FDA Report Card

Accelerated Approval Not In Danger & Price Not a Factor, Cell & Gene Therapy Prompts More CBER $, Med Device Reviews Speed Up & Biomanufacturing Focus

FDA Commissioner Robert Califf, MD, has been Commissioner of Food & Drugs for just over 6 months. His key priorities at confirmation hearings included modernizing the FDA, EUA/Accelerated Approval reform, and improving clinical trial data collection and diversity. Our take on successes, criticisms, updates on division priorities, and outlook for UFAs as well as other key initiatives can be found below.

BIOTECH & PHARMACEUTIALS

- **The agency fails to impress the biomedical community by its lack of concrete policy initiatives & the public in its mishandling of public health issues – think baby formula, tobacco, even Monkeypox**. The first 6 months of FDA Commissioner Califf's tenure has taken its toll. The agency has been playing catch up in its review of medical devices since the pandemic and remain understaffed. FDA's Food and Tobacco Centers has poorly handled major public health issues: baby formula shortages and regulation of nicotine products. The spread of Monkeypox caught the FDA off-guard and guidance on vaccines and treatment were delayed.

- **Accelerated Approval (AA) pathway is not in danger, but companies using it are expected to face greater scrutiny.** Califf has advocated for expediting follow-up trials to begin before approval and backs Oncology Center of Excellence director Pazdur's proposals to limit single-arm trials for AAs. Califf believes there are many cancer types without treatments and the use in oncology was still correct. In July, FDA launched Project Frontrunner, which expands AAs into *earlier* cancer treatments. The Oncology Center of Excellence initiative develops a framework for identifying candidate drugs for initial clinical development in the earlier advanced setting.

- **Accelerated approval and other PDUFA "riders" (CT diversity, etc.) may come into play with the PREVENTS Pandemic Act, with expected passage in Dec 2022.** FDA riders in the House passed FDA user fee bill include CT requirements for manufacturers to submit a diversity action plan and requirements for the FDA to provide guidance on conducting decentralized CTs and other innovative methods for data collection. Orphan drug grants would be reauthorized, medical device cyber security requirements as well as requiring RWE (real world evidence) policies are included.

- **Therapy prices are not a factor in AA: Dr. Califf has publicly remarked that each AA case requires individual consideration, and the agency does not and will not consider pricing in approvals.** This seems to hold with recent actions as the FDA recently approved Zynteglo, a $2.8 M gene therapy. While Califf is optimistic about AA pathway, there is an ongoing HHS' inspector general investigation into how the agency grants accelerated approvals, triggered in part by the FDA's decision last year to approve Biogen's (BIIB) Aduhelm. The report is expected to be issued in FY 2023.

- **Cell and gene therapy applications are anticipated to skyrocket, so CBER would get a bolus of dollars.** This is good news for biologic, cell & gene therapy companies. The Center for Biologics (CBER) funding comes as a part of the pending user fee bill.

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- **FDA emphasizes rare diseases, particularly in neurodegenerative space (ALS, other conditions).** In May 2022, the FDA established CDER's Accelerating Rare disease Cures (ARC) Program that works to ensure all rare disease and related programs at CDER are working together. FDA has also released an Action Plan for Rare Neurodegenerative Diseases that aims to bolster advancements. As a part of the Action plan, we can expect the creation of a Rare Neurodegenerative Diseases Task Force (FY 22) that will collect patient input and the agency has already announced a private-public partnership, the Critical Path for Rare Neurodegenerative Diseases (CP-RND) that will bring together stakeholders to improve development of treatments for amyotrophic lateral sclerosis (ALS) and other rare neurodegenerative diseases.

MEDICAL DEVICE, DIAGNOSTICS & EMERGING TECHNOLOGIES

- **Medical device review is still (somewhat) slow but improving, and the MDUFA agreement should speed approvals with enhanced funding.** In 2022, PMA and de novo approvals lagged behind 2021 rates, but the pace of 510k clearances improved. The COVID caseload appears to be mitigating as CDRH resumed review of all non-COVID In Vitro Diagnostic pre-submissions in June 2022. We expect review times to improve as CDRH resumes normalized operations, and a bump in funding via user fees (FY23-27).

- **Biomanufacturing will be a focus going forward**. The Cancer Moonshot and Biomanufacturing EO released and signed last week will bring more focus to the sector. The White House hosted a CEO summit to discuss and spur public-private partnerships on Sept 14, with an emphasis on how to spend the dollars passed as a part of the CHIPS Act.

- **The diagnostics-focused VALID Act may not come to fruition**. The new regulatory pathway for FDA approval of diagnostic tests would have started FY27, but the stalled (Senate) pathway may not make it in the Sept 2022 "clean" User Fee reauthorization. Instead, we may see it appear at year-end, or in out years. We note that large diagnostics manufacturers do not worry about "home brew" LDTs, as ABT, Roche, etc all undergo thorough FDA review.

OVERALL AGENCY INITIATIVES

- **FDA Commissioner Califf is attempting to resolve issues -- disinformation, clinical trial (CT) diversity, and health equity – but interestingly all fall outside FDA's purview**. The agency has limited authority in mandating clinical trial changes and lack tools to address disinformation & health equity beyond public guidance and communication campaigns. His recent thoughts can be found here, in a *Science* article where Dr. Califf opines & states priorities in the wake of COVID.

- **FDA has shown interest this year in improving CT data by releasing several guidances aimed at improving diversity.** We note that industry is not beholden to guidances, but many are attempting to improve diversity for robust data.

    - In March, *Inclusion of Older Adults in Cancer Clinical Trials* was released & provides recommendations to sponsors on including patients aged 65 years+ in oncology CTs.
    - In April, *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials,* requests that sponsors develop and provide a Race and Ethnicity Diversity Plan to enroll more participants from underrepresented racial and ethnic populations when submitting investigational new drug (IND) applications or investigational device exemptions (IDE). NOTE: this echoes the House UFA bill provisions

- **FDA is moving towards modernization, a key Califf priority**, **digitalization**, **improved agency transparency**. Digital reforms by the FDA include the release of an Enterprise Modernization Action Plan (EMAP) that aims to optimize business processes and a remote assessment guidance that clarifies the use of regulatory assessments beyond the current PHE. A new Resilient Supply Chain Program for medical devices will use lessons learned during the pandemic to reduce future shortages. FDA also included legislative proposals in the FY 2023 budget that will require certain firms to provide FDA with notification of potential device shortages with production volume information. Califf is also attempting to bring greater transparency to the FDA through an external review of the agency's offices on food safety and tobacco regulation. The external review was announced on July 19, and it will take the Reagan-Udall Foundation 90 days to complete its initial evaluation.

- **FDA notable approvals and actions highlighted by the agency under Califf's watch ytd.** A partial lists includes:

    - **Generic Restasis (February 2).** Restasis did not have an approved generic for 20 years. This drug is ranked #22 in the list of top Medicare Part D drug expenditures in 2020.
    - **Lumipulse G β-Amyloid Ratio (May 4)** for marketing as the first in vitro diagnostic test for early detection of amyloid plaques associated with Alzheimer's disease**.** This could be a key diagnostic tool if amyloid targeting drugs are successful in their clinical trials and reach market.
    - **Mounjaro (tirzepatide) (May 13)** for improving blood sugar control in adults with type 2 diabetes, as an addition to diet and exercise**.** Eli Lilly's key diabetes medication that is aiming to be expanded into weight management and obesity care.
    - **Enhertu (August 5)** as the first therapy targeted to patients with the HER2-low breast cancer subtype**.** Enhertu is already approved to treat lung, breast, and gastric cancer. This drug is a collaboration between AstraZeneca and Daiichi Sankyo.
    - **OTC hearing aid final guidance (August 16).** This established a new category of over-the-counter (OTC) hearing aids, enabling consumers with perceived mild to moderate hearing impairment to purchase hearing aids directly from stores or online retailers.

UP NEXT

- **NEXT STEPS**: The Senate has until September 30 (FY22) to reauthorize the FDA user fee programs.. We expect it to be a "clean" extension, with House-passed user fees riders expected to be revisited in an end of the year package. The FDA policy improvement "riders" – Accelerated Approval, allowance of AI & cell-based models, RWE – may be included in a Dec 2022 PREVENTS Pandemics Act, as a nod to retiring Sen. Richard Burr (R-NC). Rob Califf appears to have a hands-off leadership style, maintaining the agency's status quo during 2 PHEs (COVID & Monkeypox), while being called to testify on PH issues in front of Congress – COVID, Monkeypox, baby formula, tobacco. With a likely split congress in 2023+, we expect Califf to be called to testify during Oversight hearings on FDA's actions since Biden's term began. We note that Califf has drawn criticism from Democratic members e.g. Senate Majority Whip Dick Durbin (D-IL) on FDA's lax tobacco enforcement We expect Biomanufacturing to be a focus for FDA & Industry going forward, in life sciences and in other fields. The Cancer Moonshot will also feature prominently, as public-private partnerships are announced over the next 6-18 months.

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Background

Public Health Report Cards

COVID-19, Grade: B (based on fast approvals of vaccines and treatments, and expansion of treatment availability)

- **Out of all relevant issues listed, FDA handled COVID-19 the best.** It effectively used its EUA authority to approve several vaccines and treatments. The agency is proactively thinking of the fall COVID-19/flu season and have approved both PFE & MRNA COVID-19 omicron boosters this week. COVID-19 cases are trending down in lethality and in case count from the highs seen in January & February 2022. The FDA did fall short in their approval transparency and handling of disinformation which hindered vaccine uptake. Just 43% of children 5 to 17 years old are fully vaccinated, months after approval.

Baby formula shortage, Grade: C- (Based on flexibilities to mitigate shortage, delayed public response, and estimation that the shortage will continue through Fall 2022 or last even longer).

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- **The FDA has been historically criticized as prioritizing drugs over food and this was a key example of the structural inadequacies at the office on food safety.** The contamination wasn't caught until after cases arose in February. And the FDA took months to publicly act and did not issue guidance on import flexibilities until May. While their flexibilities have resulted in some mitigation (now about 20% of infant formula are in shortage), the shortage had not abated by July as originally estimated by Califf during his May 2022 HELP committee testimony. The agency's handling of the shortage was one of the triggers for the ongoing external review of its food safety center and Califf has publicly remarked that "fundamental questions about the structure, function, funding and leadership need to be addressed".

Tobacco/cigarettes, Grade: D, (based on inability to remove products from market, ongoing external review, slow implementation, and missed deadlines)

- **Califf like his predecessors is struggling to regulate nicotine products, despite taking major actions against the industry.** At the time of his confirmation, the FDA had missed e-cigarette review deadlines, and was unable to regulate synthetic nicotine (a major loophole for manufacturers). In his first 6 months, Congress closed the synthetic loophole in March and FDA made progress in their marketing reviews of nicotine products. Brian King, a known opponent of vaping, was hired to lead the office after Mitch Zeller's departure. The FDA also put forth proposed rules that prohibits menthol cigarettes and flavored cigars, engaging in a more stringent review of e-cigarette marketing products, and is planning to limit nicotine levels in FDA approved products by May 2023. However, the FDA has faced scathing criticism over failing to meet its tobacco deadlines and not using their enforcement powers to pull products from the market. A STAT investigation found that vape companies are regularly flouting the FDA's orders to remove products from the market and FDA is failing to punish these bad actors.

Opioids, Grade: C (based on recent draft guidances & released framework, more stringent review of opioid products, but lack of concrete policy changes).

- **FDA's actions on opioids fall within two major prongs: increase access to non-opioid products, decrease access to opioids.** For increase access to non-opioids, in February, FDA release their draft guidance on developing non-opioid analgesic products for acute pain. The guidance, is part of a larger Overdose Prevention Strategy from HHS and focuses on how manufacturers can generate data for an indication of management of acute pain, and the potential use of expedited programs for non-opioid approval. In decreasing access to opioids, the agency is committing to more stringent reviews of opioid products as FDA's advisory committees voted (8 yes, 14 no) earlier this year against recommending IV Tramadol. Finally, the agency released an Overdose Prevention Framework that organizes FDA's plan on addressing overdoses. FDA plans to act by promoting appropriate prescribing of medications with abuse potential, including opioids, stimulants, and benzodiazepines, expanding availability and access to overdose reversal products, and preventing counterfeit and illegal online sales of illicit drugs. This is an unsatisfactory framework with no specified deadlines and no goals to be reached. In the recent Senate HELP Monkeypox hearing, Califf stated that the agency is actively reviewing labeling changes for opioid products to make them more restrictive. Recall that this was a priority at his confirmation and his lack of dissatisfied congressional members. But Califf did promise more action on opioids in the coming weeks, and we await to see how the framework will be implemented.

Monkeypox, C (based on relatively new outbreaks, recent FDA actions)

- **Early missteps have been offset by increasing vaccine access and declining spread.** Currently, the main issues are the lack of access to Tpoxx and limited vaccine availability. The FDA has attempted to increase supply through alternative methods based on limited clinical data, but it is uncertain how vaccine efficacy will be impacted. The federal government has

ordered an additional 2.5 M doses which they hope will arrive by Fall, but vaccine shortages are expected to persist in the meantime. FDA has also been criticized for their lack of transparency in their responses as the EUA for alternative methods for the vaccine was authorized without a public meeting. Califf recently defended the agency's restrictions around Tpoxx, warning that "without human trials, we don't know if Tpoxx is beneficial for humans with monkeypox." FDA's updated guidance in September reflect additional concerns of viral resistance as the agency notes that TPOXX has a low barrier to viral resistance and must be used judicially. The next pressing issues may be spread in educational institutes (schools, colleges, daycares).