Public Stakeholder Meeting on Prescription Drug User Fee Act (PDUFA) Reauthorization

December 11, 2020

Dr. Theresa Mullin
Associate Director for Strategic Initiatives
Center for Drug Evaluation and Research
Food and Drug Administration
Outline for this meeting

• Welcome and Roll Call

• Presentation Topics:
  – CBER cell and gene therapy review programs
  – PDUFA Financial Status Update
  – CDER recent work to modernize new drug review information infrastructure (knowledge management) and reviewer talent management Discussion

• Topics for upcoming meetings

• Recap and Closing
Cell and Gene Therapy
A Regulatory Perspective

PDUFA Briefing
December 11, 2020

Wilson W. Bryan, MD
Office of Tissues and Advanced Therapies (OTAT)
Center for Biologics Evaluation and Research (CBER)
All New OTAT Investigational New Drug Applications (INDs) and Investigational Device Exemptions (IDEs)  
2016 vs. 2019
Gene Therapies
• Directly-administered Therapies
• Ex vivo Genetically-modified Cell Therapies
• Genome editing Therapies

Cell Therapies
• Structural functions
• Metabolic functions
INDs with gene therapy development programs
Gene Therapy: Scientific Advances

Human Genome Project
• Completed in October 2003
• 99% of human genes sequenced to 99% accuracy

Development of new vectors
• Adeno-associated virus (AAV)
• Lentivirus

Genome editing
Gene Therapy Approved Products

- Zolgensma (onasemnogene abeparvovec-xioi): infantile spinal muscular atrophy (SMA)
- Luxturna (voretigene neparvovec-rzyl):
  RPE65 mutation-associated retinal dystrophy

- Oncology (Leukemia/Lymphoma)
  - Kymriah (tisagenlecleucel)
  - Yescarta (axicabtagene ciloleucel)
  - Tecartus (brexucabtagene autoleucel) – under accelerated approval
CAR T Cells: A Novel Way to Treat Cancer


CTL, cytotoxic T lymphocyte; MHC, major histocompatibility complex
OTAT-Regulated Gene and Cell Therapies

Gene Therapies
- Directly-administered Therapies
- Ex vivo Genetically-modified Cell Therapies
- Genome editing Therapies

Cell Therapies
- Structural functions
- Metabolic functions
INDs with cell therapy development programs
Cellular Therapy Approved Products

- CARTICEL (Autologous Cultured Chondrocytes) (1997) for cartilaginous defects of the femoral condyle

- PROVENGE (sipuleucel-T) (2010) for asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer

- HPC (hematopoietic progenitor cells), Cord Blood licensed for unrelated donor hematopoietic progenitor cell transplantation procedures

- LAVIV (Azficel-T) (2011) for moderate to severe nasolabial fold wrinkles

- GINTUIT (Allogeneic Cultured Keratinocytes and Fibroblasts in bovine collagen) (2012) for topical treatment of mucogingival conditions

- MACI (Autologous Cultured Chondrocytes on porcine collagen membrane) (2016) for full-thickness cartilage defects of the knee
All New OTAT Investigational New Drug Applications (INDs) and Investigational Device Exemptions (IDEs) 2016 vs. 2019

- 2016: 277
- 2019: 453

- 2016: 223
- 2019: 142

Bar chart showing the number of INDs and IDEs from 1993 to 2019, with a significant increase in 2019.
Cumulative Overview of BTD and RMAT Designation Requests (excludes withdrawn and pending requests)
OTAT Meetings with Sponsors

PDUFA Meetings held in OTAT

<table>
<thead>
<tr>
<th>Year</th>
<th>Meetings</th>
</tr>
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<tbody>
<tr>
<td>2017</td>
<td>238</td>
</tr>
<tr>
<td>2018</td>
<td>270</td>
</tr>
<tr>
<td>2019</td>
<td>325</td>
</tr>
<tr>
<td>2020</td>
<td>384</td>
</tr>
</tbody>
</table>
INitial Targeted Engagement for Regulatory Advice on CBER products (previously known as pre-pre-IND interactions)
Gene Therapy Guidances (2020)

FINAL GUIDANCES
• Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)
• Testing of Retroviral Vector-Based Gene Therapy Products for Replication Competent Retrovirus (RCR) during Product Manufacture and Patient Follow-up
• Long Term Follow-Up After Administration of Human Gene Therapy Products
• Human Gene Therapy for Hemophilia
• Human Gene Therapy for Retinal Disorders
• Human Gene Therapy for Rare Diseases

DRAFT GUIDANCE
• Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations
Summary

• Scientific advances spur growth in research and development (R&D) of advanced therapies

• Growth in R&D for advanced therapies increases demand for OTAT advice

• OTAT staff are dedicated to advancing the development of cell and gene therapies
Acknowledgements

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• Ramani Sista, PhD
• Xiaofei Wang, PhD
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Questions?
Cell and Gene Therapy
Resource Needs
&
CBER Modernization

Christopher Joneckis, Ph.D.
Associate Director For Review Management
December 11, 2020
Cell and Gene Therapy
Resource Needs

December 11, 2020
Current Situation: Pace and complexity of growth forces CBER to play catch up

• The pipeline for cell and gene therapies has grown exponentially recently, and this trajectory promises to continue and lead to increases in meeting requests and regulatory submissions including BLAs.

• The complexity of applications continues to increase with genomic editing of cells, complex directly administered gene therapies, and combination products.

• The COVID Public Health Emergency has also placed additional strain on the Cell and Gene Therapy Program and crosscutting indirect functions such as post-market surveillance.

• We are meeting most PDUFA UF deadlines, but at the expense of staff working considerable overtime and facing significant burnout.

*Excluding Expanded Access
FDA’s Cell and Gene Therapy Program Goals for PDUFA VII

• Relieve the stress and strain on the Cell and Gene Therapy (CGT) program, right-sizing the baseline to get ahead of growth in the sector and ensure long-term sustainability through Resource Capacity Planning

• Add capacity to increase the average time spent on CGT submissions to account for novel development challenges, new regulatory requirements, and engagement with industry and stakeholders

• Appropriately resource all facets of the program, including indirect, such as policy and guidance, and support functions, and modernize information technology*  

• Provide resources to support development of treatments for unmet medical needs and individualized therapies

• Make resources for the RMAT program permanent to support continued success of the program

* will be discussed in Digital Health & Informatics subgroup
Assessing the near term needs of the Cell and Gene Therapy Program requires a holistic approach while leveraging current methodologies and best practices from FDA’s Resource Capacity Planning capabilities.

**Indirect FTEs**
- Indirect FTEs are tied to specific categories such as policy, communications, and science and research that scale in proportion to the amount of direct work.
- Categories are based on benchmark values from established product classes with SME input.

**Program Support FTEs**
- Overhead work, principally conducted through OCOD, OM, and in parts of OD vitally support all product classes.
- While some of this work is fixed, a portion of their time scales with direct CGT work or increases in hiring of direct or indirect FTE.

**Direct FTEs**
- Cross validated and tuned forecasts from the Capacity Planning Adjustment were paired with recent CATTS data to develop CGT specific task times for OTAT, OCBQ, and OBE.
- Adjustments were made based on SME input to account for needed increases in time dedicated to each submission review. This accounts for the strain on current staff, which results in trade offs and prioritization.
Ensure sufficient review capacity and time for expected volume

Current staffing in the Cell and Gene Therapy (CGT) program has **not kept up with growth in INDs** and **average time per submission is insufficient** to support needs for novel products.

**Current State Challenges**
- IND and meeting volume has risen drastically in recent years without corresponding increases in staff.
- CBER is starting to see corresponding increases in marketing applications, which are expected to accelerate in coming years.
- The number of REMS for CGT products growing rapidly, with no dedicated REMS review staff.
- Limited bandwidth prevents optimal use of advisory committees.
- The percentage of meeting requests that receive a written response more than doubled between 2015 and 2019.

**Benefits of Additional Staffing**
- Hire staff to support increased volume and increased time per submission.
- Setting an appropriate baseline will support long term sustainability via the capacity planning adjustment.
- Provide staff to support novel technologies and new regulatory elements, including REMS.
- Proactively engage advisory committees for recommendations on emerging topics.
- Support improved engagement with sponsors during the development lifecycle.
Sustain the RMAT Program

21st Century Cures created the Regenerative Medicine Advanced Therapies (RMAT) Designation after PDUFA VI negotiations had concluded, but resources are needed to sustain workload beyond the current five year cycle.

Current State and Challenges:
21st Century Cures established the RMAT designation program for certain cell and gene therapies for serious conditions where there is unmet need

FDA invested carryover resources to rapidly scale up staffing to support the program, but cannot sustain funding for these staff beyond the current 5-year period

This investment has facilitated an extremely successful program, but creates significant risks for CBER if the funding is not made permanent

Benefits of Additional Funding:
- The RMAT program has been tremendously popular, with growth in both requests and designations outstripping OTAT’s Breakthrough Designations

- Without funds to make the RMAT FTE permanent, CBER will have to prioritize funding for these already on board positions and scale back hiring for new vacancies in other areas

- Continued resourcing for this program is critical to build on early success
Prepare for increasing postmarket workload

As CGT products begin coming to market, they carry postmarket requirements to monitor safety and efficacy that are unique in CBER’s portfolio of products and create new resource demands.

**Current State and Challenges:**
- CBER currently has 5 active REMS programs, expected to grow substantially PDUFA VII, however CBER has no dedicated REMS staff. Post-approval submissions will grow proportionally.
- Recent guidance recommends long-term follow-up for gene therapy products, contributing in expected increase in post-market submissions.
- Adverse event monitoring also trending upwards. Patient populations for some products, e.g., CAR-Ts for oncology, are significant in size and may see a larger volume of adverse events.

**Benefits of Additional Staffing:**
- Robust monitoring of post-market safety and effectiveness is critical to FDA’s public health mission and public confidence in regulated products.
- Without additional resources, post-market safety work competes with pre-market review.
Enhance outreach and guidance development efforts

A robust program for guidance development and stakeholder engagement is critical to engage on priorities such as individualized therapies and standardization

**Current State and Challenges:**
- CBER recognizes the critical role of guidance work to provide regulatory clarity, which has been welcomed by industry (e.g., Gene Therapy Guidances finalized January 2020)
- We also aim to engage stakeholders whenever possible, but are not always able to accept invitations to speak, etc... due to bandwidth constraints
- Additional advances in technology and growing potential for treatment of ultra rare diseases will require continued engagement and leadership from CBER

**Benefits of Additional Staffing:**
- Robust guidance development providing clarity for expectations and pathways
- Strong engagement with industry, patients, and other stakeholders to promote development
- Catalyze progress on individualized gene therapies
- Take more topics to the advisory committee for input from external experts
Ensure regulatory science program is sufficient to support novel technologies

CBER's Researcher-Reviewer model supports effective regulatory review of scientific products, and is not on track to keep pace with the explosion of new products.

**Current State and Challenges:**
- FDA's cadre of experts, who both review CGT application and conduct applied research, facilitate the development of a wide variety of new and promising products and technologies.
- The regulatory science portfolio for cell and gene therapy is small relative to expected growth in submissions.

**Benefits of Additional Staffing:**
- Support evaluation of vectors for gene therapy for individualized gene therapies.
- Bring scientific expertise to bear on engagement between CBER and innovators in support of scaling of manufacturing processes.
- Ensure appropriate expertise for engagement in efforts related to standardization for CGT.
CBER Modernization

December 11, 2020
CBER Scope

- CBER has a mix of products, regulatory authorities, funding mechanisms, business, data, & IT needs.
- Most staff are not dedicated to one product.
- PDUFA is a significant part of the CBER world, but not its entire world
- Therefore, there is a need for agility and flexibility

<table>
<thead>
<tr>
<th>Biologics (PDUFA)</th>
<th>Devices (MDUFA)</th>
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<tbody>
<tr>
<td>• PDUFA defined biologics, devices &amp; drugs</td>
<td></td>
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<tr>
<td>• Cell and GT, Vaccines, Phage, FMT</td>
<td></td>
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<tr>
<td>• OBRR Diagnostic Test Kits</td>
<td></td>
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<tr>
<td>• OTAT Devices/ OVRR Devices</td>
<td></td>
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<tr>
<td>• Combination Products – device component</td>
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<table>
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<tr>
<th>Biologics (non-PDUFA)</th>
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<tbody>
<tr>
<td>• Wide variety of biologics (e.g., blood, blood components, tissues) devices</td>
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</tbody>
</table>
Current CBER Information Technology Challenges

- 35 systems on 30+ tech stacks
- 80+ servers
- 60+ technologies
- End of life technologies – over 20 legacy technologies contained in 35 systems
- Increased risk and security
- ~$150k O&M costs per system per year
- ~250 change requests per year
- ~$17k per system change
- Lengthy delivery time
- Unmet business expectations
- 11 user interfaces
Challenges

• Can’t easily provide staff (e.g., workload, workflow, data capture, data analysis).
  – Data requires extensive manual manipulation
• Difficult to support Cell and Gene Therapy growth, vaccines, business needs.
• Surge Capacity – Pandemic response – data collection and analysis
• Future regulatory submissions - incorporating novel data from a variety of sources (e.g., Real World Evidence, Digital Health information, adaptive clinical trials, bioinformatics, and other informatics)

• CBER needs to modernize its business, data and information technology to keep pace with these challenges
Integrated Modernization

Address business, data, and technology challenges in a united fashion and take advantage of the interconnectedness and dependencies that exist between and among them.

**BUSINESS**
Streamlined and harmonized business processes = effective regulatory reviews | more time for other activities

**DATA**
Less time looking for information = more time for review

**TECHNOLOGY**
Less spending fixing aging systems = more resources for implementing innovative technologies
Approach to CBER Modernization

- **Reusable Tools**: Saving time and resources by using reusable code
- **Open Source Software**: Leveraging technology best practices while making it easier to secure our systems and helping to mitigate risks
- **Automation**: Reducing time spent on redundant tasks, minimizing errors and improving data quality
- **Cloud-ready**: Preparing the Center to move to the cloud when it makes sense, avoiding additional cost incurred with a later migration to the Cloud
- **Enterprise Shared Services**: Leverage FDA-wide or other Center solutions
  - Technology
  - Governance
  - Cost
CBER Modernization Progress

- Modernization Initiated 2019
- Development of IT platforms covering product lifecycle – better integration
- Increased agility and flexibility to accommodate wide variety of CBER products and regulatory pathways
- CTF will allow us to interact with various systems

Reusable Tools
- Build once, use multiple times; Adjustable for specific needs

Common Technology Foundation
- Scalable on demand
- Secure
- Cloud Ready
- Smaller IT Footprint
CBER Modernization - Leveraging

Evolution of CBER/ FDA IT
DISTRIBUTION OF CBER IT BUDGET 2018-2020

- Operations & Maintenance: 60%
- Enhancements: 15%
- Modernization: 25%
Accelerate Modernization

• CBER has maximized use of IT dollars
  – CBER staff assume development work
  – focus contractors on technology development

• Modernization takes additional resources
  – Resources for PDUFA products
  – Resources for non-PDUFA products
Benefits Of Modernization

• REDUCE RISK

• Enhance supports of cellular and gene therapy, vaccines and other complex biologics;

• Improved internal management leading to enhanced review efficiency, effectiveness and quality;

• Ability to accept, analyze and manage newer source of data in regulatory submissions;

• Improved knowledge management harmonizing with and leveraging knowledge management efforts;

• Facilitation of external interactions with developers, manufacturers, and patients – resulting in faster information exchange, data analysis, and dissemination of safety information; and

• Better consistency of advice and decisions to guide and foster new product development, review, and approval.
Questions?
Prescription Drug User Fee Act (PDUFA)
Financial Status Update
Agenda

• Financial changes implemented in PDUFA VI
• Financial status of the program
• Resource Capacity Planning
Agenda

• Financial changes implemented in PDUFA VI

• Financial status of the program

• Resource Capacity Planning
PDUFA VI represented significant changes to financial aspects with the following objectives:

- **Enhancing the predictability** of PDUFA funding levels and sponsor invoices
- **Minimizing inefficiency** by simplifying the administration of the program
- Improving FDA’s ability to **manage program resources** and engage in **effective long-term planning**
Enhancing the predictability of PDUFA funding levels and sponsor invoices

- Increased reliability of program collections
  - Shifting fee allocation to more reliable fee types appears to have reduced variance of collections to target revenue

![Variance of Net Collections to Target Revenue Amount](image)
Minimizing inefficiency by simplifying the administration of the program

- Discontinued establishment fee
- Minimized multiple billing cycles
- Discontinued Fees-Exceed-the-Costs waiver
Improving FDA’s ability to manage program resources and engage in effective long-term planning

- Replaced 5-year offset and final year adjustment provisions with Operating Reserve Adjustment
- Established forward-looking Capacity Planning Adjustment methodology to better enable ability for resources (full-time equivalents) to keep pace with review workload growth
- Created an annualized base revenue amount
FDA has faithfully delivered on all commitments in the financial aspects of PDUFA VI

<table>
<thead>
<tr>
<th>Commitment</th>
<th>Status</th>
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<tbody>
<tr>
<td>Publish RCP/MTR implementation plan</td>
<td>Published on time</td>
</tr>
<tr>
<td>Staff an RCP team</td>
<td>Staff duties established in CDER, CBER, &amp; HQ</td>
</tr>
<tr>
<td>3rd party study of new CPA published for public comment</td>
<td>Published ahead of schedule; new CPA established for FY21 fee-setting</td>
</tr>
<tr>
<td>Allocate CPA funds to org components engaged in direct review work and report in annual financial report</td>
<td>Reported in each annual financial report</td>
</tr>
<tr>
<td>3rd party evaluation of PDUFA program resource management in FY18</td>
<td>Published; FDA action plan initiated in response</td>
</tr>
<tr>
<td>Publish 5-year financial plan with annual updates</td>
<td>Published (FY19 delayed due to shutdown)</td>
</tr>
<tr>
<td>Convene public meeting to discuss program finances (starting in FY19)</td>
<td>FY19 &amp; FY20 meetings hosted</td>
</tr>
</tbody>
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Agenda

• Financial changes implemented in PDUFA VI

• Financial status of the program

• Resource Capacity Planning
### Overview of the PDUFA Financial Plan

**Budgetary Resources**

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<tr>
<th></th>
<th>FY 2018</th>
<th>FY 2019</th>
<th>FY 2020</th>
<th>FY 2021</th>
<th>FY 2022</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target Revenue</strong></td>
<td>$911,346,000</td>
<td>$1,010,322,000</td>
<td>$1,074,714,000</td>
<td>$1,121,803,000</td>
<td>$1,168,054,000</td>
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<tr>
<td><strong>Cash Collections</strong></td>
<td>$908,077,723</td>
<td>$1,010,322,000</td>
<td>$1,015,152,012</td>
<td>$1,074,714,000</td>
<td>$1,121,803,000</td>
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<tr>
<td><strong>Recoveries</strong></td>
<td>$13,149,599</td>
<td>$10,000,000</td>
<td>$12,857,171</td>
<td>$9,000,000</td>
<td>$9,000,000</td>
</tr>
<tr>
<td><strong>Carryover Available for Use, Beginning of Year</strong></td>
<td>$232,969,623</td>
<td>$125,372,943</td>
<td>$125,372,943</td>
<td>$136,237,817</td>
<td>$133,219,097</td>
</tr>
<tr>
<td><strong>Total Budgetary Resources</strong></td>
<td>$1,154,196,945</td>
<td>$1,145,694,943</td>
<td>$1,153,382,126</td>
<td>$1,219,951,817</td>
<td>$1,264,022,097</td>
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**User Fee Obligations**

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<thead>
<tr>
<th></th>
<th>FY 2018</th>
<th>FY 2019</th>
<th>FY 2020</th>
<th>FY 2021</th>
<th>FY 2022</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Payroll &amp; Operating</strong></td>
<td>$129,543,398</td>
<td>$133,147,244</td>
<td>$132,847,629</td>
<td>$135,357,938</td>
<td>$140,880,201</td>
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<tr>
<td><strong>CDRH</strong></td>
<td>$786,091</td>
<td>$2,630,174</td>
<td>$1,501,379</td>
<td>$4,051,811</td>
<td>$4,184,089</td>
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<tr>
<td><strong>ORA</strong></td>
<td>$7,733,467</td>
<td>$8,498,654</td>
<td>$7,443,695</td>
<td>$8,628,940</td>
<td>$8,880,776</td>
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<tr>
<td><strong>HQ</strong></td>
<td>$54,211,488</td>
<td>$58,486,768</td>
<td>$55,910,342</td>
<td>$56,102,552</td>
<td>$59,097,922</td>
</tr>
<tr>
<td><strong>Total Rent</strong></td>
<td>$49,964,883</td>
<td>$65,278,320</td>
<td>$52,437,964</td>
<td>$65,931,103</td>
<td>$66,590,414</td>
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<tr>
<td><strong>Total Shared Services</strong></td>
<td>$130,936,781</td>
<td>$133,751,844</td>
<td>$134,192,042</td>
<td>$136,484,526</td>
<td>$137,611,011</td>
</tr>
<tr>
<td><strong>Total Obligations</strong></td>
<td>$1,062,111,583</td>
<td>$1,043,272,234</td>
<td>$1,017,144,309</td>
<td>$1,086,732,719</td>
<td>$1,135,105,800</td>
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**Carryover**

<table>
<thead>
<tr>
<th></th>
<th>FY 2018</th>
<th>FY 2019</th>
<th>FY 2020</th>
<th>FY 2021</th>
<th>FY 2022</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Carryover, End of Year</strong></td>
<td>$209,223,938</td>
<td>$186,273,705</td>
<td>$220,088,812</td>
<td>$217,070,092</td>
<td>$212,767,292</td>
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<tr>
<td><strong>Carryover Unavailable for Use, End of Year</strong></td>
<td>($83,850,995)</td>
<td>($83,850,995)</td>
<td>($83,850,995)</td>
<td>($83,850,995)</td>
<td>($83,850,995)</td>
</tr>
<tr>
<td><strong>Carryover Available for Use, End of Year</strong></td>
<td>$125,372,943</td>
<td>$102,422,710</td>
<td>$136,237,817</td>
<td>$133,219,097</td>
<td>$128,916,297</td>
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</tbody>
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*Numbers rounded to nearest whole dollar

### Carryover Balance
- Available carryover decreased from beginning of FY18 to end of FY20 (est.) by $99.8M
- Ending balance in FY22 accounts for roughly 9.5 weeks of operating reserves

### Impact of Fee Structure Change
- Increase in efficiency and stability
- Elimination of burdensome fees and additional “cleanup” billing
- In FY19 FDA collected 100.49% of the planned target revenue
- Through the first two years of PDUFA VI, FDA has collected 100.08% of the total planned target revenue
Agenda

• Financial changes implemented in PDUFA VI

• Financial status of the program

• Resource Capacity Planning
As part of PDUFA VI, BsUFA II, and GDUFA II, FDA committed to:

- Modernize its activity-based time reporting
- Building a resource planning capability (RCP)

The capabilities would provide FDA with the tools to better understand its future resource needs and adjust internal operations to meet the expected workload.

There was a recognition that these two capabilities, when established, would provide FDA with the data to better inform a more optimal Capacity Planning Adjustment (CPA) for its user fee target revenue for PDUFA and BsUFA.
FDA’s Journey to Excellence in Operations

FDA’s vision will be achieved by first establishing a foundation and then building additional, more mature capabilities over time.
What is Resource Capacity Planning?

RCP allows FDA to identify the resources needed **before** they are needed

**Modernized Time Reporting (MTR)**
- 52-week time reporting to provide:
  - Better measure of level of effort
  - Better analysis of available hours

**Workload Forecasting**
- Advanced analytics to forecast likely incoming work & productivity

**Operational Data**
- HR Data (attrition, hiring times)
- Financial Data

**Resource Forecast**

**Applications of Resource Forecasts**
- **Capacity Balancing**
  - Identify ops to prioritize existing resources
- **Revenue Adjustment**
- **Hiring Plans**
- **Financial Forecasting**

**Projected Demand**
- Upper bound
- Mid-point
- Lower bound

**Available Staff by Role**

**Revenue Adjustment**

**Hiring Plans**

**Financial Forecasting**
RCP near-term implementation timeline

**Done**
Build Foundational Capabilities

- Implement Time Reporting across CDER & CBER
- Develop the methodology for advanced resource capacity planning

**Ongoing**
Operationalize RCP Capabilities

- Ensure Time Reporting compliance & accuracy
- Operationalize predictive models and algorithm engines to produce resource forecasts

**Next Steps**
Develop Sustainable & Scalable IT & Support to Expand Capabilities

- Develop a technical infrastructure to enhance automation and replicability, of analysis and reporting
- Expand IT/RCP capabilities to other centers
- Build an enterprise-wide support model to sustain RCP capabilities
Program milestones to date

- Established Time Reporting within CDER and CBER
- Achieved at least 95% center-wide compliance
- Created interactive dashboard visualizations to enable leadership decision-making

- Designed predictive models for incoming regulatory submissions
- Developed models to predict upcoming future submissions (IND, NDA, BLA, supplements) and industry meetings across CDER and CBER

- Developed future-looking resource forecasts
- Created continuous forecast resource algorithms which utilize time reporting and historical submission data
- Developed resource algorithms across both CDER and CBER offices
RCP capabilities will enhance the way FDA operates

Resource capacity planning is built on the data gathered through implementation of time reporting and sets the organization up for a more structured, data-driven approach to operational decisions.

**Proactive Resource Planning**
- Reprioritization of work and resources based on time reporting and utilization data
- Targeted hiring plans based on workload forecasts

**Improved User Fee Setting Methodology**
- Data driven target revenue adjustments based on predictive modeling of resources rather than historical averages of submission volume
- Ability to incorporate increases in submission complexity into the adjustment
- Future forecasts can provide foundational data for updating of the Five-year Financial Plan

**Enhanced Management of Financial Resources**
- Increased visibility into future resource needs to inform budget
- Tracking of forecasted financial needs versus actuals
Improved user fee setting methodology

The new CPA improves upon the interim CPA by developing a forward-looking approach for the annual revenue setting.

**Legacy adjustment:**
- Lagging indicator using 3-year averages
- Compensates for increases occurring in the past
- Based on submission counts
- Timing compounded by hiring timeframes

**New adjustment:**
- Forward looking
- Compensates for likely increases
- Translates submission activity to likely resource demand
- Times resources to account for hiring and training timeframes
CPA adjustment approach

The adjustment accounts for expected direct review work – work driven directly by incoming volume of submissions.

1. **Forecast Submission Volume**
   - Predictive models estimate the volume of direct review submissions
   Includes:
   - Commercial INDs/BPDs
   - Original NDAs/BLAs
   - Efficacy Supplements
   - Labeling Supplements*
   - Manufacturing Supplements
   - Industry Meetings

2. **Calculate Future Resource Forecast**
   - FTE** forecast algorithms informed by time reporting data
   - These algorithms forecast the required FTE demand for direct review effort

3. **Assess Feasibility of Acquiring Needed Resources**
   - Compare the forecast against capacity and adjust the forecast to ensure that an adjustment is made only for what is needed and what can realistically be utilized.

4. **Convert Adjusted FTEs to Dollars**
   - Determined by FTE cost model
   - The final feasible FTEs needed will be converted to a dollar amount and added to the inflation-adjusted annual target revenue

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* New submission type included in adjustment
** Full-Time Equivalent
Fully enabling RCP capabilities

The foundational RCP capabilities have been built, however development and identification of improvement opportunities continues.

**Continually improve predictive models and resource algorithms**
- Integrate additional data sources into the workload models for enhanced accuracy
- Ensure that time reporting compliance remains high and that activities are reported accurately
- Incorporate additional drivers of effort into resource forecasting algorithms

**Build and maintain a technical environment to support RCP operationalization**
- Create an environment to store foundational data in a centralized location
- Enable an advanced analytical capability to run predictive models and resource algorithms
- Provide visualization and reporting of RCP outputs to inform operational decision-making

**Continue to incorporate RCP into FDA business processes and operations**
- Integrate RCP outputs into FDA financial processes
- Hire required talent to support RCP capability at FDA
- Change its ways of working to support and maintain the RCP capability into the future
Questions?
New Drugs Regulatory Program Modernization

PDUFA VII Stakeholder Meeting
December 11, 2020

Kevin Bugin, PhD, MS, RAC
Director, Special Program Staff
Office of New Drugs
Center for Drug Evaluation and Research

William Lewallen
International Program Analyst
Office of the Center Director
Center for Drug Evaluation and Research
Agenda

NDRP Modernization Overview and Strategic Objectives
- Impetus, Vision, and Strategic Objectives

Integrated Assessment of Marketing Applications
- Patient Experience Data Table

Knowledge Management
- Internal Efforts to Identify Knowledge Management Priorities

Talent
- OND Talent Management
- Assessing Talent
NDRP Modernization Overview and Strategic Objectives
The impetus for the Modernization...

- Rapid and sustained growth in the volume of drug development activity
- Increased complexity of innovative therapies under development
- Greater availability of observational and other “real world” data
- Increased public engagement in FDA activity
- Persistent budget constraints
- Talent shortage

...it intends to maintain the program’s status as a standard for regulatory management of drug development and review

Modernization is not a one time event, but a continuous process of improvement
Mission and Vision for the Modernization

**CDER’s Mission:**
“Protect and promote public health by helping to ensure that human drugs are safe and effective for their intended use, that they meet established quality standards, and that they are available to patients.”

**OND’s Mission:**
“To maintain and advance our global leadership in ensuring that safe and effective drugs and biologics are available to the American people.”

**Modernization Vision:**
“To Advance our leadership in the science and regulation of New Drugs.”

...is translated into six strategic objectives

- **Scientific Leadership**
  - We will grow our scientific expertise and clarify pathways to regulatory approval.

- **Integrated Assessment**
  - We will critically, collaboratively and consistently assess whether information in submissions meets statutory and regulatory requirements.

- **Benefit-Risk Monitoring**
  - We will establish a unified post-market safety surveillance framework.

- **Managing Talent**
  - We will attract, develop, and retain outstanding people.

- **Operational Excellence**
  - We will have a dedicated focus on operational excellence.

- **Knowledge Management**
  - We will facilitate knowledge management.
## Workstreams bring the Modernization to life

<table>
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<tr>
<th>Workstream</th>
<th>Scientific Leadership</th>
<th>Integrated Assessment</th>
<th>Operational Excellence</th>
<th>Benefit-Risk Monitoring</th>
<th>Managing Talent</th>
<th>Knowledge Management</th>
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<td>1 OND Reorganization</td>
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<td>2 Integrated Assessment of Marketing Apps</td>
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<td>3 Postmarket Safety</td>
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<td>5 Assessing Talent/Talent Development and Management</td>
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<td>6 Knowledge Management and WFM/MM</td>
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<td>7 Advisory Committee</td>
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Integrated Assessment of Marketing Applications
The new Integrated Assessment of Marketing Applications approach focuses on 3 guiding principles: enhanced communication, interdisciplinary collaboration, and issue-based reviews.

- The Integrated Review Template is a **three-part document** consisting of the Executive Summary, Interdisciplinary Assessment, and Appendices.

- **Phased implementation** has allowed an iterative approach through evaluation, feedback, and responsive refinement of the process and template.

- FDA requested public comment on the Integrated Review Template in 2019 and 2020 to gather feedback on how it can continue supporting our stakeholders’ needs. Respondents include patients, patient groups, scientists, academia, and industry.

  — Most recent public workshop was hosted virtually on October 30th. **Public docket** is open until **December 31, 2020**. We will be publishing a meeting summary and summary of the docket comments.

* Visit [www.federalregister.gov](http://www.federalregister.gov) and search for “FDA–2020–N–1550”
The Interdisciplinary Assessment includes a Patient Experience Data section.

Patient experience data that was submitted as part of the application, such as PROs or other COAs, qualitative studies or patient narratives submitted by the Applicant and natural history studies.

Patient experience data not submitted in the application but may have informed FDA review nonetheless, such as a PFDD meeting.

Where in the Integrated Review or appendices any discussion related to the patient experience data is included. For example, if clinical trial endpoints included PROs, reference is made to where discussion on those endpoints occurs.

Source: Rukobia Integrated Review Document

Knowledge Management
The New Drugs Regulatory Program Modernization intends to facilitate knowledge management through 4 specific aims

1. Greater **capture and integration** of knowledge in NDRP review processes

2. Faster and easier **access and searchability** of targeted information

3. Increased internal and external **transparency and shareability** of data upon request

4. Improved awareness of relevant precedents and information during decision-making
What does success look like?

Situation: A reviewer is starting an original NME application review for myelofibrosis. She wants to understand the fact base of prior reviews for this target indication, including patient inclusion/exclusion criteria, prior trial sizes, rationale for permitting or rejecting study types, etc.

From (Current State):
- No standard terminology for target indications
- Manual search of all prior myelofibrosis applications
- Individual reading of each application, searching for specific sections and key data points
- Individualized data capture/tracking without institutional knowledge being collected or shared
- Estimated 1-2 weeks to answer key question and no future use of that research

To (Future State):
- SNOMED CT is fully adopted and implemented as the standard for coding target indication
- “Google-like” search to automatically pull all former applications based on key search variables (e.g., myelofibrosis, trial design protocols)
- Consolidated results that pull consistent information/data elements per application based on structured data models of the reviews
- Continuous improvement of searches and saved inquiries to accelerate future reviewer questions
- Estimated 3-4 hours to answer key question, with most of the time spent on reviewing relevant information
Talent: OND Talent Management
OND undertook a multi-year effort to better develop and manage talent throughout OND

• As a knowledge organization, OND’s talent is its greatest resource, making OND’s approach to talent development and management critical to successfully fulfilling our public health mission.

• In the latter half of 2018, OND conducted an assessment of how we develop and manage talent, reviewing annual performance review ratings (2015-2017) and employee survey data (2017 and 2018) and conducting interviews with OND leaders and focus groups with staff and supervisors within the clinical, pharm/tox, and regulatory operations disciplines.

• In April 2019, we established an interdisciplinary group that reviewed the findings of the current state assessment, set an aspiration for the future approach to talent development and management in OND, and developed a blueprint for the future talent system and a high-level competency framework that we believe can serve as the foundation for the development and management of talent across OND.
OND’s current-state assessment found four key areas for improvement

<table>
<thead>
<tr>
<th>Does OND’s performance management system...</th>
<th>What we’ve learned...</th>
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| 1. ...establish clear and consistent performance expectations for staff? | - Performance expectations are often vague and inconsistent, but staff generally know what is expected of them day-to-day  
- PMAP objectives are not explicitly or consistently linked to career paths or professional development |
| 2. ...effectively differentiate high and low performers, with calibrated ratings across supervisors? | - OND ratings are consistently clustered to the top of the range  
- There is no common articulation or understanding of how to apply each PMAP score |
| 3. ...develop staff through feedback and coaching? | - Managers may not have been trained in how to deliver feedback  
- PMAPs often do not convey meaningful feedback  
- Giving and receiving developmental feedback is not ingrained in the culture of every division |
| 4. ...link consequences and rewards to performance? | - Staff perceive a disconnect between actual performance and recognition/rewards  
- Steps are not taken to deal with underperformers due to the burden of the remediation process |

Source: Interviews with OND CPMSs July – September 2018 and Pharm Tox reviewer, team lead, and supervisor focus groups from August – September 2018; RPM focus group April 2019; OND performance ratings data from 2015-2017; 2017 and 2018 Employee Viewpoint Survey
Aspiration and Blueprint for the future approach to talent development and management in OND

OND’s talent system should:
• Be fair, transparent, consistent, feasible, and core to OND’s strategic priorities
• Provide clear expectations for staff and managers
• Obtain accurate, evidence-based information on staff performance
• Encourage actionable feedback tied to staff development
• Provide opportunities for targeted development

Made possible through a standardized and evidence based approach to talent management

<table>
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<tr>
<th>Performance expectations</th>
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<td>• Clearly articulated performance expectations by discipline, linked to roles and career paths</td>
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<table>
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<th>Performance appraisal</th>
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<td>• Standardized evaluation rubrics that promote objective, evidence based ratings</td>
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<th>Ongoing development</th>
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<td>• Regular, actionable, forward looking feedback provided to all staff by team leads and supervisors</td>
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<table>
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<th>Consequence management</th>
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<tr>
<td>• Better recognition of high performers, both formally and informally</td>
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</table>
Talent Assessment Onboarding Pilot Overview
Our Pilot aimed to develop a systematic approach to reviewer assessment and retain new review staff

CDER’s ability to conduct thorough review work, apply sound scientific judgment, and uphold regulatory standards ultimately depends on the caliber of our reviewers

In an effort to meet PDUFA VI commitments and replace outgoing staff, the Office of New Drugs (OND) piloted a systematic pre-hire assessment of high caliber candidates to better gauge their fit with the organization

In conjunction with the pre-hire assessment, our pilot developed materials to standardize OND reviewer development and assessment during the first year, in order to support retention and new employee satisfaction
We developed a pilot approach for reviewer development and assessment based on OND feedback

Focus groups identified needs for **systematic**:
- On-boarding
- Training
- Mentoring

Extensive resources exist but are implemented unevenly.

**Key Takeaways:**
Reviewers, team leaders, and supervisors identified value in
- **Standardizing approaches** to reviewer on-boarding, development and assessment
- **Clarifying job expectations** for all staff
- **Preparing managers** to better assess and develop new staff

From September 2019-August 2020, our working group conducted an onboarding pilot with five OND divisions to test onboarding materials and processes for clinical reviewers and team leaders
Reviewer competencies will be the foundation of the pilot first year development and assessment activities

Onboarding Process
- Checklists
- Onboarding Toolkit

Assessment Tools
- Quarterly Development Templates

*Peer Mentoring

Team Leader Training

*Peer Mentoring framework developed and deployed concurrently in OND
Onboarding Toolkit

TEAM LEADER AND SUPERVISOR
ONBOARDING TOOLKIT
FOR NEW EMPLOYEE DEVELOPMENT

ONBOARDING, DEVELOPING AND ASSESSING FIRST YEAR REVIEWERS

Welcome aboard

Food and Drug Administration | Office of New Drugs
January 2020
The new reviewer onboarding toolkit and checklists were helpful

75% of new reviewers said they received the checklist and said it was helpful for understanding which systems to access and trainings to take.

Checklists were most helpful when they...

- Provided Clarity around resources
- Pointed them to what key trainings to take and when to take them
- Provided contacts and links to other resources to address new reviewer questions
New reviewers and Team Leads spoke very highly of OND’s peer mentor program

94% of new reviewers surveyed said they had a peer mentor.

Having a mentor allowed new reviewers to ask questions and express concerns without feeling like they were being evaluated or bothering their supervisor.

Mentors helped by answering day-to-day questions about assignments and resources, setting up 1:1 meetings, providing feedback, explaining onboarding expectations.

Team Leads noted that peer mentors took some of the burden off themselves (TLs) and provided new reviewers with another perspective on how to coordinate their workload.
Overall recommendations of the pilot include expanding pilot material and process for use across OND

- **Amend onboarding checklists**
  Integrate suggested recommendations to onboarding checklists as feasible.

- **Amend structure of development check-ins**
  Hold check-ins only at the six and twelve month marks.

- **Create a shared knowledge base for each division**
  New reviewers recommended that a shared knowledge base be established for each division, including examples of different types of deliverables, particularly the wording of responses.

- **Consider additional recommendations**
  Recommendations regarding having the TL check in on onboarding logistics, and creating division-specific learning opportunities - such as examples and informal meetings for new reviewers - should be considered.

- **Expand pilot materials to all of OND**
  Tls throughout OND should be trained on how to use pilot materials and they should be housed in a central, easy-to-access repository.
Questions?
Discussion/Any Other Business
Upcoming Topics

Friday, January 15, 2020
12:30-2:30 PM EST

• Efforts to make clinical trials more inclusive and diverse
• Recent guidance on use of decentralized clinical trials (CT), other potential clinical trial flexibilities, and opportunities for greater efficiency
• Strength and reach of patient and rare disease programs (including rare disease cures accelerator) to improve diversity in patient engagement and encourage greater data sharing
PDUFA VII Closing Remarks

December 11, 2020

Dr. Theresa Mullin
Office of the Center Director
Center for Drug Evaluation and Research
Food and Drug Administration