FDA/GPhA
Quarterly Meeting on GDUFA

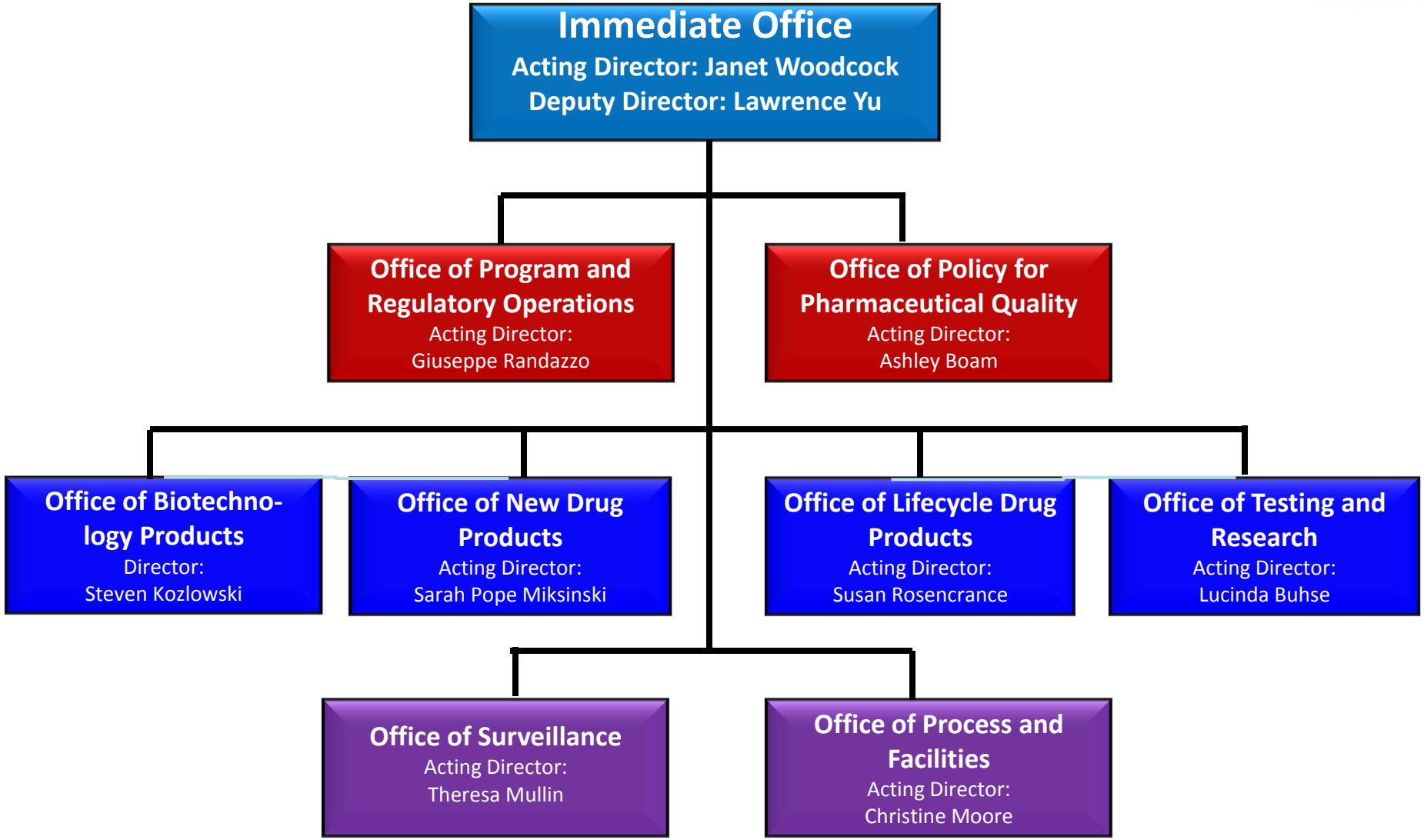
March 23, 2015

Meeting Agenda

I.	Introductions	All
II.	OPQ Organizational Structure	FDA
III.	Time To Approval/Action	FDA
IV.	GDUFA 1 Operations Update	FDA
	Break	
V.	QMS Update	FDA
VI.	Mechanics and timing of Paragraph III and IV approvals	FDA
V.	Wrap-up and Next Steps	All

OPQ Organization Structure

Office of Pharmaceutical Quality



Time to Approval/Action

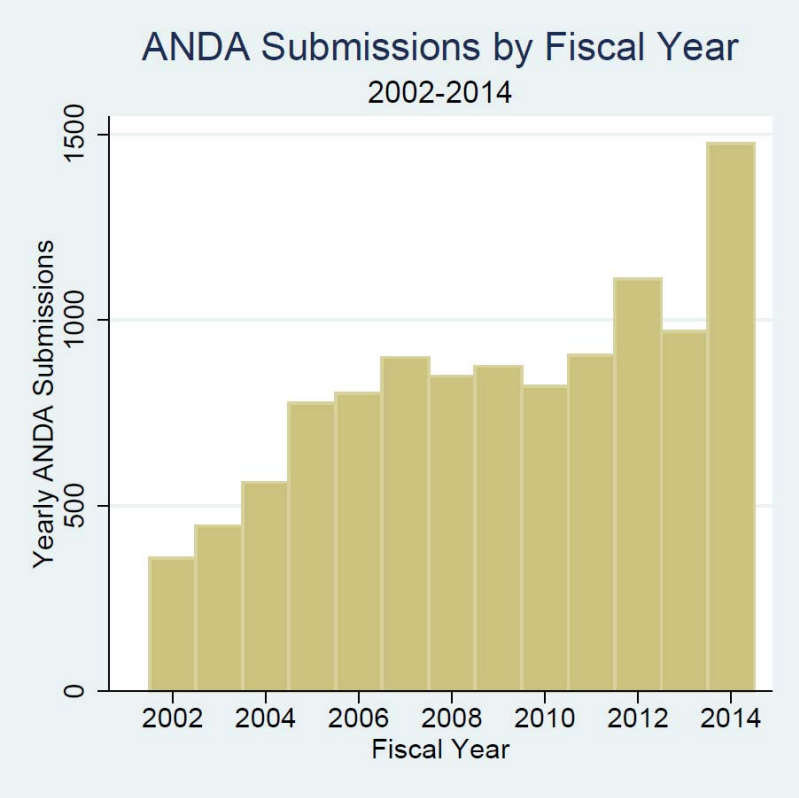
- Ryan Conrad

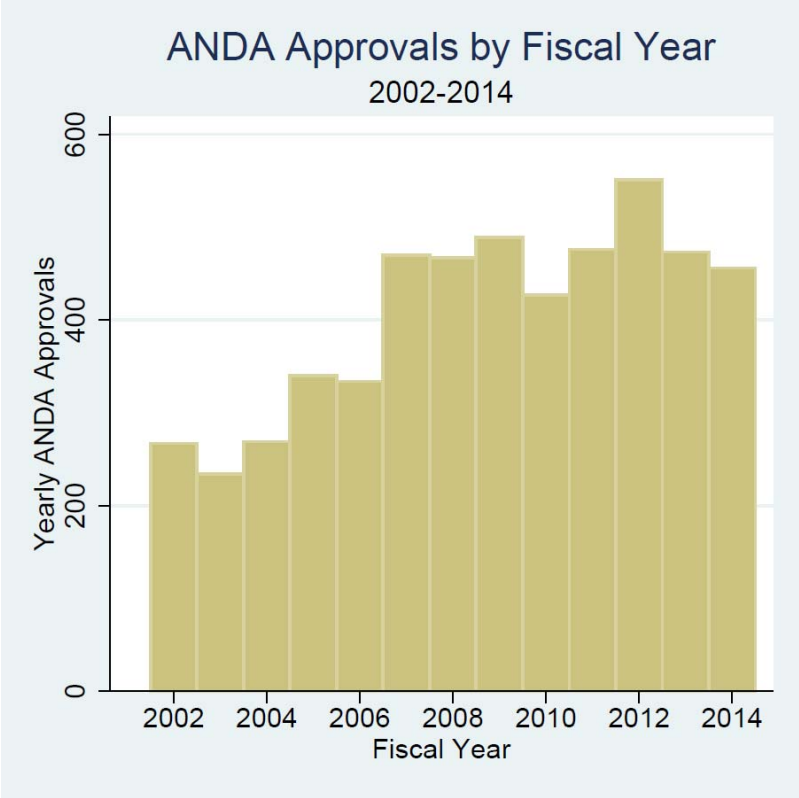
Meaningful Measurements of ANDA Review Timelines

23 March 2015 – FDA/GPhA Quarterly Meeting

Prepared and presented by: Ryan Conrad, PhD, Office of Strategic Programs, CDER

The market for generic drugs has expanded greatly over time





Time to approval has increased – but consider review times

Time to approval ≠ review time

- Many factors are related to how long it takes for an ANDA to be granted approval
  - Incomplete or insufficient applications can result in multiple review cycles
  - Reviewer workload

- We will consider two ways to look at review times
  - Submission to approval (full and tentative)
  - Submission to end of first review cycle event

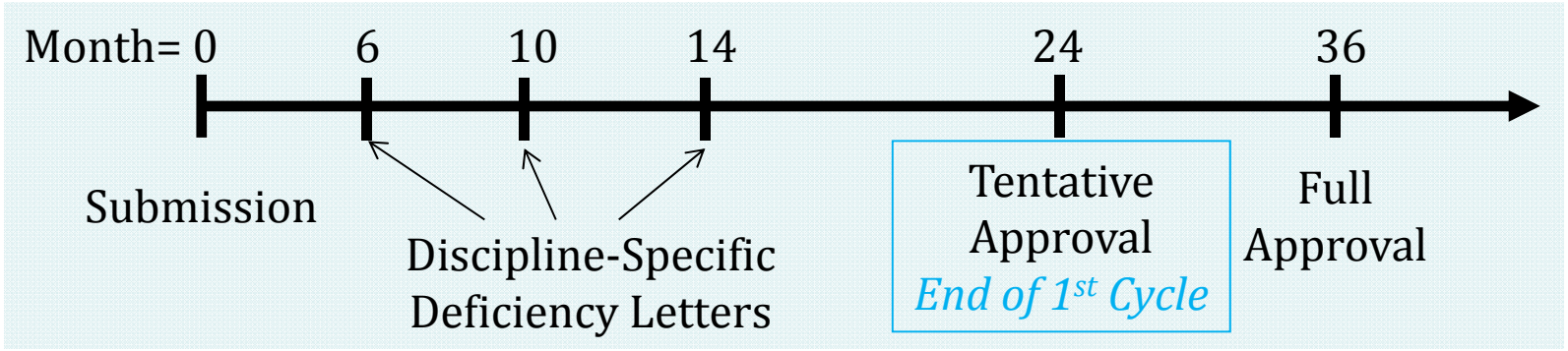
Compare approval to first cycle review outcomes

- We define the end of the first review cycle to occur when one of the following actions occurs:
  1. Full or tentative approval (AP, TA)
  2. Complete response or withdrawal (CR, WD)

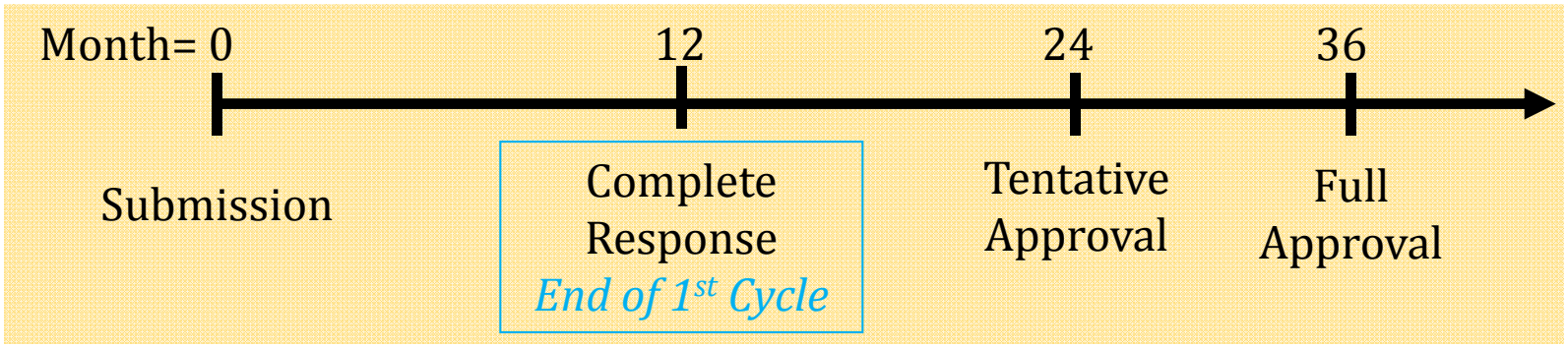
- Tentative approvals are issued when patents or exclusivities are blocking full approval, application is otherwise complete
- Complete responses are issued when applications have deficiencies that must be corrected
- Withdrawals are only considered here when no other action (CR, TA, AP) has been taken

The first review cycle has changed since CR was introduced

1. Before the Complete Response Era (Before Oct 2010)



2. After the Complete Response Era (After Oct 2010)



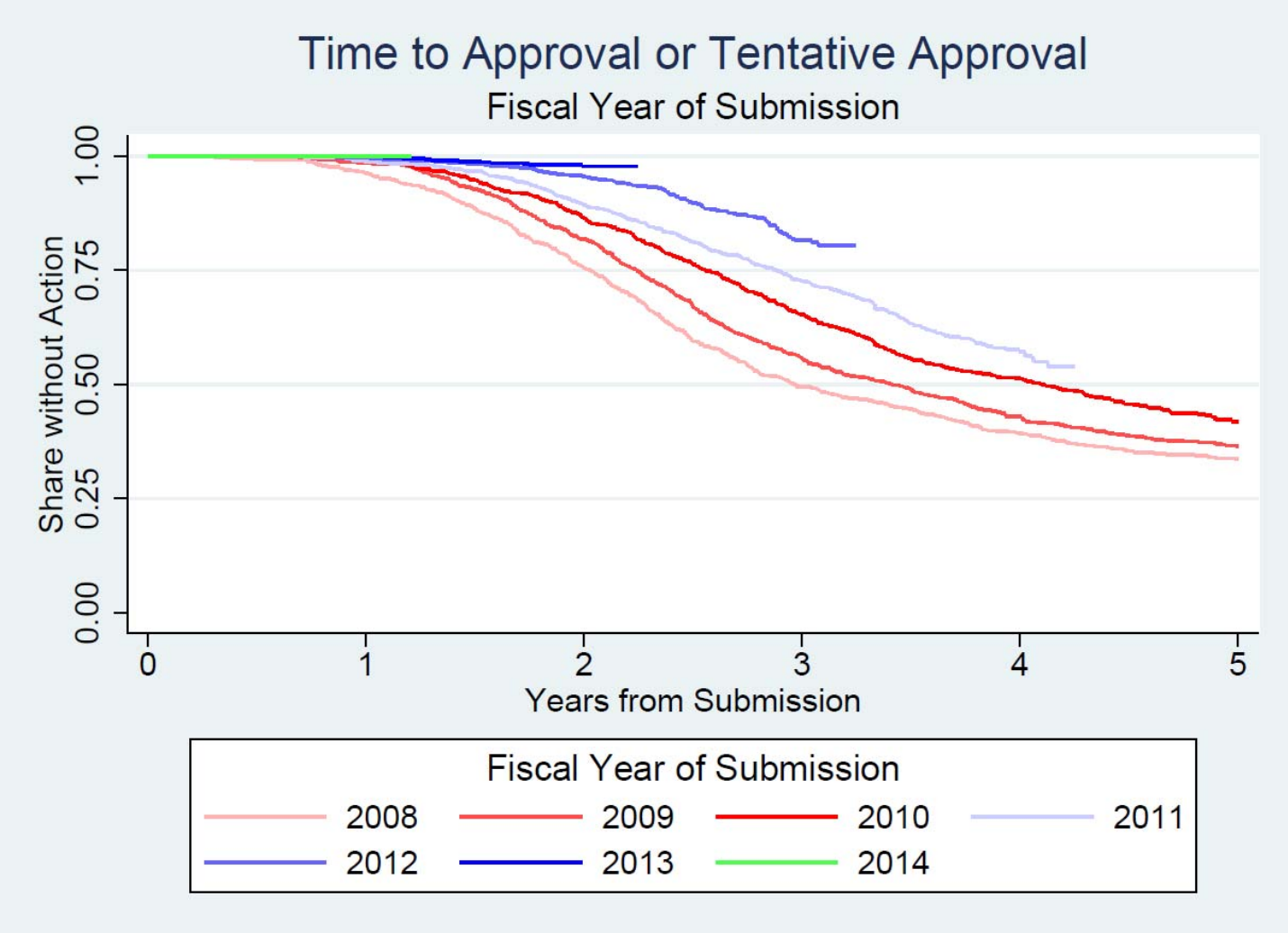
We analyze reviews for all ANDAs submitted from FY 2008-2014

- 6,780 total ANDA submissions
- Looks at outcomes stratified on fiscal year of submission

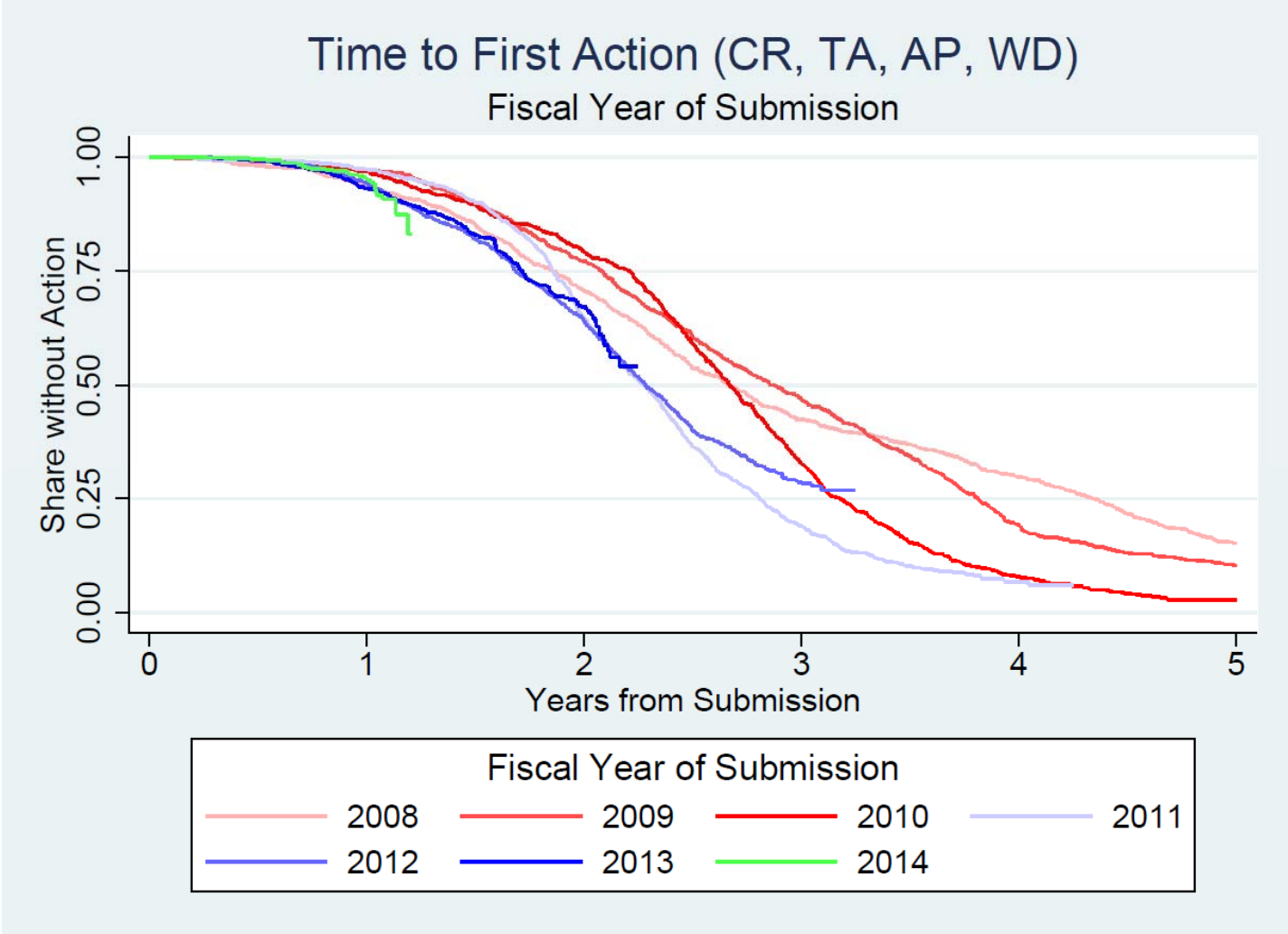
	FY of ANDA Submission						
	2008	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**
Submissions	827	850	798	885	1,077	925	1,418

- Plot two survival curves comparing submission cohorts
  1. **Time to approval or tentative approval**
  2. **Time to first action (CR, WD, TA, AP)**
- Note: CRs not issued until FY2011

Time to tentative or full approval

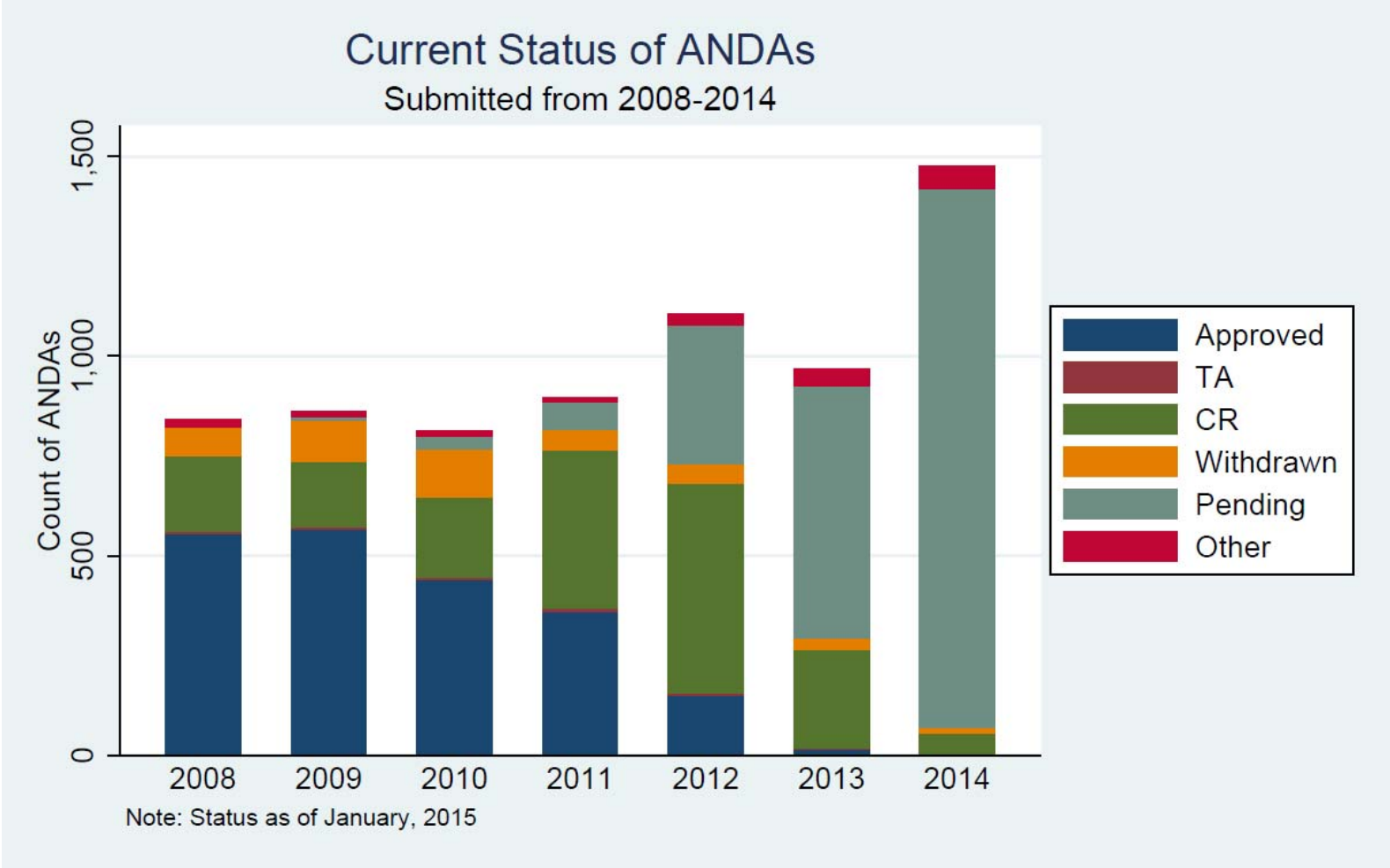


Time to earliest of CR, WD, TA, or Full Approval



Let's now briefly consider the current status of all ANDA submissions since 2008…

Current status of ANDA submissions since 2008



GDUFA 1 Operations Update

- Edward Sherwood
- Carol Holquist
- Denise McKan-Toyer

From the Last Meeting

Next Steps:

- Assign Target Action Dates (TADs) to all pre-Year 3 submissions. (With caveats, and not all at once. See next slide.)
- Base TADs on workload management factors, with one exception: For big first generics, assign TADs roughly corresponding with expiry.
- In early CY15, start notifying applicants of TADs.
- "Launch planning updates" for big first generics 6 and 3 months before TAD.
- Certain other pre-launch "go/no go" communications.
- Iterative, "real-time communications" re deficiencies in current review cycle. Already started in CMC, scale this out to Bio next.
- Update Communications with Industry MAPP to formalize and clarify these changes.

Operations Activities

- Filing Decision
- Target Action Dates (TADs)
  - Setting
  - Communicating
- No Go
- Information Requests (a.k.a. Real Time Communications)
- Easily Correctable Deficiencies
- Health of Application/Status Update (a.k.a. Launch Planning)
- Go/Action Letter Expected
- Complete Responses
  - Post CR meetings
- Approval/Tentative Approvals

Caveat

- Notification of a Target Action Date does not constitute a commitment or guarantee that FDA will take action on the application by the Target Action Date.
- Any amendments submitted after the notification may affect whether FDA will take action on the application by the Target Action Date.

Caveat

- When contacted for an additional status update 3 or 6 months prior to the Target Action Date, RPM will provide the total number of discipline reviews needed for the application and the number of reviews pending.
  - RPM cannot provide specifics on which disciplines are pending.
- All outstanding ECDs and IRs must be addressed before action can be taken.

Caveat

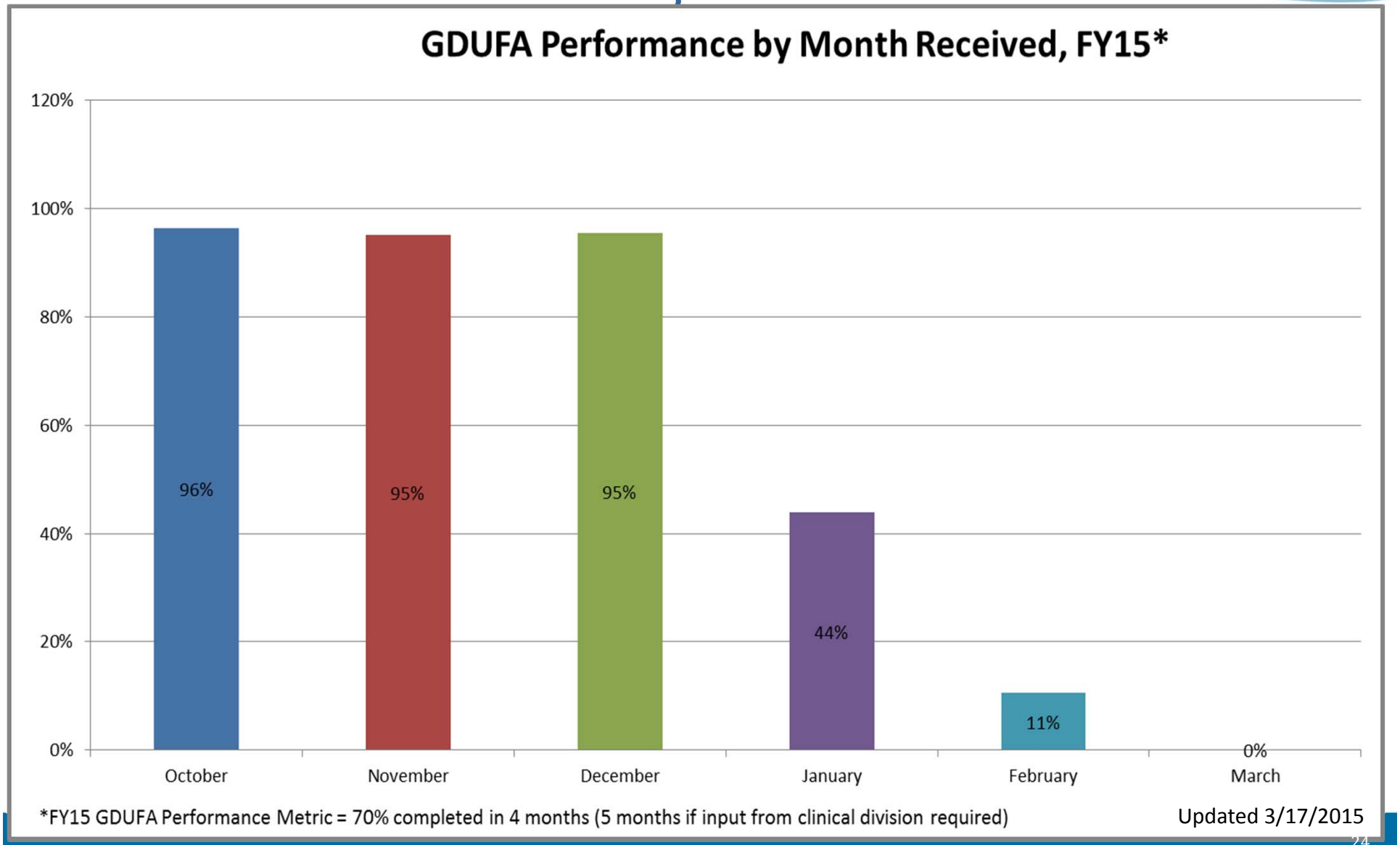
- When an application is in the clearance phase, RPM will notify the applicant by phone that FDA is on track to provide an action.
  - RPM may request assurance that the application's labeling, patent information, Type II DMFs, and inspections are up-to-date.
  - RPM cannot provide additional information other than that the application is on track to receive an action.
  - Not a guarantee of approval.

Controls

Controls as of 3/3/2015

- Controls Closed 309
- Controls – open 212
- Not a Control 229

Closed Controlled Correspondences FY15



Original ANDA Stats

Actions	Oct. 14	Nov. 14	Dec. 14	Jan. 15	Feb. 15
CR	43	76	95	104	100
TA	10	7	5	5	13
AP	45	28	29	25	28
Total	**98**	**111**	**129**	**134**	**141**

Filing Decision Time for Y3 ANDAs

27 days

Break Time

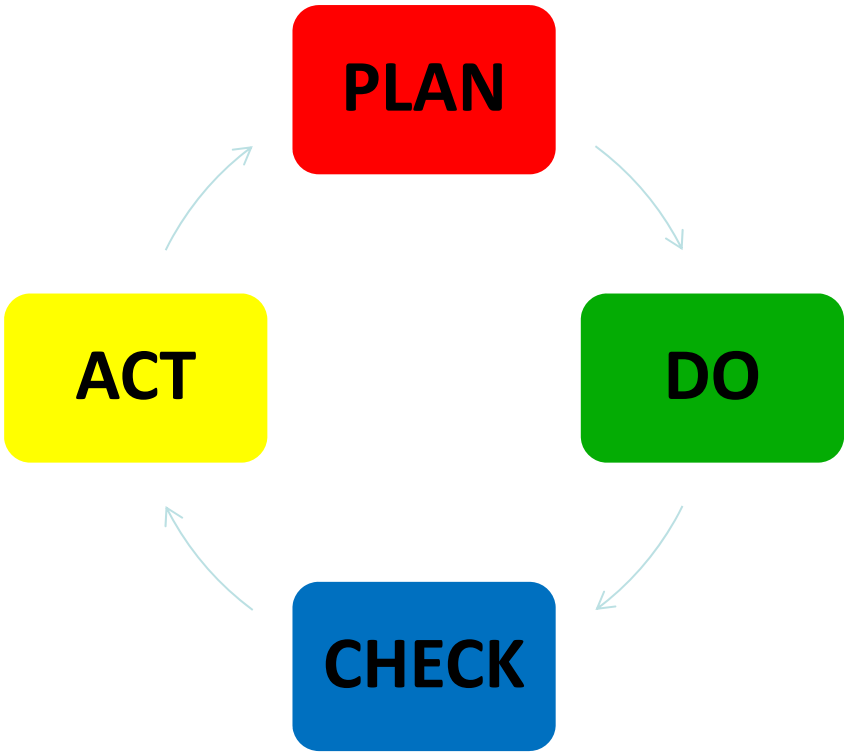
Quality Management System (QMS) Update

- Edward Sherwood
- Ashley Boam
- Giuseppe Randazzo

From the Last Meeting

SUCCESSFULLY IMPLEMENTING GDUFA …BUILDING A QUALITY SYSTEM

- **Hire & Train**
- **Process & Policy**
- **Inspectorate**
- **Informatics ("Platform")**
- **Regulatory Excellence**
- **Agency Alignment**



What Does the CDER ANDA Program Mean by QMS?

- The ANDA QMS is a collection of processes and procedures designed to facilitate the making of safe, effective, quality generic drug products available to the American public.

Elements

- Say what you do **PLAN**
  - Create shared understanding of mission, work, tools/resources, policies and procedures
  - Capture and document the understanding
- Do what you say **DO**
  - Train to the understanding
  - Execute, perform to the understanding

Elements (cont.)

- Prove it **CHECK**
  - Check
  - Audit
- Improve it **ACT**
  - Understand impact (internal and external) of current activities on systems and policies
  - Align quality policies, objectives, and processes
  - Re-evaluate, recapture, retrain, repeat…

Capture and Document

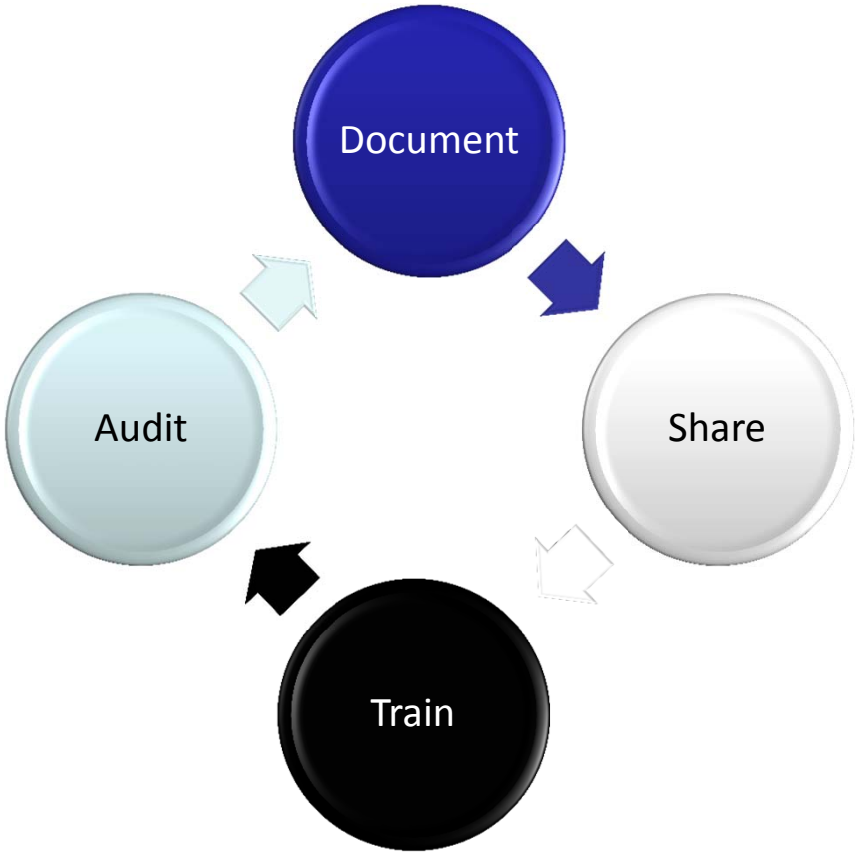
- Process mapping
  - Drafting of SOPs*
  - Creation of documents (forms, checklists, etc.)
  - Standardization of letter templates
  - Cross-division/office (collaborative) revision of documents and communication templates
- Shared CDER/ORA electronic document and workflow management through the CDER Informatics Platform

* SOP: Standard Operating Procedures

Training

- All staff
  - GDUFA requirements met
  - New & newly mapped processes and procedures (concepts such as team based review, risk based approaches, integrated quality assessment)
  - New & revised resources/tools
- New employees
  - Formal series of orientations
  - Resources/tools
  - Long-term mentorship
- New managers – roles and responsibilities

Continue to Improve



- All content, expectations, processes, procedures, etc.
- All levels of the ANDA organizations
- All staff members involved with ANDAs

Monitoring for Consistency

- OPQ/OGD provide formalized QMS activities
- Regular assessments of completed applications will:
  - Monitor for consistency of decisions across similar products/applications with established policies
  - Identify opportunities for improvement in quality assessment processes and/or approaches, need for additional training and/or reviewer tools

Mechanics and timing of Paragraph III and IV approvals

- Maryll Toufanian
- Marty Shimer

First Generics

March 23, 2015 FDA/GPhA Board Quarterly Meeting

Goal of Today's Discussion

- Review complex issues relating to First Generic ANDAs
- Discuss mechanisms to ensure timely First Generic approvals

Why We Are Here

- Timely approval of First Generic ANDAs is in everyone's best interest
- Commitment Letter addresses First Generics, but not in detail

Today's Agenda

I. Overview of Hatch-Waxman: How It Works
II. GDUFA and First Generics
III. Institutionalizing Prioritization of First Generics
IV. Managing Complexity and Unpredictability of First Generic Landscape
V. Next Steps

I. Overview of Hatch-Waxman: How It Works

Hatch-Waxman Amendments

Grand bargain for Brand and Generic Industries

- Brand Industry Gains:
  - 5-year New Chemical Entity (NCE) Exclusivity
  - 3-year New Clinical Studies Exclusivity
  - Patent Term Extension to account for time patented product is under review by FDA
- Generic Industry Gains:
  - Ability to challenge brand drug patents prior to marketing in court
  - 180-day Generic Drug Exclusivity

I. How Hatch-Waxman Works

What brand must do: "list" patents

- NDA sponsor must identify in NDA those patents reasonably related to drug product, drug substance, or method of using drug for which approval is sought.
- FDA "lists" patents identified by NDA sponsors in "Orange Book" (OB).
- NDA referred to as "reference listed drug" or RLD.

I. How Hatch-Waxman Works

What generics must do: "certify"

- Certify with respect to each patent listed for that RLD in the OB:
  - patent information has not been filed ("paragraph I certification") = FDA can approve ANDA when ready
  - the patent has expired ("paragraph II certification") = FDA can approve ANDA when ready
  - the date the patent will expire ("paragraph III certification") = FDA can approve ANDA when patent expires and ANDA is ready
  - the patent is invalid or not infringed by the drug product proposed in the ANDA ("paragraph IV certification") = complex approval landscape

I. How Hatch-Waxman Works

What follows from PIV certification

- After FDA notifies applicant that ANDA is sufficiently complete to review, applicant must notify NDA/patent holder of Paragraph IV certification.
- NDA sponsor can sue when it receives notice.
- Infringement lawsuit can start prior to ANDA approval and marketing
- If NDA sponsor sues within 45 days of notice, ANDA approval is stayed for 30 months.
- No lawsuit with 45 days = FDA can approve ANDA when ready

I. How Hatch-Waxman Works

What follows from PIV certification

- ANDA approval depends on patent litigation

Litigation Status	Regulatory Action
Lawsuit pending before 30-month stay expires	We can only tentatively approve ANDA
Lawsuit still pending at 30 months	We can approve ANDA
Generic wins	We can approve ANDA
Dismissal/Settlement	We can usually approve ANDA on agreed date
Brand wins	We can only tentatively approve ANDA

I. How Hatch-Waxman Works

Tentative Approval

- ANDA ready for approval but blocked by patent, exclusivity, or stay = only eligible for tentative approval (TA)
- Full approval not automatic after TA – must show ANDA still meets requirements for approval at time of full approval, e.g., cGMPs still good
- TA'd ANDAs must request full approval

I. How Hatch-Waxman Works
180-day Exclusivity

- Reward for ANDA applicants that challenge patents, potentially hastening generic market entry
- 180-day exclusivity is only available to "First to File" (FTF) ANDAs containing PIV certification
- Commonly there are multiple FTFs = shared exclusivity for FTF cohort

I. How Hatch-Waxman Works

Shared 180-day exclusivity

- FTF ANDAs may enter market at once if approval-ready

- or sequentially, depending on approvability

- or sequentially depending on intent to market

- All exclusivity ends at first triggered 180-day mark

I. How Hatch-Waxman Works

Other Important Concepts: Forfeiture

FTF can forfeit 180-day exclusivity:

- Failure to obtain a tentative approval in 30 months – impacted by multiple factors external to FDA
- Failure to market within a specified time after approval
- Expiration of all patents with which exclusivity is associated
- Withdrawal of the ANDA or all paragraph IV certifications
- Entering into an agreement that is in violation of antitrust laws as determined by FTC

Pediatric Exclusivity

Exclusivity for pediatric studies requested under Best Pharmaceuticals for Children Act (BPCA)

- Will result in six months of exclusivity when sponsor "fairly responds" to the written request regardless of changes to labeling
- Attaches to existing NCE and three-year exclusivity and most patents
- Study that results in six months of pediatric exclusivity may also result three-year exclusivity for pediatric patients

II. GDUFA and First Generics

Background on GDUFA Commitment Letter

Pursuant to CL, FDA has three obligations re review prioritization for First Generics

#1: expedite year 1 + 2 FTF

#2: expedite all FTF ANDAs within 30 months of submission to avoid forfeiture

- The above obligations overlap and are familiar. We have always tried to make sure FTFs don't "slip through the cracks."

Background on CL (cont.)

#3: Expedite at submission and over course of review applications that are/become eligible for approval as a result of no blocking exclusivities, patents and/or applicable stays

- This is new. It usually concerns not FTFs, but – instead – subsequent applicants that become eligible for FA based on change with FTF.
- Impacted by variables outside FDA control.

III. Institutionalizing Prioritization of First Generics

Opened First Generics Docket

Challenge: "First Generic" means different things to different people

- Received informal statements demonstrating different understandings, desired definition
- Opened First Generics docket to enhance transparency and gain clear industry expectations
- Expansive definition (discussed below) well-received

Patent and Exclusivity Team

Established dedicated group within OGD Policy

- A-team: DLRS Deputy Director, a former team leader in regulatory support branch, and pharmacists with significant ANDA regulatory management experience
- Purpose: proactively identify, track, and facilitate timely resolution of issues related to First Generic approvals
- Driving long-term planning in First Generic Space

DLRS Regulatory Counsels

Built team of dedicated, experienced regulatory counsels

- Recruited from within: OCC, OGD, and experienced FDA regulatory counsel management
- Recruited from private sector: Attorneys from highly credentialed law firms, patent litigation firms, with Hatch-Waxman knowledge
- Purpose: Analyze Hatch-Waxman issues and document decisions to ensure timely First Generic approvals

IT Enhancements

Significant enhancement to IT underway to support efficient analysis of First Generics issues.

- Data tracking, updating functions
- Nimble, real-time information available to decision makers

OGD Hatch-Waxman Training

- Providing training to all OGD disciplines on Hatch-Waxman, including regulatory project managers and operations team.
- Providing updated information on developments in legal and regulatory space

Take away – We are strongly institutionalizing the First Generics function that previously was ad-hoc and under-resourced.

IV. Managing Complexity and Unpredictability of First Generic Landscape

Proposed Criteria for First Generic Prioritization Category

Any received ANDA:

- that is eligible for 180-day exclusivity (FTF); OR
- for which there are no (or no longer) blocking patents or exclusivities AND there is no previously-approved ANDA for the drug product.

Benefits and Challenge of Proposed Criteria

Benefits:

- Focuses on getting generics to market as fast as possible
- Consistent with broad scope of Commitment Letter
- Adds focus on quick approval of subsequent applicant given 180-day forfeiture, other shifts in landscape

Challenge:

- Variables outside of FDA control affect status over lifetime of ANDA; can change often and quickly
- FDA does not control approvability (e.g., quality of submissions, inspection status, timing of industry response to deficiencies, patent litigation)

Variables in Determining First-Generic Status

- Changes in patent certification, litigation status, and settlement agreements/waivers between the NDA holder and ANDA applicant(s) can immediately delay or accelerate approval dates.
  - Change by first applicant could result in multiple subsequent applicants becoming immediately eligible for full approval
  - Order by court could temporarily or significantly delay ability to approve
- Forfeitures by FTF PIV applicants can result in subsequent applicants becoming immediately eligible for full approval.
- Late-in-the-game submission of revised patent information; added pediatric or 3-year exclusivity
- Approvability of ANDAs

Case Study

Key Take-Aways from Case Study

- ANDAs submitted on the same day won't necessarily be approved on the same day.
- Each ANDA in a FTF cohort has a distinct patent/legal status.
- This status can change often, and without our knowledge.
- Multiple variables – most outside of FDA's control – need to be tracked and updated in real time.

V. Next Steps

Next Steps on First Generics

- FDA will continue to develop, enhance capacity to ensure timely First Generic Approval
- FDA seeks a conversation with industry on continued improvement:
  - What else FDA can do?
  - What can Industry do?

Wrap-Up and Next Steps

Next Meeting:

- June 11, 1-4pm, WO75, RM 1540

Agenda:

- Mutual Reliance Update
- ORA Inspection Update
- Surveillance Selection
- Office of Process and Facilities Inspection (pre-approval and post-approval)