

# **FDA Office of Generic Drugs (OGD) Keynote Address**

## **GDUFA: Past, Present and Future**

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**GPhA Annual Meeting**  
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# 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

*Some data represent FY2016 while others are for CY2016.  
FY2017 data represent preliminary data that are being further reviewed and validated for official reporting purposes.*

# Introductory Comments

## THANK YOU

- For working with us on GDUFA I implementation
  - Your engagement and feedback improved the program
- For your patience and resilience during the past four years of tremendous change
- For working with us on GDUFA II
  - Numerous, major program enhancements to reduce cycles to approval (AP)



# GDUFA Overview

1. Past
2. Present
3. Future
4. Closing Thoughts



# GDUFA Overview

- 1. Past**
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# GDUFA: Past

- In 2012, GDUFA was enacted as part of FDASIA
- In 2013-2014, FDA restructured ANDA review program to prepare for goal dates
- FDA also worked with GPhA to improve communications and transparency – e.g., agreed to TADs
- 2015 to present: GDUFA goal dates, TADs, other formal and informal commitments

# GDUFA Overview

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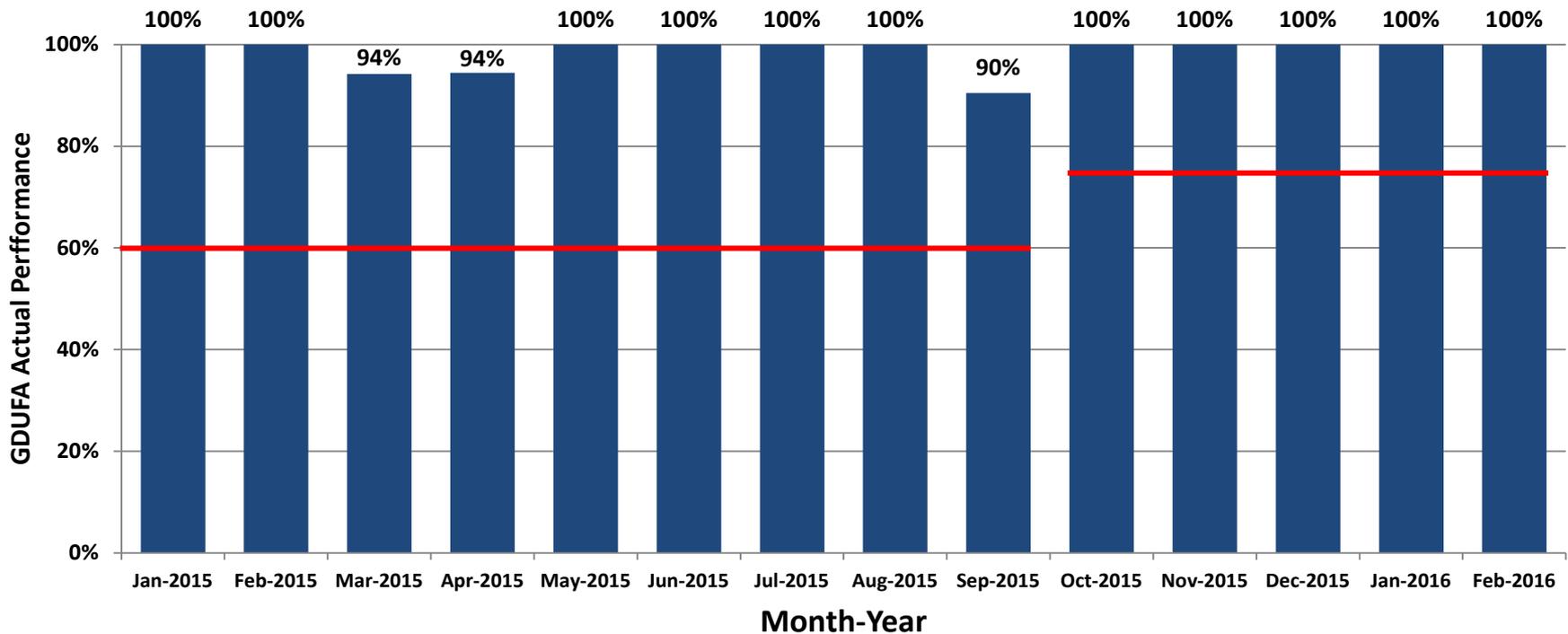
# GDUFA: Present

- FDA is meeting or exceeding the GDUFA goals
- Numerous other significant accomplishments
- Main outstanding challenge is multiple review cycles
  - Leads to a huge amount of re-work for FDA and applicants alike

# GDUFA Goal: Original ANDAs

- GDUFA goal: Review and act on 60% of FY2015 Original ANDAs within 15 months of submission
- FDA acted on 97% of FY2015 Original ANDAs within 15 months of submission
- FY2016 original submissions are just now starting to hit their GDUFA goal dates

# GDUFA Goal: PAS



**— GDUFA PAS Goal**

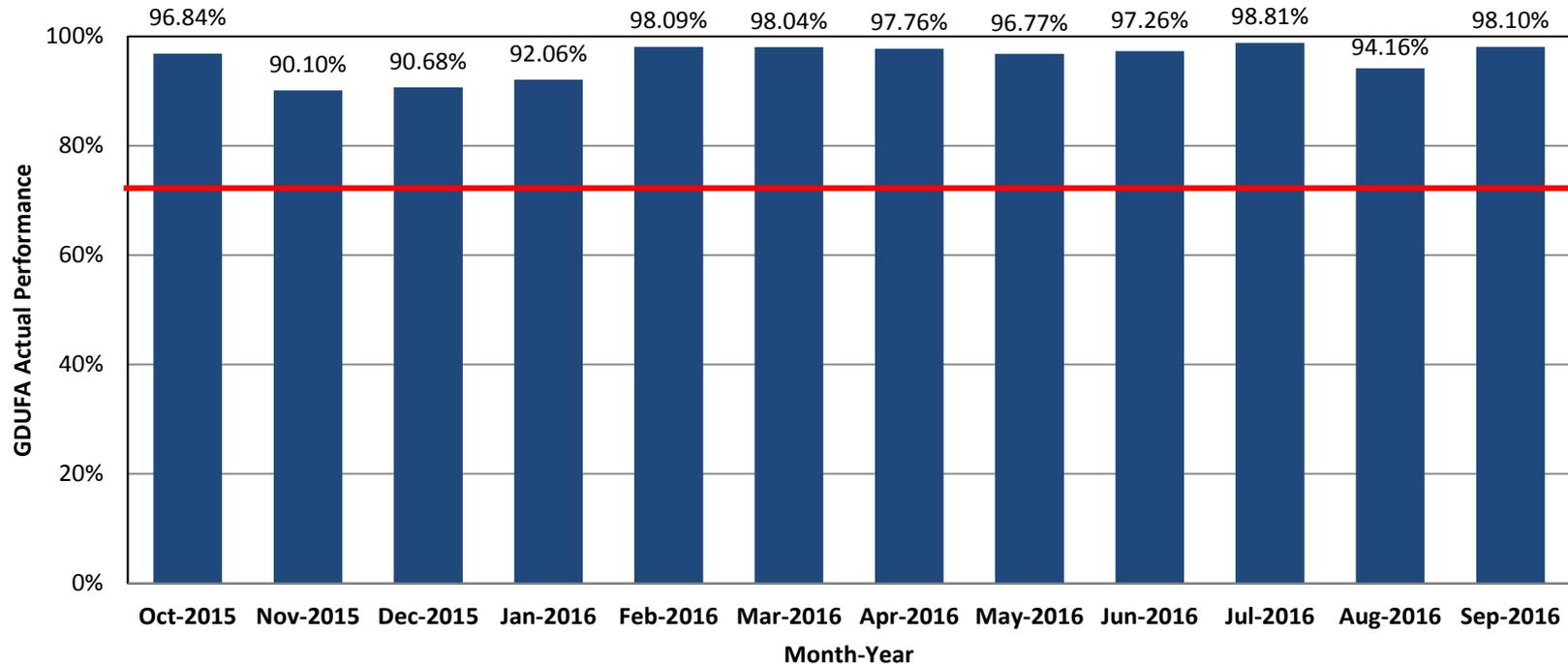
\* Goal dates provided on submissions received through February 2016, as those are the goal dates that have actually occurred. The cohort data is not mature enough to report on whole year data

\*Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.

# GDUFA Goal: Controlled Correspondence

## Controlled Correspondence

### FY 16 GDUFA Performance by FDA Receipt Date – All Disciplines

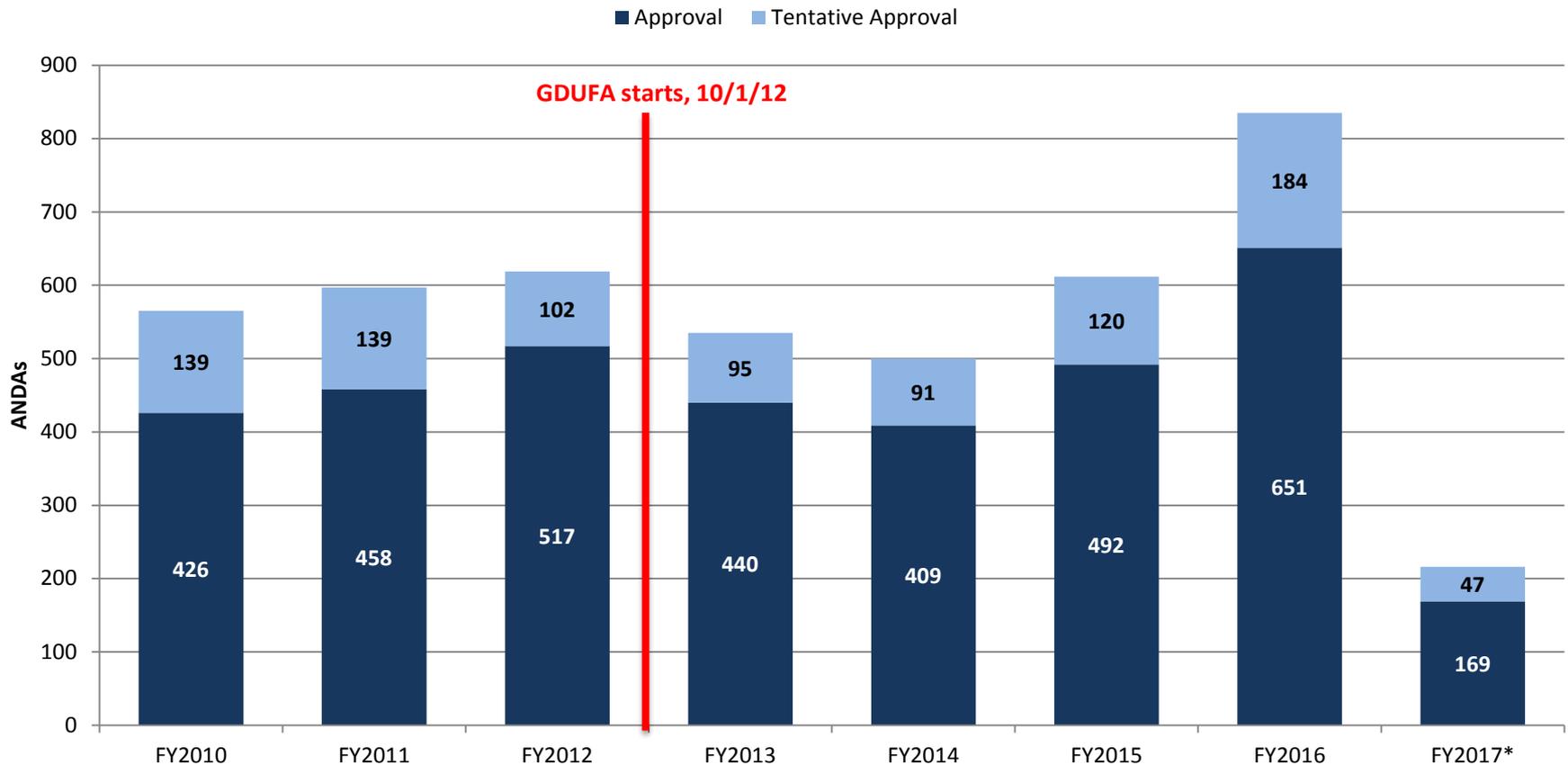


**— GDUFA Controlled Correspondence Goal**

\* Goal dates provided on submissions received in FY2016.

\*Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.

# Other Accomplishments: Approvals and Tentative Approvals



\*As of 1/1/17. Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.

# Other Accomplishments: Notable FY2016 “First Generic” Approvals

Generic Name	Reference Listed Drug
Bendamustine Hydrochloride for Injection, 25 mg/vial and 100 mg/vial	Treanda for Injection
Dasatinib Tablets, 20 mg, 50 mg, 70 mg, and 100 mg	Sprycel Tablets
Dofetilide Capsules, 0.125 mg, 0.25 mg, and 0.5 mg.	Tikosyn Capsules
Efavirenz Tablets USP, 600 mg	Sustiva Tablets
Imatinib Mesylate Tabelets, 100 and 400 mg	Gleevec Tablets
Lacosamide Tablets, 50 mg, 100 mg, 150 mg and 200 mg	Vimpat Tablets
Mometasone Furoate Nasal Spray, 50 mcg	Nasonex Nasal Spray
Olopatadine Hydrochloride Ophthalmic Solution USP, 0.1%	Patanol Ophthalmic solution
Oseltamivir Phosphate Capsules USP, 30 mg, 45 mg and 75 mg	Tamiflu
Rosuvastatin Calcium Tablets, 5 mg (base), 10 mg (base), 20 mg (base) and 40 mg (base)	Crestor Tablets
Rufinamide Tablets USP, 200 mg and 400 mg	Banzel tablets
Sildenafil Citrate Tablets, 25 mg, 50 mg and 100 mg**	Viagra Tablets

\*<http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/drugandbiologicapprovalreports/andagenericdrugapprovals/default.htm>

\*\*ANDA approved but listed in Discontinued section of Orange Book



# Other Accomplishments: Starting to See First Cycle Approvals

(FY2015 cohort)

**1<sup>st</sup> cycle**

First Cycle RTR Rate	20%
First Cycle AP/TA Rate	9%
First Cycle CR Rate	71%

N=523

**2<sup>nd</sup> cycle**

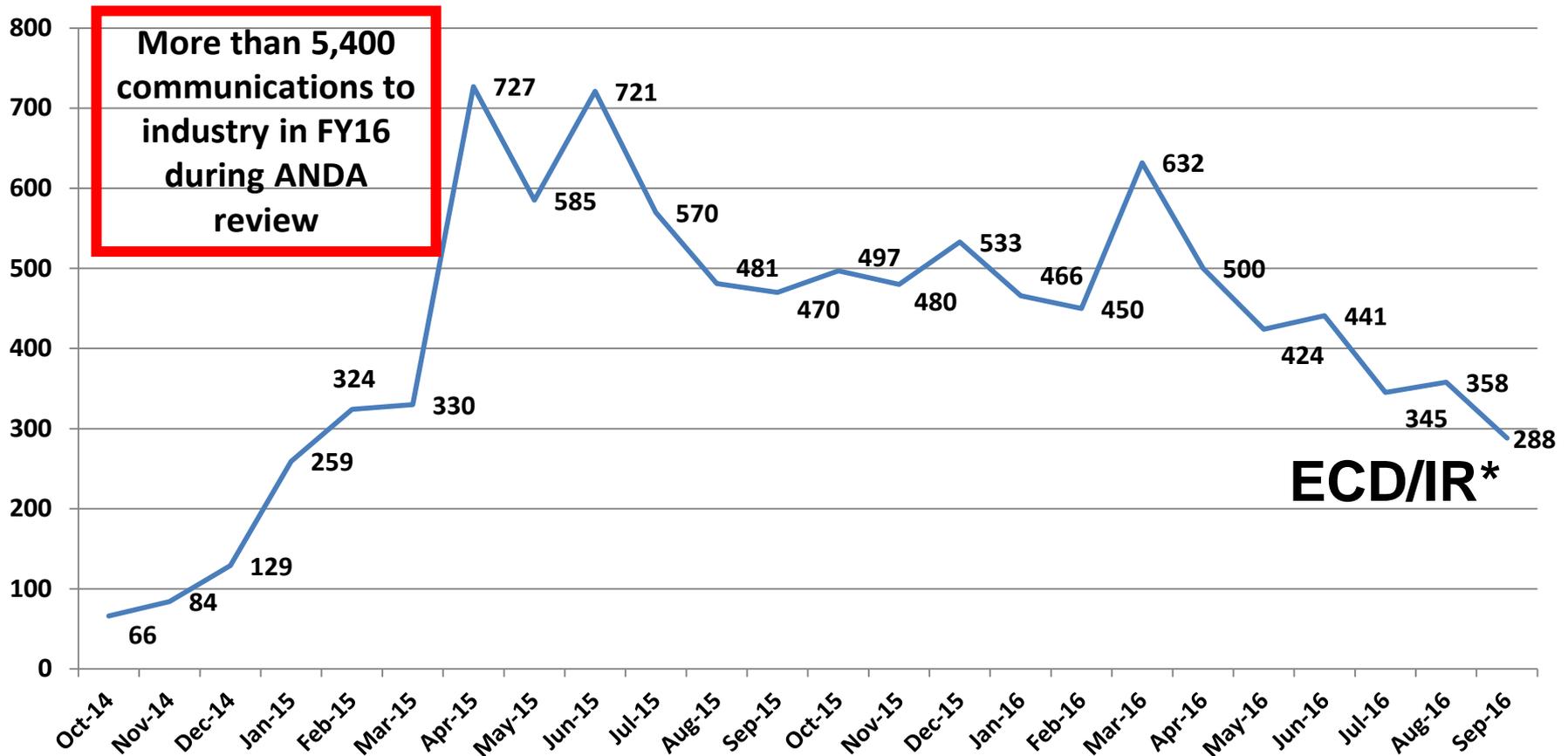
Second Cycle AP/TA Rate	42%
Second Cycle CR Rate	56%
Withdrawn	2%

N=67\*\*

\*As of 1/23/17. Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.

\*\*Completed reviews of second submissions; most others are pending with industry or under review at FDA and within goal.

# Other Accomplishments: Expanded Communications with Industry



\*Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.



# Other Accomplishments: Overall Actions

	Pre-GDUFA			GDUFA		
	FY2012	FY2013	FY2014	FY2015	FY2016	FY2017*
ANDA approvals	517	440	409	492	651	169
PAS approvals	275	535	659	624	496	115
Tentative Approval (TA)	102	95	91	120	184	47
Complete Response (CR) ‡	84	1251	1254	1180	1725	446
<b>TOTAL **</b>	<b>978</b>	<b>2321</b>	<b>2413</b>	<b>2416</b>	<b>3056</b>	<b>777</b>
<b>DMF Completeness Assessment (CA)</b>	<b>0</b>	<b>1699</b>	<b>1706</b>	<b>901</b>	<b>886</b>	<b>102</b>

\* As of 1/1/17. Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.

\*\* 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.

# Other Accomplishments: PAS Actions

	FY2013	FY2014	FY2015	FY2016	FY2017 <small>(as of Jan 30, 2017)</small>
<b>Received</b>	482	436	563	567	160
<b>Approved</b>	532	654	616	542	145
<b>CR Letter</b>	8	18	185	242	75

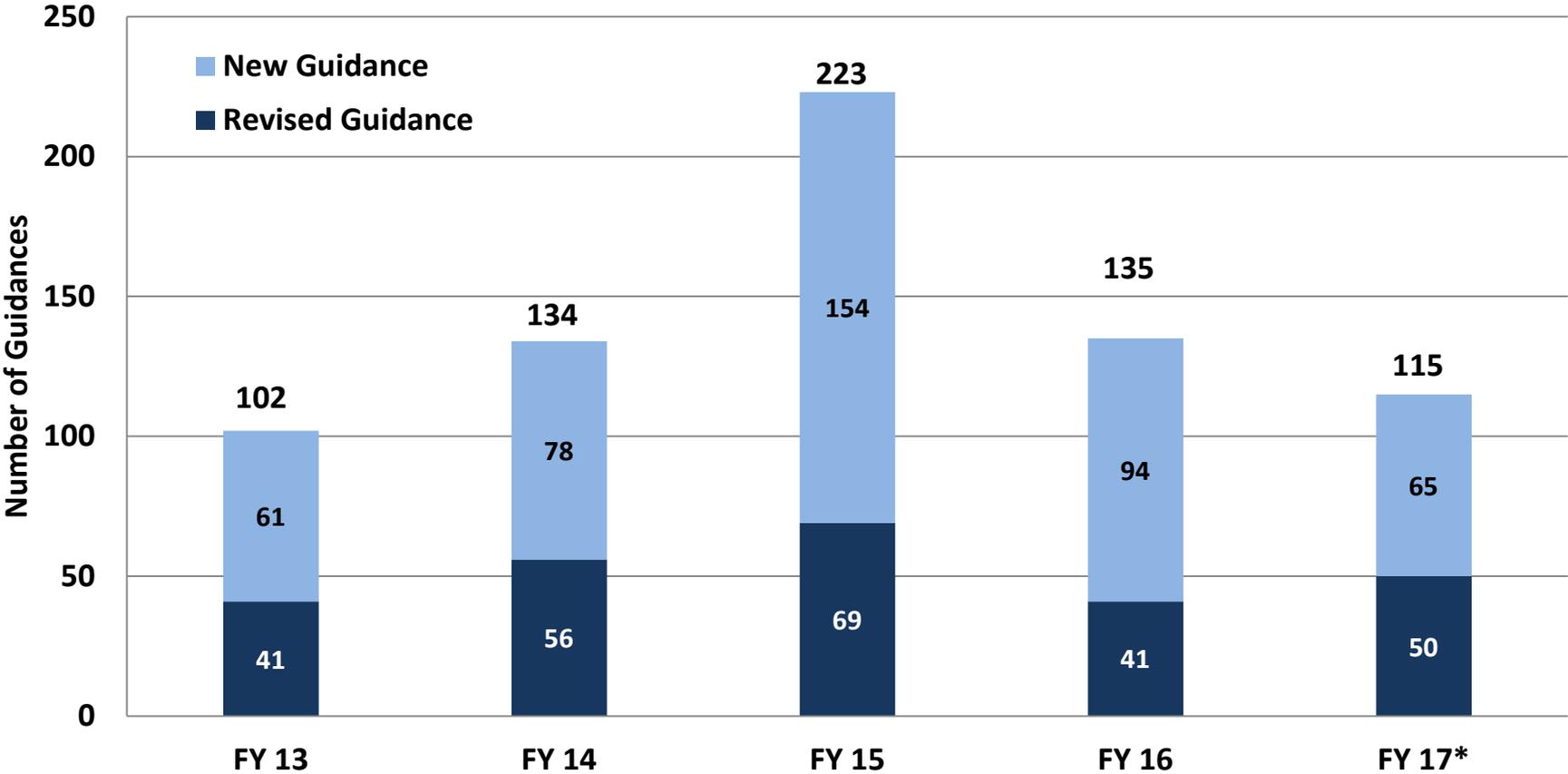
# Other Accomplishments: Filing

- > 900 original ANDAs, resubmissions, and PASs underwent filing review in FY2016
- Also, OGD has eliminated large filing backlog

# Other Accomplishments: Filing

- Revised Refuse To Receive (RTR) Guidance published 12/21/16
- Implementing Good Review Practices on Filing Review:
  - Robust training and review practices for staff, including strong documentation
  - Intense engagement with OGD Policy on regulatory and legal framework
  - Internal procedures to ensure consistency with filing determinations
  - Resulting in **very few rescissions of RTR** in FY2016 and FY2017
- DFR heavily involved with Controlled Correspondence
  - Success here should translate into industry submitting ANDAs that will less likely be RTR'ed for the question raised in the Control

# Other Accomplishments: Product-Specific Guidances



# Other Accomplishments:

## GDUFA Regulatory Science → FDA standards

- **“Product-specific” guidances**
  - ~200 per year
  - Developing more for complex products
    - ~15 for inhalation products
- **New “general” product or BE guidances**
  - Evaluating Abuse Deterrence of Generic Opioid Products (March 2016)
  - Assessing Adhesion for Generic TDS and Topical Patches (May 2016)
  - Comparative Analyses and Human Factors Studies for Drug-device Combinations submitted in an ANDA (January 2017)
  - rDNA peptides (on public guidance agenda, in progress)

## Other Accomplishments:

# GDUFA Reg. Science → Access to Generics

- Each area in portfolio is a **\$billion/year market** without generic competition
- Coordinated internal and external research drives progress
  - ~90 active contracts and grants
- Huge public health impact with small regulatory science investments -- leads to large return on investment (ROI)
  - Guidance on complex products
  - Internal CDER & FDA alignment on complex issues
  - Confidence in generic substitution
  - Review tool development and use
  - Faster and smarter generic drug development and review

# Other Accomplishments: Policy Transparency & Predictability

- REGULATIONS ISSUED
  - MMA Final Rule (September 2016)
- GUIDANCES ISSUED
  - RTR for Lack of Justification of Impurity Limits (August 2016)
  - Updated RTR Guidance (December 2016)
  - 180-Day Exclusivity Guidance (January 2017)
  - Referencing Products in ANDAs Guidance (January 2017)
- GUIDANCES IN DEVELOPMENT
  - Determining 505(b)(2) or 505(j) Pathway

# Other Accomplishments:

## OGD Communication Enhancements

- Monthly [Activities Report](#) of the Generic Drug Program
- ANDA [First Generic Drug Approvals](#)
- Quarterly [Generic Drug Review Dashboard](#)
- Generic Drugs [listserv](#)
  - OGD RPMs using in signature block
  - >800 signed up in first month
- GDUFA [Regulatory Science Annual Report](#)
- Office of Generic Drugs 2015 [Annual Report](#)
- GDUFA Annual [Performance Report](#), 2015

# Notable Comms. Accomplishment:

## Generic Drug Review Dashboard

Review productivity and current workload with FDA and with industry

Updated Quarterly

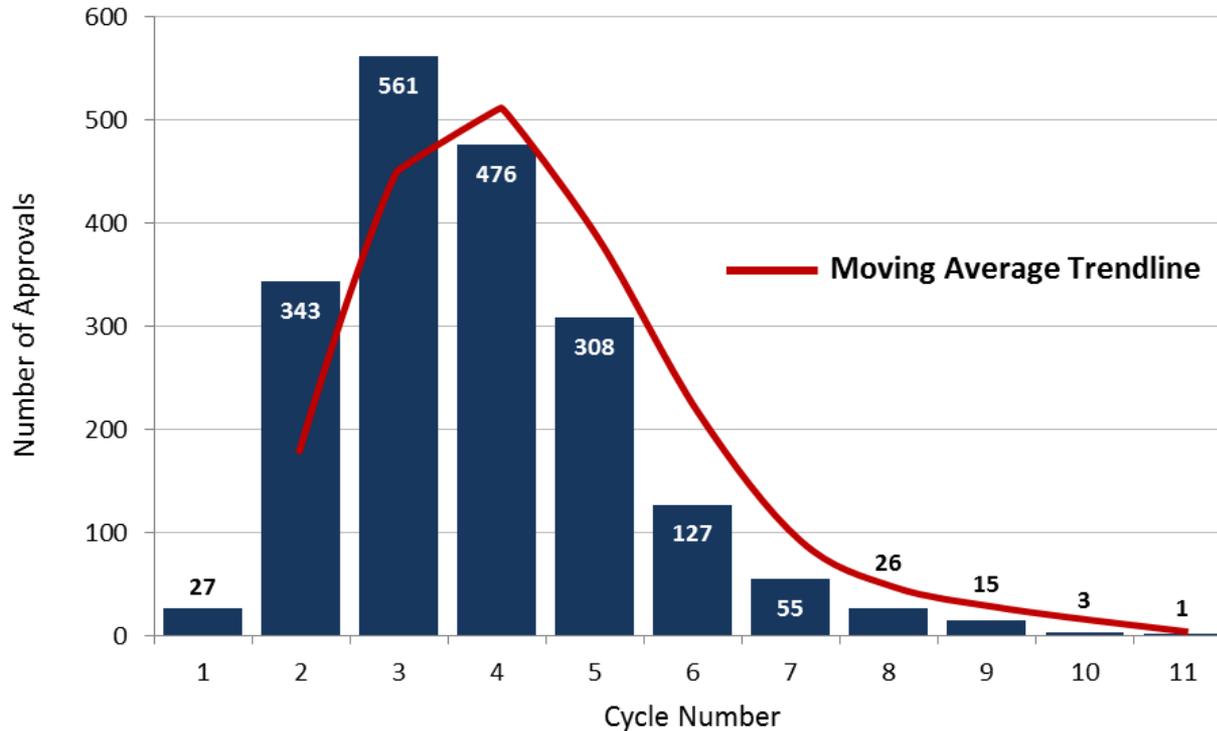
Four reports available:

- Total Original ANDA Workload Activity for Pre-GDUFA Year 3 Application Cohorts
- Total Original ANDA Workload Activity for All Unapproved Applications
- Original ANDAs - Total Agency Actions for the Most Recent 12 Months
- ANDA Prior Approval Supplements - Total Agency Actions for the Most Recent 12 Months

<http://go.usa.gov/cunHT>

# Outstanding Challenge: Multiple Review Cycles

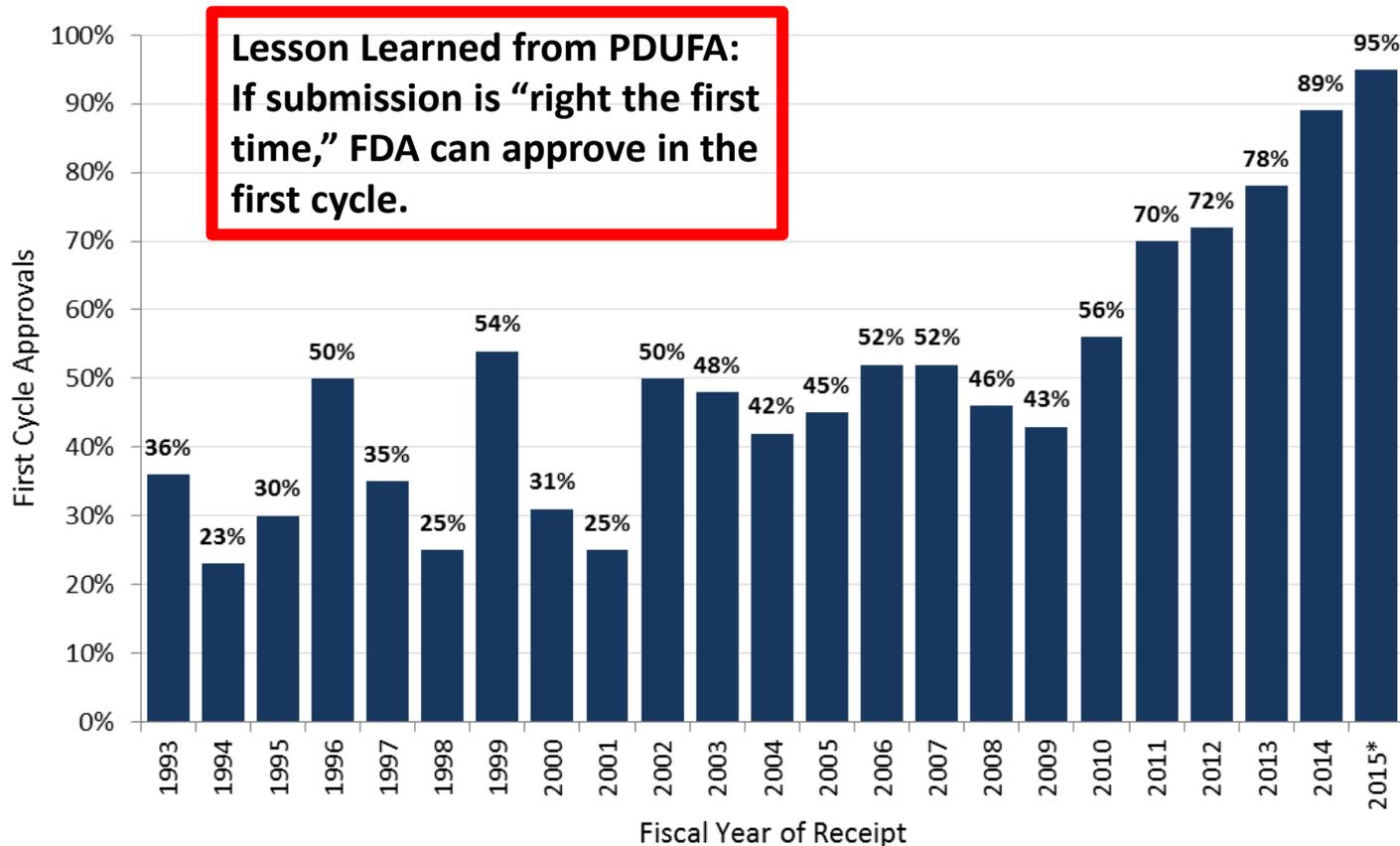
**Chart 15. Review Cycles for ANDAs**  
2009 through July 2014



# Outstanding Challenge: Multiple Review Cycles

Chart 26. First Cycle Approval Rate Under PDUFA

CDER NME NDAs/BLAs First Action Approval Rate  
First Action Approval Rate

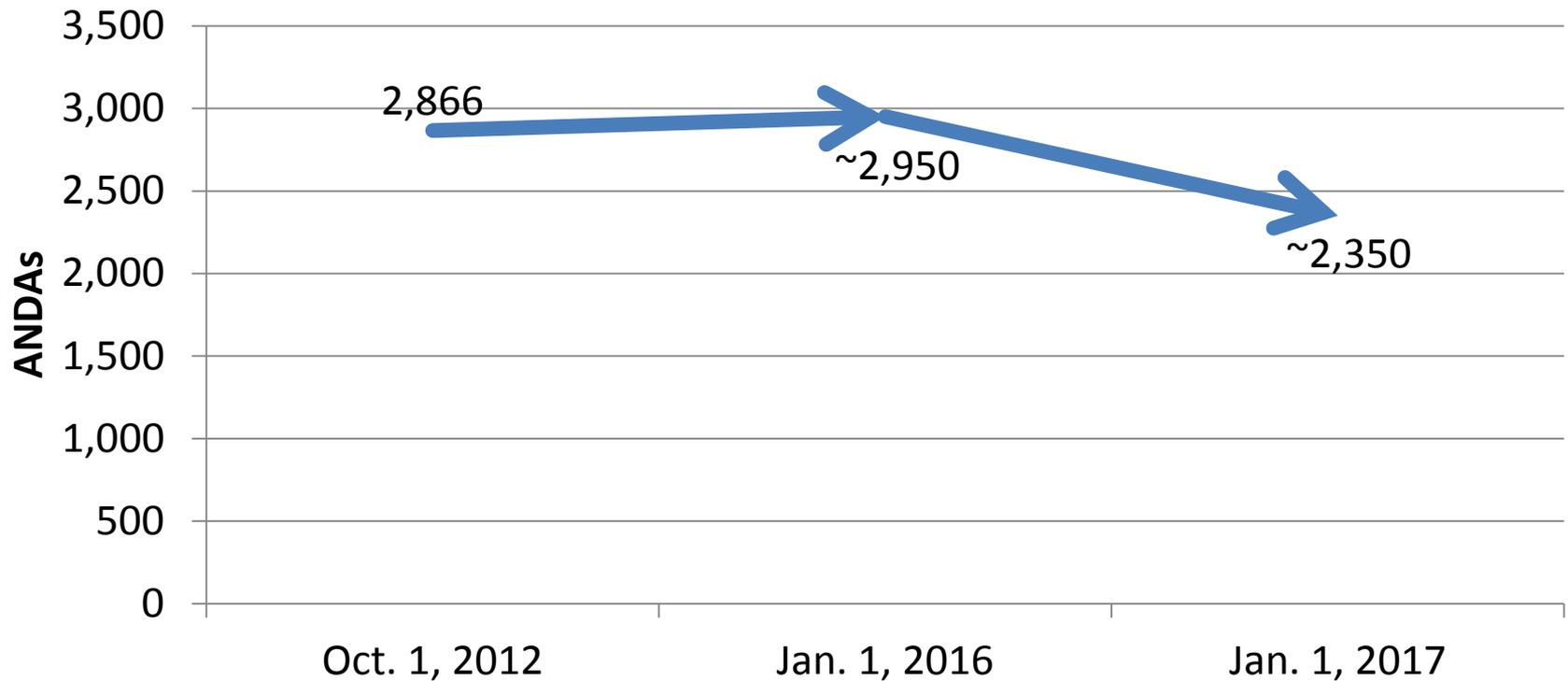


# Outstanding Challenge: Multiple Review Cycles

- Substantially all of the ANDA workload is:
  - At FDA and within the GDUFA goal, OR
  - With the applicant
- Many ANDAs are not lawfully approvable yet, because patent/exclusivity have not expired
- The main challenge is: It usually takes several review cycles to get to approval
- While UFAs count actions, approval is the ultimate objective
- The good news is: The older ANDAs are now on their second or third review cycle and therefore should be ripe for approval

# Outstanding Challenge: Multiple Review Cycles

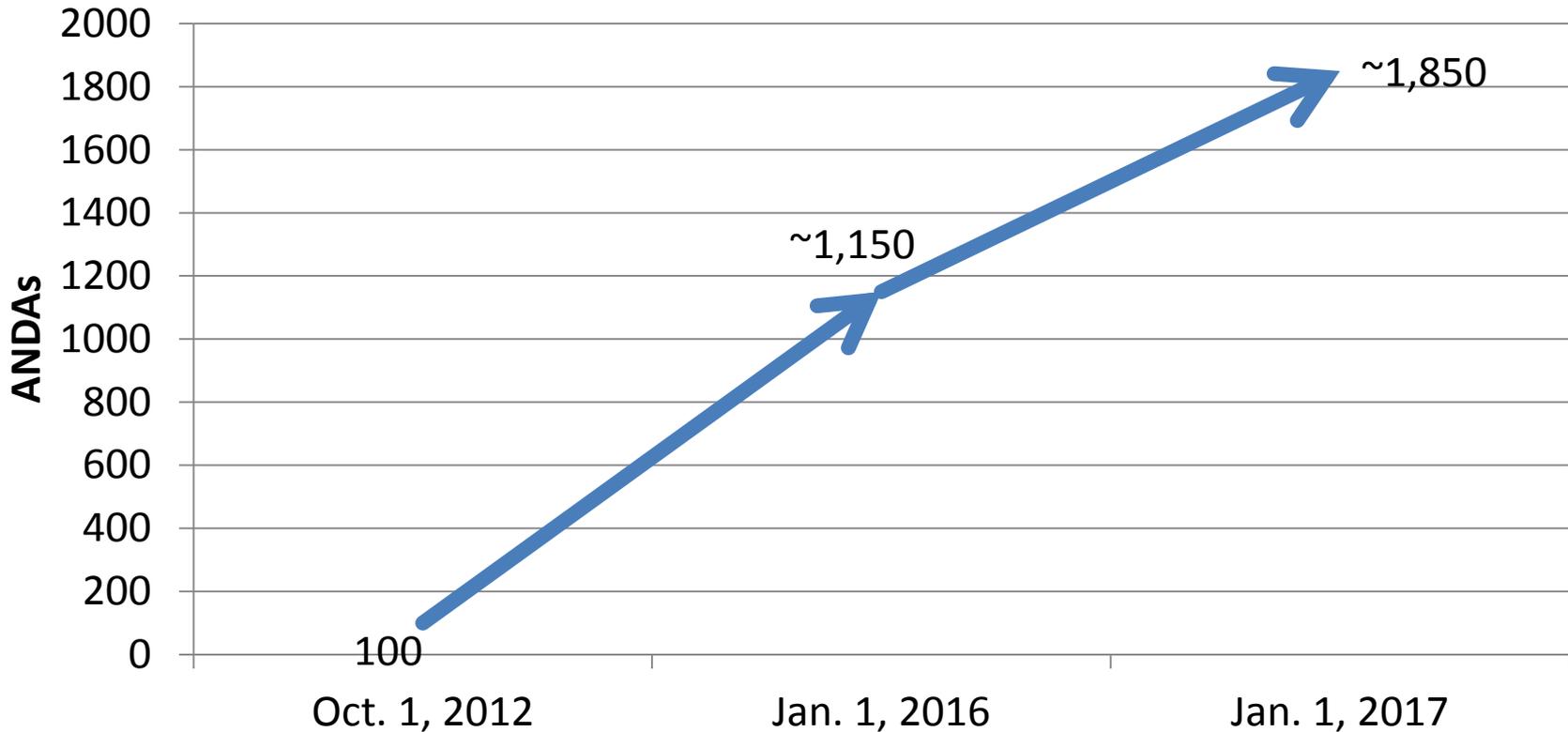
## ANDAs Under FDA Review



\*Approximate Values, January 2017

# Outstanding Challenge: Multiple Review Cycles

Complete Response Letters (CRs) & TAs



\*Approximate Values, January 2017

# Outstanding Challenge: Multiple Review Cycles

The most common deficiencies are:

- Inadequate CMC
  - Stability
  - Dissolution
  - Inactive ingredients
- Inadequate facilities

# Outstanding Challenge: Multiple Review Cycles

## Next Steps --

- FDA and GPhA have a strong track record of working together to overcome GDUFA challenges
- For example, in 2013-14, we improved review communications and transparency, revised “Communications with Industry MAPP”
- Let’s work together to convert the CRs into Approvals (Aps)
- Trade press has noted the challenge here -- applicants also need to respond to high volume of IRs/DRLs on ANDAs that are under active review and might be imminently approved
- FDA-GPhA quarterly meetings stopped during negotiations
  - These will resume soon including GDUFA II negotiators and FDA
- GDUFA II will help a lot for new, incoming submissions
- We can do this!

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# GDUFA II

Proposed agreement between FDA and industry stakeholders

- Generic Pharmaceutical Association (GPhA)
- Bulk Pharmaceutical Task Force (BPTF)
- Pharma and Biopharma Outsourcing Association (PBOA)
- European Fine Chemical Group (EFCG)

# GDUFA II

- While there is a proposed agreement between FDA and industry stakeholders, Congress needs to reauthorize by October 1, 2017 -- otherwise, GDUFA expires
- “Goals” or “Commitment” letter:

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

# GDUFA II Highlights

## Faster review of priority submissions: 8 months

- “Priority” defined in MAPP – includes first generics, sole source, shortages
- To obtain priority review, applicants must submit Pre-submission Facility Correspondence (“PFC”) at least 2 months prior to submission

Why 8 months?

So ANDA can be approved in the first review cycle.

- FDA must plan and conduct facility inspections (many are overseas) and facility often needs opportunity to correct deficiencies
- FDA review team must communicate – and applicant must address – deficiencies
- “Real time” communication to fix and approve ANDA now, not later

# GDUFA II Highlights

## ANDA Review Program Enhancements

- Refine and enhance efficiency of review process from start to finish
- New procedures for filing, review communications, review status communications, timely AP and TA, post-CRL t-cons, and dispute resolution
- Many concepts drawn from PDUFA: Create more opportunities for applicants to address deficiencies in current review cycle, instead of waiting to receive them in a later-issued CRL
- Increase first cycle approvals
- Reduce number of cycles to approval

# GDUFA II Highlights

## “No submission left behind”

- GDUFA Goals for all ANDAs and amendments
- GDUFA I “*Bridging*” – E.g., any pre-FY2015 ANDAs with missed/never assigned TADs as of Oct. 1, 2017 will get a GDUFA II goal date NLT July 31, 2018

# GDUFA II Highlights

## Pre-ANDA Program

- Clarify regulatory expectations early in product development, so ANDA can be “right the first time”
- Increase odds of first cycle approval
- Reduce number of cycles to approval
- More efficient and effective review process

# GDUFA II Highlights

## Features of Pre-ANDA Program

- “Complex Product” defined in the proposed GDUFA II Commitment Letter
  - Products with complex active ingredients, formulations, routes of delivery or dosage forms
  - Complex drug-device combinations
  - Other products where complexity or uncertainty concerning the approval pathway or other alternative approach would benefit from early scientific engagement
- Meetings
  - Product development, pre-submission, mid-review cycle -- FDA will issue guidance
- Product-Specific Guidance
  - Product-specific guidance for NCEs (not complex)
  - Identify the methodology for developing drugs and generating evidence needed to support generic approval
- Other enhancements include:
  - Controlled correspondence
  - Regulatory science
  - Inactive Ingredients Database (IID)
  - Safety Determination letters for REMS applications

# GDUFA II Highlights

## DMF Review Program Enhancements

- DMF program enhancements were developed in collaboration with API manufacturers
- New efficiencies and better coordination with ANDA review will benefit ANDA sponsors

# GDUFA II Highlights

## Facility Assessment Enhancements

- FDASIA eliminated longstanding minimum inspection frequency requirements and directed FDA instead to inspect facilities globally on the *basis of risk*
- The transition to a new paradigm was disruptive -- over time Industry had developed expectations and business practices based on the old model

To mitigate ANDA sponsor concerns regarding the transparency and speed of facility assessment and its impact on ANDA approvability and product launch, FDA would:

- Communicate outstanding facility issues that could prevent approval of an ANDA or PAS through an IR, DRL or CRL
- Communicate to the facility owner final inspection classifications that do not negatively impact approvability of any pending application within 90 days of the end of the inspection
- Provide updates to and seek feedback from Industry stakeholders concerning facility assessment -- FDA understands strong GPhA concerns and looks forward to the dialogue
- To enhance transparency concerning the compliance status of GDUFA self-identified facilities and sites, FDA would update its existing, publicly available database

# GDUFA II Highlights

## Accountability and Reporting Enhancements

Build internal capacity to enable improved productivity and performance through:

- Transparent and efficient administration, allocation, and reporting of user fee resources
- Resource management planning
  - Modernized time reporting
- Independent third-party evaluations of program
- Robust and expanded program performance reporting
  - Monthly, quarterly, annually

# GDUFA II Highlights

## Program Size Commensurate with ANDA Workload

- ANDAs are the primary workload driver of the program
- GDUFA I assumed that FDA would receive approximately 750 ANDAs per year
- Over the first 4 years of GDUFA, ANDA receipts have averaged approximately 1,000 per year
- In order to maintain current productivity and implement proposed GDUFA II improvements, FDA and Industry agreed that user fees should total \$493.6 million annually, adjusted each year for inflation

# GDUFA II Highlights

## Modifications to User Fees

- To maintain a predictable fee base and better align fee responsibility with program costs and fee-paying ability, FDA and Industry propose to shift the burden more towards annual ANDA holder  
“Program Fees”
- Sponsors with one or more approved ANDAs would pay an annual fee
- Changes to facility fees
- Elimination of supplement (PAS) fees

# GDUFA II Highlights

## Small Business Fee Considerations

- No facility or ANDA sponsor would be charged an annual fee until an ANDA in which it is listed is approved
- Annual program fee would have three tiers based on number of approved ANDAs owned by a firm and its affiliates: large (20+), medium (6 – 19), and small (1 – 5)
- Contract Manufacturing Organizations (CMOs -- hired by ANDA sponsors to manufacture their generic drugs) would pay one-third of the annual facility fee paid by manufacturers that produce their own ANDAs

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# Closing Thoughts

- We are on the right track: More approvals than ever before
- Unfinished business -- Convert CRs to APs, reduce cycles to approval
- **THANK YOU** for your engagement, commitment, and support
- Generics are more important than ever
- GDUFA II will make a big difference
- Together, we can do it!

