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21 Apr 2020 | **News**

Real-World Evidence On COVID-19: US FDA Approaching With 'Sense Of Urgency'

by Sue Sutter

Agency is going outside its 'comfort zone' to leverage different streams of existing real-world data sources to quickly assess the impact of potential treatment approaches, Amy Abernethy says; pandemic experience could lead to a more open embrace of RWE beyond the current public health emergency.

The COVID-19 pandemic is forcing the US Food and Drug Administration to step outside its comfort zone when it comes to using real-world evidence to inform rapid regulatory decision-making and clinical trial design. This experience could have a potentially lasting and positive impact on the agency's view of the utility of RWE to support – or even guide – drug approvals and labeling expansions beyond the context of the current public health emergency.

The agency is trying to leverage existing real-world data sources, such as electronic health records, to quickly assess the impact of potential therapeutic approaches as well as the downstream effects of the disease itself, Principal Deputy Commissioner Amy Abernethy told a webinar sponsored by the Duke-Margolis Center for Health Policy on 20 April.

> ***"We're really in the setting where we need to figure it out right now and acknowledge that this may take us out of our comfort zone." – FDA's Amy Abernethy***

"Within the context of COVID-19, we've got this urgency to learn what we can as soon as we can,

and that means that we need to be learning from the patients that are receiving care right now and trying to understand how do we apply that as quickly as possible," Abernethy said.

"It certainly takes us out of our comfort zone at FDA, where we usually contemplate very careful work that has been carefully thought through and vetted, and we've also really thought through the precedent of what happens when we make a decision on real-world data," she said. However, in the context of COVID-19, "we're really in the setting where we need to figure it out right now and acknowledge that this may take us out of our comfort zone."

From Step-Wise Approach To A 'Sense Of Urgency'

With its release of a real-world evidence framework in December 2018 and initiation of numerous demonstration projects, the agency has taken a step-wise approach to exploring how RWE can be used in the drug regulatory context. (Also see "*Real-World Evidence: US FDA Framework Emphasizes Data Fitness And Study Quality*" - Pink Sheet, 9 Dec, 2018.) (Also see "*RWE: Comparators, Therapeutic Area May Be Key For Trial Replication*" - Pink Sheet, 14 Oct, 2019.)

Yet, the agency has remained cautious about the utility of RWE, particularly from observational studies, to support efficacy claims given concerns about data quality and reliability, methodological issues and transparency. (Also see "*Real-World Evidence: Sponsors Look To US FDA Drug Reviews For Potential Pitfalls*" - Pink Sheet, 7 Oct, 2019.)

However, the morbidity and mortality resulting from the SARS-CoV-2 virus could mark a turning point in how the FDA approaches RWE.

In response to questions from the *Pink Sheet*, the FDA said the Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research are using existing RWD sources and initiatives to assist with COVID-19, while the Office of the Commissioner is coordinating agency-wide initiatives to develop novel data and analytical solutions to address urgent questions related to the disease.

In the postmarketing space, the FDA is using RWD for COVID-19 natural history, drug use and shortages, and treatment impact studies through the Sentinel System of distributed data networks. In addition, the FDA is working with the Centers for Medicare and Medicaid Services to apply rapid analysis of Medicare claims data to support the agency's mission.

The agency also pointed to the CURE ID app as enabling clinicians to share their real-world experiences treating patients with COVID-19. Although there was only limited use of the app for reports on the novel coronavirus a month ago, activity has since picked up. (Also see "*Coronavirus Hasn't Sparked CURE ID Physician Social Network Interest*" - Pink Sheet, 17 Mar, 2020.) As of 21 April, there were 23 case reports, 77 discussion posts and 323 clinical trials listed

on the site.

Abernethy said the agency is approaching RWE on COVID-19 "with a sense of urgency"

The pandemic is "a story that keeps changing," she said. "So rather than sit around and wait until we learn how to use RWE and make some of the hard decisions, one of the approaches that we've taken right now is to start learning from the data that are currently available, and what does that teach us about what decisions we can confidently make with the data that are available as well as what do we need to do in the future."

Three Buckets Of Questions

Abernethy said the agency is looking to RWE to answer three buckets of critical questions (including epidemiological, treatment, safety and operational) related to COVID-19:

- Questions that can be answered within two weeks because the data are available;
- Questions that can be answered within three to 12 weeks with available data that require some clean up or new analytic techniques; and
- Questions that are going to take more than three months to answer.

"By dividing the questions in that way, what it's allowed us to do is figure out what data sources are already out there and how can we start to put them to bear, and also figure out how do we practice answering the questions," she said.

Having a list a questions matters because it tells the agency what variables are needed and what kind of work needs to be done, she said. For instance, there needs to be agreement on common data elements in RWD sources, and these same data elements should be incorporated into clinical trials to enable a future comparison between the RWE and traditional clinical trial evidence, she said.

Reagan-Udall Steps Up

Identifying key questions and core data elements is at the heart of a new initiative launched by the Reagan-Udall Foundation and Friends of Cancer Research.

The COVID-19 Evidence Accelerator provides a venue for major data organizations, government and academic researchers, and health systems to gather and design queries that can be quickly turned around and their results shared.

"Since the beginning of the pandemic, data scientists around the country have been engaged in

an intense effort to capture real-world data and rapidly deploy data analytics to help answer key questions related to the management of COVID-19 patients," the Foundation said in announcing the program. "While over time each of these individual efforts will likely develop into valuable insights, by banding together we can collectively accelerate and maximize the utility of this information in the near term."

The group is developing a set of common data elements that can be uniformly embedded into data collection efforts to allow for rapid aggregation and analysis.

The 'Bubbling Up' Effect

The FDA has been trying to organize different data streams – such as through the Sentinel network, pharmaceutical companies and other data holders – into a series of critical categories "where ultimately the results then bubble up and get merged together in ways that we haven't historically thought about," Abernethy said.

"What we've been thinking about is how do we bubble up the information coming from all of these different areas and start to put it together to look for consistent findings that provide enough signal that we should get it" to the White House Coronavirus Task Force, the Centers for Disease Control and Prevention and the National Institutes of Health, she said.

Those findings also will inform the next set of critical questions that needs to be answered.

"I think part of the challenge here is recognizing that the questions are going to keep coming, and so we not only have to develop systems to answer those questions but also systems to rapidly say here's the next thing we need to know," she said.

Hydroxychloroquine As A RWE Platform

The widespread use of the antimalarial drugs hydroxychloroquine and chloroquine as potential therapeutic agents for COVID-19 has provided a jumping off point for various RWE initiatives.

"We've used this critical question around hydroxychloroquine as what I call the platform for figuring it out," Abernethy said. "Practically speaking, hydroxychloroquine is being prescribed by many physicians in America outside the context of a clinical trial. So that means the patients are receiving hydroxychloroquine or not, and their care is being picked up within the electronic health record."

Querying different datasets about treatment patterns, safety concerns and potential effects with hydroxychloroquine "will teach us what datasets make that possible, how can we standardize the questions in the common data elements, what results do we find reliable and compelling enough, and also replicable enough against different datasets, that we can actually answer potentially questions around hydroxychloroquine with confidence but also then use that same platform

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approach for other questions," Abernethy said.

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The use of hydroxychloroquine with or without azithromycin versus control among hospitalized COVID-19 patients is the focus of the first parallel analysis project by Reagan-Udall's COVID-19 Evidence Accelerator. This project will involve collaborators repeating analyses in parallel, using different analytical techniques and data sources, to characterize: the COVID-19 patient populations treated with the drugs; nature of the treatment; safety signals; comparative effectiveness on key outcomes; potential predictors of treatment safety and effectiveness; and validation of a COVID-19 risk stratification score.

Payers also are turning to RWD to probe questions about the utility of hydroxychloroquine.

Steve Miller, chief clinical officer at *Cigna Corp.*, told the Duke webinar that payers are pooling their claims data to look at off-label use of hydroxychloroquine, chloroquine and other approved drugs that may have utility in treating COVID-19.

For example, insurers are using a case-controlled approach to look at whether hydroxychloroquine provides a prophylactic effect against COVID-19 among rheumatoid arthritis and lupus patients who were already using the drug to treat their underlying conditions.

"It's not a true definitive trial, but it just gives you a kernel of knowledge to say are these things actually working the way you hope they are, or are they not and should we be looking in a different direction," Miller said.

Sarah Karlin-Smith contributed to this story.