CDER New Drug Review: 2015 Update

John K. Jenkins, M.D.
Director
Office of New Drugs
Center for Drug Evaluation and Research

FDA/CMS Summit
December 14, 2015
Housekeeping

- Data and analyses presented on the following slides are thought to be accurate. In order to provide the most up-to-date information the analyses have not undergone the same thorough quality control as is performed for official FDA reports.
- Many staff in CDER provided data, analyses, and PowerPoint expertise for this talk; their work behind the scenes makes me look good each year. Special thanks and acknowledgement to:
  - The Performance Analysis and Data Services Staff in CDER’s Office of Program and Strategic Analysis
  - Mike Lanthier in the Office of the Commissioner
- Pay attention to fiscal year (FY) or calendar year (CY) and cut-off dates on data presentations
Themes in new drug review for 2015

- The PDUFA V NME Program is widely viewed as a success
  - Positive interim report issued by an independent contractor\(^1\)
- Continued growth of breakthrough designations/approvals
  - Workshop held to help clarify FDA’s decisions on designations\(^2\)
- Continued interest in Priority Review Vouchers (PRVs)
  - GAO study of rare pediatric PRV program ongoing
- NME first-cycle approval rates at historically high levels
- US continues to lead the world in first approval of NMEs
- Continued growth of biosimilar program
- Despite successes, significant challenges remain
  - Increasing workload placing strain on program resources
  - Recruitment and retention of staff remains a major challenge

\(^2\) [http://www.brookings.edu/events/2015/04/24-fda-breakthrough-therapy-criteria](http://www.brookings.edu/events/2015/04/24-fda-breakthrough-therapy-criteria)
Topics to be covered

- How is CDER doing with regard to meeting PDUFA goals?
- What are the trends in new drug approvals?
  - IND activity, NME submissions, and NME approvals
  - Utilization and impact of expedited programs
- Implementation of PDUFA V/FDASIA programs
  - “Program” for NME review
  - Breakthrough Therapy Designation Program
What about PDUFA Goals?

- FDA continues to meet or exceed nearly all PDUFA goals for application review
- We continue to implement new programs under PDUFA V and FDASIA as resources and competing priorities allow
  - Continued budget uncertainty due to CRs, shutdown threats, etc.
  - Some progress in improving staffing in OND
    - 916 FTEs on board at start of PDUFA V/FDASIA (FY13)
    - 1014 FTEs on board at start of FY16
    - Still below current authorized ceiling of 1067 FTEs
      - FTE ceiling does not adequately reflect staffing requirements to meet increasing workload and expectations; e.g., meetings, BT, biosimilars, PFDD, PRVs, stakeholder engagement, staff training and PD, guidance ............
  - Federal hiring system, HHS pay caps, outdated GS pay system, etc. continue to adversely impact our ability to recruit and retain the highly trained staff we need to do our important public health work
What About New Drug Approvals?

• The commercial IND pipeline remains strong
  – Growth driven mostly by biologics

• For CY15, through December 9th, 2015, CDER has:
  – Received 36 NME applications
  – Approved 41 NMEs*, including 19 Orphan Drugs

• First cycle approval rates are at historic highs
  – Median time to approval up slightly as expected due to NME Program filing review “off the clock”

• From start of BT program through November 30, 2015:
  – CDER has received 307 requests for BT designation
  – CDER has granted a 95 BT designations
  – Approved 20 BT original/supplemental applications

* This information is accurate as of December 9, 2015. In rare instances, it may be necessary for FDA to change a drug’s new molecular entity (NME) designation or the status of its application as a novel new biologics license application (BLA). For instance, new information may become available which could lead to a reconsideration of the original designation or status. If changes must be made to a drug's designation or the status of an application as a novel BLA, the Agency intends to communicate the nature of, and the reason for, any revisions as appropriate. This note applies to all references to NME/Original BLAs in this presentation.
## CDER PDUFA V

### Review Performance

<table>
<thead>
<tr>
<th>Submission Type</th>
<th>FY 2014</th>
<th></th>
<th>FY 2015</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number Filed</td>
<td>Performance (Current)</td>
<td>Number Filed</td>
<td>Performance (Potential)**</td>
</tr>
<tr>
<td>Priority NME NDAs/original BLAs</td>
<td>24</td>
<td>96%</td>
<td>25</td>
<td>100%</td>
</tr>
<tr>
<td>Standard NME NDAs/original BLAs</td>
<td>14</td>
<td>93%</td>
<td>19</td>
<td>100%</td>
</tr>
<tr>
<td>Priority non-NME NDAs/BLAs*</td>
<td>10</td>
<td>80%</td>
<td>8</td>
<td>100%</td>
</tr>
<tr>
<td>Standard non-NME NDAs/BLAs*</td>
<td>72</td>
<td>97%</td>
<td>69</td>
<td>99%</td>
</tr>
<tr>
<td>Class 1 NDA/BLA Resubmissions</td>
<td>6</td>
<td>100%</td>
<td>6</td>
<td>100%</td>
</tr>
<tr>
<td>Class 2 NDA/BLA Resubmissions</td>
<td>32</td>
<td>97%</td>
<td>35</td>
<td>100%</td>
</tr>
<tr>
<td>Priority Efficacy Supplements</td>
<td>40</td>
<td>100%</td>
<td>37</td>
<td>98%</td>
</tr>
<tr>
<td>Standard Efficacy Supplements</td>
<td>146</td>
<td>90%</td>
<td>94</td>
<td>100%</td>
</tr>
<tr>
<td>Class 1 Efficacy Resubmissions</td>
<td>7</td>
<td>100%</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Class 2 Efficacy Resubmissions</td>
<td>8</td>
<td>88%</td>
<td>7</td>
<td>100%</td>
</tr>
<tr>
<td>Prior Approval Mfg Supplements</td>
<td>542</td>
<td>93%</td>
<td>455</td>
<td>94%</td>
</tr>
<tr>
<td>CBE Mfg Supplements</td>
<td>1017</td>
<td>95%</td>
<td>1017</td>
<td>97%</td>
</tr>
</tbody>
</table>

Data as of 9/30/2015
*Beginning in FY 2013, the new tracked metrics are non-NME Priority and non-NME Standard NDAs.
† Includes submissions pending filing.
**Potential Performance refers to the level of performance that could potentially be achieved if all the actions currently pending are reviewed within their required goal date. Submissions with unknown review schedules are excluded.
Commercial INDs With Activity Based On PDUFA Workload Adjuster Data

Data represent 12 month period of July 1st - June 30th
CDER PDUFA
Formal Meeting Requests

Data as of 9/30/2015

*BLAs were not included as they transferred to CDER in FY2004

Data as of 9/30/2015
CDER NME NDAs/BLAs†
Filings and Approvals as of 12/9/15

This information is accurate as of December 9, 2015. In rare instances, it may be necessary for FDA to change a drug’s new molecular entity (NME) designation or the status of its application as a novel new biologics license application (BLA). For instance, new information may become available which could lead to a reconsideration of the original designation or status. If changes must be made to a drug’s designation or the status of an application as a novel BLA, the Agency intends to communicate the nature of, and the reason for, any revisions as appropriate. This note applies to all references to NME/Original BLAs in this presentation.

*Since applications are received and filed throughout a calendar year, the filed applications in a given calendar year do not necessarily correspond to an approval in the same calendar year. Certain applications are within their 60-day filing review period and may not be filed upon completion of the review.

† Multiple applications pertaining to a single new molecular/biologic entity are only counted once. Original BLAs that do not contain a new active ingredient are excluded.
Number of NMEs Concurrently Under Review

* Data as of 11/30/2015
CDER NME NDAs/BLAs†
First Action Approval Rate

Data as of 12/9/2015
† Multiple applications pertaining to a single new molecular/biologic entity (e.g., single ingredient and combinations) are only counted once. Therefore, the numbers represented here for filings are not indicative of workload in the PDUFA V Program.
† Original BLAs that do not contain a new active ingredient are excluded.
Percentages exclude pending applications from the denominator.
* FY 15 Cohort has 25 pending applications.
CDER First Action Approval Rates
For Priority NME NDAs/BLAs†

Data as of 12/9/2015
† Multiple submissions pertaining to a single new molecular/biologic entity (e.g., single ingredient and combinations) are only counted once. Therefore, the numbers represented here for filings are not indicative of workload in the PDUFA V Program.
‡ Original BLAs that do not contain a new active ingredient are excluded.
Percentages exclude pending applications from the denominator.
* FY 15 Cohort has 11 pending priority applications.
CDER First Action Approval Rates For Standard NME NDAs/BLAs†

Data as of 12/9/2015

† Multiple submissions pertaining to a single new molecular/biologic entity (e.g., single ingredient and combinations) are only counted once. Therefore, the numbers represented here for filings are not indicative of workload in the PDUFA V Program.

Original BLAs that do not contain a new active ingredient are excluded.

Percentages exclude pending applications from the denominator.

* FY 15 Cohort has 14 pending standard applications.
NME Actions and Approvals

*Data as of 12/09/2015

Includes discrete actions on a given date for an active ingredient which, if approved, would constitute a new molecular entity. Actions for original submissions and resubmissions as well as actions for new BLAs are included. Multiple actions which occur on the same date for multiple dosage forms or indications are counted as a single regulatory action.
CDER NME/New BLA Complete Response* Letters Issued

Data as of 11/30/2015

* Complete Response letter figures include “approvable” and “not approvable” letters issued for NDA actions prior to August 11, 2008, the date the Complete Response Letter rule was finalized.
CDER New Molecular Entity Approval Rates by PDUFA Cohort

* Data as of 11/30/2015. PDUFA IV estimates based on 77 NMEs submitted in FY 2013 - 2014 (it is too early to estimate performance on FY 2015 submissions). Projection estimates account for actions to date and elapsed time to date for non-approvals and assume an additional 6 months of review time at a minimum for unapproved applications after resubmission. Currently no unapproved NMEs from the FY 2013 - 2014 submission cohort are pending review as of 11/30/2015.
Why are first-cycle NME approval rates so high?

- CDER has **not** changed its interpretation of the statutory standard for approval – we are **not** a “rubber stamp”
- Factors that may be contributing
  - FDA guidance/meetings during IND to clarify expectations for development programs – improves quality of NDAs/BLAs
  - NME Program – **complete** applications at time of filing and more time for interactions with sponsor to address deficiencies
  - Targeted therapies – greater benefit/less risk in selected patients
  - More orphan drugs – alters benefit/risk balance
  - BT designation – “all-hands on deck” for sponsor and FDA
  - Focus of sponsors away from “me too” drugs and diseases with available treatment options with less favorable B/R balance
    - Not necessarily a good outcome from a public health perspective
  - Other factors?

- Other factors?
CDER Overall NME NDA/BLAs†
Median Total Time to Approval

Data as of 12/9/2015
† Original BLAs that do not contain a new active ingredient are excluded.
CDER Priority NME NDAs/BLAs†
Median Total Time to Approval

Data as of 12/9/2015
† Original BLAs that do not contain a new active ingredient are excluded.
CDER Standard NME NDA/BLAs†
Median Total Time to Approval

Data as of 12/9/2015
† Original BLAs that do not contain a new active ingredient are excluded.
USA Share of New Active Substances Launched on World Market

Data as of 11/30/2015

Global New Active Substances
First Launches by Region 2001 – 2014

% Approved by Region

Calendar Year

Median NDA Review Times AND Priority Reviews Received By Drug Review Division

Percentage of NDAs That Qualified For Priority Review vs. Median NDA Review Time (Days)

R-squared: 0.53
### Snapshot of CY 2015 NME NDAs/BLAs† Drug Approvals (1/3)

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Met PDUFA Goal Date*</th>
<th>Approved on First Cycle</th>
<th>Priority Approval</th>
<th>Fast Track</th>
<th>First in Class</th>
<th>Approved First in the U.S.</th>
<th>Accelerated Approval</th>
<th>Orphan Drug</th>
<th>Breakthrough Therapy</th>
<th>QIDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVAYSA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COSENTYX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NATPARA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBRANCE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LENVIMA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FARYDAK</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVYCAZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRESEMBA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNITUXIN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHOLBAM*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CORLANOR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KYBELLA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIBERZI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KENGREAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data as of 12/9/2015

† Multiple submissions pertaining to a single new molecular/biologic entity (e.g., single ingredient and combinations) are only counted once. Therefore, the numbers are not indicative of workload in the PDUFA V Program.

† Original BLAs that do not contain a new active ingredient are excluded.

* A PDUFA Goal Date is marked as met if the NME is acted upon within its approval cycle due date.

QIDP - Qualified Infectious Disease Product

* Cholbam- Currently listed as not first in class, but subject to change. The first in class status for cholic acid is still under consideration by the DASH LOE committee.

Approved in 2014 in EU for SED but not PE
## Snapshot of CY 2015
### NME NDAs/BLAs† Drug Approvals (2/3)

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Met PDUFA Goal Date*</th>
<th>Approved on First Cycle</th>
<th>Priority Approval</th>
<th>Fast Track</th>
<th>First in Class</th>
<th>Approved First in the U.S.</th>
<th>Accelerated Approval</th>
<th>Orphan Drug</th>
<th>Breakthrough Therapy</th>
<th>QIDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORKAMBI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENTRESTO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REXULTI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRALUENT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ODOMZO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAKLINZA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADDYI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REPATHA *</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VARUBI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XURIDEN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VRAYLAR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LONSURF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRESIBA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data as of 12/9/2015

† Multiple submissions pertaining to a single new molecular/biologic entity (e.g., single ingredient and combinations) are only counted once. Therefore, the numbers are not indicative of workload in the PDUFA V Program.

† Original BLAs that do not contain a new active ingredient are excluded.

* A PDUFA Goal Date is marked as met if the NME is acted upon within its approval cycle due date.

QIDP - Qualified Infectious Disease Product

*Repatha was submitted with two indications. One indication received Orphan designation while the other did not. Application received a priority review due to redemption of a PRV.
## Snapshot of CY 2015 NME NDAs/BLAs† Drug Approvals (3/3)

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Met PDUFA Goal Date*</th>
<th>Approved on First Cycle</th>
<th>Priority Approval</th>
<th>Fast Track</th>
<th>First in Class</th>
<th>Approved First in the U.S.</th>
<th>Accelerated Approval</th>
<th>Orphan Drug</th>
<th>Breakthrough Therapy</th>
<th>QIDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARISTADA</td>
<td></td>
<td></td>
<td>Purple</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRAXBIND</td>
<td></td>
<td></td>
<td>Red</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VELTASSA</td>
<td></td>
<td></td>
<td>Green</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YONDELIS</td>
<td></td>
<td></td>
<td>Orange</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STRENSIQ</td>
<td></td>
<td></td>
<td>Yellow</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NUCALA</td>
<td></td>
<td></td>
<td>Blue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GENVOYA</td>
<td></td>
<td></td>
<td>White</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COTELLIC</td>
<td></td>
<td></td>
<td>Grey</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAGRISSO</td>
<td></td>
<td></td>
<td>Brown</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DARZALEX</td>
<td></td>
<td></td>
<td>Pink</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NINLARO</td>
<td></td>
<td></td>
<td>Mauve</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PORTRAZZA</td>
<td></td>
<td></td>
<td>Gold</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPLICITI</td>
<td></td>
<td></td>
<td>Dark Blue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KANUMA</td>
<td></td>
<td></td>
<td>Coral</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data as of 12/9/2015

† Multiple submissions pertaining to a single new molecular/biologic entity (e.g., single ingredient and combinations) are only counted once. Therefore, the numbers are not indicative of workload in the PDUFA V Program.

† Original BLAs that do not contain a new active ingredient are excluded.

* A PDUFA Goal Date is marked as met if the NME is acted upon within its approval cycle due date.

QIDP - Qualified Infectious Disease Product
In CY 2015, CDER Continued To Ensure The Efficiency Of First Cycle Review

- All but two (95%) of the novel drugs approved to date in CY15 met their PDUFA goal dates for the approval review cycle

- Almost nine out of ten of the novel drugs (88%) approved to date in CY15, were approved in the first review cycle
CDER Ensures That Novel Drugs Receive Expedited Review

- More than half (56%) of the novel drugs approved to date in CY15 were approved under Priority Review
- Almost one – quarter (22%) of the novel drugs approved to date in CY15 received Breakthrough Therapy designation
- About a third (34%) of the novel drugs approved to date in CY15 received Fast Track designation
2015 Continues A Strong Track Record For Drug Innovation

- Nearly half (46%) of the novel drugs approved to date in CY15 are for rare diseases
- Over one-third (37%) of the novel drugs approved to date in CY15 are the first in their class
- Two-thirds (66%) of the novel drugs approved to date in CY15 were first approved in the U.S.
Selected PDUFA V/FDASIA Programs That Impact Drug Development and Review
Review Program for NME NDAs and Original BLAs

Goal

• “Improve the efficiency and effectiveness of the first cycle review process and decrease the number of review cycles necessary for approval, ensuring that patients have timely access to safe, effective, and high quality new drugs and biologics.” (PDUFA V Goals Letter)

Concept

• Better planning before application submission, submission of complete applications, improved communication and transparency between applicant and review team during review, and additional review time will improve the efficiency of the first review cycle, which may decrease the number of additional review cycles prior to approval.
Review Program for NME NDAs and Original BLAs

Components

- Pre-submission meeting strongly encouraged
- Complete application at time of submission; incomplete subject to RTF
- 60-day filing review period “off the clock”
- 74-Day Letter
  - Planned review timeline, planned date of internal mid-cycle meeting, preliminary plans on need for AC meeting, early communication of deficiencies/information requests
- Mid-Cycle Communication
  - Within 2 weeks of internal mid-cycle meeting
  - Communication of significant issues identified to date/information requests, preliminary thinking on risk management/REMS, proposed dates for late-cycle meeting, updates on AC plans
- Discipline review letters
  - Summarize preliminary findings/deficiencies by discipline
- Late-cycle meeting (LCM)
  - Focus on information sharing, planning for AC, and planning for the remainder of review
Sample Program Review
Timeline – Standard Application

1. Pre-Submission Activities
   - Day 0
   - for Priority

2. Process Submission
   - Day 45
   - Day 30
   - for Priority

3. Review Plan
   - Month 5
   - Month 3
   - for Priority

4. Conduct Review

5. Primary Reviews Complete
   - 7 Weeks prior to Action Date
   - 5 Weeks prior to Action Date
   - for Priority

6. Wrap-Up Activities
   - Late Cycle Meeting
   - AC Meeting

7. Take Official Action
   - Month 12
   - Month 8
   - for Priority

8. Post Action Feedback

PDUFA CLOCK
   - 1 month
   - 2 month
   - 3 month
   - 4 month
   - 5 month
   - 6 month
   - 7 month
   - 8 month
   - 9 month
   - 10 month

Action Date
   - Month 12
   - Month 8
   - for Priority
# Cumulative Activity in the Program

<table>
<thead>
<tr>
<th></th>
<th>FY2013 (9/30/13)</th>
<th>FY2014 (9/30/14)</th>
<th>FY2015 (9/30/15)</th>
<th>Through 11/30/15</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSMs</strong></td>
<td>42</td>
<td>96</td>
<td>137</td>
<td>141</td>
</tr>
<tr>
<td><strong>Receipts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>33 NDAs</td>
<td>20 BLAs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>106 NDAs</td>
<td>38 BLAs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>166 NDAs</td>
<td>60 BLAs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>110 NDAs</td>
<td>64 BLAs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RTFs</strong></td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Day 74</strong></td>
<td>44</td>
<td>98</td>
<td>157</td>
<td>163</td>
</tr>
<tr>
<td><strong>MCCs</strong></td>
<td>33</td>
<td>80</td>
<td>135</td>
<td>150</td>
</tr>
<tr>
<td><strong>DR letters</strong></td>
<td>5</td>
<td>8</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td><strong>LCMs</strong></td>
<td>17</td>
<td>64</td>
<td>111</td>
<td>121</td>
</tr>
<tr>
<td><strong>FCAs</strong></td>
<td>6</td>
<td>64</td>
<td>115</td>
<td>133</td>
</tr>
<tr>
<td>4 APs</td>
<td>0 CRs</td>
<td>46 APs</td>
<td>92 APs</td>
<td></td>
</tr>
<tr>
<td>2 WDs</td>
<td></td>
<td>14 CRs</td>
<td>18 CRs</td>
<td></td>
</tr>
<tr>
<td>4 WDs</td>
<td></td>
<td>5 WDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>108 APs</td>
<td>20 CRs</td>
<td>5 WDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PAIs</strong></td>
<td>6</td>
<td>106</td>
<td>196</td>
<td>211</td>
</tr>
<tr>
<td>3 FDA</td>
<td>3 applicant</td>
<td>56 FDA</td>
<td>103 FDA</td>
<td></td>
</tr>
<tr>
<td>3 APs</td>
<td></td>
<td>50 applicant</td>
<td>93 applicant</td>
<td></td>
</tr>
<tr>
<td><strong>Major Amendments received</strong></td>
<td>3</td>
<td>18</td>
<td>35</td>
<td>37</td>
</tr>
<tr>
<td>3 APs</td>
<td>18 APs</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 CR</td>
<td>2 CRs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Amendments</strong></td>
<td>166</td>
<td>2684</td>
<td>4740</td>
<td>5263</td>
</tr>
</tbody>
</table>

1. Major Amendments are categorized by the quarter in which they were received. The status (AP, CR, Pending) reflects the status of each application as of close of FY2014.

- **AP** = Approval
- **CR** = Complete Response
- **WD** = Withdrawal
- **FSA** = Late-Cycle Meeting
- **PSM** = Pre-Submission Meeting
- **FCAs** = First Cycle Action
- **PAI** = Post Action Interview

Note: Because 3 applications were split at action, 48 applications generated 51 actions. Includes CDER as well as CBER data.
Program Modifications to Address Learnings

- Mid-cycle communication
  - Intended to be an informal communication between FDA project manager/CDTL and sponsor
  - Meeting has taken on greater importance than anticipated
  - Often involves more attendees from sponsor and FDA
  - Internal FDA guidance modified to encourage providing sponsor with meeting agenda in advance to facilitate improved communication/discussion of preliminary review issues

- Program negotiation in PDUFA V pre-dated Breakthrough
  - Program “timeline” based on full 8 or 12-month review cycle
  - Original construct not well aligned with expedited reviews
  - Modifications of FDA desk reference guide posted on 10/20/14 to accommodate expedited reviews while still honoring Program commitments
Breakthrough Therapies

- FDASIA program to expedite development and approval of new drugs intended to treat a serious condition where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies.
- FDASIA endorsed and extended FDA’s long-standing policy of expediting promising new drugs for serious and life-threatening conditions.
- Final guidance “Expedited Programs for Serious Conditions—Drugs and Biologics” issued May 2014.
Breakthrough Approvals to Date* (1)

• 2013
  - Gazyva: CLL
  - Imbruvica: Mantle Cell Lymphoma
  - Solvaldi: Chronic Hepatitis C

• 2014
  - Kalydeco, supplement: CF
  - Arzerra, supplement: CLL
  - Zykadia: NSCLC, alk+
  - Zydelig: CLL
  - Inbruvica, supplement: CLL
  - Promacta, supplement: Aplastic Anemia
  - Keytruda: Metastatic Melanoma
  - Ofev: Idiopathic Pulmonary Fibrosis
  - Esbriet: Idiopathic Pulmonary Fibrosis
  - Blincyto: ALL

* Data as of 12/9/2015
Breakthrough Approvals to Date* (2)

• 2015
  - Ibrance: Metastatic Breast Cancer
  - Orkambi: Cystic Fibrosis
  - Xuriden: Hereditary Orotica Aciduria
  - Imbruvica, supplement: CLL
  - Lucentis, supplement: Diabetic Retinopathy
  - Kalydeco: Cystic Fibrosis
  - Eleya, supplement: Diabetic Retinopathy
  - Rapamune, supplement: Lymphangioleiomyomatosis
  - Technivie: HCV
  - Keytruda, supplement: NSCLC
  - Opdivo, supplement: NSCLC, Renal Cell Carcinoma
  - Praxbind: Reversal of anticoagulant effects of dabigitran
  - Strensiq: Hypophosphatasia
  - Tagrisso: NSCLC
  - Darzalex: Multiple Myeloma
  - Empliciti: Multiple Myeloma
  - Kanuma: Lysosomal Acid Lipase Deficiency

*Data as of 12/9/2015
Current Status of 307 CDER Breakthrough Therapy Requests

- Granted: 31%
- Denied: 48%
- Withdrawn: 14%
- Pending: 7%

Data as of 11/30/2015
CDER Breakthrough Therapy Requests by Division

Data as of 11/30/2015
CDER Breakthrough Therapy Requests Granted by Division

Data as of 11/30/2015

- Oncology: 28%
- Antiviral: 19%
- Hematology: 18%
- Pulmonary / Allergy / Rheumatology: 6%
- Gastroenterology / Inborn Errors: 3%
- Psychiatry: 2%
- Neurology: 2%
- Dermatology / Dental: 2%
- Anti-Infective: 2%
- Transplant / Ophthalmology: 1%
- Anesthesia / Analgesia / Addiction: 1%
- Cardiovascular / Renal: 0%

www.fda.gov
CDER Has Granted 95 Breakthrough Therapy Designations Since Inception

Data as of 11/30/2015

### 307 Requests
- Pending: 48%
- Granted: 31%
- Denied: 14%
- Withdrawn: 7%

### 95 Grants
- Oncology: 28%
- Dermatology / Dental: 19%
- Gastroenterology / Inborn Errors: 18%
- Anti-Infective: 12%
- Transplant / Ophthalmology: 3%
- Pulmonary / Allergy / Rheumatology: 3%
- Psychiatry: 2%
- Neurology: 2%
- Anesthesia / Analgesia / Addiction: 2%
- Cardiovascular / Renal: 1%
- Psychiatric: 1%
- Ophthalmology: 1%
- Cardiovascular: 1%
- Gastroenterology: 1%
- Antiviral: 1%
- Hematology: 1%
- Pulmonary: 1%
- Oncology: 1%
- Antiviral: 1%
- Hematology: 1%
- Pulmonary: 1%
- Oncology: 1%
- Antiviral: 1%
- Hematology: 1%
- Pulmonary: 1%
- Oncology: 1%
- Antiviral: 1%
- Hematology: 1%
- Pulmonary: 1%
- Oncology: 1%
- Antiviral: 1%
- Hematology: 1%
- Pulmonary: 1%
- Oncology: 1%
- Antiviral: 1%
- Hematology: 1%
- Pulmonary: 1%
- Oncology: 1%
- Antiviral: 1%
- Hematology: 1%
- Pulmonary: 1%
- Oncology: 1%
- Antiviral: 1%
- Hematology: 1%
- Pulmonary: 1%
- Oncology: 1%
- Antiviral: 1%
- Hematology: 1%
- Pulmonary: 1%
- Oncology: 1%
- Antiviral: 1%
- Hematology: 1%
- Pulmonary: 1%
- Oncology: 1%
- Antiviral: 1%
- Hematology: 1%
- Pulmonary: 1%
- Oncology: 1%
- Antiviral: 1%
- Hematology: 1%
- Pulmonary: 1%
- Oncology: 1%
- Antiviral: 1%
- Hematology: 1%
- Pulmonary: 1%
- Oncology: 1%
- Antiviral: 1%
- Hematology: 1%
- Pulmonary: 1%
- Oncology: 1%
- Antiviral: 1%
- Hematology: 1%
- Pulmonary: 1%
- Oncology: 1%
- Antiviral: 1%
- Hematology: 1%
- Pulmonary: 1%
- Oncology: 1%
- Antiviral: 1%
- Hematology: 1%
- Pulmonary: 1%
- Oncology: 1%
- Antiviral: 1%
- Hematology: 1%
- Pulmonary: 1%
- Oncology: 1%
- Antiviral: 1%
- Hematology: 1%
- Pulmonary: 1%
- Oncology: 1%
- Antiviral: 1%
- Hematology: 1%
- Pulmonary: 1%
- Oncology: 1%
- Antiviral: 1%
- Hematology: 1%
- Pulmonary: 1%
- Oncology: 1%
- Antivarial: 1%
Breakthrough Development Program Continues to Grow at a Steady Pace

* Figures includes total # of granted breakthrough designations at the beginning of each month that have yet to have reached either a marketing approval, rescission decision, or discontinued IND development.
Breakthrough Therapies: Three-year Assessment

- “Bar” for designation remains unclear for applicants/public
  - Statutory criteria are subjective, require judgment by FDA
  - BT submission/review under IND impedes clarity/transparency
  - CDER MPC provides consistency for internal decisions
  - Brookings workshop on April 24, 2015, “Breakthrough therapy designation: Exploring the qualifying criteria”
    - [http://www.brookings.edu/events/2015/04/24-fda-breakthrough-therapy-criteria](http://www.brookings.edu/events/2015/04/24-fda-breakthrough-therapy-criteria)

- Pace of requests and % granted for BT designation have remained steady

- Clinical development often NOT the rate-limiting step
  - CMC/GCP deficiencies often delay review completion/approval
Breakthrough Therapies: Three-year Assessment (2)

- Program commitments are very resource intensive for FDA
  - No resources for BT program were provided under PFUFA/FDASIA
  - Growing number of “all-hands on deck” development programs and NDA/BLA/supplement reviews are straining FDA’s resources
  - Resource needs must be addressed for continued success

- Common reasons for denial of BT requests
  - Evidence does not include clinical data
  - Evidence is too preliminary to be considered reliable
    - e.g., small numbers of patients or inadequate duration of follow up
  - Failure to demonstrate “substantial” improvement over available therapy vs “expected” incremental benefit of development programs
  - Reliance on a novel biomarker or surrogate endpoint without sufficient evidence to support benefit to patient
  - Post-hoc analyses of failed studies
Thank You!