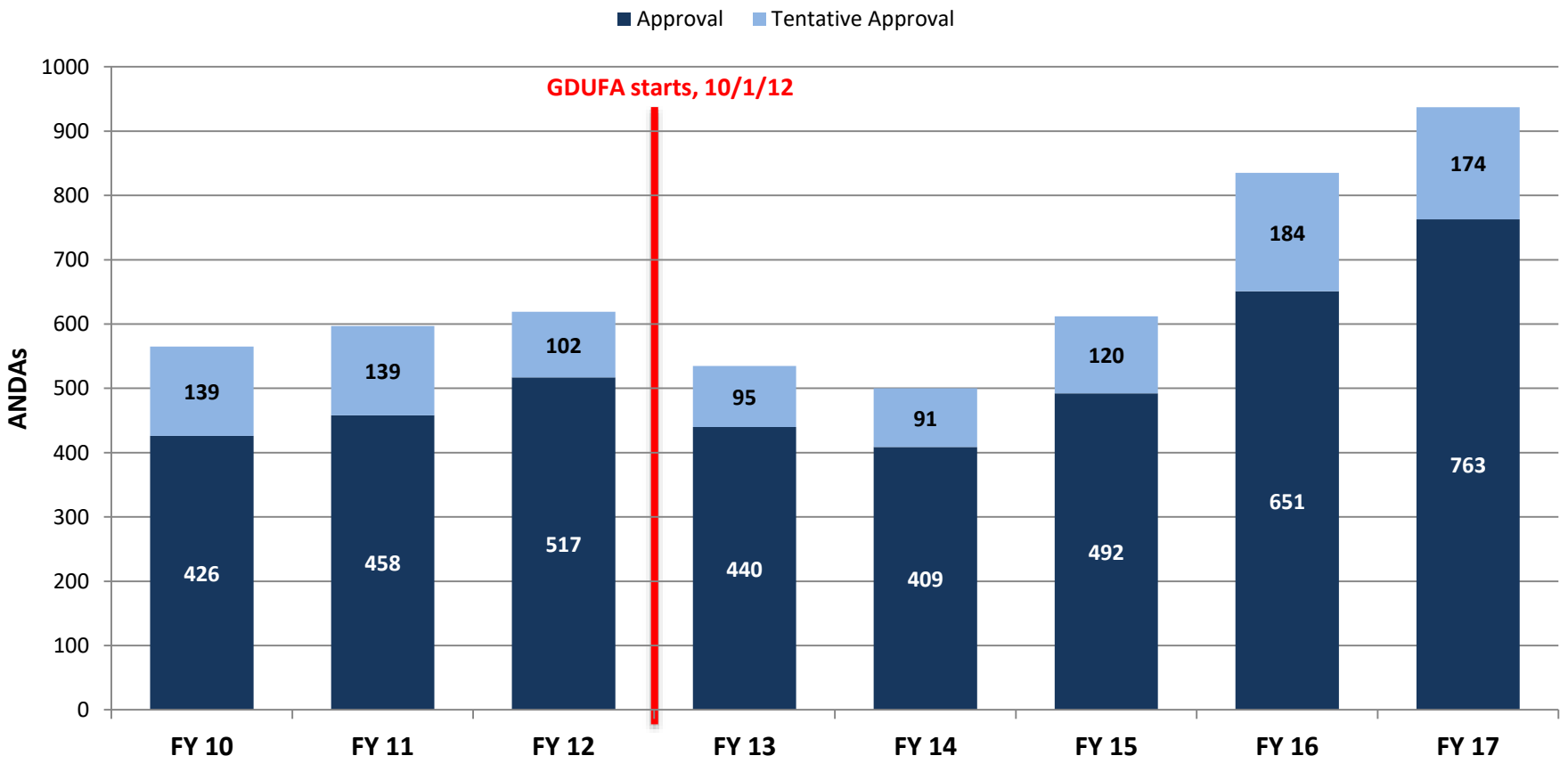
GDUFA I

Original ANDA - Median Time to First Action



Analysis of GDUFA I as of 12/22/2017, Data Source: ANDAs originally submitted during GDUFA I, internal FDA database.
Data generated by CDER/OTS/OB, Jingyu (Julia) Luan, PhD, Jing Han, PhD, and Stella Grosser, PhD

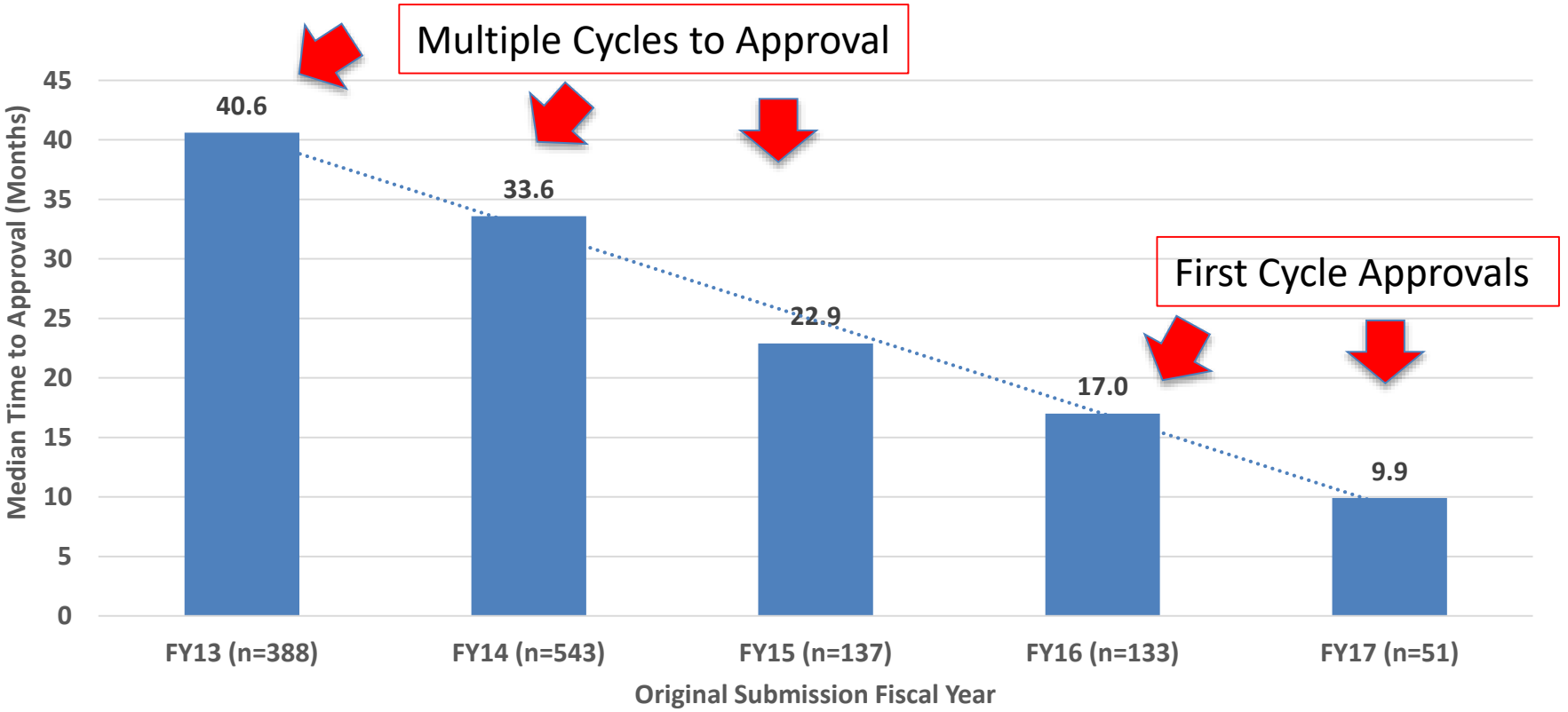
Annual Approvals & Tentative Approvals



*Updated 10/1/2017. Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.

ANDA Median Time to Approval per GDUFA I cohort year

(n=1,252, median=32.1 months, data cut off 12/22/2017)



NOTE:

- Trend over time is likely to flatten reflecting CRL response times and multiple cycles to approval
- Industry response to CR letters: 50% w/in 6 months, 33% 7-12 months, 17% greater than 12 months
- Future data will depict time with FDA and time with industry

Data generated by CDER/OTS/OB, Jingyu (Julia) Luan, PhD, Jing Han, PhD, and Stella Grosser, PhD
*Data Source: ANDAs originally submitted during GDUFA I as of 12/22/2017, internal FDA database.

MEDIAN TIME TO APPROVAL

- Best case:
  - Years 4 and 5 data on previous slide
  - Fastest 5% and 10%
  - Median time to approval c/w GDUFA goals and 1st cycle approvals

- Realistic case:
  - 1st review cycle (CRL "major") = 10 months
  - Time with industry before responding to CR = 12 months
  - 2nd review cycle for "major" amendment = 10 months
  - TOTAL TIME TO APPROVAL = 32 months

FIRST CYCLE APPROVALS*

Prior to GDUFA	**<1%**
FY2015	**10.7%**
FY2016**	**14.7%**
FY2017**	**10.7%**

- Low %
- Inefficient use of Agency and industry resources
- Critical to improve the ANDA Quality UP FRONT, before submission

*Updated 1/25/2018. Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.
**Percent represents the current percentage of regulatory actions FDA completed within the review-time goal. Final performance will depend on the outcome of pending submissions. For cohort Year 5 (FY2017), many ANDAs are still under review and within goal; all mature by July 31, 2018.

First Cycle Approval Definition: The percentage of AP and TA original and original-response to RTR ANDAs that were received for extensive review and were given a regulatory decision (excluding ANDAs under review).

INTERVAL BETWEEN CR LETTER AND AMENDMENT

- CRs result in more work and re-work by both industry and FDA
- If long time before amendment to CR submitted, more likely to have:
  - Change in review/assessment staff
  - Changes in standards
    - Change in Product Specific Guidance (PSG) or other FDA guidance
    - Change in USP monograph, ICH or other requirements
  - Change in RLD labeling
  - Change in facility status or need to add new facilities
  - Change in or new CMO

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GDUFA Regulatory Science

- During GDUFA II negotiations questioned by industry to continue or not
- Substantial value added to generic drug program, with considerable ROI for industry developing generic drugs
  - $100M program over 5 years
  - GDUFA I: published ~800 product-specific guidances (PSGs)
    - 295 for complex generic drug products
  - GDUFA I work provided the foundational elements and infrastructure for GDUFA II Pre-ANDA program
    - “Pre-ANDA” meetings
    - Timelines for PSGs after NDA approval

GDUFA Regulatory Science

1. Develops and validates methodologies to demonstrate “sameness” and “bioequivalence” -- Standards setting
2. Streamlines generic drug product development, regulatory review/decision making, and approval/TA
3. Enhances public and medical community acceptance of generic drugs

GDUFA Regulatory Science

Develops and validates methodologies
Standards Setting

- FDA "science" conducted in the public domain
- Keeps abreast of scientific advances in the field
- Program using robust scientific methods
  - Reproducible findings:
    - Conducted at different locations with several investigators
    - 8 way cross over studies to develop robust standards
- Alignment across FDA – e.g., among CDER offices and review disciplines, CDRH, etc.
- Agency's current thinking on how to develop specific generic drug products
- Leads to many Product Specific Guidances (PSGs)

GDUFA Regulatory Science

Streamlines development, review, and AP/TA

- Adhesion guidance revision, 600 vs. 60 subjects
- In vitro characterization (Q3) vs. large clinical endpoint study
- Work leads directly to ANDA approvals; for example, following PSG results in:
  - ~75% Bioequivalence "adequate" after 1st review cycle
  - Higher AP rate vs. ANDAs not following PSGs

GDUFA Regulatory Science

Enhances acceptance of generic drugs

- Epilepsy Foundation 2016 position statement endorsing generic substitution in patients with seizures:

"…not only confirms that the FDA's standards for BE are appropriate for persons with epilepsy, but it also supports ongoing research and makes practical recommendations for HCPs who prescribe or dispense generic forms of AEDs."

Epilepsy Curr. 2016 May-Jun; 16(3): 209–211.

GDUFA Regulatory Science

- Like most science, it evolves over time, as we learn more about specific drug products:
  - Data on use of drugs in a real world and postmarket setting
  - PMRs/PMCs completed for RLD
  - Scientific advances in the field

- At the time of approval, an ANDA needs to meet the Agency's *current* approval standards, and not the standards from when ANDA submitted and/or accepted for filing.

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GDUFA II

"Goals" or "Commitment" letter:

http://www.fda.gov/downloads/forindustry/userfees/genericdruguserfees/ucm525234.pdf

PLEASE READ!

GDUFA II HIGHLIGHTS

- Numerous Review Program Enhancements
  - Discipline Review Letters (DRLs)
- Pre-ANDA program for complex products
- "PFC" – Pre-submission Facility Correspondence
- "Bridging Goals" for GDUFA I Pre-Year 3 ANDAs, i.e., those with no official GDUFA I goal dates
- DMF enhancements
- Accountability and reporting enhancements
- Small business relief for fees

ORIGINAL ANDA REVIEW

- FDA committed to:
  - Information requests (IRs) as well as mid-cycle discipline review letters (DRLs) from disciplines assessing/reviewing ANDAs

AMENDMENTS REVIEW

- Major vs. Minor designation reflects the time FDA anticipates it will take to review the amendment, not the time industry takes to respond

AMENDMENTS REVIEW

- There are no GDUFA II commitments to provide IRs and DRLs during amendment review; those were commitments unique to original ANDA review

- FDA will strive to provide IR and DRLs when possible, e.g., during major amendments
  - Issued at the discretion of a discipline or sub-discipline
  - See MAPP 5220.5, Issuance of Information Requests and/or Discipline Review Letters for Abbreviated New Drug Applications

- For minor amendments, with 3 month review goal, unlikely to see IR or DRL from FDA, and may see CR letters with deficiencies from one discipline
  - For example, Labeling is not always “easy”
    - Carve out, patents and exclusivity

ANDA REVIEW

- Responses to IR's and/or DRLs, FDA has the option to:
  - *Review responses*
  - *Defer to the next review cycle*
  - *Set a new review goal date*

- FDA can determine that amendments submitted during ANDA review **MAY** extend the review goal

  See GDUFA II Guidances on Amendments
  https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM578371.pdf
  and MAPP 5220.5 on IR/DRL

- We encourage industry to submit amendments during review cycle vs. going into a next review cycle (e.g., Elemental Impurity Data)

GDUFA II POLICY DOCUMENTS

- Published 10 GDUFA II-related guidances for industry
- Issued 6 MAPPs

GDUFA II Outreach Videos

Brief videos by FDA staff highlighting new features in GDUFA II on FDA.gov:

- GDUFA Overview
- Pre-ANDA Program for Complex Products
- Type II Drug Master Files (DMF) Update
- Performance Goals
- Goals Integration
- Review Status Updates
- Post Complete Response Letter (CRL) Meeting
- Requests for Reconsideration
- Review Classification
- More to come!

DIA Podcasts/Webinars

"Innovation in Generics"

OGD Speaker		
Maryll Toufanian, JD	**An Introduction to Generic Drugs – Hatch Waxman Overview**	Podcast- Recorded
Xiaohui (Jeff) Jiang, PhD	**An Overview of Challenges and Opportunities in the Development of Complex Generic Drug Products**	March 6, 2018 2:00 pm
Kim Witzmann, MD	**Overcoming Barriers to Entry for Complex Generic Oral Inhalation Drug Products**	March 15, 2018 3:00 pm
Sam Raney, PhD	**FDA Champions Research to Make Complex Generic Transdermal Products Available to Patients***	April 25, 2018 2:00 pm
Liang Zhao, PhD	**Pioneering Modeling Methodologies in Generic Drug Development***	May 17, 2018 1:00 pm

*Free registration available when posted on:
http://communities.diaglobal.org/events/calendar

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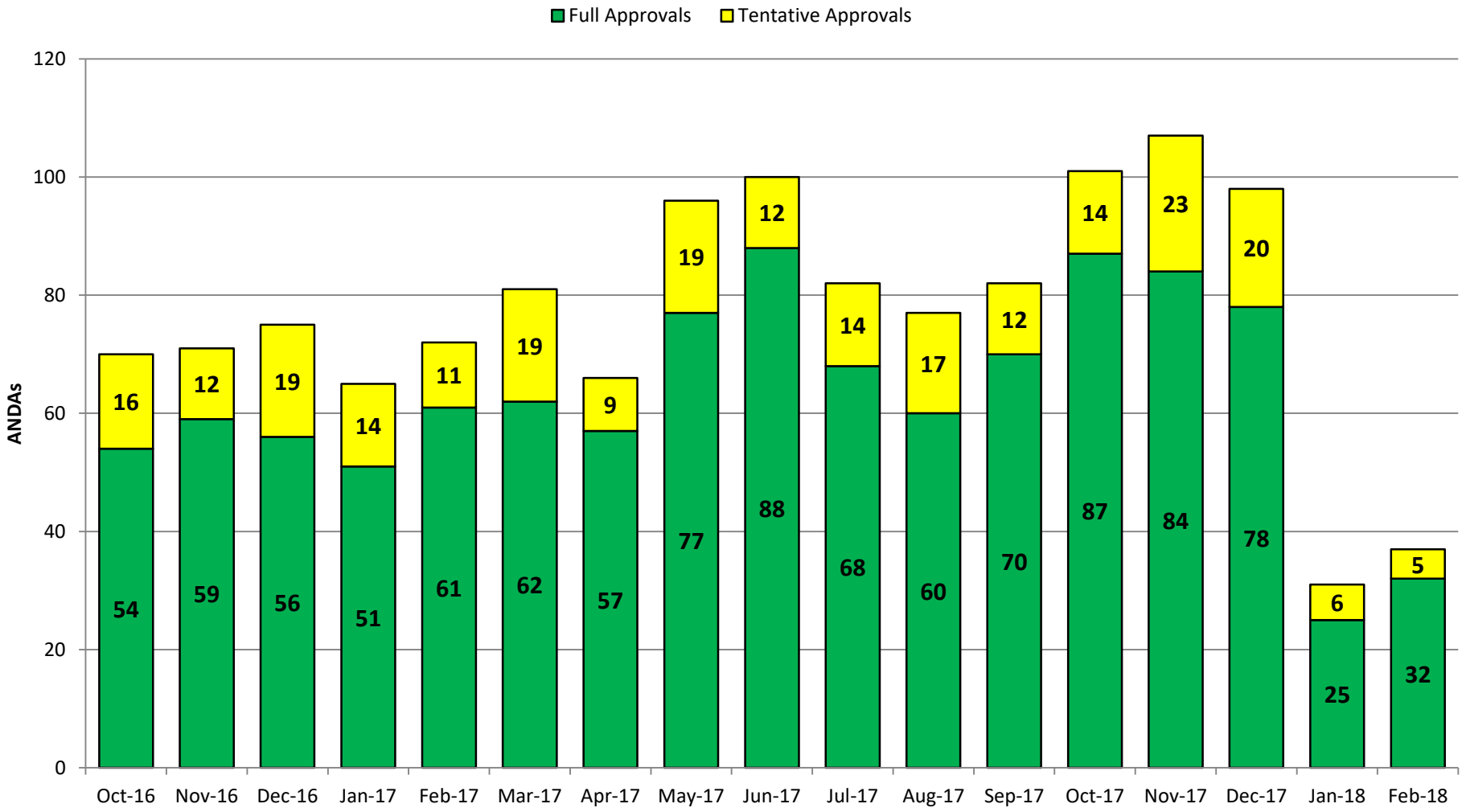
COMPANIES THAT HAVE A ROBUST UNDERSTANDING OF THE REGULATORY ENVIRONMENT HAVE THE COMPETITIVE EDGE

BE PROACTIVE

Stay up to date with:

- What is going on at FDA
  - Frequently monitor Federal Register, FDA websites and Twitter feeds
  - Subscribe to GDUFA, Generic Drug Updates, SBIA listservs
- FDA and CDER guidances
- Changes in US Pharmacopeia (USP) monographs
- RLD label
- REMS modifications
- International Conference for Harmonization (ICH)
  - ICH Q3D – Elemental Impurities, implemented 1/1/2018

Monthly Approvals & Tentative Approvals*



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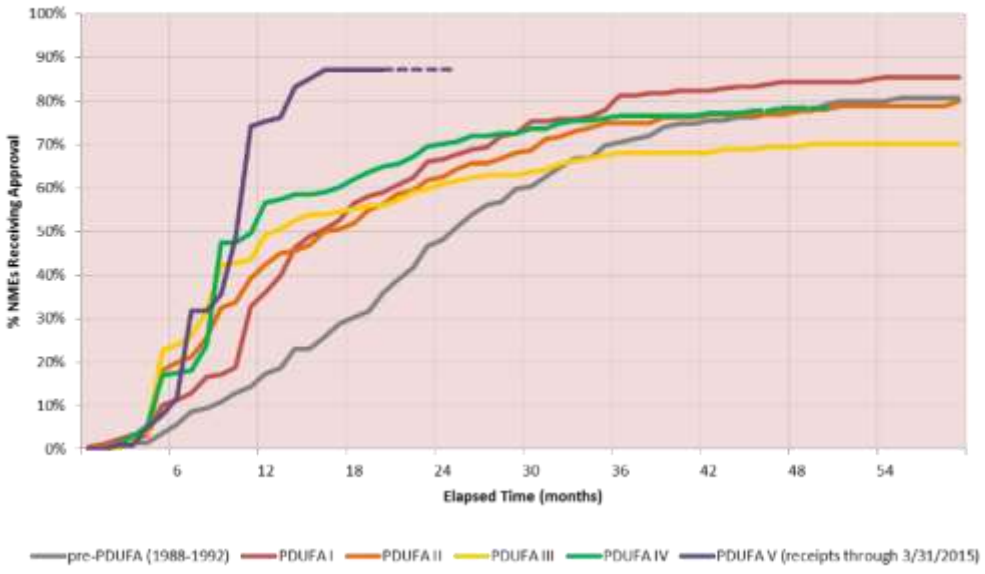
PDUFA EXPERIENCE: ACHIEVABLE HIGHER 1ST CYCLE APPROVAL RATE

CDER New Molecular Entity Approval Rates by PDUFA Cohort



- Applications right the first time are successful
- Benefits from PDUFA resources and efficiencies
- *Benefit of goal date extensions – keeping application under review and addressing deficiencies during review cycle*

Data as of 9/30/2016. PDUFA V estimates based on 77 NMEs submitted in FY 2013 – mid FY 2015 (it is too early to estimate performance for later submissions)
Projection estimates account for actions to date and elapsed time to date for non-approvals

FDA's GENERIC DRUG PROGRAM

- FDA built a HIGH quality Generic Drug Program during GDUFA
- Issued record numbers of approvals and tentative approvals
- However, at the end of GDUFA I:
  - High Rate of Refuse to Receive (RTR)
  - Low first cycle approvals and large number of Complete Response letters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