GDUFA: Moving from the Present to the Future

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SBIA Generic Drug Forum
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PRESENTATION OUTLINE

1. Present

   (GDUFA I implementation)

2. Future

   (GDUFA II)

3. Closing Thoughts

PRESENTATION OUTLINE

1. **Present**

   (GDUFA I implementation)

2. Future

   (GDUFA II)

3. Closing Thoughts

GDUFA: Present

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

GDUFA I -- goal dates

Powerful tool to improve the timeliness and predictability of review
Generic Drug Program is a REVIEW Program

Goals	Review Time	Year 3 FY2015	Year 4 FY2016	Year 5 FY2017
Original ANDA submission	15 months~	60%	75%	90%~
Tier 1 first major amendment	10 months	60%	75%	90%
Tier 1 minor amendments (1st-3rd)	3 months*	60%	75%	90%
Tier 1 minor amendments (4th-5th)	6 months*	60%	75%	90%
Tier 2 amendment	12 months	60%	75%	90%
Prior Approval Supplements	6 months*	60%	75%	90%
ANDA teleconference requests	10 business days	200	250	300
Controlled correspondence+	2 months	70%^	70%	90%
ANDAs, amendments and PASs in backlog on Oct 1, 2012	*Act on 90% by end of FY2017*			

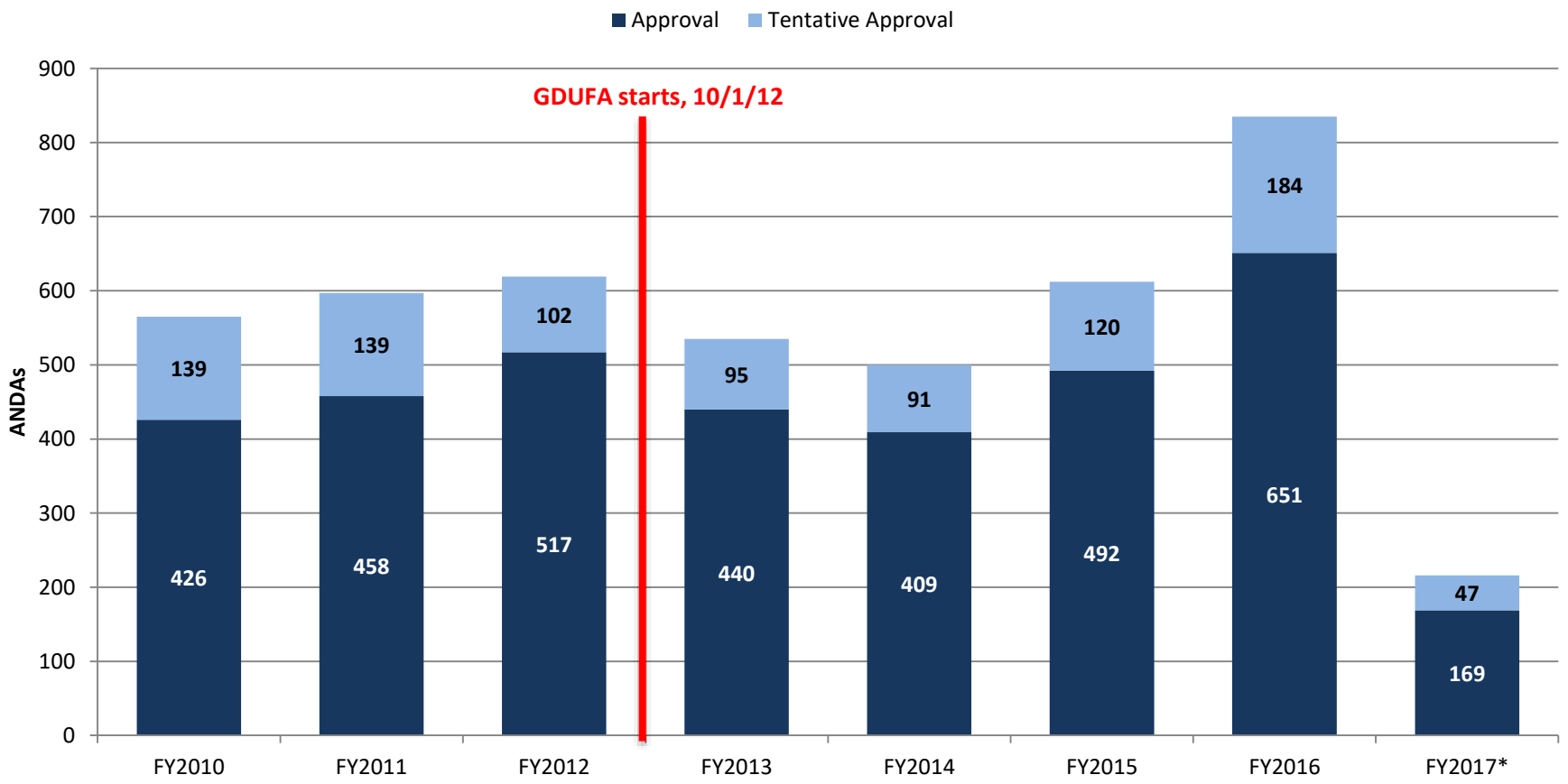
Note: Performance goals in the chart means FDA should take a "first action" (as defined above) on a certain percent of applications, etc. within timeframes listed; it does not mean FDA should approve applications, etc. within such timeframes.
+If no input required from clinical division
***10 months if inspection required**
^4 months
~10 months

NOW

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
  - Exceeding GDUFA goals for FY2015
- FY2016 original ANDAs are just now starting to reach their GDUFA goal dates
  - We will report out on FY2016 cohort in the future

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

(CY2016 OGD approved 73 "First Generics")

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)

1st cycle

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

N=523

2nd 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/amendment to original ANDA after receiving CR; most others are pending with industry or under review at FDA and within goal.

Prior to GDUFA, First Cycle Approvals were less than 1%.

OTHER ACCOMPLISHMENTS

Overall Generic Drug Program "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
TOTAL **	978	2321	2413	2416	3056	777
DMF Completeness Assessment (CA)	0	1699	1706	901	886	102

* 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

¥ Complete Response both with and without inspections for ANDAs.

What are the reasons for the increase in Complete Response letters?

1. GDUFA
2. ANDAs have deficiencies that need to be corrected before the Agency can approve/TA
3. Multiple review cycles to get to AP/TA

OTHER OGD 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
  - Successes here should translate into industry submitting ANDAs that will less likely be RTR'ed for the question raised in the Control
- More on "Filing" by Rosanne Chandra (Day 2)

OTHER OGD ACCOMPLISHMENTS
GDUFA Reg. Science →Access to Generics

- Coordinated internal and external research drives progress
  - ~90 active contracts and grants
- Each area in portfolio is a **$billion/year market** where there is NO generic competition
- 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
- More on “GDUFA Regulatory Science” by Stephanie Choi

OTHER OGD 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)

OTHER OGD 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)
- More on “Policy” by Martha Nguyen and Maarika Kimbrell

OTHER OGD 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 2016 Annual Report
- GDUFA Annual Performance Report, 2016

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
- More on “Performance/Operations” by Ted Sherwood

http://go.usa.gov/cunHT

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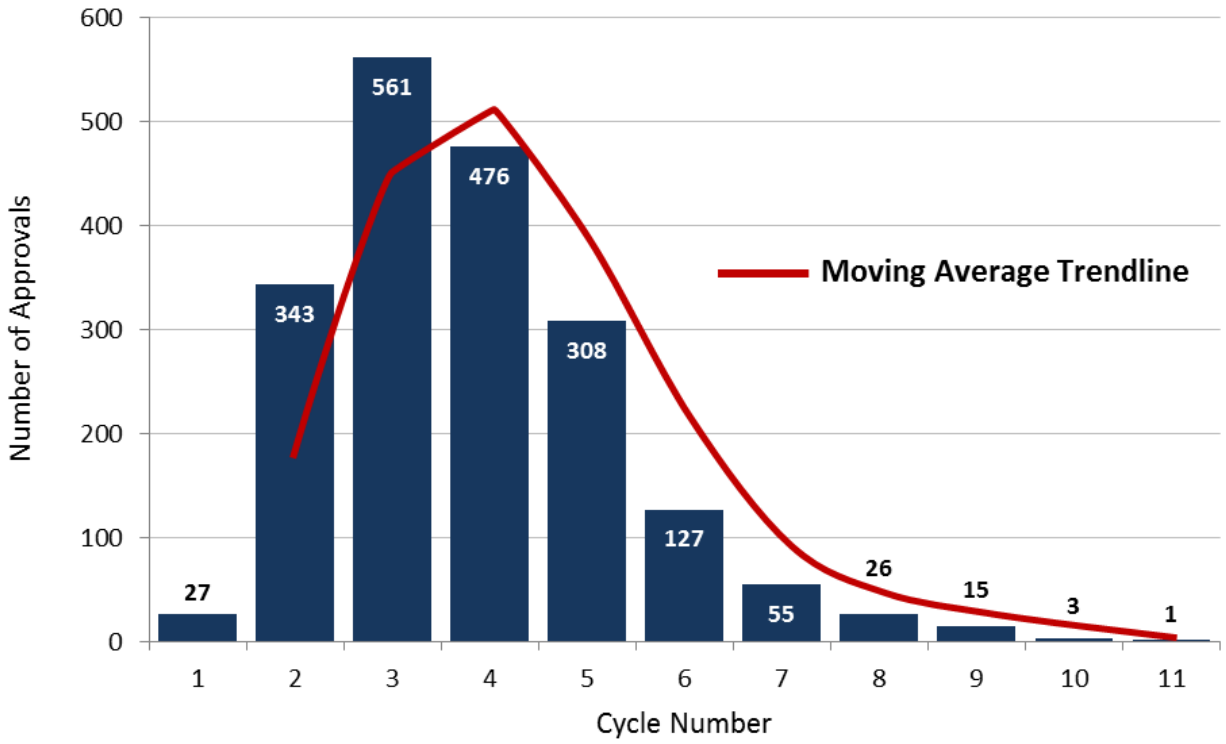
Despite GDUFA I successes…..
Challenges remain

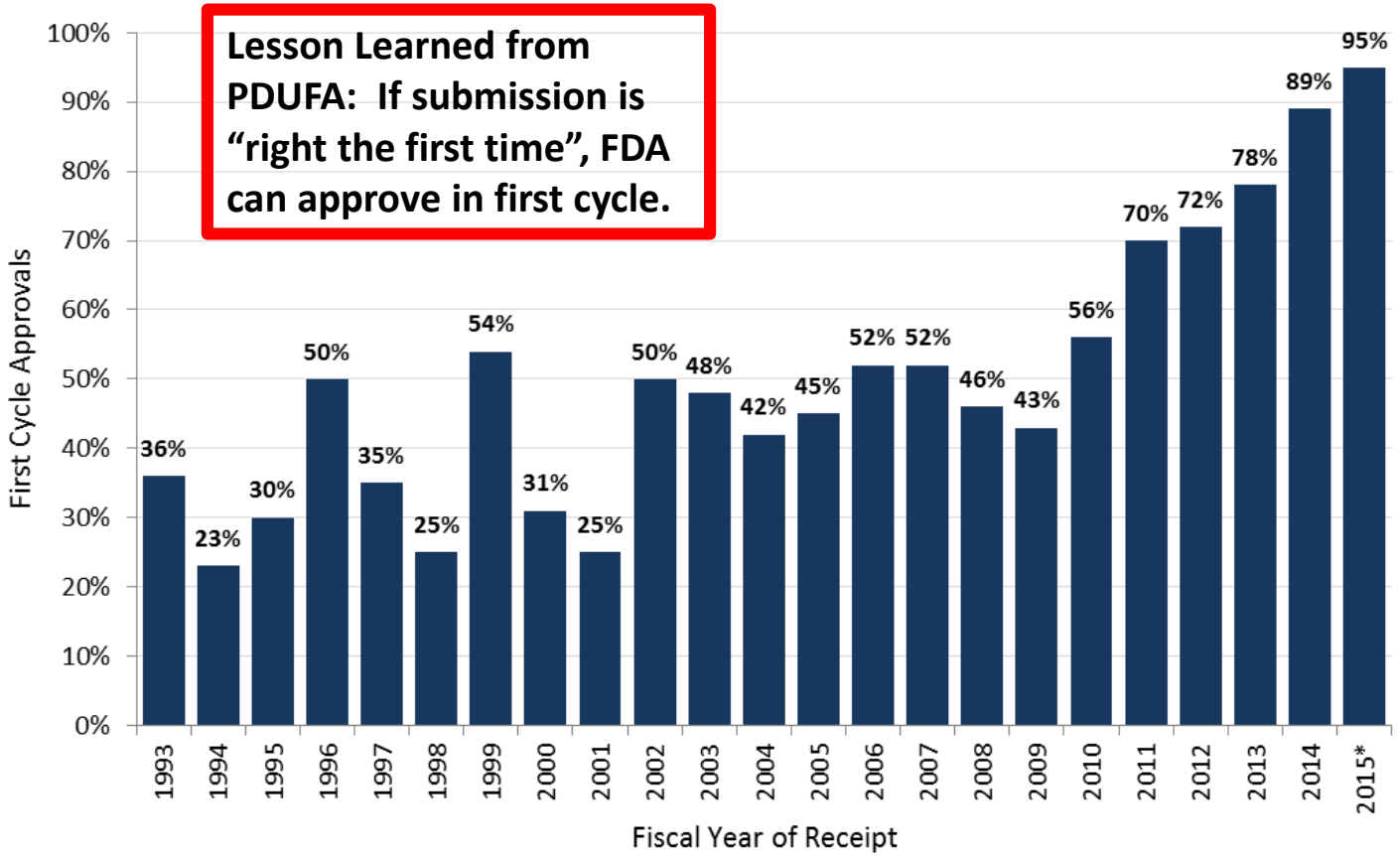
OUTSTANDING CHALLENGE: Multiple Review Cycles

CMC Review Cycles to ANDA Approval
2009 through July 2014



OUTSTANDING CHALLENGE: Multiple Review Cycles

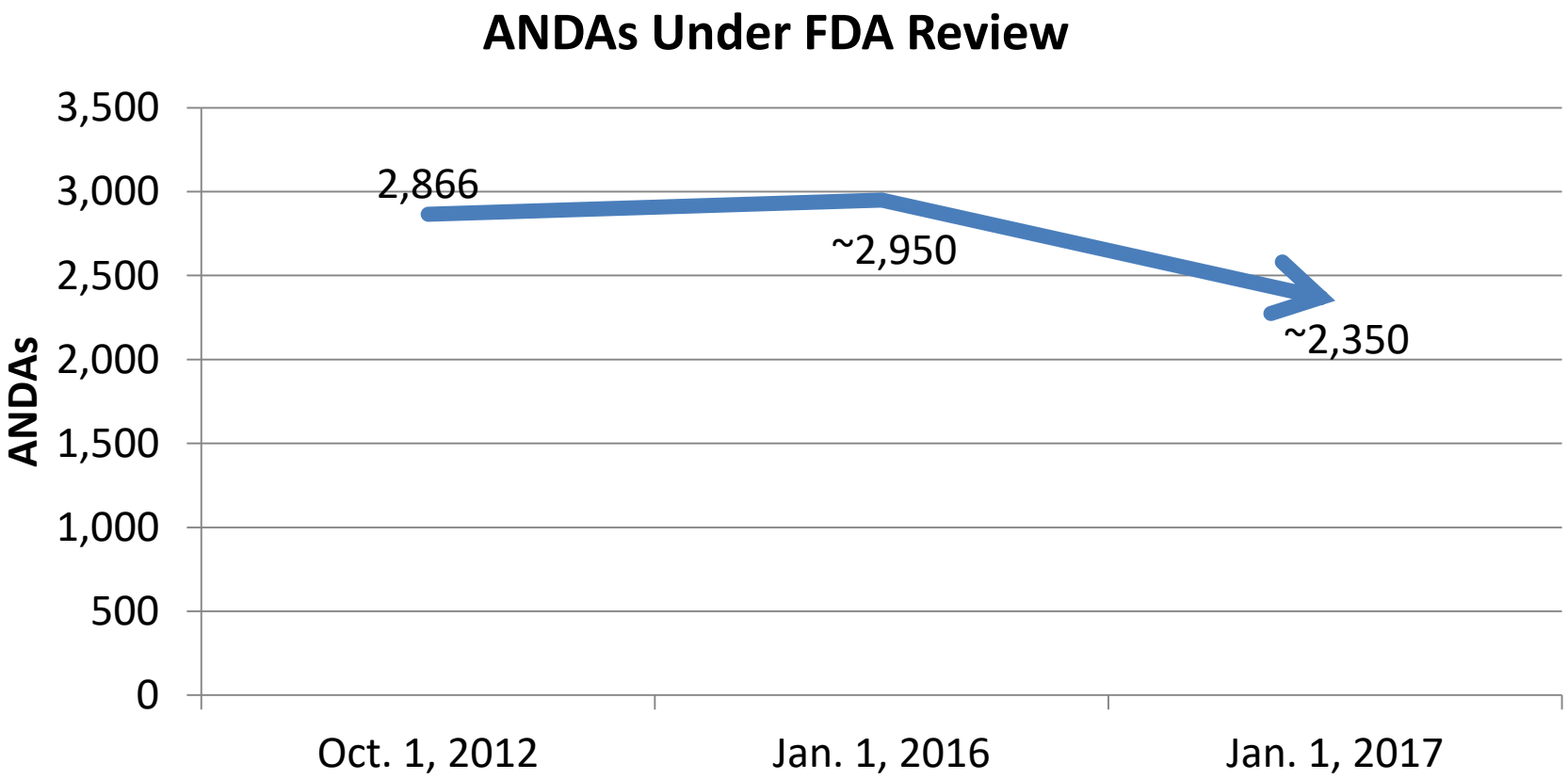
CDER NME NDAs/BLAs First Action Approval Rate



OUTSTANDING CHALLENGE: Multiple Review Cycles

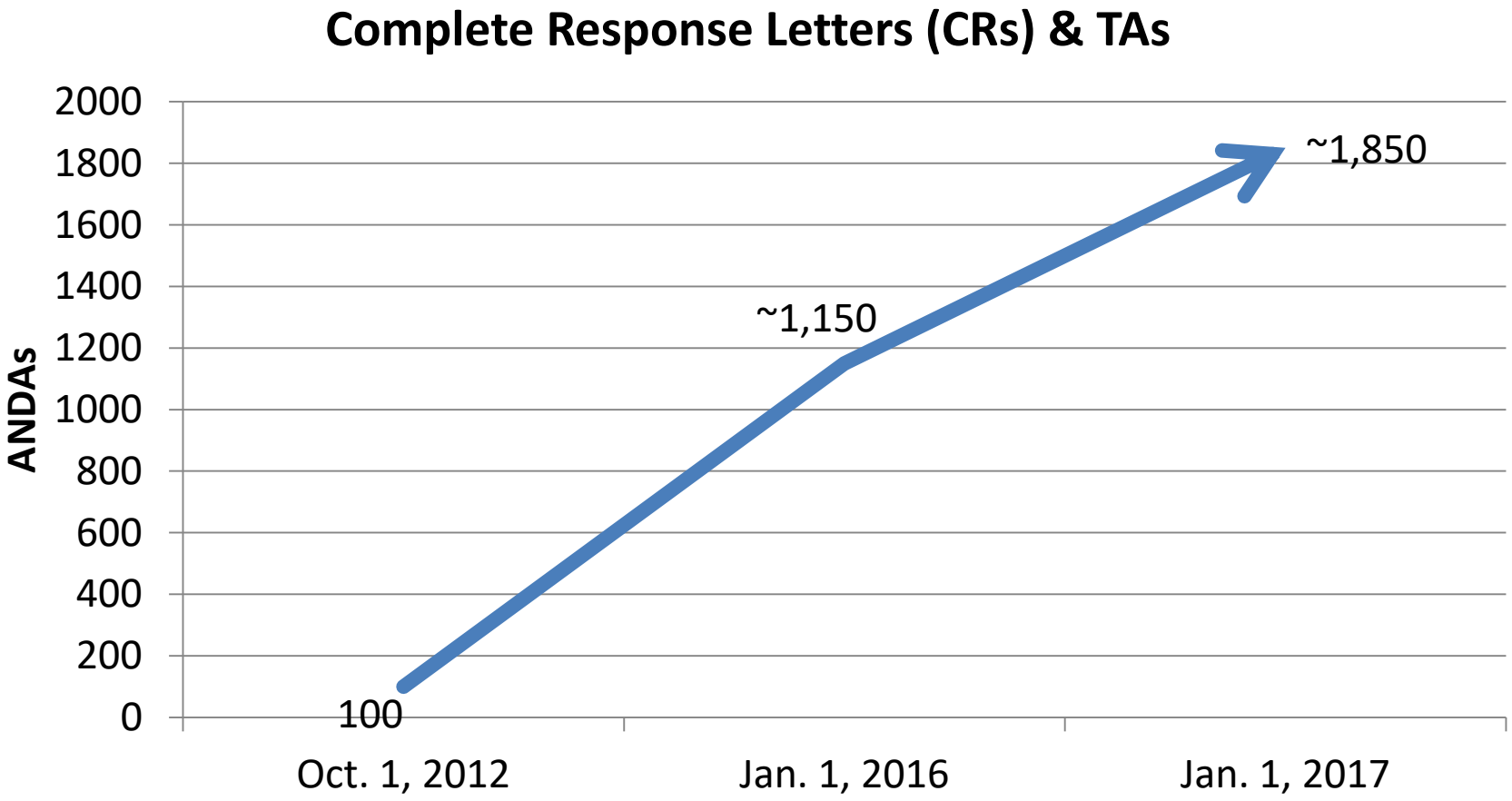
- Substantially all of the ANDA workload is:
  - At FDA and within the GDUFA goal, OR
  - With the applicant
- Many ANDAs are not lawfully approvable yet, because patent/exclusivity have not expired
- The **main challenge** is: It usually takes several review cycles to get to ANDA approval
- While UFAs count "regulatory actions", approval is the ultimate public health objective
- The **good news** is: The older ANDAs are now on their second or third review cycle, as evidenced by the large number of CRs in FY2016, and therefore should be ripe for approval

OUTSTANDING CHALLENGE: Multiple Review Cycles



*Approximate Values, January 2017

OUTSTANDING CHALLENGE: Multiple Review Cycles



*Approximate Values, January 2017

OUTSTANDING CHALLENGE: Multiple Review Cycles

The most common deficiencies are:

1. Inadequate facilities
2. Inadequate CMC
   - Stability
   - Dissolution
   - Inactive ingredients

PRESENTATION OUTLINE

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GDUFA II

Proposed agreement between FDA and industry stakeholders

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

GDUFA II

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

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

Main features of proposed GDUFA II

- ANDA review goals
- ANDA review program enhancements
- Enhanced Pre-ANDA process for complex products
- DMF review program enhancements
- Facility assessment enhancements
- Enhanced accountability and reporting
- Program size commensurate with overall ANDA workload
- Modifications to user fee structure
- Small business considerations
- More on “GDUFA II” by Ted Sherwood, Donal Parks, and Amy Bertha

GDUFA II Highlights

Faster review of priority submissions: 8 months

- "Priority" defined in MAPP 5240.3 – 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 to get to approval

GDUFA II Highlights

ANDA Review Program Enhancements

- Standard and Priority reviews
  - 10 months for new "standard" submission
  - 8 months for new "priority" submission
- "Priority" reviews contingent on Pre-Facility Communication (PFC)
  - Facilities data package submitted >2 months prior to ANDA submission
  - Complete (includes ALL facilities in ANDA), accurate, and remain unchanged

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”
- More efficient and effective review process
  - Increase chances for first cycle approval
  - Reduce number of cycles to approval

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

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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3. **Closing Thoughts**

FDA Delivering on GDUFA

- FDA is successfully fulfilling all its GDUFA I commitments
- In many cases, going above and beyond our negotiated commitments
- We are building a robust, modern generic drug regulatory program
  - Sustainable and predictable
  - Clear and consistent communication
  - Fairness across applications and applicants
- Work in progress now to be ready for GDUFA II on October 1, 2017

CLOSING COMMENTS

THANK YOU to Industry for:

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


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