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12 Nov 2021 | **Analysis**

Robert Califf Likely To Find Many Familiar Problems Upon His Return To US FDA

by Derrick Gingery

President Biden's pick for FDA commissioner should remember many of the hot-button issues that he would face upon confirmation, such as drug pricing and approval standards.

Should Robert Califf gain a second term as FDA commissioner, he likely will find that many of the issues demanding attention remain the same as when he left the agency five years ago, even though the names of the products now linked with them are different.

As expected, President Biden announced his intention to nominate Califf for FDA commissioner on 12 November. If confirmed, he will become *only the second commissioner* to serve two non-consecutive terms and the first to gain Senate approval twice.

A swift confirmation could offer Califf several years to address long-standing public health issues as well as affect change at the FDA, well more than the 11 months he had at the end of the Obama Administration.

Califf resigned when President Trump took office, although he made clear that he would have liked to stay in the job. (Also see "*Califf Maintains Desire To Stay At FDA, But Would Either Presidential Candidate Keep Him?*" - Pink Sheet, 5 Nov, 2016.)

Several drug-related issues will continue to confront Califf if he reaches the office again, but others, such as tobacco and nutrition, also are expected to garner his

Calculating Califf's Course To Confirmation

By M. Nielsen Hobbs

12 Nov 2021
Robert Califf got 89 votes in the Senate last time – but that's also the least a Democratic nominee has ever gotten.

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attention. E-cigarettes remain a priority for the agency going forward, and its recent policy moves could have long ripple effects, even as the FDA's response to the coronavirus pandemic continues.

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Drug Pricing Remains Front And Center

Drug pricing likely will be a focus of the confirmation process, even though the agency has limited ability to lower drug costs. Califf will have to decide whether to aggressively push the mantra that former commissioner Scott Gottlieb brought to the FDA's White Oak headquarters: that the agency should include drug affordability in its public health mission.

Califf faced drug pricing issues during his first term, which ran from 24 February 2016 to 20 January 2017.

Outrage over the rising price of EpiPen (epinephrine), then owned by *Mylan Pharmaceuticals Inc.*, which now is *Viatris Inc.*, sparked criticism that the agency did not make competitors available sooner, including whether ANDAs were prioritized. (Also see "*EpiPen Outrage In Congress Puts Spotlight On FDA Generic Review*" - Pink Sheet, 29 Aug, 2016.)

The FDA eventually approved a generic version, marketed by *Teva Pharmaceutical Industries Ltd.*, in 2018. (Also see "*Teva Launches Generic EpiPen At Same Price As Mylan's Generic* " - Scrip, 27 Nov, 2018.)

Califf Confirmation Hearing Round Two: Industry Ties Once Again May Bark Loud, Bite Lightly

By Derrick Gingery

12 Nov 2021

The cardiologist seeking another term as FDA commissioner has been working in the pharma industry since leaving the post, but Senators have tended not to question nominee's work history extensively during previous confirmation hearings.

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The FDA has tried in recent years to streamline the complex generic drug approval process, in part by increasing communications and issuing more guidance. More changes are planned for the upcoming generic drug user fee program renewal. (Also see "*GDUFA III Talks Completed; Fees will Fund Inspection, Complex Generic Improvements*" - Pink Sheet, 2 Sep, 2021.)

The drug price negotiation legislation worked out by congressional Democrats could mean the issue will recede from prominence (having already been "addressed" by Congress), but how those negotiations could reshape product development may impact FDA in the future. (Also see "*The End Of Small Molecule Drugs? Potential Implications Of US Price 'Negotiation'*" - Pink Sheet, 5 Nov,

2021.)

Other avenues exist to affect drug prices, such as more aggressive enforcement within the patent system, if the Biden administration wants to continue to aggressively push the topic.

Acting Commissioner Janet Woodcock appealed to the Patent and Trademark Office for help with patent thickets and product hopping, but the extent either agency could affect the problem without legislative changes remains unclear. (Also see "*USPTO Faces Growing Pressure To Enter Battle Over Drug Pricing*" - Pink Sheet, 23 Sep, 2021.)

Approval Standards Critics Not Going Away

Califf was near the center of criticism of an approval, seen as pushing the agency's marketing bar too low, during his tenure, but did not actively influence the final decision, suggesting the hands-off approach likely would continue.

When *Sarepta Therapeutics, Inc.* gained an accelerated approval for Exondys 51 (eteplirsen) as a treatment for Duchenne muscular dystrophy, despite questions about its efficacy and rejection by the primary reviewers, Califf was forced to make the final determination of an appeal by assessment staff.

He deferred to Woodcock, at the time Center for Drug Evaluation and Research director, who wanted to approve the product, saying political appointees should not be making those decisions. (Also see "*Political Appointees Shouldn't Influence Approval Decisions, Califf Says*" - Pink Sheet, 20 Oct, 2016.)

When some at the FDA raised concerns that Woodcock suggested Sarepta may need an approval for its financial health and to drive research in the disease, Califf defended her judgment, saying he thought she considered all sides of the issue. (Also see "*Woodcock's 'Bias' In Sarepta Case Made Jenkins Worry About Future Drug Reviews*" - Pink Sheet, 31 Jul, 2017.)

Not surprisingly, questions about the FDA's relationship with sponsors as it relates to drug development continue to plague the FDA. The most high-profile recent example was the accelerated approval of *Biogen, Inc.*/*Eisai Co., Ltd.*'s Aduhelm (aducanumab-avwa) for treatment of Alzheimer's disease, which came despite an overwhelmingly negative vote from the agency's advisory committee. (Also see "*Power To The (Adcomm) People: Members Believe Votes Should More Directly Affect US FDA Decisions*" - Pink Sheet, 17 Aug, 2021.)

Many stakeholders criticized the agency for working with Biogen during the review, and Woodcock eventually requested an Inspector General review of FDA interactions with Biogen. Califf most likely would be commissioner when the findings are issued. (Also see "*Beyond Aduhelm: OIG Review Will Put FDA's Entire Accelerated Approval Program Under Microscope*" - Pink

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Sheet, 4 Aug, 2021.)

The Aduhelm approval also elevated calls for changes to the accelerated approval pathway. While Califf likely does not agree they are necessary, he may prefer better illuminating the current accelerated approval standard. During the Exondys 51 approval controversy, Califf acknowledged that the agency should better outline its interpretation of the regulations for the public and ensure it is applied consistently across review divisions.

Califf said in 2016 that establishing a bar for accelerated approval was not appropriate, but more discussion of FDA thinking was necessary. (Also see "*Accelerated Approval Should Be Less 'Wide Open,' Califf Says*" - Pink Sheet, 20 Oct, 2016.)

Califf also could influence a revamp of the advisory committee system used in the approval process. CDER Director Patrizia Cavazzoni has said that committees should refocus on the scientific discussion rather than emotion. (Also see "*US FDA Advisory Committees Could Get Revamp With A Focus On Science Over Emotion*" - Pink Sheet, 15 Jun, 2021.)

Policies describing when a meeting is appropriate already are under consideration. (Also see "*US FDA Adcomm Modernization Includes How Meetings Are Scheduled*" - Pink Sheet, 17 Aug, 2021.)

Expect More Clinical Trial Reform

An area where Califf could be aggressive is clinical trial reform. As a former clinical trialist, Califf pushed for improvements to the research system, including expanded use of real-world evidence (RWE), during his first stint as commissioner. Califf advocated for designs allowing randomization of patients within the practice setting to obtain real-world evidence and assess a drug's benefits and risks.

The idea should fit well with recent efforts to improve the diversity of clinical trials, which gained attention when the coronavirus vaccines were being tested. (Also see "*Pfizer COVID-19 Vaccine Trial Diversity Slips As Enrollment Rises, Unlike Moderna*" - Pink Sheet, 18 Sep, 2020.)

Califf also warned while commissioner that the rising cost of clinical research was not sustainable. (Also see "*US FDA's Califf On Real-World Evidence: 'Use It For The Right Purposes'*" - Pink Sheet, 21 Jun, 2016.)

Robert Califf Offers 'A Few Words In Favor Of The Tortoise' When Conducting Clinical Trials

By Brenda Sandburg

01 Nov 2021

Califf continued his research reform message after leaving the FDA. Google's *Verily*, where Califf now is head of clinical policy and strategy, works with health care companies

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on RWE, clinical trial reform and other issues.

The FDA also is in the midst of expanding its use of real-world evidence in decision-making. The upcoming prescription drug user fee reauthorization devotes more funding toward RWE issues. (Also see "*US FDA's Stein 'Excited' About Real-World Evidence, Rare Disease Endpoint Pilot Programs*" - Pink Sheet, 14 Sep, 2021.)

The once and likely future FDA commissioner emphasizes value of randomized controlled trials, the fact that not all trials are good for people, and how decentralization and digitization are leaving people behind. Takeda exec questions if industry is being bold enough.

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Woodcock has also advocated for clinical research system reform. She said that became apparent during the coronavirus pandemic, when many clinical trials had to be stopped, paused or reconfigured because of lock-downs and travel restrictions. (Also see "*US FDA's COVID Master Protocol Guidance To Maintain Influence Post-Pandemic*" - Pink Sheet, 17 May, 2021.) Califf is likely to continue her work.

Another Chance To Shape Opioid Response

Opioid policy once again could delay Califf's path to the FDA's top job, as in 2016. The epidemic and the agency's response remain a top issue for many members of Congress and stakeholders.

The complicated problem has many facets, some of which are outside FDA control or influence. Califf will be forced to maintain the tough balance between the need to prevent opioid abuse, while still maintaining access for those who legitimately need the products.

The FDA's strategy has many prongs, including creating prescribing standards, increasing the availability of naloxone, and changing opioid packaging.

A policy to mandate using blister packs instead of the traditional orange bottles for opioid pills has been stalled for some time, amid objections from manufacturers' and providers about cost and limiting patient access. (Also see "*Opioid Blister Packs Need Study Before Mandate, Groups Urge* " - Pink Sheet, 11 Aug, 2019.)

The FDA's 2018 approval of *AcelRx Pharmaceuticals, Inc.*'s Dsuvia (sufentanil sublingual), a highly potent opioid, continues to be criticized. (Also see "*Dsuvia Gets Warning Letter As US FDA's Opioid Decisions Complicate Commissioner Race*" - Pink Sheet, 16 Feb, 2021.)

But Califf faced a similar issue upon taking over as commissioner in 2016. At that time, the agency faced ongoing concerns about its approval of *Zogenix, Inc.*'s Zohydro ER (hydrocodone) despite advisory committee objections.

Califf defended the decision, saying that the agency resolved concerns about the postmarketing system for opioids prior to approval. But he indicated the agency should have met with the advisory committee again to outline the new plan before approval. (Also see "*FDA's Opioid Regret? Skipping Another Zohydro Meeting, Califf Says*" - Pink Sheet, 2 Mar, 2016.)

Califf's Legacy May Be Shaping The FDA Staff

Califf also could face a substantial brain drain during his term, which could allow him to shape the direction of the agency for years to come.

Woodcock is expected to remain acting commissioner until the confirmation process is complete, but she likely will not remain at FDA long after Califf's return. Upon departure, Woodcock would take more than 30 years of institutional knowledge and expertise out the door with her, which will be difficult to replace.

Other senior, as well as rank-and-file, staff likely will leave in the coming months, especially as the US emerges from the pandemic. FDA officials already have warned that pandemic-related burn-out is growing among employees, which is lowering short-term expectations for hiring and retention. (Also see "*US FDA Lowers FY '22 PDUFA Fees Due to Hiring, Attrition Concerns*" - Pink Sheet, 13 Aug, 2021.)

Among the more prominent recent departures were the director and deputy director of the Center for Biologics Evaluation and Research's vaccine review office. Marion Gruber and Philip Krause apparently left because of disagreements on COVID-19 booster shots. (Also see "*US FDA's Top Two Vaccine Officials Announce Surprise Retirements*" - Pink Sheet, 31 Aug, 2021.)

Chief Scientist Denise Hinton also recently left the agency to become deputy surgeon general. (Also see "*US FDA Chief Scientist Hinton's Departure Leaves Vacancy Atop Makena Decision Tree*" - Pink Sheet, 1 Nov, 2021.)

In addition, the lack of a confirmed commissioner appears to have left several other positions at the agency in temporary hands, such as chief counsel. (Also see "*FDA Chief Counsel Stacy Cline Amin Guided Agency Through COVID-19 EUAs And Guidances*" - Pink Sheet, 11 Jan, 2021.)

A challenge for Califf and others will be to ensure the institutional knowledge that is departing is not lost, as well as find new leaders both inside and outside the agency.

Shortly after becoming commissioner, Califf suggested the FDA's mission should be a powerful recruiting tool for many physicians and scientists. He also said that the various disciplines across the FDA's centers should share ideas and best practices, which will make the environment more attractive to job prospects. (Also see "*Califf Lowering FDA Drawbridge To Work With External Expertise*" - Pink Sheet, 18 Apr, 2016.)

The FDA's senior staff was more stable during Califf's first term, and he did not have an opportunity to fill many positions or change the leadership structure. (Also see "*FDA Chief Scientist Post A Chance For Califf To Make Mark*" - Pink Sheet, 1 Sep, 2016.)

But Califf will now be in position to shape the agency's recruitment and retention strategy. He will preside over a substantial user-fee mandated hiring initiative. The upcoming prescription drug user fee reauthorization calls for 352 new full-time equivalent employees to be hired. (Also see "*PDUFA VII Commitment Letter Outlines Real-Time Review Expansion, Hiring Goals*" - Pink Sheet, 23 Aug, 2021.)

The generic drug user fee renewal will include 128 additional employees. Most of the additions are planned during fiscal year 2023. (Also see "*GDUFA III: Convening Enhanced Mid-Cycle Meeting Will Cost Sponsors*" - Pink Sheet, 29 Oct, 2021.)

Depending on the timing of his confirmation and the energy Congress puts into the user fee reauthorization, Califf could find himself making a quick return trip to Capitol Hill to discuss that five-year plan for the agency. Given how short his time as commissioner was first time around, Califf may welcome the opportunity.