Efficient Generic Drug and Biosimilar Review and Surveillance Processes

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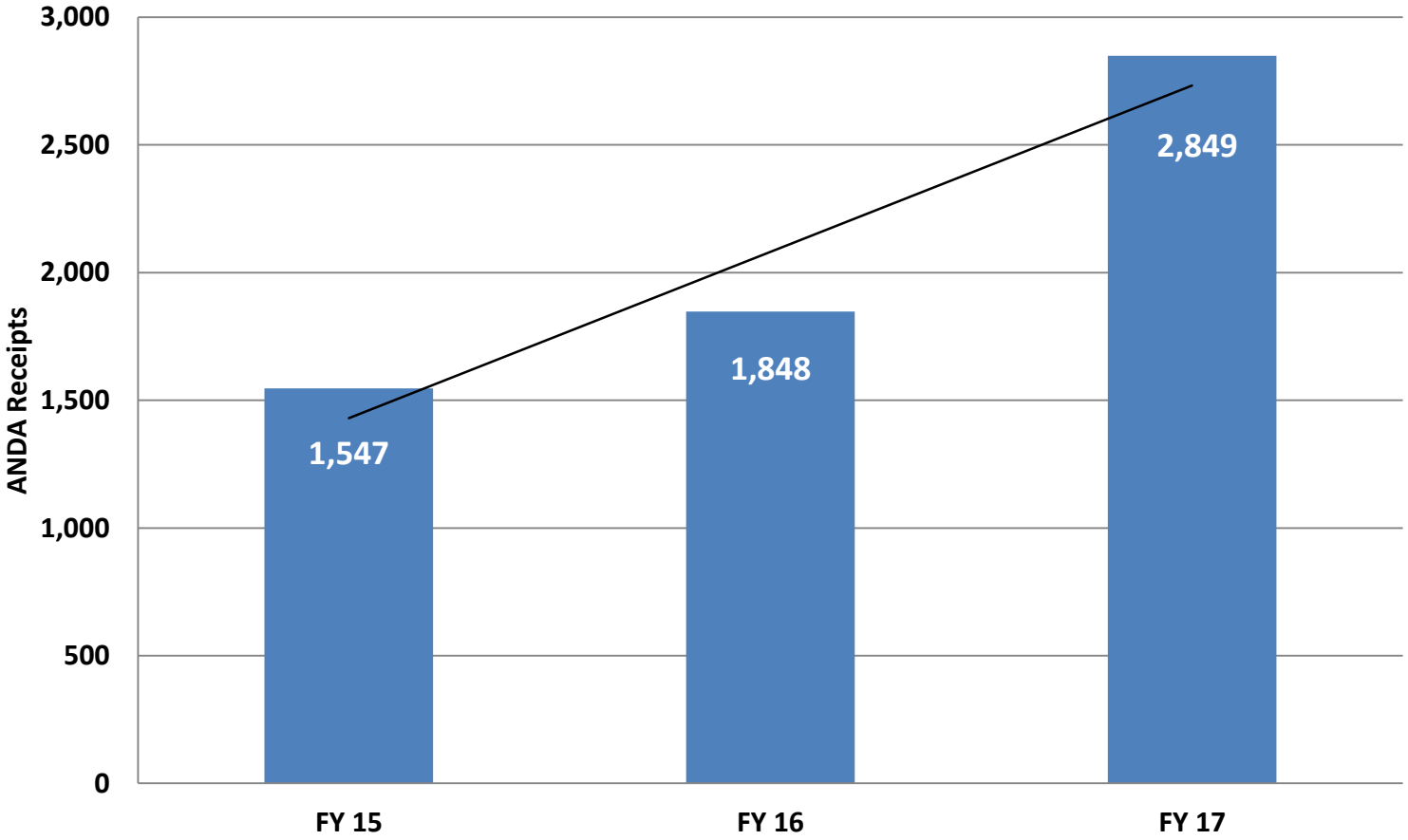
Agenda

- Towards a structured assessment process
- Facility assessment and surveillance
- Current status and challenges for biosimilars program

TOWARDS A STRUCTURED ASSESSMENT PROCESS

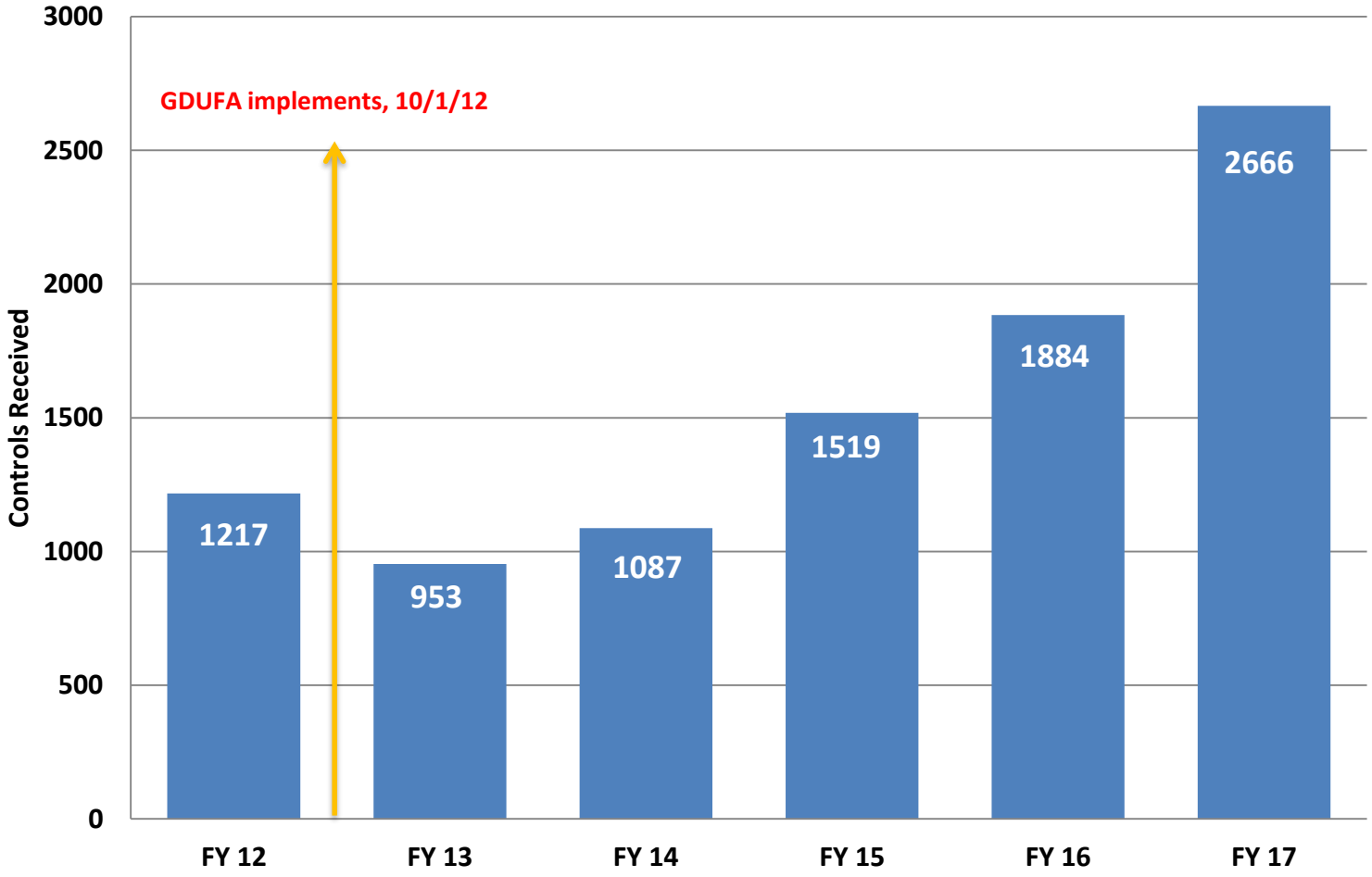
ANDA Receipts

(Originals + CR Responses/Amendments)



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

Controls Received



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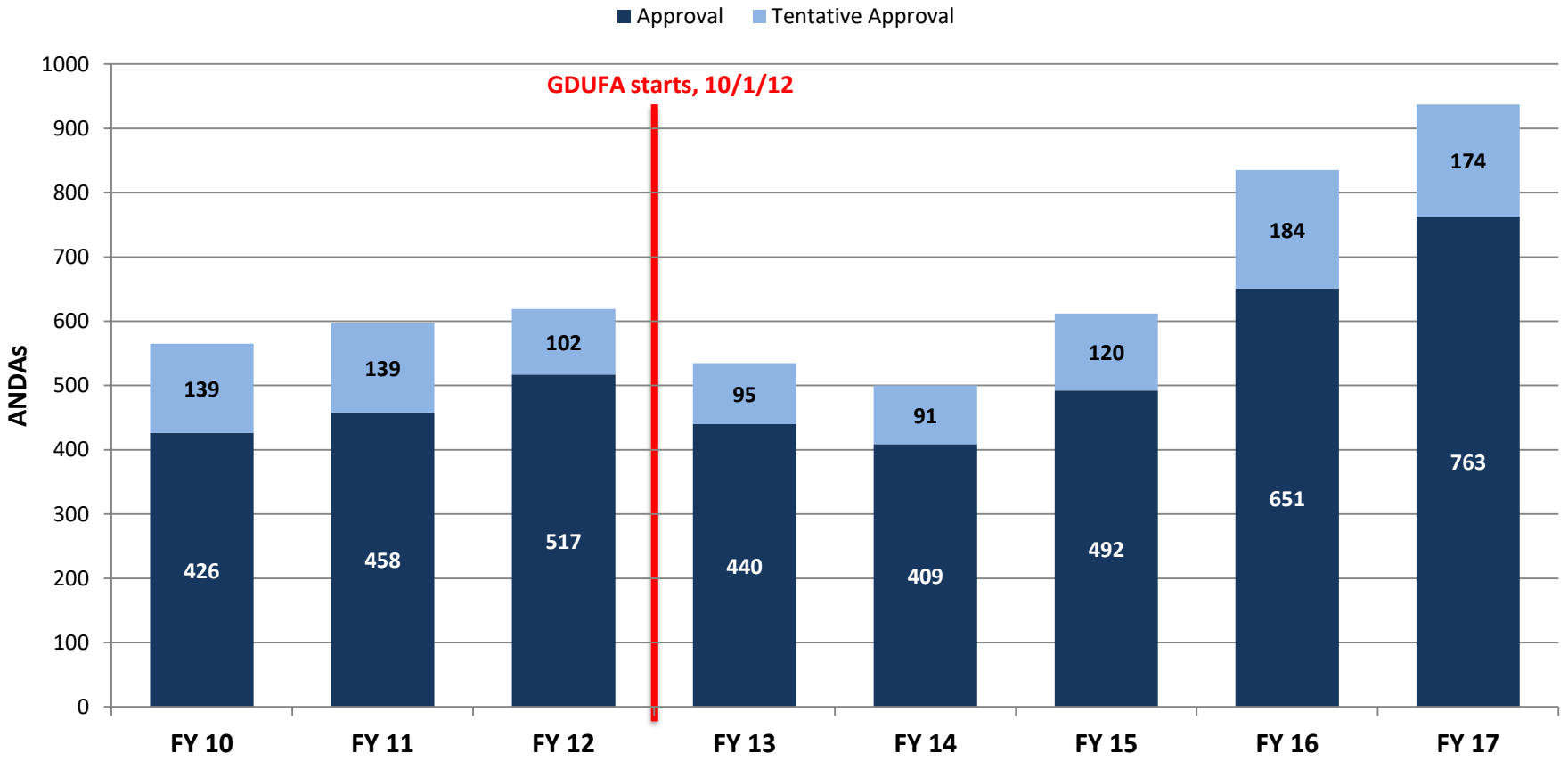
Annual Approvals & Tentative Approvals



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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**

*Updated 10/1/2017. Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.
**Cohort Year 5 (FY2017) – Given the large number of ANDAs submitted in the end of FY2017, many ANDAs undergoing Filing Review.

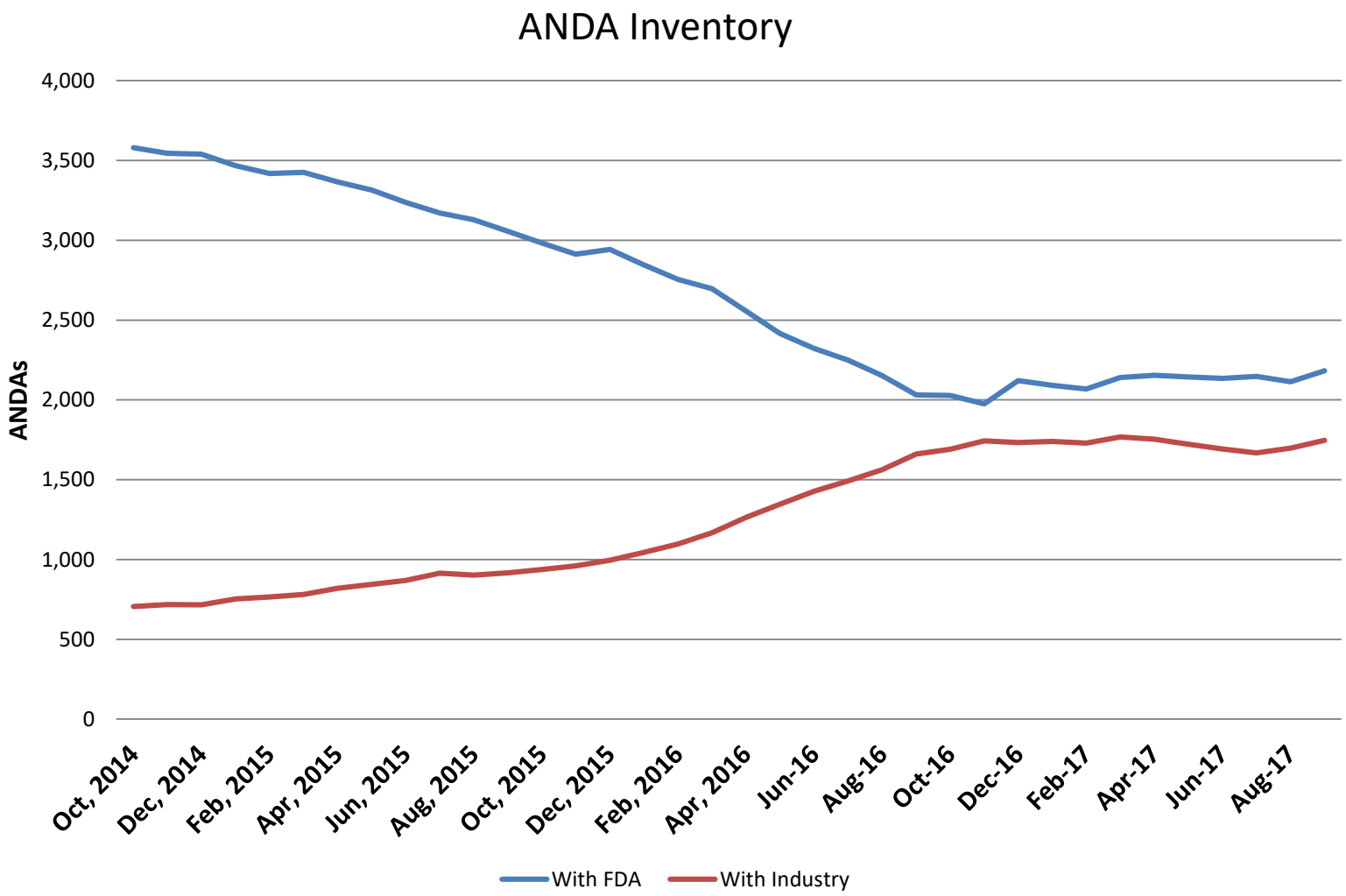
FIRST CYCLE APPROVALS*

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

*Updated 10/1/2017. Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.
Cohort Year 3 (FY2016) – Some are still under review and within goal; all mature by December 31, 2017.
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 decision (excluding ANDAs under review).

Getting to “Stable Footing”



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Trajectory Probably not Sustainable under Current Practices

- GDUFA 2 adds additional expectations
- Staff still working flat out
- Still many inefficiencies in review process
- Need to get to more 1st cycle approvals and decrease RTR's to minimize workload on both sides of the application process—industry and FDA
- Clarity of expectations and structuring/standardization of review process key

Current Application Assessment Process—Particularly Quality—very Labor Intensive

- Involves creation of review documents by multiple scientists
- Text documents not very amenable to knowledge management
- Many parts of assessment process relatively standard or could be standardized

Knowledge-aided Assessment and Structured Application (KASA)

- Need a new paradigm for performing quality assessments of applications
- Move toward structured assessment rather than text document
- Allow for knowledge management over the lifecycle AND high efficiency of processing
- Will help in communicating requirements clearly to industry sponsors

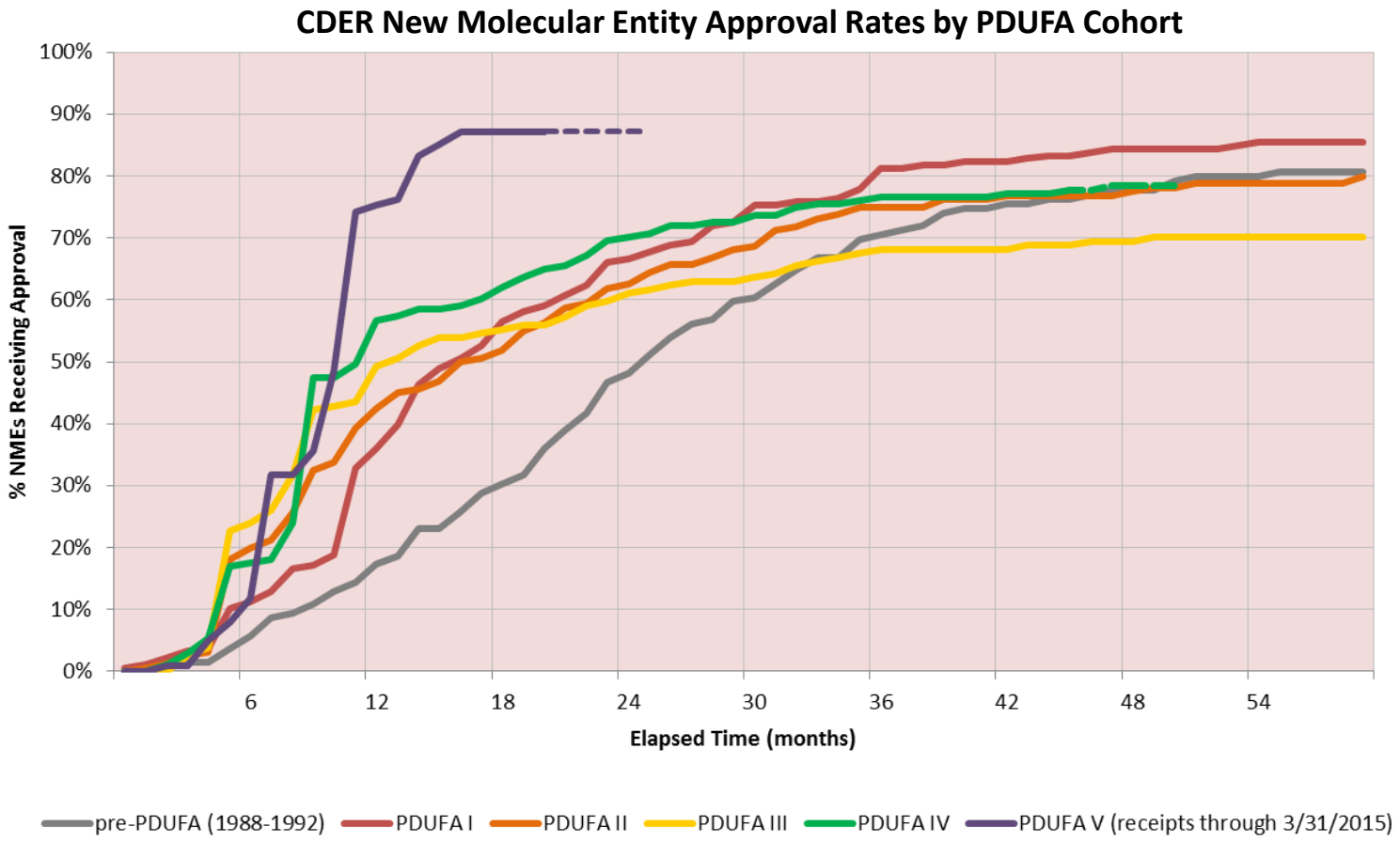
Progress

- Have designed a computer-aided interface to enable lifecycle management and standardized ANDA quality assessment
- Developed and piloted dashboard interface centered around
  - Quality risk assessment for critical quality attributes and corresponding mitigation strategies
  - Control strategies for drug substance and drug product

Initiative

- Plan to develop and implement modules over the next several years
- Without this streamlining, program will be the victim of its own success
- Next steps (post internal FDA implementation) would be to assist industry in better structuring submissions
- Reduce RTR rate and decrease number of cycles before approval

PDUFA Experience: Higher first cycle approval rate achievable



* 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

FACILITY ASSESSMENT AND SURVEILLANCE PROCESS IMPROVEMENTS

Progress on Facility Assessment and Surveillance

- Goal: understand facility inventory and inspect on a regular schedule-ACHIEVED
- Goal: Develop a new “concept of operations” with the re-organized ORA organization and implement—ACHIEVED
- Goal: New compliance program developed and published--ACHIEVED
- Goal: Notify facilities in writing of status 90 days after conclusion of inspection—ACHIEVED so far, since Nov 2017

Additional Objectives

- Develop more sophisticated risk metrics so we can better target higher risk facilities
- Better knowledge management among Office of Surveillance, Office of Process and Facilities, and ORA (some of the information is still in District file cabinets)
- Implement more standardized inspection protocols
  - Better international harmonization of inspection practices

New Inspection Protocol Project (NIPP)

- Goal: Standardized, eventually GRADED processes and categories of observations to ensure better consistency among observers and better communicate assessment of facility status and deficiencies
- Pilot: Sterile facility inspections, continuing to do pilots in this area
- Plan: expand to addition dosage forms
- Would again provide better clarity for industry on requirements
- Across all types of products, not just generic drugs

NIPP

- Ultimately, hope to implement knowledge management so inspectional information will be seamlessly integrated with other data from applications, annual reports, and so forth
- We are currently working on implementation of agreement with the EU on surveillance inspections in countries found to have equivalent inspectional practices
- Currently, not able to integrate this information

PROGRESS ON BIOSIMILARS

Biosimilar Program

- Currently, as you know, we have approved nine biosimilars, no interchangable biosimilars
- Not all currently marketed due to additional hurdles
- Multiple development programs underway
- We are in the process of adding staff to this review program
- Still have numerous additional guidances, policies, possibly regulations to issue to fully implement program

Acceptance by Medical Community

- We have been conducting targeted outreach programs
- We are seeing acceptance and understanding growing in US practitioners
- Positive experience with early products critical to practitioners and to uptake
- Due to the costs of the innovator products most are subject to “prior authorization” and formulary control--we will see how this all plays out in the US market

Scientific Challenges

- Analytical methods evolve over time
- Better lens to evaluate innovator products and biosimilars alike
- When you look at something with a more powerful microscope, you will find things you did not know about before
- As always, need to understand critical quality attributes and their relationship to clinical outcomes
- Fortunately we have a very scientifically strong scientific staff and policy group and we will be able to sort these issues out

Biosimilars Program

- The standardization we are working towards in the generic drug and facility areas will not be achievable soon in the biosimilar space
- Need to recognize how early we are in this program
- For example, product-specific guidances are not possible until we accumulate more knowledge about the issues
- We continue to learn more about the control of these products and their variability

Summary

- Standardization and streamlining essential for efficient application and facility assessment
- FDA has initiative to carry this out—progress somewhat impeded by workload but efforts are moving forward
- Critical to overall program success
- Biosimilar program is at a different stage—laying out policies and gaining scientific understanding