

CDER Update and Priorities: 2016

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Operations

CDER, FDA

CDER has Multiple Important Priorities

- Statutory: FDAAA, FDASIA, DQSA, Sunscreen Innovation Act, appropriations bill language; more under consideration currently with 21st Century Cures
- Operational: Three user fee programs with multiple ongoing goal commitments and now new agreements to implement
- Mission oriented both on macro and micro scales, from organizational to cultural and policy orientation

Front Burner Priorities: 2016

- User Fees
 - Complete PDUFA VI and GDUFA II agreements will be delivered to Congress by January 15, 2017 (statutory deadline)
 - Complete the second BSUFA program agreement
- Statutory
 - Continue to implement new (and clarified) statutory provisions on drug compounding and outsourcing facilities
 - Continue to meet milestones of Sunscreen Innovation Act
 - Continue implementation of Track and Trace program
 - Respond as needed and participate as requested in Congressional inquiries and FDA-related legislative initiatives

Front Burner Priorities

- Re-evaluate our regulation of drug advertising and promotion in light of current jurisprudence around the 1st Amendment: ongoing, progress made, but more work needed
- Prescription opioid epidemic:
 - Have issued guidance on evaluation of abuse deterrent formulations
 - Finalize the draft guidance on generic versions of abuse-deterrent opioid formulations
 - Evaluate opioid labels and REMS
 - Work on appropriate prescribing through our Safe Use group
 - Support the secretary's initiative and FDA strategic plan
- Improve staffing:
 - Continue to have more than 670 staff vacancies
 - Recruiting for multiple executive positions

Important Priorities (in no order)

- Drug Safety
 - Integrate Sentinel Network into routine drug safety activities
- Continue Drug Label Improvement Initiative
 - Patient Medication Information (PMI) project
- Continue to develop policy approach for antimicrobials to treat drug-resistant organisms
- Improve combination product Inter-Center review process
- OTC monograph reform: discussion of new approach with Congress and industry ongoing
- International Harmonization: recent meeting

Important Priorities

- Make significant progress on FDA-EU mutual reliance initiative
- Refine biomarkers qualification program
 - Develop a process and ultimate policy documents on evaluation of a biomarker as a surrogate endpoint for accelerated approval
- Modernize clinical evidence development, fully utilizing electronic health data and real world evidence
- Further develop use of Bayesian statistics, adaptive designs, modeling approaches, etc. for difficult drug evaluation issues
- Implement a broad IT platform for operations across the center
- Establish broader governance of the center

FURTHER INFORMATION ON SELECTED PRIORITIES

PDUFA Review Performance

Drug Development in 2015 remained strong

- FDA met 98% of its PDUFA goals
- 45 New Drugs (NMEs)
- 36% were first in class
- About 87% approved in first cycle of review
- 47% were for orphan diseases
- 64% of all new molecular entities are approved in the US first
- New “program” for reviews of NME’s progressing well
- PDUFA 6 negotiations progressing well.



CDER Ensures That Novel Drugs Receive Expedited Review

- 60% of new drug approvals in 2015 used an expedited pathway
 - More than half (53%) of the novel drugs approved to date in CY15 were approved under **Priority Review**
 - About one-third (31%) of novel drugs approved to date in CY15 received **Fast Track** designation
 - 13% were **Accelerated Approvals**
 - 22% were **Breakthrough** designated products

Breakthrough Therapy Designation Program

- Pace of submissions and designations continue
- Utilized a process to provide advice to sponsors before Breakthrough Therapy Designation requests are submitted
- Evaluation as of 9/30/16
 - Received 388 requests for breakthrough therapy designation
 - CDER granted 137
 - Hem Onc and antivirals lead but orphan diseases also frequent
 - 52 original/supplemental applications approved

Impact of Breakthrough Designation

- Friends of Cancer Research
 - Review time approximately 3 months faster
 - Development time 2.2 years less
 - Greater use of phase 1:2 data
 - Greater use of accelerated approval
- FDA internal analyses
 - Approximately 3 years less development time
 - Review times about 1-2 months less

CDER-ORA PAG Agreement

- Integrate ORA facility pre-approval inspections into OPQ team review—one overall quality assessment.
 - Pilots ongoing; new inspectional template under development
- Specialized pharmaceutical inspectional personnel in ORA will work closely with the Center
 - ORA undergoing change process
- Share data from various systems seamlessly

Biosimilar Development Programs

- As of November 30, 2016, 66 programs were in the Biosimilar Product Development (BPD) Program.
- CDER has received meeting requests to discuss the development of biosimilars for 21 different reference products.
- Since program inception and as of November 30, 2016, 8 companies have publicly announced submission of twelve 351(k) BLAs.
- Four 351(k) BLAs for biosimilar products have been approved.
 - Zarxio (filgrastim-sndz)
 - Inflectra (infliximab-dyyb)
 - Erelzi (etanercept-szzs)
 - Amjetiva (adalimumab-atto)
- FDA has issued four final and five draft guidances since enactment of the BPCI Act.



Generic Drug User Fee Act (GDUFA)

- New review performance goals (10 m review) now in play as of Oct
 - required process change and hiring
 - on track in hiring (about 1000 hires) and guidance goals, fee collection
- GDUFA Backlog
 - 2,866 Original ANDAs; 1,868 PAS Supplements
 - New submissions each year far ahead of GDUFA assumptions
 - > 1000 new ANDAs ; > 400 PASs
- Actions, on track for all GDUFA Goals
 - >4000 DMFs have been evaluated for completeness under GDUFA.
 - **>90% backlog applications received a review**
 - Those submitted after Oct. '14 on track for 15 m review
 - Some Year 3 ANDAs already approved (15 month goal dates in Jan 16)
 - Now (since Oct) tracking for 10 m reviews of new ANDAs
 - Regulatory science agenda established for \$20 million

Overall Actions

Pre-GDUFA

GDUFA

	FY2012	FY2013	FY2014	FY2015	FY2016*
ANDA approvals	517	440	409	492	651
PAS approvals	275	535	659	624	496
Tentative Approval (TA)	102	95	91	120	184
Complete Response (CR) †	84	1251	1254	1180	1725
TOTAL **	978	2321	2413	2416	3056
DMF Completeness Assessment (CA)	0	1699	1706	901	838



*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.

Drug Quality and Security Act: Compounding

- Since 2012 FDA has taken aggressive action to increase oversight and implement compounding provisions of the law
 - Conducted over 425 inspections and issued more than 130 warning letters
 - Issued 18 draft and revised draft guidances, 7 of which have been finalized
 - Issued 2 proposed rules and 1 final rule regarding list of drugs that cannot be compounded
 - Convened 4 intergovernmental working meetings with states
 - Held 4 sets of listening sessions with over 75 stakeholders
 - Held 6 meetings of the Pharmacy Compounding Advisory Committee (PCAC)
- We continue to identify insanitary conditions at many of the compounding facilities we have inspected and receive reports of adverse events associated with sterile and non-sterile compounded drugs

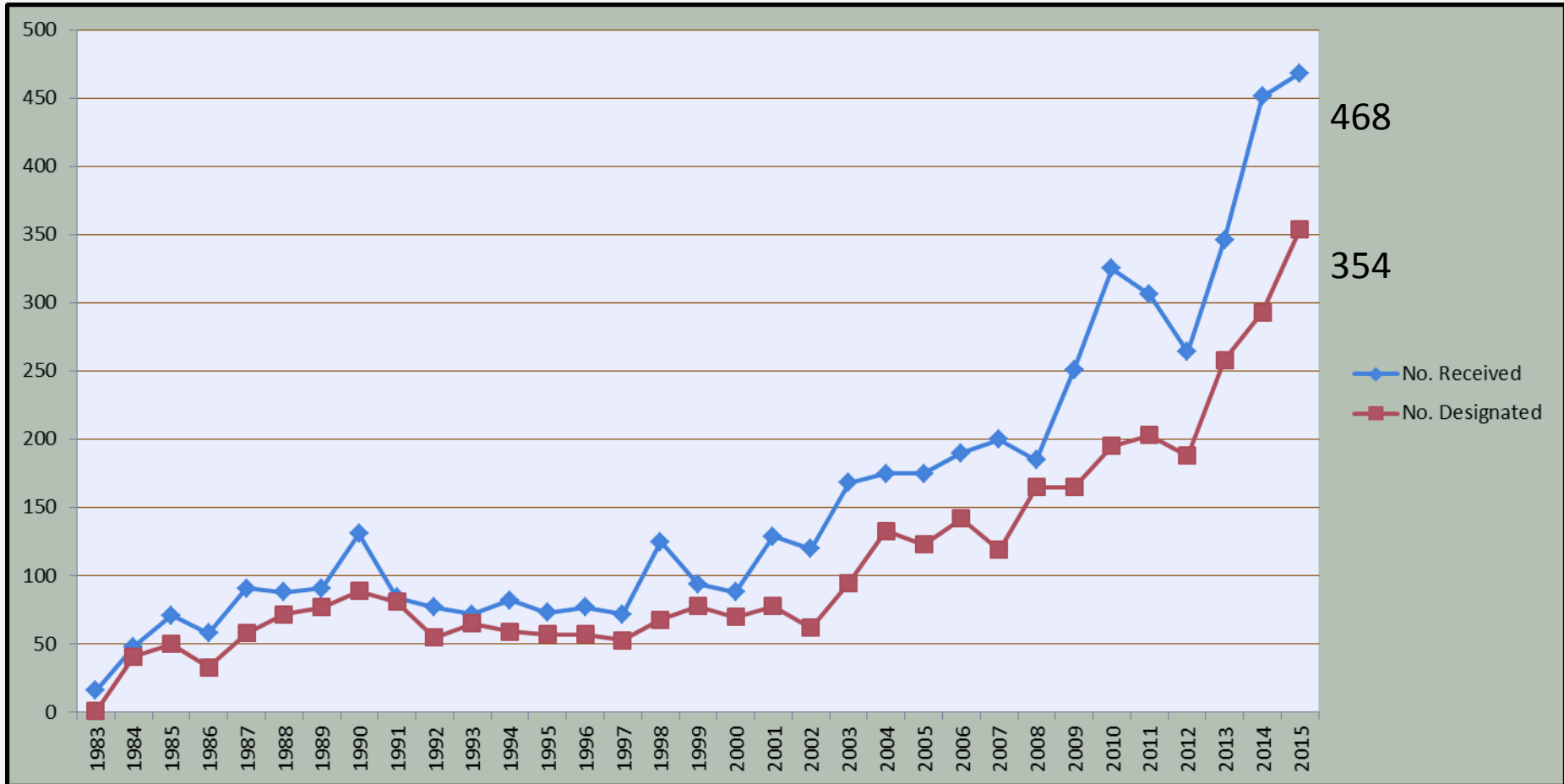
“Patient-focused” Drug Development

- We understand that people with chronic diseases are “experts” in that disease, as far as the symptoms and the impact on QOL, and what might be acceptable tradeoffs
 - On risk
 - On uncertainty
- Have held >20 of 24 PFDD meetings, more to go, reports generated
- Working with multiple patient organizations who are pioneering patient-focused guidance development for their disease of focus
- How to meaningfully collect that knowledge, in rigorous manner, given that there is a spectrum of opinions and a spectrum of disease burden in any given disease? How to do this for the many thousands of diseases?
- Next step externally led patient focused drug development meetings
- Develop guidances, develop the science of patient input, translate to PROs

Progress in Rare Disease

- Significant percentage of novel product approvals: 45% (n=17) in 2015
 - Most ever in a year
- High use of expedited pathways (86% vs 35% for non rare diseases, (2008-2016) and incentive programs
- High degree of flexibility by the agency: 82% vs 35% for non rare diseases, 2008-2016)
- Targeted therapies increasingly common in drug development
 - Smaller subsets available for clinical trials, smaller clinical development programs
 - Larger magnitude of effects anticipated but needed
 - Safety, R-B assessments
- Need for flexibility, novel trial designs, translational science development, recent FDA workshop on statistical approaches to small populations

Statistics: Orphan Drug Designations





Rare Pediatric Disease Priority Review Voucher Program

- The OOPD received 102 RPD request, which resulted in 51 RPD determinations
- Voucher requests are managed by the OND RDP
 - 11 Voucher requests were submitted with an NDA or BLA
 - 7 Vouchers awarded, 3 denied and 1 pending review
 - Two PRVs have been redeemed
- Future
 - 21st Century Cures legislation has extended the sunset date to 30 September 2020 for designation and to 30 September 2022 to receive marketing approval.

Important Lessons Learned in Rare Disease Drug Development

- Early natural history studies are invaluable
 - Rigorous prospective protocol driven collection best
- Better translational development
 - Biomarker assays SHOULD be validated/qualified before clinical studies begin if they are to be seriously considered for regulatory purposes
- Need to consider randomization and placebo controls from the very beginning of clinical studies when equipoise clearly exists

“Personalized Medicine” Policies

- CDER is approving significant number of “targeted therapies”
- These drugs target pathways or specific genetic mutations and thus are less disease-specific
- Target populations tend to be narrow sub-populations of specific diseases; and developers then seek to get additional indications
- Efficacy requirements for these additional “small slices” are under consideration. Have used case-by case evaluation up to now, but broader policy development is needed

Streamlining Clinical Trials: Multiple Projects Ongoing

- **Work with stakeholders on:**
 - “Basket trials” and “master protocols”
 - Adaptive trials including seamless development
 - Randomized clinical trials embedded in healthcare system
- **Use of new IT**
 - Use of personal devices for patient input
 - Use of telemedicine in clinical trials
 - Use of electronic data capture, data standards
- **“Monitoring and Data Cleaning Practices”:**
 - Traditional monitoring may not be most effective way of ensuring data quality: building quality in; developing risk-based approaches, and focusing on the most important data points may provide better quality
 - Remote monitoring of electronic data
- **Real World Evidence**
- **Integrated networks and systems**

Evidence Generation

- Randomized clinical trial – parallel universe
 - CRFs, eligibility criteria, customized endpoint, etc.
 - Internal validity
 - Controlled environment to detect incremental benefit
- Healthcare system
 - External validity
 - Data is messy
- Disease-specific patient registries

Sentinel System

- Mandated by FDAAA in 2007 –launched 2008
- Active post market risk identification and analysis system
- Common data model & distributed data network
- Secure querying behind data partner's firewall
- Near real time monitoring
- > 190 million patients and 351 million person-years
- Now engaged in routine regulatory decisions

Innovation in Medical Evidence Development and Surveillance



- IMEDS is sponsored by the Reagan-Udall Foundation for the FDA which was established by Congress to advance regulatory science
- The framework provided by IMEDS is modeled on the Sentinel system and provides governance so private-sector entities gain access with appropriate oversight and transparency
 - Sentinel data partners are invited to participate
 - The analytic/coordinating center utilized by the FDA through the Sentinel System also participates in IMEDS
 - Private sector entities may sponsor rapid queries or complete studies
- IMEDS has sponsored methods research on the limitations and strengths of real world evidence derived from secondary healthcare data

Incorporating *Real World Data* into RCTs

- Selection of study sites
- Enrichment
- Medical history
- Reducing duplication of data input
- Automated adverse event reporting
- Endpoint ascertainment

Summary

- CDER has numerous priority initiatives for 2016 along with ongoing workload
- Outstanding progress has been made in many areas, but we are all quite pressed
- Large number of staff vacancies also require VERY significant amount of work to fill
- Attention to continuous improvement in management and IT support will enable accomplishment of a broad agenda