

STATE OF OGD:

Pivoting to GDUFA II

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AAM Fall Technical Conference
November 6, 2017

Disclaimer

- This presentation reflects the views of the speaker and do not reflect official FDA, HHS, or other government opinion or policy.
- I have nothing to disclose.
- FY2017 data represent preliminary data that are being further reviewed and validated for official reporting purposes. October 1, 2017 used as cut-off.

Overview

1. Update on GDUFA I
 - Receipts
 - Actions towards Goals
 - Other accomplishments
2. Brief comments on GDUFA II
3. Closing Comments

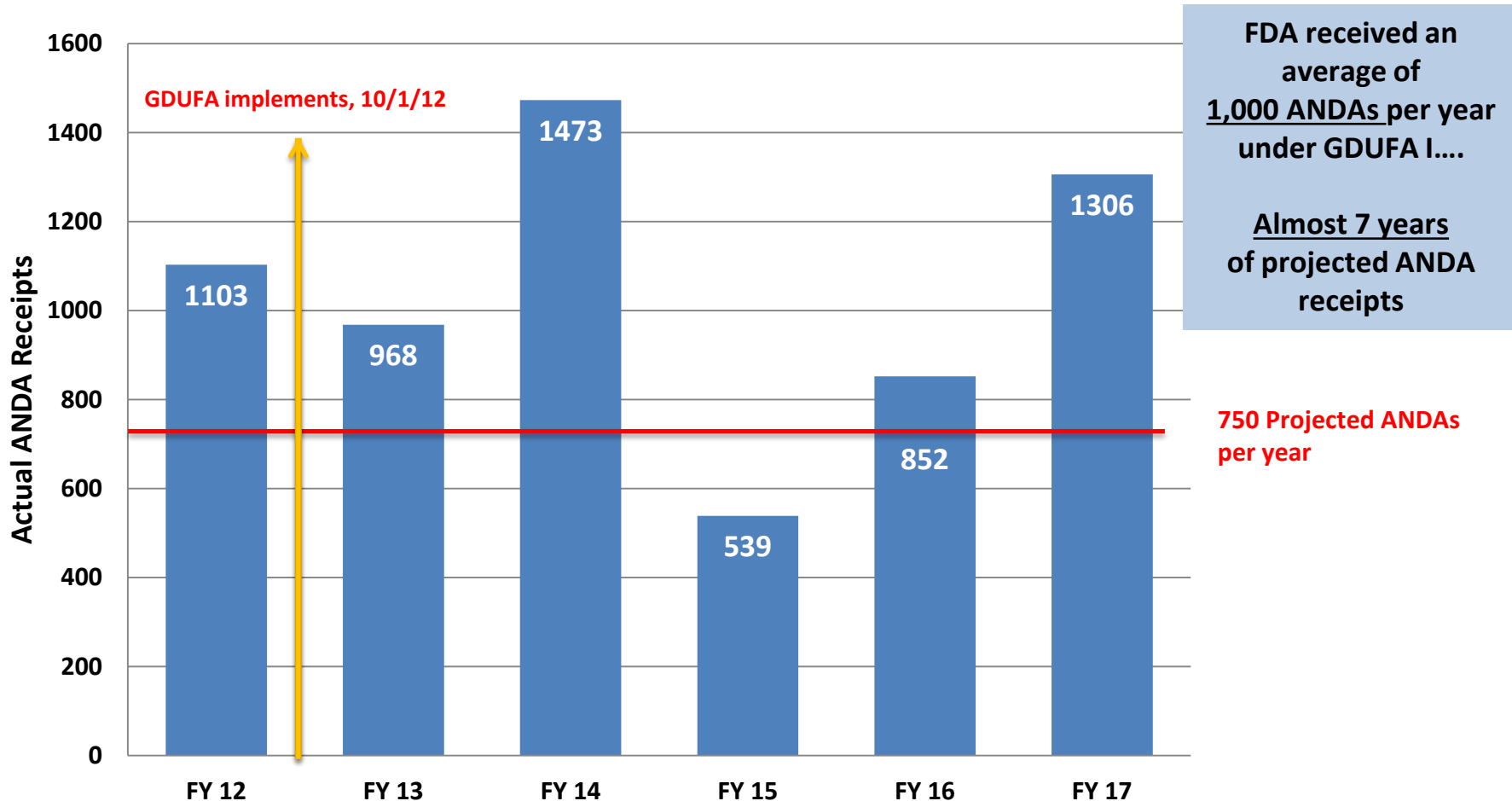
Generic Drug Program: Current State

- FDA is meeting or exceeding the GDUFA goals
- Numerous other significant accomplishments
- Standing up/implementing GDUFA II
- Evaluating FDARA - this will take time
- Main outstanding challenge is multiple review cycles
 - Inefficient and leads to a huge amount of re-work for FDA and applicants alike

GDUFA I workload

- Number of original applications exceeded estimates
- Number of applications continues to rise
- Number of amendments continues to rise
- Number of controls continues to rise
 - More complex controls
- Number of companies increasing
- Number of facilities increasing

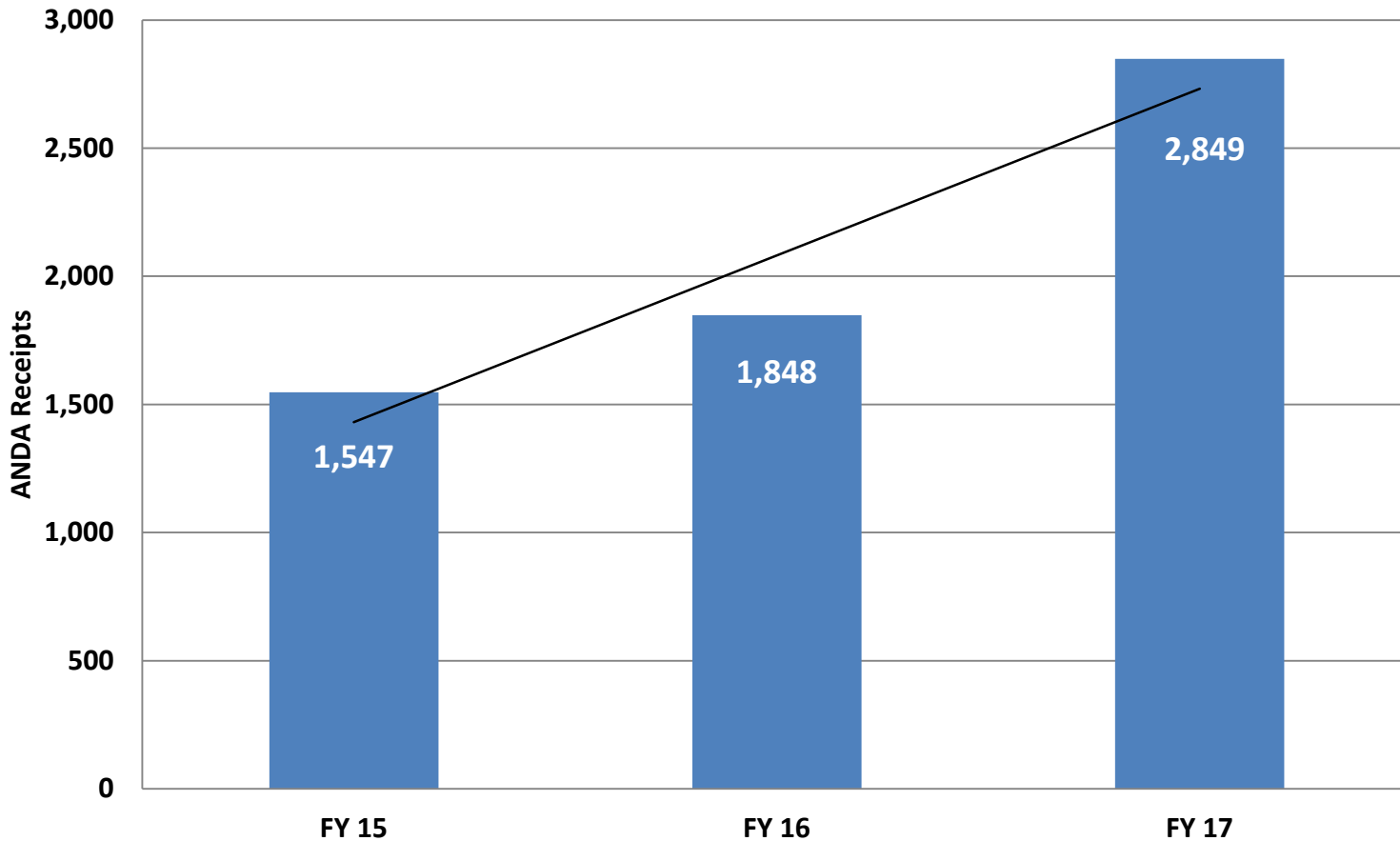
Projected vs Actual* ANDA Receipts



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

ANDA Receipts

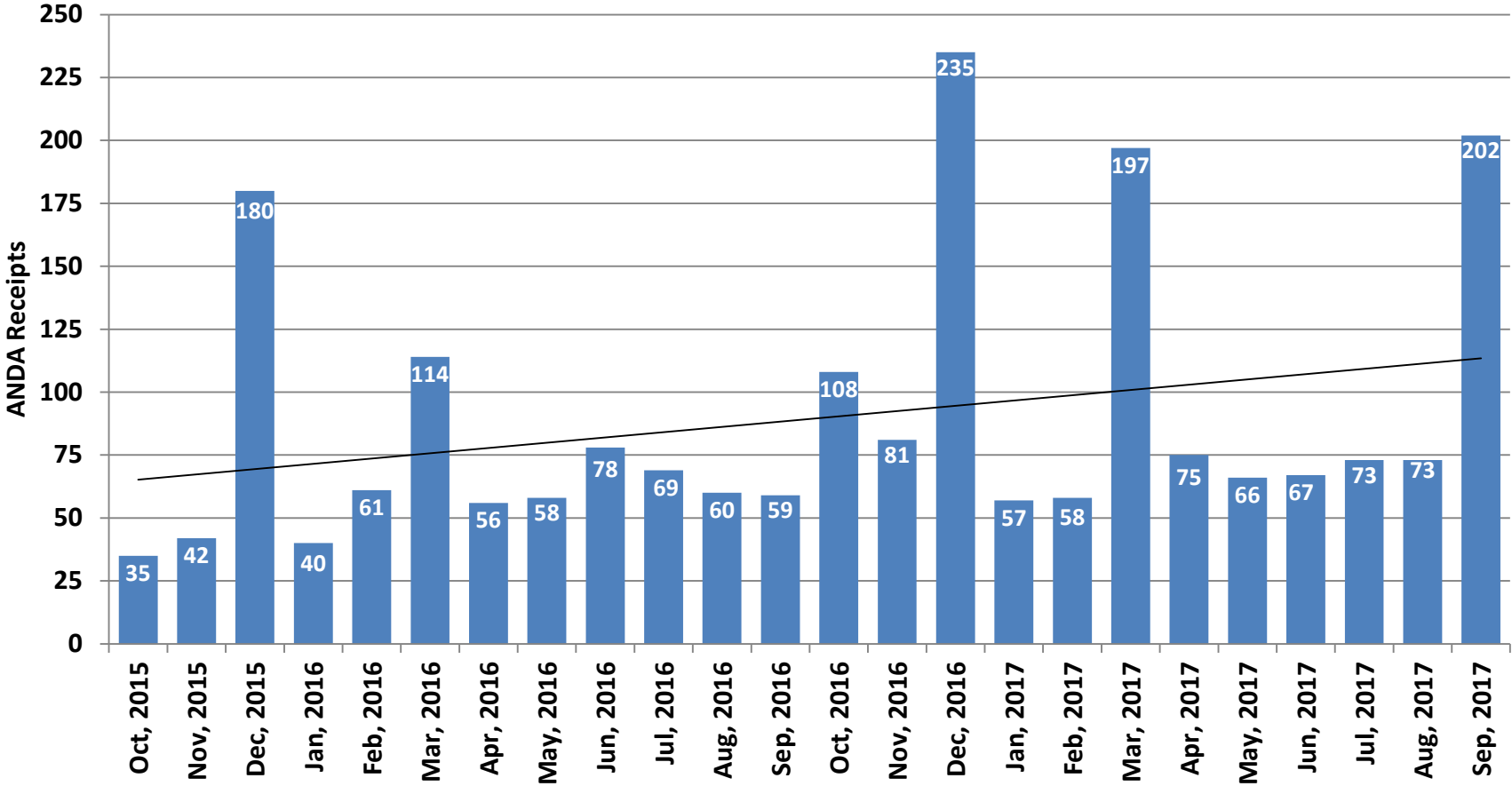
(Originals + CR Responses/Amendments)



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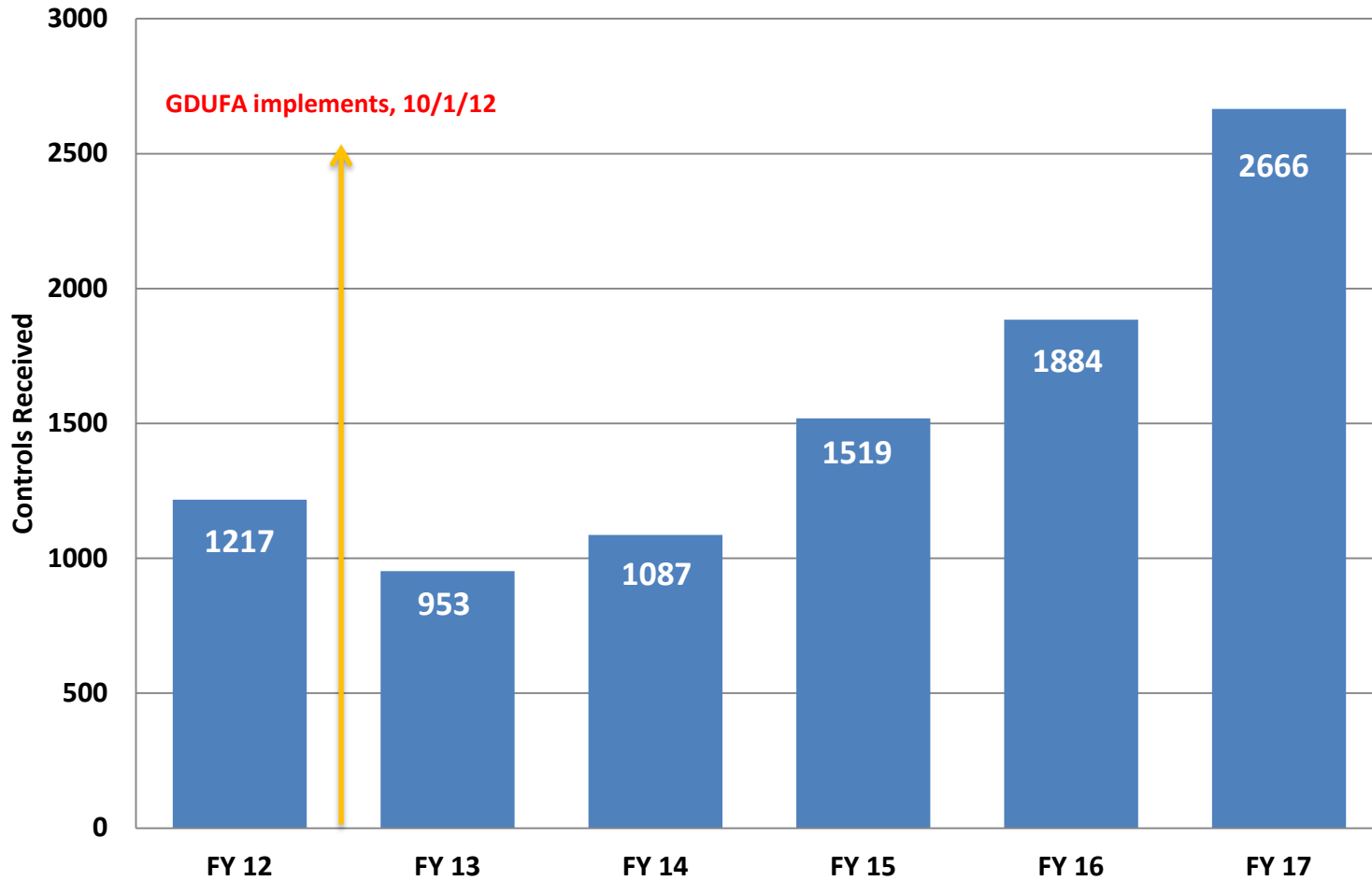
Monthly ANDA Receipts

(New Originals)



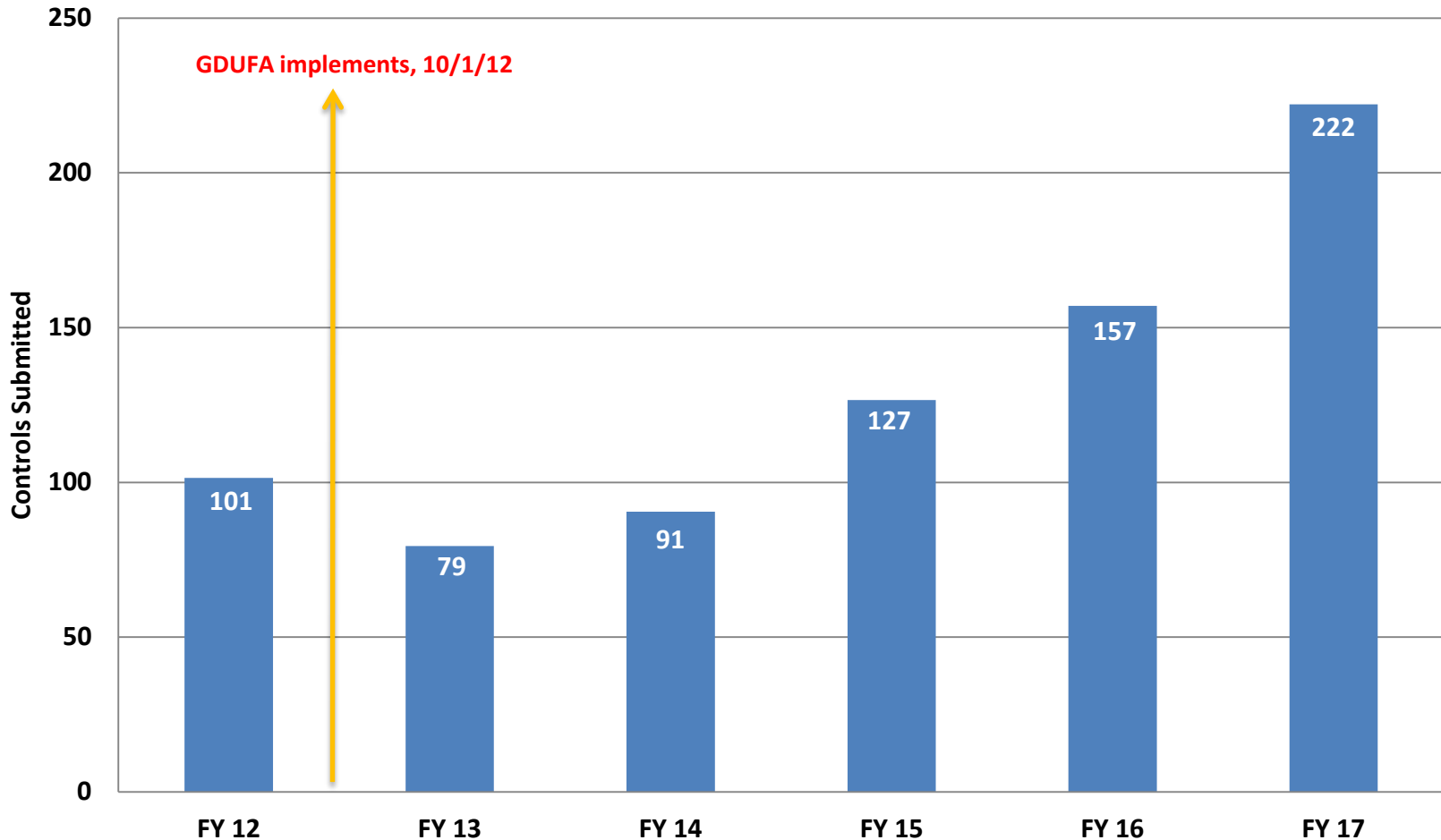
* Updated 10/1/2017. Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.

Controls Received



* 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.

Average Monthly Controls Submitted



* 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.

To date, FDA has met or exceeded EVERY formal negotiated GDUFA goal

Original ANDAs

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

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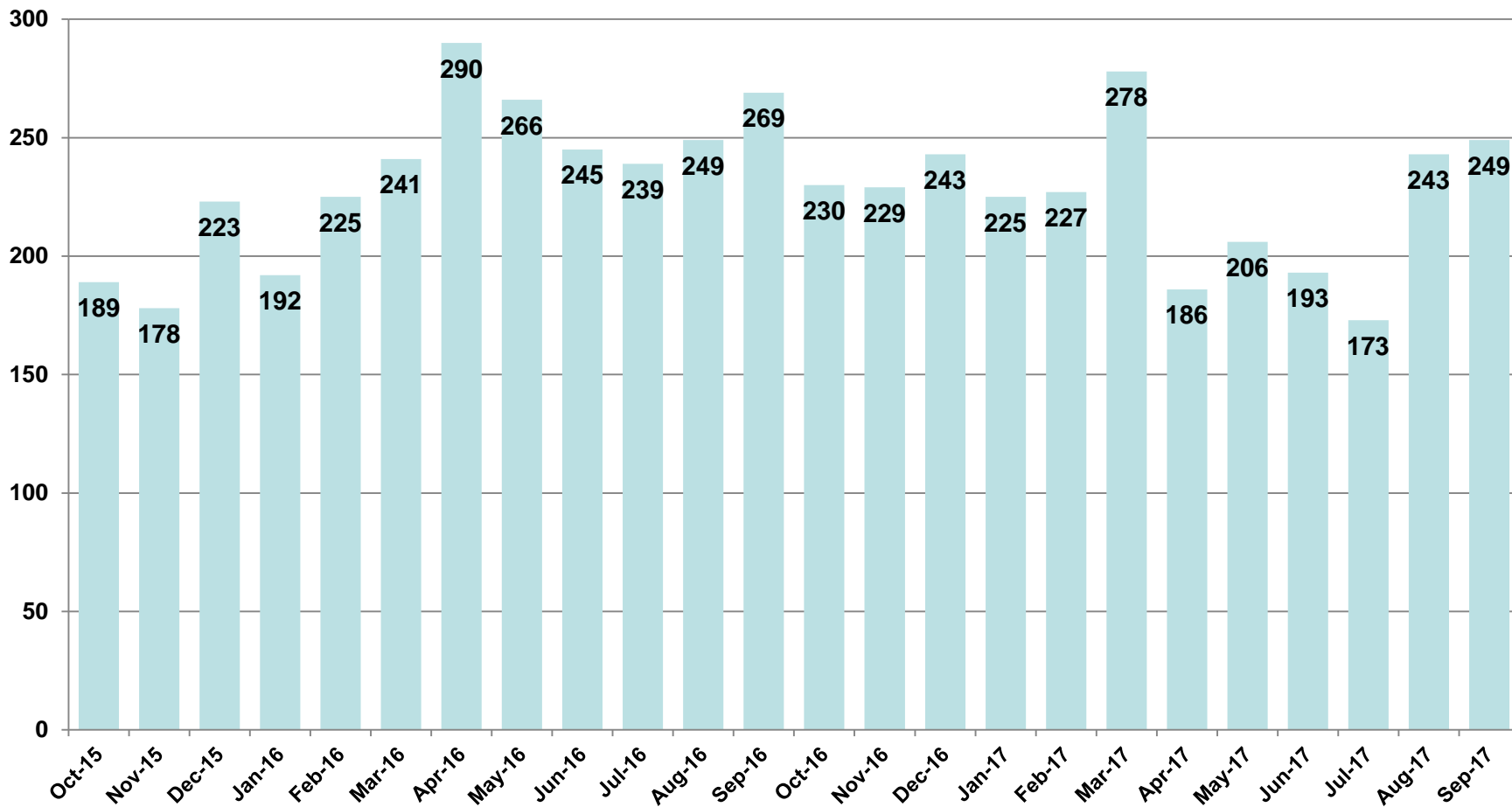
Cohort Year 4 (FY2016) – Some are still under review and within goal; all mature by December 31, 2017.

Cohort Year 5 (FY2017) – Many are still under review and within goal; all mature by July 31, 2018.

**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.

Total ANDA Regulatory Actions per Month

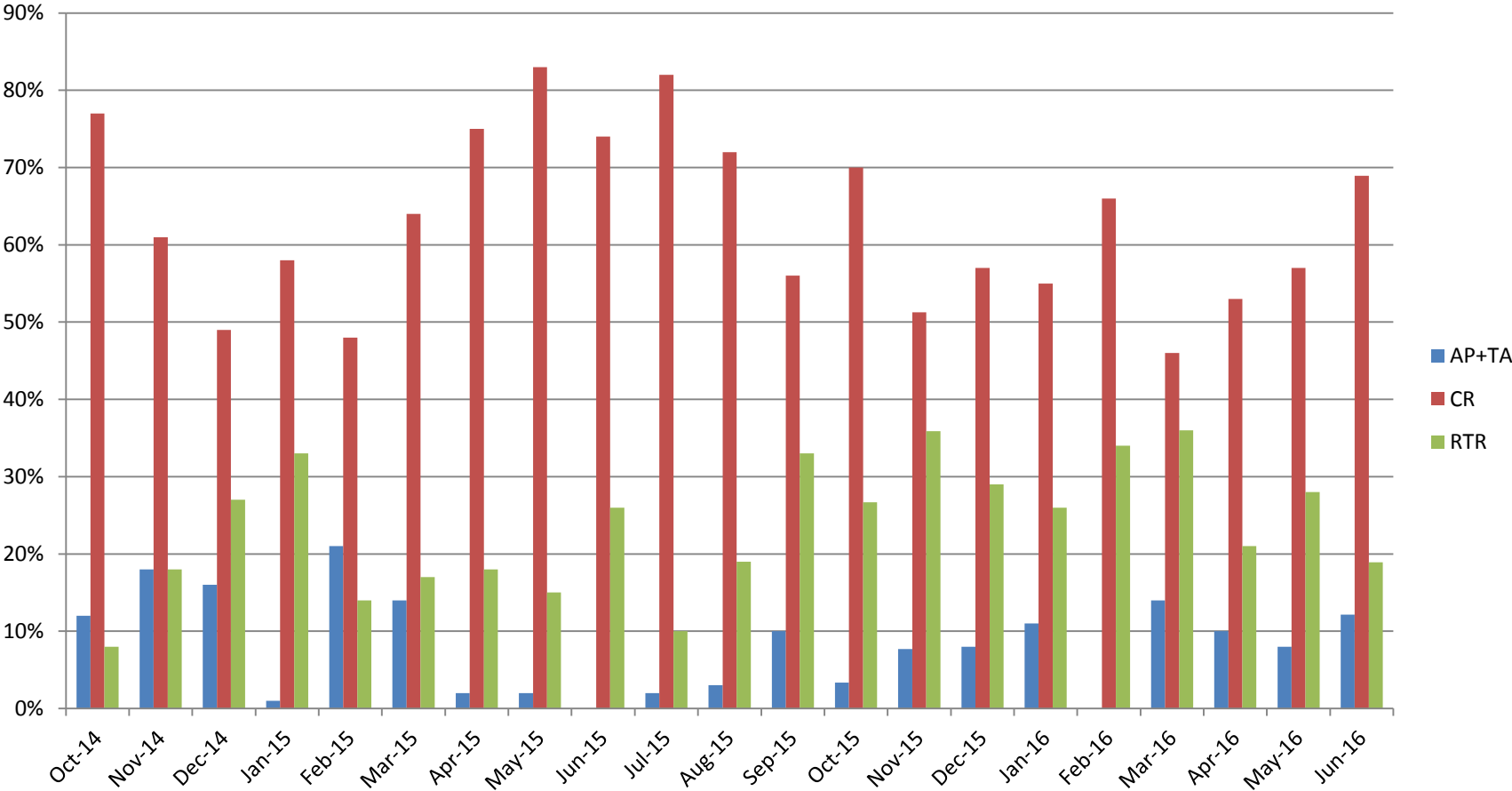
(AP+TA+CR+RTR)



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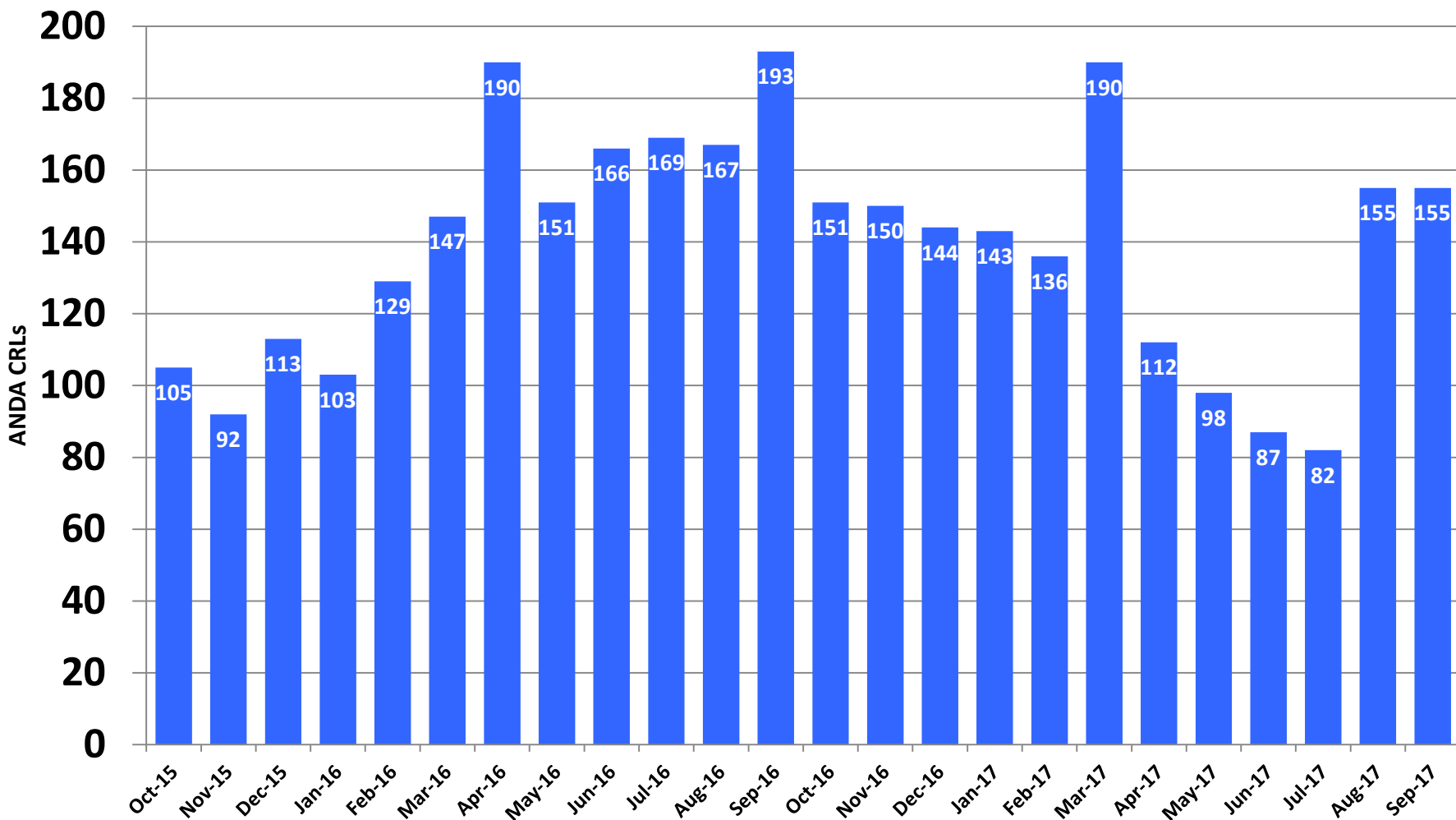
First Regulatory Action – Rates

Rate for all original ANDAs submitted for the respective month of submission



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 Cohort Year 4 (FY2016) – Some are still under review and within goal; all mature by December 31, 2017.
 Cohort Year 5 (FY2017) – Many are still under review and within goal; all mature by July 31, 2018.

ANDA Complete Response Letters (CRLs)



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Overall Regulatory Actions.... Another Record Year

Pre-GDUFA

GDUFA I

	FY2012	FY2013	FY2014	FY2015	FY2016	FY2017
ANDA approvals	517	440	409	492	651	763
PAS approvals	275	535	659	624	481	431
Tentative Approval (TA)	102	95	91	120	184	174
Complete Response (CR) †	84	1251	1254	1180	1725	1603
TOTAL **	978	2321	2413	2416	3056	2971
DMF Completeness Assessment (CA)	0	1699	1706	901	886	820*

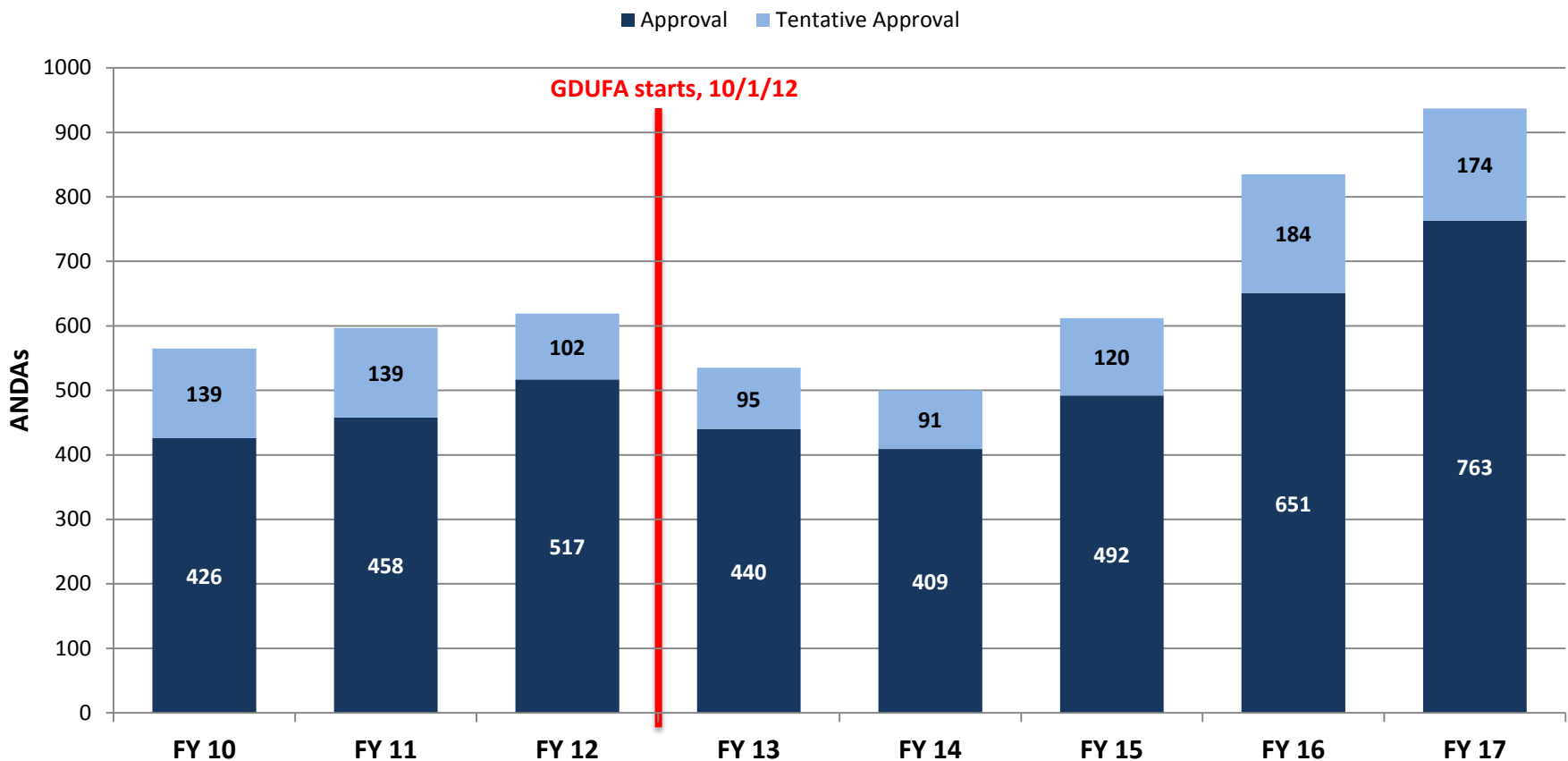
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** FDA will aspire to the extent possible to **maintain levels of productivity at least similar to pre-GDUFA levels**, while hiring and training incremental staff necessary to achieve the program performance goals, building necessary systems and implementing outlined program changes in years 1 and 2 of the program (GDUFA Commitment Letter, page 3)

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm375079.htm> 16

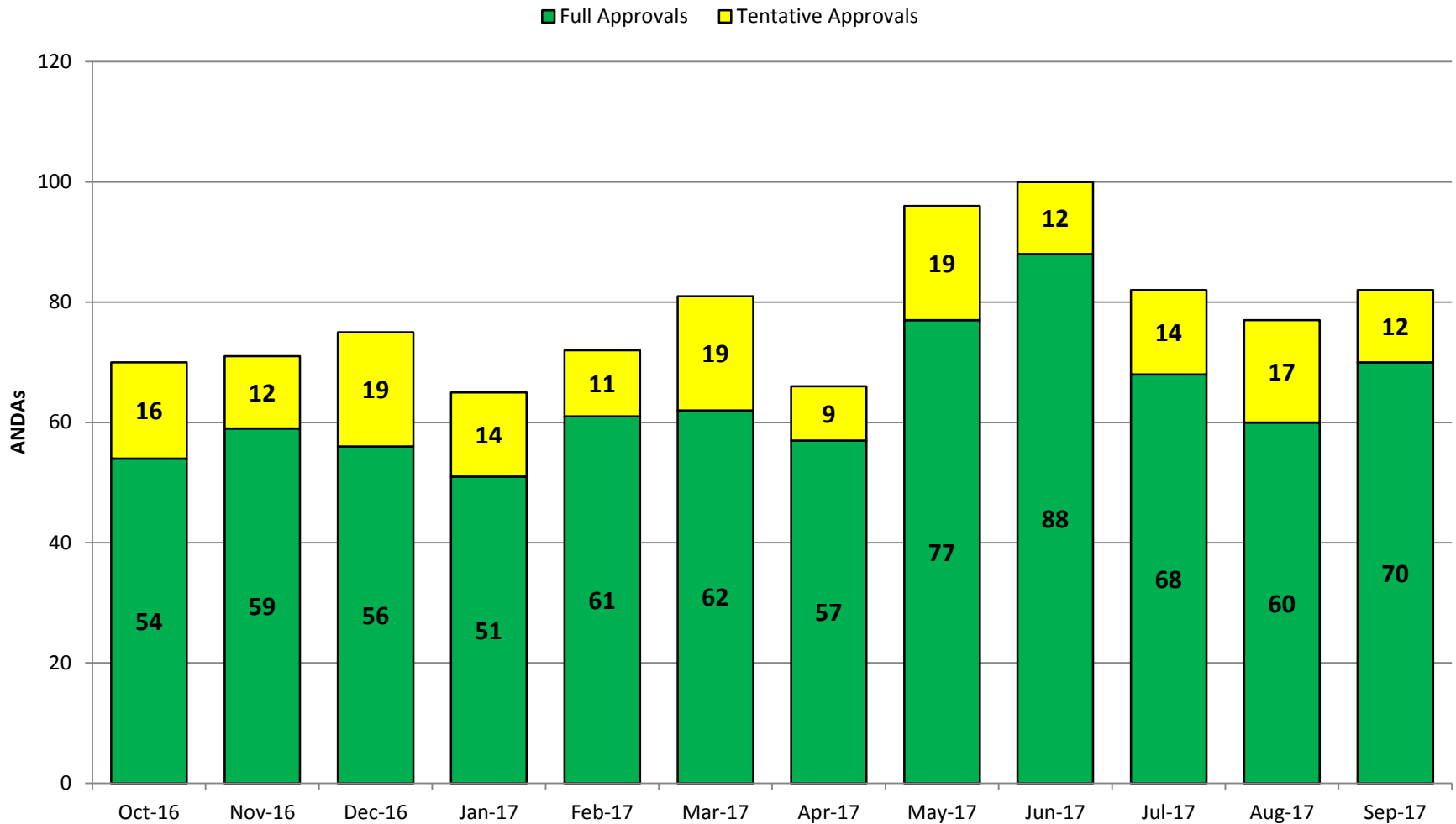
† Complete Response both with and without inspections for ANDAs.

Annual Approvals & Tentative Approvals



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

Monthly Approvals & Tentative Approvals*



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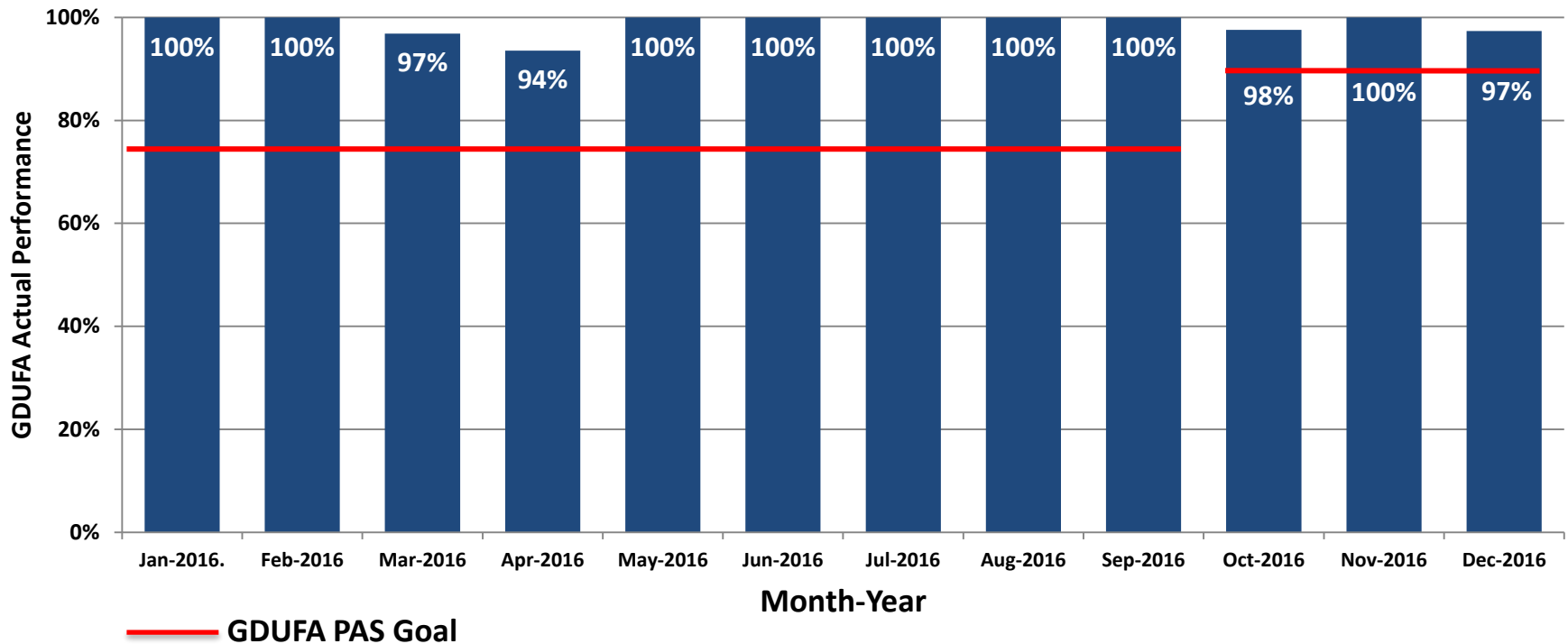


FY2017 - Notable ANDA Approvals

Generic Name	Reference Listed Drug
Olmesartan Medoxomil Tablets, 5 mg, 20mg, and 40 mg	Benicar Tablets
Quetiapine Fumarate Extended-release Tablets, 50 mg, 150 mg, 200 mg, 300 mg, 400 mg	Seroquel XR Tablets
Dexlansoprazole Delayed-release Capsules, 60 mg	Dexilant Capsules
Atomoxetine Capsules, 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, and 100 mg	Strattera Capsules
Mesalamine Delayed-release Tablets USP, 1.2 g, and 800 mg	Lialda and Asacol HD Delayed-release Tablets
Emtricitabine and Tenofovir Disoproxil Fumarate Tablets, 200 mg/300 mg	Truvada Tablets
Sevelamer Carbonate Tablets, 800 mg; Powder for Oral Suspension, 0.8 g and 2.4 g Pouches	Renvela Tablets and Powder for Oral Suspension
Prasugrel Tablets, 5 mg, 10 mg	Effient Tablets
Isoproterenol Hydrochloride Injection, USP 0.2 mg/mL and 1 mg/5 mL (0.2 mg/mL) (single-dose vials)	Isuprel Injection
Ezetimibe and Simvastatin Tablets, 10mg/10mg, 10mg/20mg, 10mg/40mg, 10mg/80mg	Vytorin Tablets
Oseltamivir Phosphate for Oral Suspension, 6 mg (base)/mL	Tamiflu for Oral Suspension

Prior Approval Supplements (PASs)

GDUFA Goal: PAS



* 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

PAS Actions

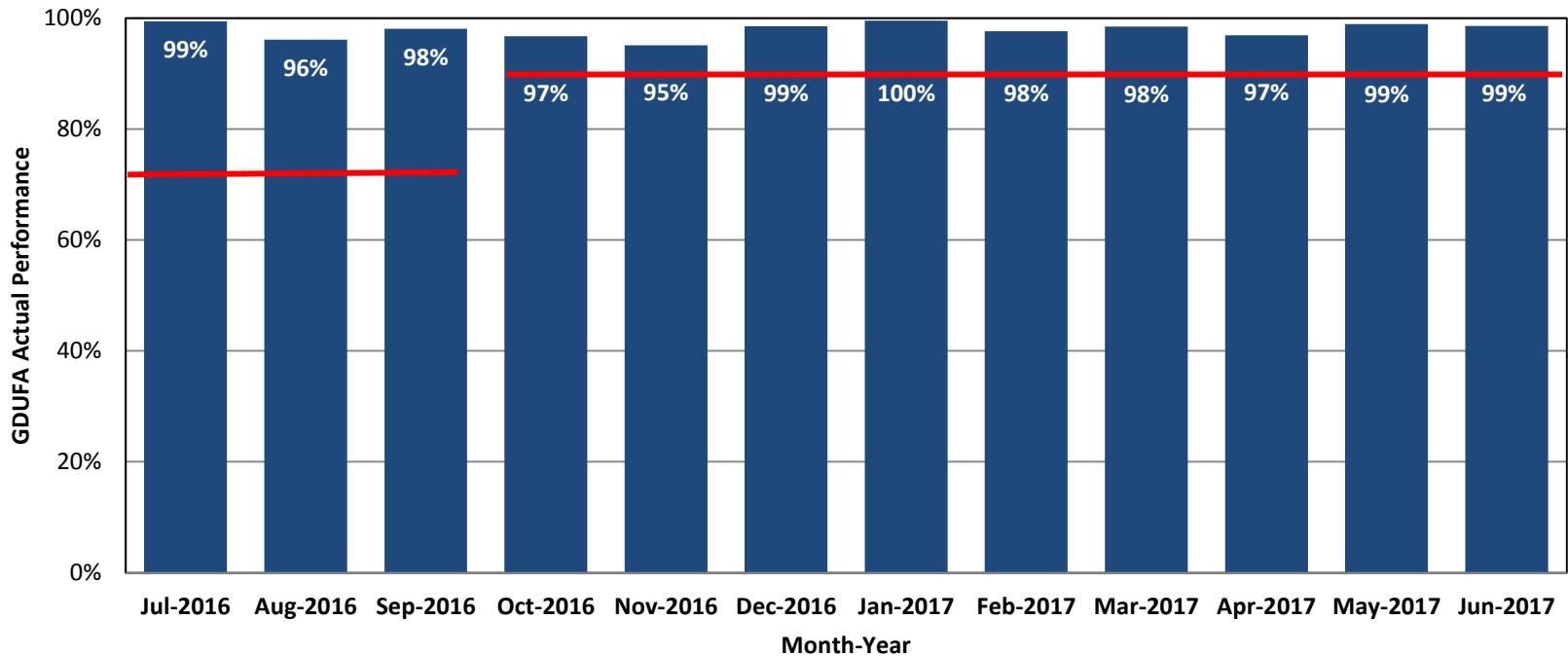
	FY2013	FY2014	FY2015	FY2016	FY2017
Received	482	436	480	478	415
Approved	535	659	624	481	431
CR Letter	8	18	185	228	223

Controlled Correspondence “Controls”

GDUFA Goal: Controlled Correspondence

Controlled Correspondence

GDUFA Performance by FDA Receipt Date – All Disciplines



— GDUFA Controlled Correspondence Goal

* Goal dates provided on submissions received in FY 2016 and 2017.

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CONTROLS

- Increasing number of “control” submissions
 - >8,000 controls submitted in GDUFA I
- Increasing complexity
- Approximately 20% controls do not follow FDA guidance
- PLEASE READ and FOLLOW GUIDANCE –
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM411478.pdf>

OGD FILING REVIEW

- > 1,100 original ANDAs, resubmissions, and PASs underwent filing review in FY2017

REFUSE TO RECEIVE (RTR)

- ~10-30% of ANDAs submitted get RTR
- ~1% fees not paid

	% ANDAs RTR-ed*
FY2015 (cohort Year 3)	34.3
FY2016 (cohort Year 4)	28.3
FY2017 (cohort Year 5**)	10.5
Overall RTR % FY15-17	20.9

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**Cohort Year 5 (FY2017) – Given the large number of ANDAs submitted in the end of FY2017, many ANDAs undergoing Filing Review

REASONS FOR REFUSE TO RECEIVE (RTR)

DEFICIENCY	%
Inadequate Stability	31.1%
Inadequate Dissolution	17.8%
Incomplete English translation	17.4%
No response with 7 calendar days	6.4%
Incomplete Response	5.5%
Not Q/Q Same	4.6%
Incomplete DMF	4.1%
Inadequate EA or Categorical Exclusion	3.2%
Incomplete/Failed BE studies	2.7%
Inadequate justification of excipients	2.7%

RTR is a CRITICAL “Vital Sign”

- If ANDA received RTR....
 - Less 1st cycle AP or TA
 - More deficiencies in CRL
 - Worse (“major”) deficiencies
 - If RTR resubmitted quickly to FDA, even lower likelihood for AP or TA





RTR is a CRITICAL ANDA “Vital Sign”

Regulatory Action	<u>WITH</u> prior RTR	<u>WITHOUT</u> prior RTR*
Approved or Tentative Approval	3.8%	11.5%
Complete Response Letter (CRL)	96.2%	86.9%

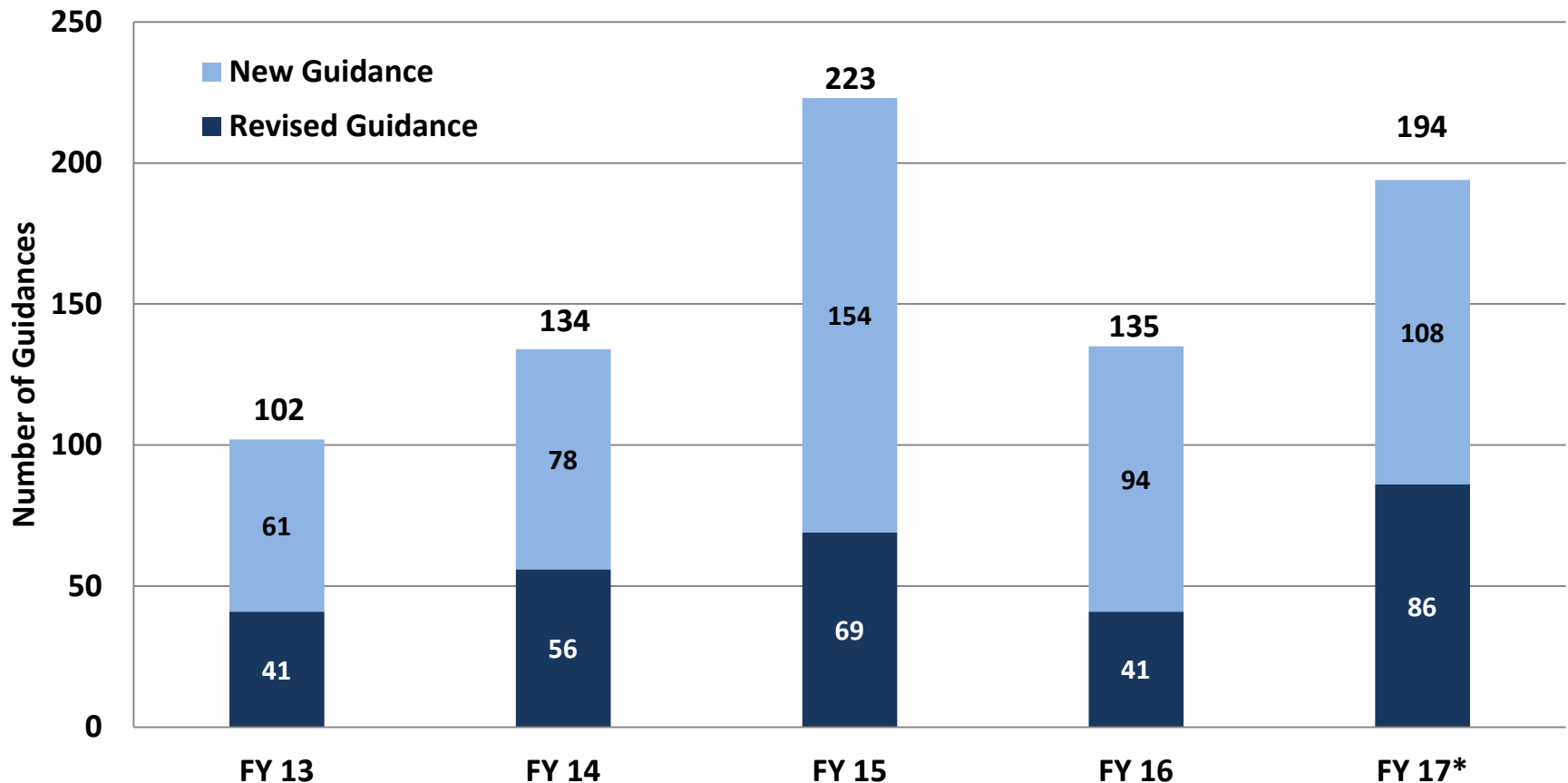
Analysis of FY2015 Year 3 cohort, conducted 8/9/2017; n=400 ANDAs, all underwent extensive review.
Results of First Regulatory Action following first cycle review.

*Does not total 100%; at time of analysis 1.6% were under active review.

GDUFA I Regulatory Science Accomplishments*

- Issued 108 external research grants and contracts
 - Prepared OGD for industry interaction on complex drug products
- Published 788 Product Specific Guidances (PSGs)
 - 495 new PSGs and 293 revised PSGs
 - Increased number for complex drug products each year
- Reviewed 127 pre-ANDA meeting packages
 - Almost all for complex drug products

Product-Specific Guidances (PSGs)

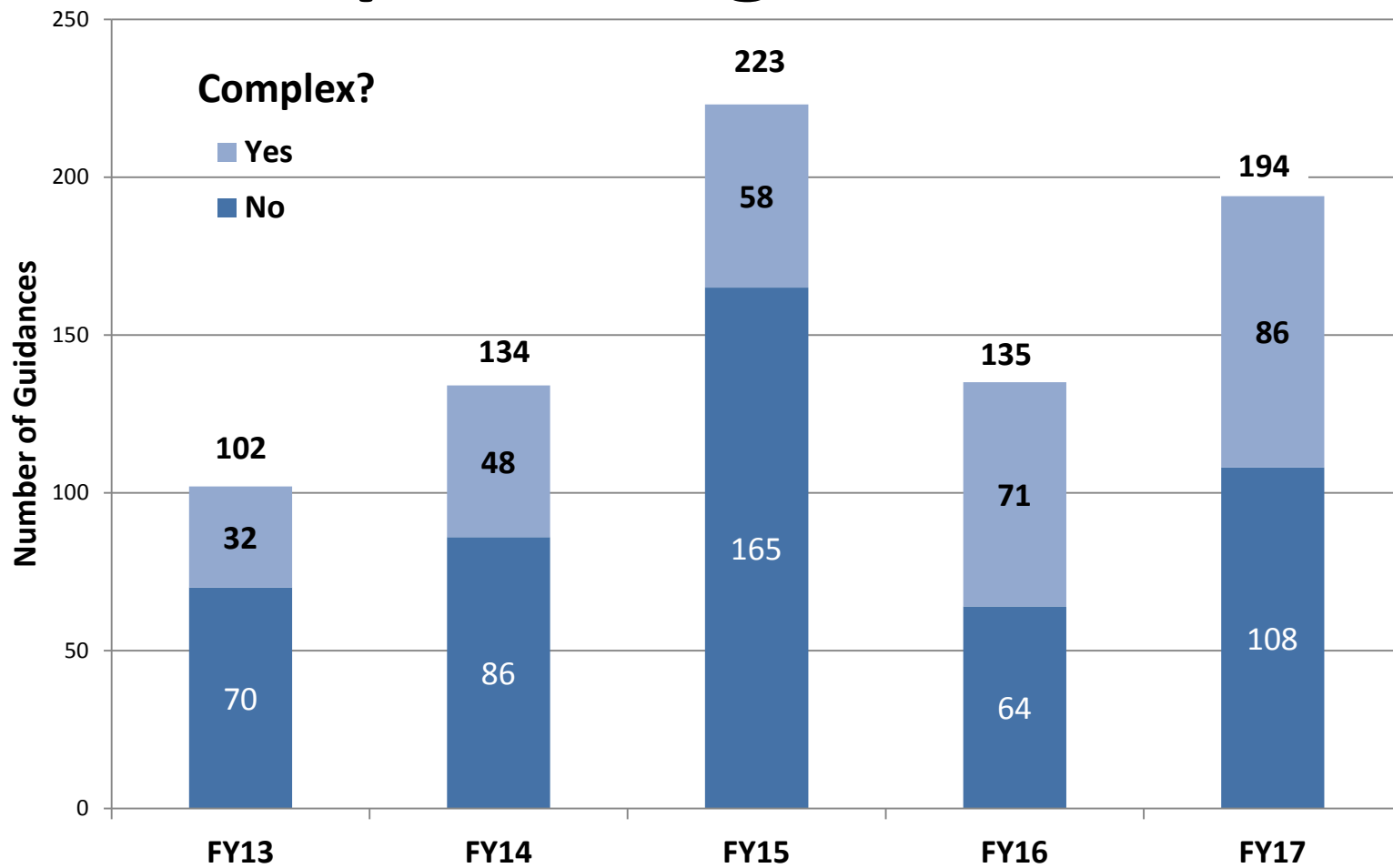


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Product-Specific Guidances (PSGs)



Complex Drug Products



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GDUFA I Regulatory Research



“Game Changers”

(\$Billion Impact)

- PSGs for:
 - 17 inhalation products
 - Conjugated estrogens
 - In vitro equivalence for topical ointments, topical creams, GI binding agents, ophthalmic emulsions
- Stand alone guidance for:
 - Generic abuse deterrent opioid formulations
 - BCS class III biowaivers
 - Synthetic peptides referencing rDNA RLDs
 - Adhesion for transdermals
- ANDA Approvals for:
 - Generic glatiramer acetate
 - Nasal spray suspension based on novel particle size methods
 - Topical ointments (in vitro approach)
 - GI binding agents (in vitro approach)
- Scientific Advances
 - Polymer characterization for long-acting injectables
 - First open flow microdialysis BE study for a topical cream

FY2017 OGD Policy Accomplishments*



- Co-led successful re-negotiation for GDUFA II
- October 2016 - Final Rule on ANDAs and 505(b)(2) Applications
- Developed policy and procedures to streamline the publication of Federal Register notices announcing the voluntary withdrawals of ANDAs under 21 CFR 314.150(c)
- Published 15 guidances
 - 7 - GDUFA II related
- Issued 7 MAPPs
- Orange Book Modifications
 - ~ 5,600 NDAs and ANDAs to add RS and RLD designations and ~ 840 discontinued NDAs to provide RLD designations
- Supporting the Commissioner's Drug Competition Action Plan

FDA Commissioner Scott Gottlieb, MD



- Huge interest and focus on Generic Drugs
- Numerous internal briefings provided regarding the generic drug program, GDUFA, Hatch-Waxman, and other activities
- Attendance at OGD All Hands
- Drug Competition Action Plan



Communicating FDA's Generic Drug Program



REQUIRED:

- [GDUFA Performance Reports](#)
- [GDUFA Financial Reports](#)

COMING SOON

GDUFA II Dashboards:

- More metrics
- Different reporting
- Not OGD reports

ENHANCED:

- GDUFA [Regulatory Science Annual Report](#)
- [Activities Report of the Generic Drug Program](#)
- [Quarterly Meeting Minutes Between FDA and Industry](#)
- Quarterly [Generic Drug Review Dashboard](#)
- ANDA [First Generic Drug Approvals](#)
- Office of Generic Drugs [Annual Report](#)
- Generic Drugs Updates and GDUFA [listserv](#)
- [Generic Drug Outreach Campaign](#)

Communicating FDA's Generic Drug Program

- [GDUFA Outreach Videos](#)

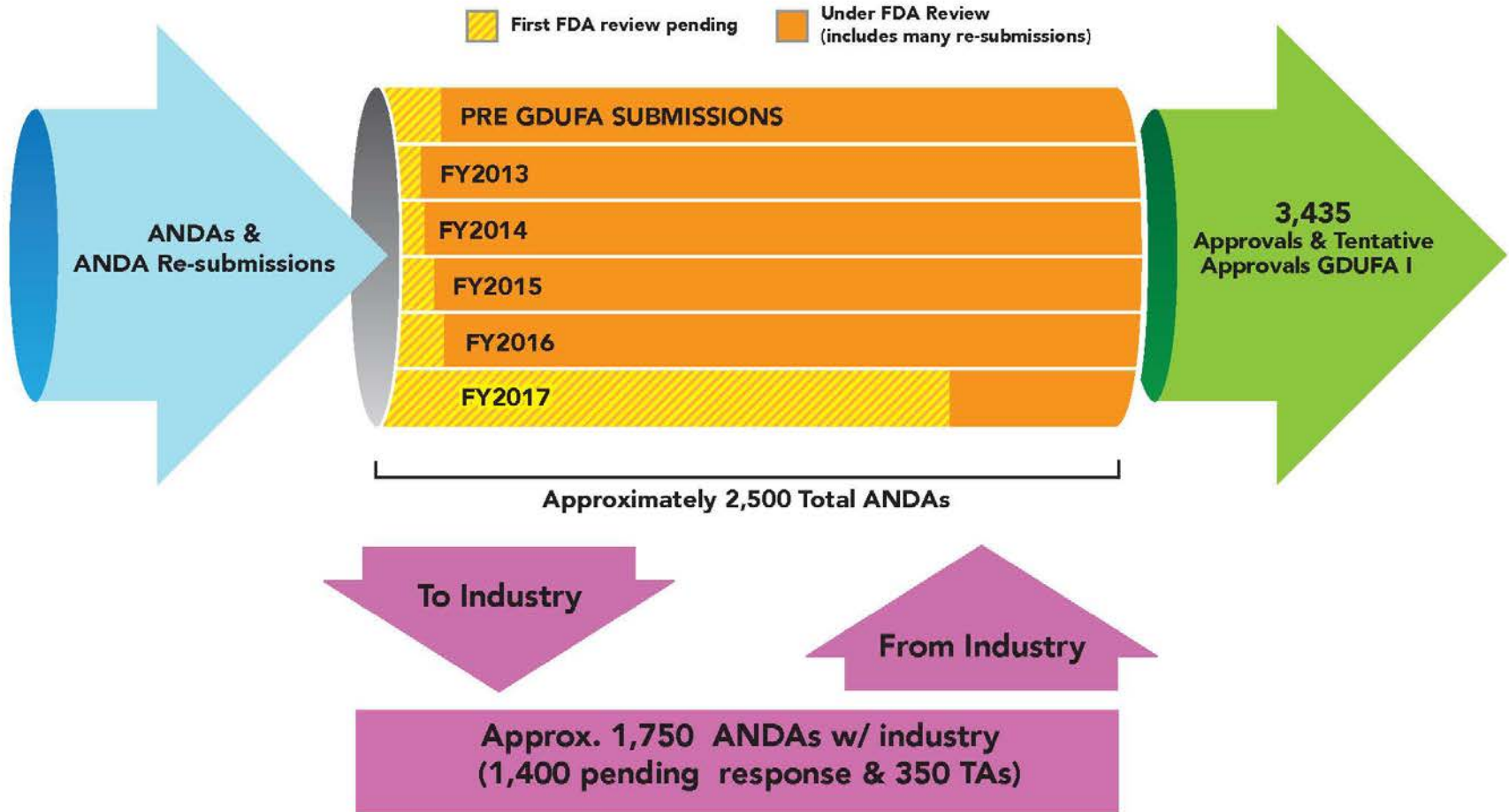
- Brief videos by FDA staff highlight new features in GDUFA II on FDA.gov.

- Topics include:

- [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!

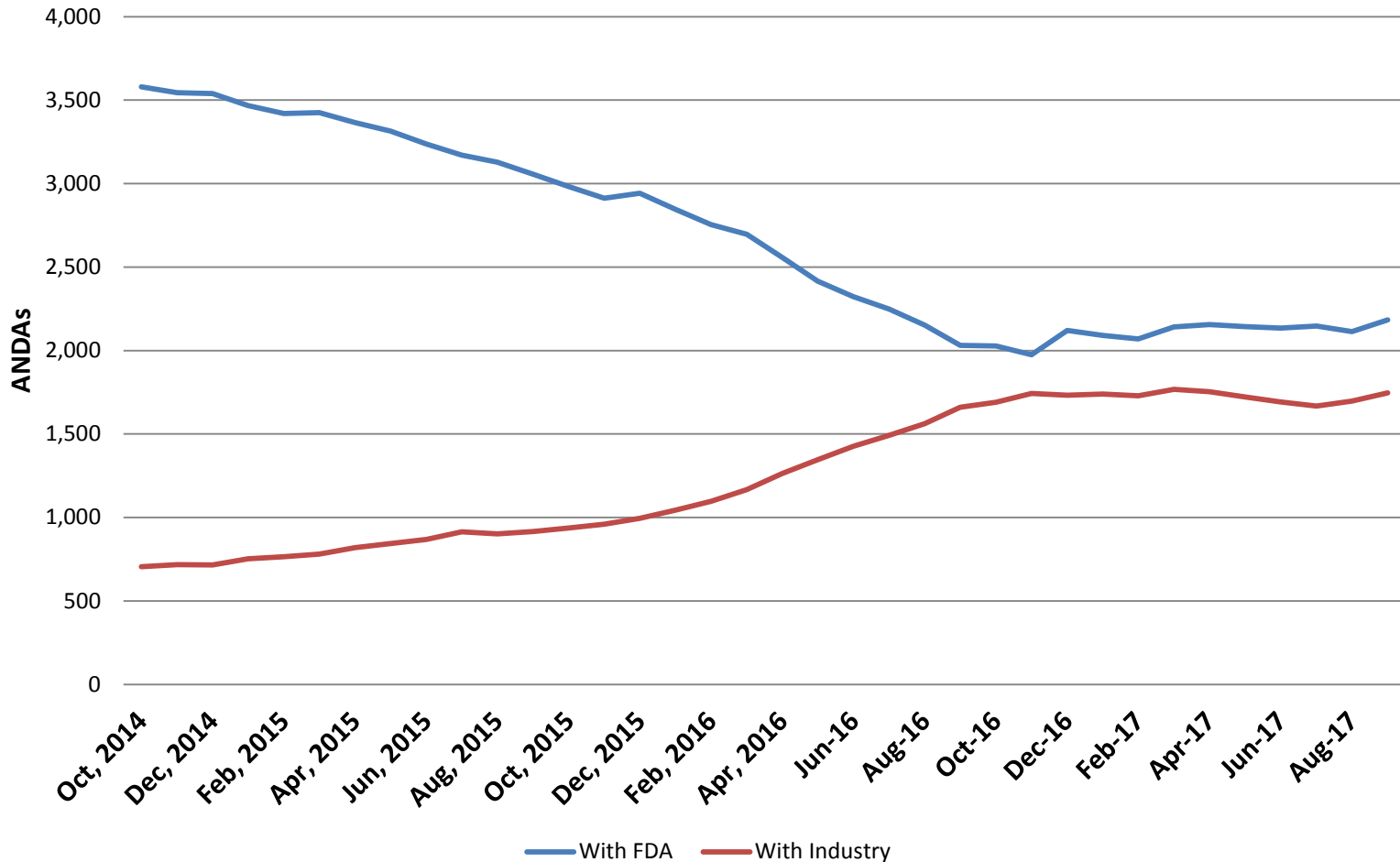
FDA's Generic Review Pipeline

By Submission Cohort as of September 30, 2017



Getting to “Stable Footing”

ANDA Inventory



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

ANDAs in CR status with industry

- FDA needs a better understanding of this
 - Predictors of when amendment will be submitted to FDA
 - Workload predictions and forecasting, capacity analytics, etc.
- FDA asked industry for data/analysis during QTR
GDUFA II FDA-industry meeting

Application “approvability”

**FDA will Approve or TA an ANDA
WHEN
it meets the Agency’s standards
for approval**

FIRST CYCLE APPROVALS*

FY2015	10.7%
FY2016**	14.3%
FY2017**	12.8%

- Low %
- Lots of rework
- Inefficient use of resources
- Large number of ANDAs “pending” with industry, issued CR letters
- Critical to improve the ANDA Quality UP FRONT

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Cohort Year 4 (FY2017) – Many are still under review and within goal; all mature by July 31, 2018.

**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.

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 decision⁴³ (excluding ANDAs under review).

Overview

1. Update on GDUFA I
 - Receipts
 - Actions towards Goals
 - Other accomplishments
2. **Brief comments on GDUFA II**
3. Closing Comments

GDUFA II

- Numerous Review Program Enhancements
 - Mid-cycle & post CR t-cons, ability to dispute a variety of CDER actions
 - More touch points with industry pre-, during, and post-submission
- Pre-ANDA program for complex products
 - Meetings, timeframes for Product-Specific Guidances, updates to Inactive Ingredients Database (IID)
- “PFC” – Pre-submission Facility Correspondence
 - Priority Submission with PFC - 8 month goal
- All Pre-Year 3 ANDAs get a hard GDUFA II goal date vs. TADs
- DMF enhancements
- Accountability and reporting enhancements
- Small business relief

GDUFA II

“Goals” or “Commitment” letter:

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

PLEASE READ!





GDUFA II Pre-ANDA Program

- **Session:**
 - Tuesday November 7, 2017, 9:00am-10:00am

GDUFA II Review Program Enhancements

- Sessions:
 - Tuesday November 7, 2017, 10:30am-12:30pm
 - Tuesday November 7, 2017, 1:30pm-3:30pm

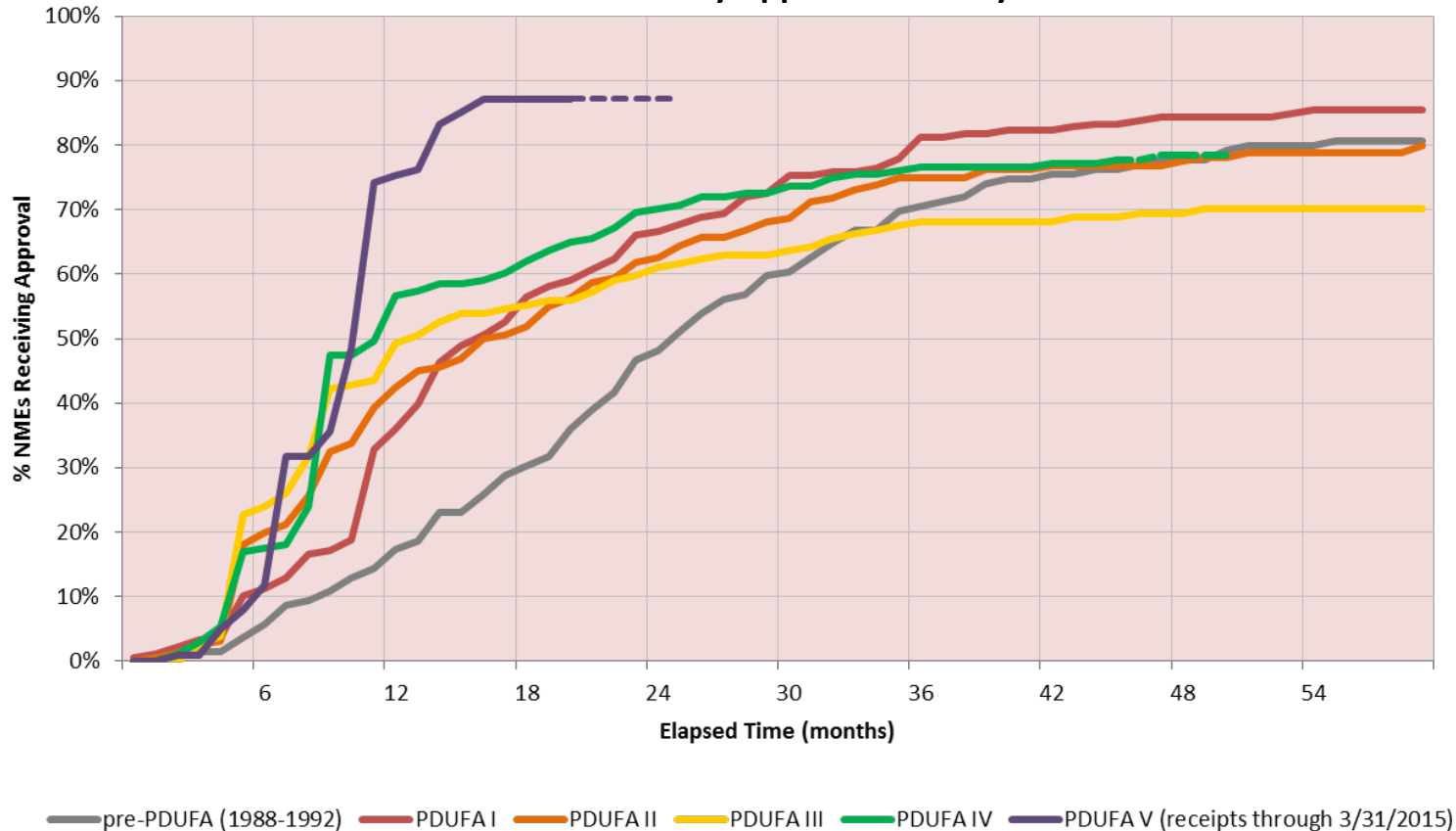
Lessons learned from PDUFA I-V & GDUFA I

- Critical/Pivotal role of RPM
- Complete Application is critical
- High quality NDA & ANDA applications result in:
 - Low Refuse To File (RTF)/Refuse to Receive (RTR) rates
 - First cycle approvals
 - Shorter time to approval

PDUFA Experience: Higher first cycle approval rate achievable with high quality submissions



CDER New Molecular Entity Approval Rates by PDUFA Cohort



* 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

Data as of 9/30/16

CURRENT OGD & GDUFA CHALLENGES

- Continue to Deliver on GDUFA I deliverables
 - Year 4 cohort with 15 month goals all due by December 2017
 - Year 5 cohort with 10 month goals all due by July 2018
- Complex scientific issues with complex active ingredients, routes of delivery, dosage forms, formulations
- Complex regulatory and legal issues unique to the generic/HW space

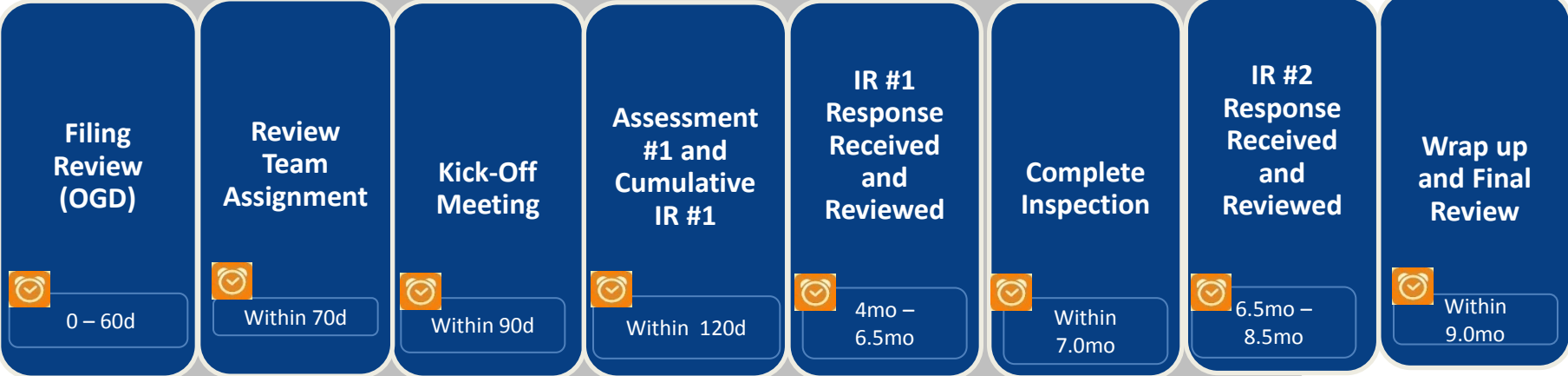
CURRENT CHALLENGES

- High Rate of Refuse to Receive (RTR)
 - RTR'ed ANDAs:
 - Require more cycles to approval when finally received
 - Contain more/worse deficiencies than non-RTR'ed ANDAs
- Hidden facilities
 - Not identified on 356h form
 - Risk getting a new/later GDUFA goal date when hidden facilities are found during review
- Limited awareness of benefits of Product-Specific Guidances
- Increasing workload: ANDAs, amendments, controls

ANDA “Approvability”

Build in Quality Up Front

GDUFA I Cohort Year 5 timeline:



Majority of deficiencies issued in CR letters:

- 1. Dissolution
- 2. Stability
- 3. Excipients
- 4. Facilities



All are Quality-related (OPQ)

**“RIGHT
THE FIRST
TIME”**

FDA is Successfully Delivering on GDUFA

- FDA continues to fulfill GDUFA commitments
- Continue to see increasing submissions, companies, workload, etc.
- Created a high functioning generic drug program
 - Robust, modern, state of the art tools
 - Sustainable and predictable
 - Clear and consistent communication
 - Fairness across applications and applicants





- For your feedback and endurance during the tremendous processes changes under GDUFA
- Your engagement and input were critical to its success
- It was a team effort with FDA and industry
- There is still plenty of work to go around with GDUFA II

