MMIT RADAR

Spotlight on Market Access

Actionable understandings from AIS Health's in-depth coverage

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COVID Emphasizes Collaborative Approach That's Needed to Assess Health Care Value

With the COVID-19 pandemic affecting a variety of health care stakeholders, the cost of their services is becoming even more important. Payers tightening their budgets are trying to make sure that they are truly paying for value. But that's easier said than done. All industry stakeholders, including pharma companies, should work to make changes in the health care system to bring value to the forefront of decision making, maintain industry experts.

Pointing out that people may never agree on the issue of whether prices for innovative drugs are too high, Kate Dion, value communications lead at 3D Communications, a company that provides strategic regulatory and value communications services to pharmaceutical, device and biologic companies, maintained that "what's really at stake, and COVID-19 is pushing this into sharp focus, is how urgently we need to get medicines to patients. And not just medicines for the pandemic. The challenge is formidable. All at the same time, we need to make medicines more accessible to patients, incentivize scientific innovation and keep investors happy."

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COVID-19 Manufacturer Market Access Challenges Include Speed, Scale, Pricing

As pharmaceutical manufacturers gear up to develop and bring to market vaccines and therapeutics that address the COVID-19 pandemic, they're facing both unique opportunities and significant challenges relating to speed, scale and pricing, three Avalere experts say. Those sources, who spoke as part of a webinar on July 22, noted that companies need to consider how the pandemic is likely to evolve and whether they want to potentially gamble big to attempt to develop a vaccine or therapeutic for COVID-19.

"I think the challenges and opportunities of some of these products really differ, when you take them in the context of the current public health crisis, or when you think about the future, when COVID might actually be just a routine disease that we might be treating," explained John Neal, managing director at Avalere.

Pharmaceutical manufacturers also need to consider pricing, distribution and access in the context of how to proceed "within the context of whether you're a new molecular entity that's seeking your first indication — which

might be for COVID — you're not on the market, you're doing clinical development and then seeking that first indication, versus whether you're currently on the market and maybe indicated for some other therapeutic area," Neal told the webinar audience.

Vaccine, Drug Pipelines Are Robust

The COVID-19 vaccine and therapeutic pipelines are robust. According to Avalere, there are at least 510 active pre-investigational (pre-IND) treatments in development, with another 230 that have received "safe to proceed" IND status.

Two COVID-19 treatments have been cleared for limited use, although one since has been withdrawn. The FDA on May 1 issued an emergency use authorization (EUA) for Gilead Sciences, Inc.'s investigational antiviral drug remdesivir for the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease. In addition, the FDA on June 15 revoked its EUA for chloroquine and hydroxychloroquine, saying the two controversial drugs "are unlikely to be effective in treating COVID-19 for the authorized uses in the EUA."

Meanwhile, on the vaccine front, Avalere lists at least 145 COVID-19 vaccines in pre-IND development, another 18 in Phase I and Phase II trials, and five initiating Phase III trials (see infographic, p. 3).

Kelly George, Ph.D., consultant at Avalere, said that a large amount of basic coronavirus research over the last 60 years has banked enough knowledge to give researchers an advantage. This head start, fueled by very preliminary knowledge about this specific coronavirus, allowed the pharmaceutical industry to screen products for repurposing and quickly ramp up the development process, she said. "That brought us to where we are today, with over 500 products in development."

Beyond the repurposing process, pharma manufacturers have used the virus genome, published on Jan. 10, to move quickly to structure-based drug design that potentially can attack the virus quite specifically, George said. Still, she added, it has been somewhat challenging to get solid results.

"I think — as we all were initially — the system for clinical trials, as well as the agency, has been overwhelmed at the beginning. And much of the data reflected that — we had clinical trials without control arms, various standards of care, and there was a level of ambiguity in the data interpretation at the very onset," George said.

Now that research is generating more data, she said, "we see far more collaborative efforts globally and far more clear guidance from FDA on their expectations for pre-IND, IND, EUA or full approval." Clinical trials are beginning to have more unified protocols and inclusion/exclusion criteria and more standardization, she said. "We're seeing more umbrella trials, and excitingly, we see endpoints reflecting various levels of efficacy so we can ensure a full understanding of the clinical outcomes."

EUA Can Be Seen as Interim Step

Neal pointed out that manufacturers can choose what path to pursue. An EUA can be seen as an interim step on the way to full approval, he said. In the case of COVID-19, the two EUAs that have been granted were based on a very limited data set for safety and efficacy, Neal said, adding that EUAs also can be revoked as data matures, as occurred in the case of hydroxychloroquine. This experience shows the potential risk to manufacturers of seeking an EUA on very limited data.

Sponsors considering which route to pursue should take into consideration the varying levels of data burden, financial burden, time to market, promotional options and various downstream implications, and it's ultimately the FDA's decision whether or not to allow the product to market for COVID-19, said George. "And that's going to absolutely rely on that risk-benefit profile, but with the risk of the drug being just as important as the benefit of the drug."

Assuming more products receive EUAs and potentially are licensed, it also could get more difficult for manufacturers to obtain EUAs for competing products, George said. She noted that one of the four criteria for issuance of an EUA is that there are no alternative treatments available, "so this opens up the door for the possibility of scenarios where there's a product already on the market that could weigh into the agency decision for additional EUAs."

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How Close Are We to a Coronavirus Vaccine?

by Jinghong Chen

With 16.8 million confirmed cases of COVID-19 and counting, researchers are racing to develop a vaccine for the new coronavirus. Currently there are more than 165 vaccines in preclinical testing, and 27 are in human trials. In May, the Trump administration rolled out Operation Warp Speed to accelerate vaccine development, an effort funded by billions of dollars. Meanwhile, some leading candidates overseas have delivered promising clinical results. Here's a look at key coronavirus vaccine candidates:

Phase	Developer	Vaccine Type	Development Timeline
			Mar. 2020 · Apr. · May · June · July · Aug. · Sept. · Oct. · Nov. · Dec. 2020 · Early 2021 · End of 2021
Limited Approval	CanSino Biologics	Non-replicating viral vector	Phase I clinical trial began · Phase II trial began · Phase I study data published · Approved for Chinese military use · Phase II study data published
Phase III	Univ. of Oxford & AstraZeneca	Non-replicating viral vector	Phase I/II clinical trial began · Phase II/III trial began · Phase I/II study data reported · Available for U.K. · Available for U.S. · Will make & distribute 300M doses
Phase III	Sinopharm	Inactivated virus	Phase I/II clinical trial began in China · Phase I/II study data disclosed · Phase III trial launched in the United Arab Emirates
Phase III	Sinovac	Inactivated virus	Phase I and Phase II clinical trial began in China · Phase I study data disclosed · Phase III trial launched in Brazil
Phase II	Moderna	Messenger RNA	Phase I clinical trial began · Phase I data disclosed & Phase II trial began · Phase I study data published & Phase III trial to begin · Will have vaccine doses ready
Phase II	BioNTech & Pfizer	Messenger RNA	Phase I/II clinical trial began in Germany · Phase I/II clinical trial began in U.S. · Phase I/II study data published; FDA granted fast track status & Phase III trial to begin · Will make up to 100M doses · Will make more than 1.2B doses
Phase II	Johnson & Johnson	Non-replicating viral vector	Phase I clinical trial to begin · Late-stage human trial to begin · Will manufacture 1B doses
Phase II	Novavax	Protein-based	Phase I/II clinical trial began in U.S. · Phase I/II study data expected; U.S. government awarded $1.6B · Will make 100M doses for U.S. · Will make 1B doses globally
Phase II	Imperial College London	Messenger RNA	Phase I/II clinical trial began · Vaccine moved to the next phase
Phase II	Inovio	DNA	Phase I clinical trial began · Phase I study data disclosed · Phase II/III trial expected to begin in the summer

Other Phase II Vaccines	Vaccine Type
AnGes & Osaka University & Takara Bio	DNA
Anhui Zhifei Longcom & Chinese Academy of Medical Sciences	Protein-based
Institute of Medical Biology at the Chinese Academy of Medical Sciences	Inactivated virus
Bharat Biotech & Indian Council of Medical Research & National Institute of Virology	Inactivated virus
Zydus Cadila	DNA

Other Frontrunner Vaccines	Vaccine Type	Development Timeline
CureVac	Messenger RNA	Phase I clinical trial began in June in Germany and Belgium. The Coalition for Epidemic Preparedness Innovations (CEPI) awarded CureVac $8M.
Clover Biopharmaceuticals	Protein-based	Phase I clinical trial began in June. CEPI awarded Clover nearly $70M.
Merck & Co.	Replicating viral vector	Phase I clinical trial is expected to begin in July.
Sanofi & GlaxoSmithKline	Protein-based	The two manufacturers partnered in April. They plan to begin human clinical trials by September.

SOURCES: News releases of manufacturers; "The Coronavirus Vaccine Frontrunners Are Advancing Quickly. Here's Where They Stand," BioPharma Dive. Visit https://bit.ly/2ZLTgvL. "Coronavirus Vaccine Tracker," The New York Times. Visit https://nyti.ms/2BnZEA6.

Firms Face Market Access Issues

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Similarly, vaccine guidance indicates that vaccines approved after the first vaccine would be expected to be no less than 10% less efficacious than the first vaccine. However, said George, that might be difficult to determine from clinical trial data.

Overall, the FDA is working hard with manufacturers to compress the time frame for product development and clinical trials, using adaptive trial designs and speeding some of the phase progression while articulating the expectations for the quantity and quality of data expected, said Richard Hughes IV, managing director at Avalere.

The U.S. government has spent more than $9 million so far on COVID-19 vaccine development, manufacturing and infrastructure. Hughes said the pipeline is extremely impressive: "We're not just talking about live viruses or kill-the-virus antigens, but we're talking about RNA technologies, DNA technologies, virus particles, protein-based vaccines, and we're combining them with really novel adjuvants."

The effort is unprecedented. Prior to COVID-19, only one EUA ever has been issued for a vaccine, and that was for an anthrax vaccine, which never was administered to the general civilian population, he said.

January Vaccine Delivery Is 'Ambitious'

Given the nature of the pandemic crisis, vaccines' paths to market — and their pricing, at least at first — will not be conventional. As vaccines begin to come online, potentially this fall, Hughes said he anticipates "a progression," with some of the vaccine candidates receiving an EUA while the Phase III trials are completed to further establish safety and efficacy. "You'll see this playing into some of the prioritization and allocation decisions," he added. "Hundreds of millions of individuals will not receive this vaccine on day one."

The Trump administration's Operation Warp Speed is aiming to deliver 300 million doses of vaccine by January, which Hughes noted is "a very ambitious timeline." Some manufacturers' announcements clearly are targeting an EUA this fall for their vaccines, with "potentially hundreds of thousands of doses coming available through those EUAs" and potentially a licensure application filed with the FDA, he said.

In fact, HHS and the Department of Defense (DOD) on July 22 unveiled a $1.95 billion deal with Pfizer Inc. to acquire 100 million doses of the COVID-19 vaccine candidate it is developing with German drugmaker BioNTech. The two companies, which are receiving $20 per dose under the deal, said they could seek an EUA as early as October. The contract includes an option that would allow the government to acquire an additional 500 million doses. Consumers would pay nothing for the vaccine.

Two Doses of Vaccines May Be Needed

Even if Operation Warp Speed delivers 300 million doses, the vaccines under development may require two doses to be effective, which means that only 150 million people could receive the full course of shots.

Both the DOD and the HHS Biomedical Advanced Research and Development Authority (BARDA), which runs the Strategic National Stockpile, may play a role in vaccine procurement and distribution decisions and efforts alongside the Centers for Disease Control and Prevention (CDC).

As vaccines begin to be distributed late this year or in 2021, Neal said he anticipates government-controlled distribution to a tightly managed population. The CDC is likely to head up distribution, using a model similar to the one used for the H1N1 influenza vaccine. States, meanwhile, will consult with the CDC on how to prioritize populations as part of this process, and the CDC then would distribute the vaccine doses to the states, said Hughes.

This likely will differ from state to state, he said: "What we know based on the experience with H1N1 is that every state is different, and every state will prioritize populations differently. They have different infrastructure and approaches to distributing a product. So what we could see is in one state, health systems prioritized, in another state, we see pharmacies prioritized or public health clinics prioritized. If we're really trying to make sure that certain populations such as health care workers get the vaccine first, we might see preregistration requirements to receive the vaccine."

In June, the Advisory Committee on Immunization Practices (ACIP), which advises the CDC on vaccine use, proposed priority groups for a tiered-distribution vaccine approach. The top-tier priority groups include highest-risk medical, national security and other essential workers. Second-tier high-priority groups include health care personnel, essential workers and people with high-risk medical conditions. Additional proposed priority groups include adults ages 65 and older, long-term care facility residents, children, pregnant women and high-risk racial and ethnic groups.

Of course, it's possible that the Trump administration might decide to distribute differently, Hughes noted, citing the recent experiences around personal protective equipment distribution for the pandemic. Still, following this phase, "hopefully we see candidates fully licensed and additional candidates with EUAs and licensure, and ultimately by some point next year, we would have sufficient vaccine to vaccinate a substantial portion of the population," Hughes said, noting that manufacturers need to consider vaccine allocation across countries.

Drugs Have No Established Pathway

At the time of the H1N1 pandemic, there was a process for vaccine development and delivery but not for rapid therapeutic advancement, so there's no path already in place for potential COVID-19 therapeutics, said Neal.

There are two types of therapeutics to consider, he said. The first is a product that's new to the market, with COVID-19 as its only indication, while the second is a product that's already on the market, being used for other disease states, with a new indication for COVID-19. "They're probably going to follow two fundamentally different pathways," he said.

Hydroxychloroquine, for example, was already in drug channels and in pharmacies, Neal said. "At that point, there was no way to control distribution or take that product and give it all back to the government to allow them to parse it out where it should be used."

Therefore, drug supply was managed — or was attempted to be managed — via public health messaging, he said: "Don't take it prophylactically, don't overuse it, don't overprescribe it, because it's actually needed for other disease conditions. So that's probably going to be a challenge for manufacturers as they think about therapeutic line indications for products that they currently have in the distribution channels."

Remdesivir, however, was not in distribution channels when it received its EUA. Once Gilead got the EUA for the product, the U.S. government decided where doses would go. "We've heard that there were some challenges with that. We've heard that there was product that went to the wrong place. This is all public information," Neal said. "We also heard that there were some community hospitals that needed the product and never received any of the donated product. So that's a bit of a history lesson on how that method worked, at least in this early phase."

Still, "time will tell" how this process will evolve as there's more supply of remdesivir and potentially of other new molecular entities that get an indication, Neal said. "But my speculation would be that if we're to improve and control distribution in a better manner, leveraging how we're potentially going to do it for vaccines might be a good solution for how we might also manage therapeutics."

He added, "our sense is that as more product and more supply become available, and as lessons are maybe learned from how things may have been done in the past, we would hope for stronger guidance from public health agencies like HHS to be much more clear on the type of patients that actually should get these products."

Cocktail of Drugs May Be Needed

George noted that viral diseases pose additional challenges. "We've got to keep in mind that most of the current therapeutics for viral diseases are cocktails," George said. "This means they have several products — it's fairly complex and they have various mechanisms of action." Pharma manufacturers may need to develop a cocktail of therapeutics, rather than just one single product, she said.

In addition, many of the viral disease treatments on the market — for example, for HIV or hepatitis C — require extended treatment times, George pointed

out. Since COVID-19 progresses so rapidly, this model wouldn't work for it, she said.

Product pricing for COVID-19 vaccines and therapeutics is a murky area right now, although the Institute for Clinical and Economic Review (ICER) is playing a larger role. "They've been pretty vocal, especially around providing private pricing and value guidance within the context of COVID," Neal said. ICER provided guidance on remdesivir pricing when that drug first received an EUA and has adjusted pricing guidance based on positive data on dexamethasone, an older steroid that has seen some positive COVID-19 data.

ICER Has Weighed In on Pricing

ICER published a white paper on July 2 detailing alternative policies for therapeutic and vaccine pricing during a pandemic, and it is holding a series of meetings on that topic through the summer. The paper analyzes the advantages and disadvantages of six alternative approaches to pricing, ranging from "status quo unrestricted pricing" to compulsory licensing and advanced market commitments and subscription models.

Factors that may be considered in price negotiations include efficacy; differences between the product in question and other already-approved products; the specific patient population targeted; the number of doses needed for effectiveness; the overall unsatisfied demand for treatments or vaccines; the burden of disease and demand; research and development, manufacturing and scale-up funding; whether the end-user purchaser is government or private commercial; whether the product is new-to-market or represents an indication extension; and whether there's a stockpiling opportunity.

According to ICER, the pre-FDA approval/EUA phase likely would feature U.S. government contracting, distribution and priority treatment, with highly managed and tightly controlled distribution. Once the FDA grants approval, but assuming supplies still are limited, ICER expects product administration to high-risk target populations, with the government purchasing and potentially distributing novel products.

"I think ICER is going to become a very, very important organization," Neal said. "They get a lot of press when they do publish. Whether it's sort of a bully pulpit position or whether they actually are used by the U.S. government will remain to be seen. But I think for drug manufacturers and potentially even vaccine manufacturers, understanding what ICER is going to say about your product, especially in the context of an ongoing public health emergency, is going to be an important consideration."

The ACIP also has played a role in vaccine pricing, starting with the varicella vaccine in the mid-1990s, said Hughes. "We've seen over time that they have really incorporated cost-effectiveness into their decisions, and they are making decisions in large part because of some of the economics studies that they've reviewed."

Still, when considering value-based contracting for vaccines, "it's really important to think about the nature of vaccines and the herd effect," Hughes said. "If you're contracting for a specific population, but you're talking about a routine vaccine that is going to have a tremendous herd effect outside of the immediate population, that's a very unique consideration, versus if you're talking about a vaccine that's very targeted toward a very specific patient who we know is very much at risk for a condition, and we can prevent that condition. When you start to talk about broad population benefits and COVID, it becomes a lot harder to talk about how to structure something that's value-based involving a vaccine."

Ultimately, as the public health emergency lifts and diagnosis of COVID-19 shifts to routine, use restrictions would be lifted, and product distribution and payer management will normalize, according to ICER.

HHS Will Make Distribution Decisions

The first phase in ICER's scenario — pricing and distribution under an EUA — is reflected in the way remdesivir has been purchased and distributed in the U.S. HHS said in late June that it had secured more than 500,000 treatment courses of the drug for American hospitals, representing 100% of drugmaker Gilead's projected production for July, 90% of August production and 90% of September production.

HHS decides which states and territories will receive the medication, which then is shipped by AmerisourceBergen, with state health departments making the final decisions on how to allocate it to specific hospitals. Hospitals pay no more than Gilead's Wholesale Acquisition Price of around $3,200 per treatment course.

Meanwhile, therapeutic and vaccine manufacturers are seeking to partner with outside companies across national borders to ensure product access, particularly in the face of what's being called "vaccine nationalism," Neal added. Gilead, for example, has formed some partnerships in other parts of the world in an attempt to boost supply of remdesivir.

Manufacturers, Providers Face Hurdles

One challenge for therapeutics operating under an EUA is that there isn't a reimbursement pathway established, Neal said. "Use of these products and the acquisition of these products without a reimbursement pathway established for these products puts additional cost burden on these hospitals," he explained.

It also adds to the challenges for manufacturers thinking about developing these products. "Typically during a launch, you plan for these things and they're part of your launch planning," but the COVID-19 situation has evolved too quickly for any of that, Neal said.

"As more vaccines become available, as more therapeutics become available, the government control over pricing, supply and distribution will ease, and we can expect it to become a much more routine market over time," he said. "The exact trigger points are unknown."

Still, Hughes pointed out, as manufacturers decide whether to get involved in the COVID-19 therapeutics and/or vaccine space, they need to take into account their history and experience, particularly in relation to the dose and timing commitments that will be required to develop products in this space. "These are really ambitious commitments," he said. "It's putting a lot of pressure on developers and manufacturers."

In addition, Neal added, working in this space has the potential for huge effects on corporate reputation, particularly when it comes to pricing and access for vulnerable populations. "Whether it's pricing for profit or whether you're going to give it away, there's lost opportunity cost for developing these things," he said. "This is truly a global public health emergency. There is a corporate reputation issue. That's going to be a very, very fine needle to thread."

Nonetheless, innovation is occurring at a time when it potentially can help the overall pharma industry, Hughes said, particularly in novel delivery mechanisms. "We've seen investment in oral tablet development and needle technologies. We've been hoping for these technologies for a long time for what they can do for routine vaccination. We could see those technologies move a lot faster, which could be great for COVID but also great long term for vaccine access."

Contact George, Neal and Hughes via Avalere spokesperson Liz Moore at lmoore@avalere.com. ✧

by Jane Anderson

DOJ, Pharma Renew Disputes Over Charitable Foundations

Two lawsuits — one against federal health regulators by a drugmaker and the other against a drugmaker by the Department of Justice — represent the latest salvos in the dispute over whether and how drug company-supported charities can help patients pay for expensive medications.

The two suits may ultimately offer a chance to clarify what manufacturers can and cannot do to fund copay assistance charities, particularly for patients with rare diseases, says Lance Grady, who leads the market access practice at Avalere Health.

"I think you're going to continue to see patient advocacy groups and manufacturers fight for the right for patients to obtain these drugs, including the fight to have these patients either be able to get a copay card or be able to be considered eligible for third-party foundation [help] or be able to be considered eligible for free drug," Grady tells AIS Health.

Jayson Slotnik, partner at Health Policy Strategies, Inc., tells AIS Health that arguments on both sides hinge on how close the drugmaker is to the charity that's actually paying for the medication. "It's very simple....Where is that line where it's true patient as-

sistance and appropriately balances policies to get the outcome we want for society versus just ripping off the government?"

In one lawsuit, filed June 26 against HHS in U.S. District Court in New York, Pfizer Inc. argued that it should be able to provide financial assistance to Medicare beneficiaries who are otherwise unable to afford Vyndaqel (tafamidis meglumine) or Vyndamax (tafamidis), which are the only two FDA-approved treatments for transthyretin amyloid cardiomyopathy, a rare and fatal heart condition.

OIG Considers Programs Kickbacks

Pfizer said it can't offer such help to beneficiaries "because of a significant risk of a criminal or other government enforcement action arising from erroneous legal restrictions imposed by" the HHS Office of Inspector General (OIG). "As a consequence, without relief from this court, Medicare beneficiaries who are unable to afford copay obligations under the Medicare Part D prescription drug benefit will continue to be denied access to their Medicare benefits and these life-changing medical breakthroughs," the lawsuit stated, noting that OIG has prohibited copay assistance programs "on the theory that such assistance constitutes an unlawful kickback."

Meanwhile, the U.S. Attorney's Office in Boston said June 24 that it had filed a civil False Claims Act complaint against Regeneron Pharmaceuticals, Inc., alleging that Regeneron paid tens of millions of dollars in kickbacks for its macular degeneration drug Eylea (aflibercept), using a foundation as a conduit to cover copays for the drug. The anti-kickback statute prohibits pharma companies from offering or paying either directly or indirectly any remuneration — including coverage of copays — to induce Medicare patients to purchase companies' drugs.

"According to the allegations in today's complaint, Regeneron funneled tens of millions of dollars in kickbacks through a third-party foundation to ensure that few Medicare patients paid a copay on Eylea and that physicians who prescribed and purchased the drug did not have to collect Medicare copays from their patients," U.S. Attorney Andrew Lelling said in a statement.

The complaint alleges that soon after the launch of Eylea in 2012, Regeneron considered how much to pay a foundation that covered Medicare copays for patients taking macular degeneration drugs. At the time, Regeneron and Genentech, with its drug Lucentis (ranibizumab), were the leading manufacturers of drugs for macular degeneration. Regeneron's senior management was willing to pay the foundation only enough to cover Medicare copays for Eylea patients, and Regeneron senior management wanted assurances that the company's payments to the foundation would generate "a handsome ROI," the complaint alleges.

To satisfy senior management, the complaint alleges, Regeneron employees repeatedly contacted the foundation to learn the amount of money the foundation would need to cover the copays of Eylea patients. "They then determined the Medicare revenue that Regeneron would derive from those patients and calculated that the company would earn a return of over 400% on its payments to the foundation," the complaint alleges. "Over the course of 2013 and through the beginning of 2014, Regeneron paid the foundation exactly what it said it needed to cover Medicare expenses for Eylea patients only."

"Furthermore, senior company executives allegedly took extensive measures to cover up the scheme," Lelling's statement said.

Regeneron said in a statement that there was no merit to the complaint, and that it would "vigorously defend" against the allegations. "It is unfortunate that a misguided lawsuit is attempting to assign wrongful intent to entirely legal conduct," the company said. "Regeneron has fully cooperated with the government's investigation and will vigorously defend the company's case."

Company Has Refused to Settle

The drugmaker had said in 2017 that it was among a large group of companies that received subpoenas in connection with a governmental inquiry related to charitable organizations that provide financial assistance to patients. "Regeneron has not settled the case because the company did not engage in illegal or wrongful conduct," the company said in its statement.

Grady says the genesis of these types of patient assistance programs harkens back to the formation of the Medicare Part D drug benefit and "the government's unwillingness to allow for copay support for those patients." When patients couldn't afford their medication, that "created this market of biopharmaceutical manufacturers expanding their existing patient assistance programs" with third-party foundations that weren't necessarily giving away medications but were providing out-of-pocket support to eligible patients. "And the funding of that out-of-pocket support often flows from contributors, and those contributors are often the manufacturer," he adds.

Charity, Marketing Should Be Distinct

Most drug manufacturers have a charitable giving strategy, but "it should be part of your corporate affairs and not necessarily part of your brand budget or your marketing budget," Grady says. "That's where we see inconsistencies in how some pharmaceutical manufacturers approach this." Charitable giving that helps to provide out-of-pocket support should be part of a division within the company "that is separate and distinct from advertising and marketing," he says.

From the perspective of HHS, federal regulators in OIG and elsewhere want to see "appropriate firewalls or guideposts in place so that [patient assistance] is not seen as an inducement but is truly utilized as an affordability support tool for patients," Grady says.

"The difficulty gets to how diverse the contributors are to the third-party copay foundations, and ensuring that those dollars are not tied to a specific drug and that there isn't a linear flow from the manufacturer, the donor to the third-party copay foundation, to the patient who is going to be prescribed that drug and needs direct dollar support for that drug," he says. "That is the key. That is the fundamental line that should not be crossed."

Diseases that have numerous treatments, such as rheumatoid arthritis, might have up to a half dozen third-party copay foundations with multiple manufacturers contributing, Grady says. "This is less of an issue than when you see these disease funds established that are for a very small patient population — there may be only one or two manufacturers and therefore only a handful of donors. Then I think that's where you start to see that bright line form that gives attorneys pause and gives the government pause."

Slotnik says that in the Regeneron case, "we now have what the government thinks is too close. But we only heard one side of the story." Regeneron has yet to make its case in court, he points out. "There are many people who are following this case to learn what this [DOJ official's] definition of 'too close' is. And there's a lot of patient access and health care at stake here."

The issue will continue to evolve until more direct guidance is available on copay assistance eligibility, particularly as patient out-of-pocket costs continue to rise, Grady says. It ties into the use of copay accumulator programs, he notes.

"So the question becomes, who is your end customer?" Grady says. "Is it the government? Is it the health plan? Is it a pharmacy? Or is it the consumer who needs access to the medications? I think that's the way biopharmaceutical companies will continue to look at it and continue to try to identify solutions and tactics… to address this burden of out-of-pocket [costs] that continues to grow across multiple payers here in the U.S."

View the Pfizer complaint at https://bit.ly/2Z-6K7NT and the Regeneron complaint at https://bit.ly/2Z7HOKP. Contact Grady via Avalere spokesperson Liz Moore at lmoore@avalere.com and Slotnik at jayson@healthpolicystrategiesllc.com. ✧

by Jane Anderson

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Collaboration on Value Is Needed

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Dion moderated a recent webinar sponsored by 3D Communications titled "COVID-19: Will It Be a Catalyst That Moves Us Forward in the Drug-Pricing Debate? Or the Barrier That Slows Us Down?" She pointed out that the last decade has seen "some spectacular innovation in science. But what about innovation in the way we pay for medicines?"

"There are many unknowns on how COVID-19 will impact health care in general, and I think pricing is just one piece of health care," said Indranil Bagchi, Ph.D., senior vice president and head of global value and access at Novartis Oncology. "But the longer the crisis lasts," it will only add pressure to parts of the health care system, including payer budgets. "It's a little hard to look at this and say nothing will change at all."

COVID Is Accelerating Existing Trends

He noted some trends were in place before the pandemic. "If you think of the Affordable Care Act and the goals of improving quality of life, ensuring satisfaction, reducing costs, that was all already happening. What we see is COVID-19 being an accelerator" of these.

"I think budgets will come under increasing pressure," said Edmund Pezalla, M.D., former Aetna senior executive and founder and CEO of Enlightenment Bioconsult, LLC. "The self-insured employers are under pressure to keep costs down generally, but now their revenues are decreasing, so they are keeping a lot of costs down, including health care costs. In this coming year, I think it will be difficult for many of them to sustain their current levels of contribution to health care."

According to Pezalla, measures they will take to reduce health care costs will include implementing "restrictive provider networks and leaner formularies, and this does put pressure on manufacturers to avoid pricing much above the existing therapies. COVID is bringing out components we haven't thought about before in terms of how much everything in the health care system is costing. So we're going to need to align drug pricing with other things, other values in the health care system. I think it's going to bring a lot of this into sharp relief."

Valentino Confalone, general manager at Gilead Sciences, Inc., Italy, said he sees three emerging trends that COVID is accelerating: "One is an evolution of value-based [pricing] that was already there, that's been there for a long time, but I see an evolution and a change in pace. Another one is for the first time, we're seeing drug spending, pharma spending…as an investment for the long term rather than a current expenditure for the short term. And last but not least is an increasing momentum toward international pricing coordination by payers and regulators alike."

Michael Schroter, Ph.D., founder of Swiss investment firm VIOPAS Partners AG, drew a parallel between COVID and another history-altering event: "I think COVID will be for health care what 9/11 was for the defense sector. There will be a flurry of investments to develop innovative treatments and build capacity to prevent the next crisis. But at the same time, the economic burden from COVID-19 will be forcing payers to spend more prudently. Innovation at rising costs will no longer work in this context. However, products from companies that offset existing costs will be in high demand. The pressure is really going to be on pharma and biotech to develop and deliver medicines with great clinical benefit that at the same time help reduce overall health care costs."

Asked if COVID will change the way payers and other stakeholders value innovative therapies, Pezalla replied, "I think the evaluation process will stay the same. We're still going to be looking for the same sorts of things in a medication: effectiveness, what's the benefit to the patient, are there cost offsets and other important things like that. But there's going to be an increased emphasis on comparative effectiveness — on choosing either the best product or reducing coverage of multiple products with similar efficacies."

Good Model to Assess Value Is Needed

He asserted that stakeholders need "to work on a model that will align value and prices because we still don't have a way of valuing drugs that's universally accepted….We have to determine is this medication, or any other treatment for that matter, a good value for money, and that's important, but the other thing is that it doesn't necessarily mean that we can afford it." Payer budgets are going to be tight, and "we don't really have a good framework or starting point" for payers to make decisions on the value of a therapy.

Schroter said he thought the pandemic would alter the way that payers and other stakeholders value innovative medicines. "One thing that COVID's shown us is the importance of the entire health care system to work together. All the subsectors, from pharma to hospitals to insurers, are dependent on each other. And what

we need to overcome is the challenge that we are so siloed. We need to start looking at cost savings across the entire health care spectrum in order to make a real difference. Time has come to take a much more holistic approach to deliver health care.

Payers Need to View Costs Differently

"Just to put this into perspective," he continued, "about 85% of health care expenses are other than medicines, and we have to look at the total expenses rather than look at just one single cost element. That means payers need to look at costs differently and look at medicines rather as an investment than a cost."

Confalone agreed. "I think for the first time, it has emerged dramatically how much a health challenge can impact the whole of society. And spending on pharmaceuticals in terms of budget impact is definitely going to undervalue what is the real impact holistically of novel new and effective medicines on all of society."

"COVID has certainly made public health very public," observed Bagchi. "I mean, when can you turn on the TV and not hear a discussion about how everybody seems to be very conversant about when a vaccine is likely to hit the market or when treatments are going to be available? So I think people generally have a much broader understanding of what's at stake if large swaths of the population fall ill at the same time. We have seen our hospitals getting more burdened due to lack of extra capacity, which is something over the years as we're driving toward efficiency, you get an efficient health care system, but then the pandemic shows up, and the hospital system is just incapable of handling all that. So I would think — I would hope — there's a broader understanding from the public on the overall value of the health care system, including what role medicines play in it." Pointing to the 15% that drugs make up in overall health care costs, he noted that "cost-wise, it's a small piece, but in terms of contribution, the piece is significant."

The biggest obstacle to change in the United States, said Pezalla, "is a lack of clear understanding. Determining the value of medical interventions, whether it's a drug or procedure, we just don't have a good handle on that. And we haven't been able, therefore, to reconcile that with our ability to pay."

He added that "this is not just about drugs. This is really about things across the spectrum of health care services [such as] diagnostics and hospital admissions. We can't just focus on drugs here. We've got to talk about the entire thing and how we value all of that and then how we reconcile that value with what we're willing and able to pay for it."

According to Bagchi, "we all know the U.S. has had over the years a relatively fragmented health care system. Often the medical budgets and the pharmacy budgets are separated, and when it comes to the budgeting process, often the focus is two to three years. So the system the way it was set up didn't lend itself to recognition of value within the system. So if I'm looking to put a medicine on the formulary, and my length of responsibility is two to three years, how am I going to understand the value of a medicine that might report out in five to 10 years? These days, we are talking about CAR-Ts and cell and gene therapies…with a one-time administration today, whose efficacy and effectiveness are supposed to last for a lifetime."

Capturing Data Is Another Challenge

The fragmented and short-term-focused U.S. health care system "doesn't lend itself to recognizing value," he maintained. "And then the other piece is data requirements." With single-treatment cell and gene therapies, "how do we capture the right data that helps us prove their efficacy and effectiveness over a long time? That's something that's a challenge that we need to work on. And then the last piece when it comes to the U.S. is the increasing amount of patient copay and coinsurance, which is a significant challenge. Especially as we move into specialty medicines, oncology medicines," coinsurance and copayments "can become significant for the patient. That's something that needs to be addressed."

Within emerging markets, the challenges may be different, said Bagchi. In many markets, it comes down to "improving infrastructure" within the existing health care system, "making sure we have the right personnel, making sure we have the right diagnostics," and ensuring affordability and availability.

In Europe, "sustainability is certainly a big, big challenge," said Confalone. Coordination among

countries "can be very helpful," as seen recently with COVID, "when the European Union started to think about using joint procurement agreements to achieve one single agreement for all the member countries, and this could definitely be a way to speed up access" to COVID therapeutics once they are available.

Asked whether prices for medicines are sustainable for health care systems, Schroter said, "yes, they can be sustainable — even high-priced drugs can be sustainable for health care systems — but only if the prices of these medicines offset other costs in the system. And that's the challenge with the way we look at pricing today."

He contended that "we need to fully embrace value-based health care in a much broader way….This approach needs to apply to the entire patient journey, not just when the person shows up at the doctor. This is especially true for chronic diseases and diseases that require long-term care." For example, he pointed to Alzheimer's disease, where caregivers carry a tremendous burden, often suffering from depression and sometimes losing their job. "Today, most payers would not consider the costs borne by caretakers since it does not hit their budget, but ultimately, we as a society still pay for these costs."

Approach Needs to Be More Holistic

Schroter asserted that "we need to think more holistically as we do with COVID and think beyond individual siloed budgets and start thinking across these silos. Our common goal should be maximizing health and reducing costs….And as we've seen with COVID, we all have to work together on it, or otherwise it won't work."

As for pharma's role in getting their drugs on formularies, payers "really need to have medications that are addressing problems, and part of that is are they actually addressing the cost of the health care system and its inefficiencies," said Pezalla. "I think if we were more convinced that medications were addressing those issues, it would be a lot easier to deal with."

However, he continued, "many drugs are developed because of the scientific issues. The technology is right for something to come along now. It's very hard to say, 'I want the magic bullet to do this or that.' Instead, we get magic bullets that do very specific things because that's where the science takes us."

Pezalla maintained that "pharma really needs to think about how we price those things. The pricing policies are resulting in prices that many people kind of think are hitting the ceiling at this point. I think it would be helpful to have more transparency in the sense that in the U.S., many payers and a lot of other people really don't have much of a good feel for how drug prices are set and what they really reflect. Do they reflect the cost of development, in which case can we make development more efficient? Or do they actually reflect something else, their value, in which case we need to demonstrate their value better?"

When Gilead came under fire for pricing its hepatitis C drug Sovaldi (sofosbuvir), the drug became known as the $1,000-per-day drug instead of a cure for hepatitis C, pointed out Dion. "Some of the messages coming from the pharma industry are not always clear. Do you think that's still the case today?" she asked.

Clarity Around Pricing Is Needed

"We need to do a much better job in explaining what value-based [pricing] is and how do we set the price for drugs," said Confalone. Value-based pricing, he said, is simply just "setting a price that reflects the true value of a medicine for patients, for physicians, for the society as a whole. I must say, we're getting a little bit better at doing this, to be honest." He said after he had spent "months and years" explaining the value of Gilead's hepatitis therapies, patients, payers and authorities agreed that the drugs represented "the best investment health care did in the last decade. We're finally seeing the long-term impact for society, for health systems of investing in a drug so effective. So, yes, we are improving, but there's still a long way to go for sure."

Bagchi said that pharma companies "absolutely" could be clearer in explaining how they set drug prices. "We are getting better, but historically pharma has not been good in terms of either explaining the value of our medicines or how we price our medicines. We are in favor of transparency as it comes to how we price our medicines and how we communicate [that informa-

tion]. Partially the challenge has been a lot of pharma-led initiatives have been very technical. While there is technical underpinning data that drives the pricing process, that shouldn't preclude us from developing, demonstrating and communicating the value proposition of our medicines in a very clearly understandable way."

Manufacturers, he maintained, "have to be clear at how those benefits will touch patients, how they will touch physicians, all the different components of the health care system, as well as society." Novartis, explained Bagchi, has four pillars it uses in developing and pricing medications: clinical data that providers are looking for, improvements that patients will see, cost savings for health care systems and the benefit to society of returning people to work.

When investors are evaluating pharma companies, they "don't want to see a company price a drug so high that they are likely to see access restrictions by payers," said Schroter, such as limiting eligible patient populations. With such restrictions, "payers, patients, industry and ultimately also investors are losing."

Access Restrictions Can Hurt Innovation

He pointed to the PCSK9 inhibitors, which upon launch had "great clinical data but piddly sales due to access restrictions until the companies struck their prices by about 60%. Not a very cheerful moment for investors. So I think there's a lot of talk about how low prices hurt innovation, but equally access restrictions, which hit a company's bottom line, also hurt innovation, as well as investors."

Initiatives such as value-based agreements and outcomes-based deals "sound like they could be perfect" solutions to make drugs affordable for payers, said Dion, "but many don't like them."

Such deals "certainly make sense" for payers, said Pezalla, "because they are focused on the outcomes for patients. But there are some serious problems with implementation." One of the issues is around Medicaid best price, although CMS recently released a proposal intended to address that *(SMA 7/20/20, p. 1)*. That proposal "might help this a lot," he said.

"The other thing is that it's difficult for payers to measure clinical outcomes because mostly what payers get are transactional things about somebody did a service, they saw a patient, a drug was delivered, and they get a bill for it," Pezalla noted. "So they may not be getting the information that we really need to know if the outcome is better or not. So better connectivity, better data transfer, information from providers and patients about how they're doing is really going to be necessary."

"The landscape is evolving."

In Italy, Gilead struck a deal with the Italian Medicines Agency (AIFA) for its CAR-T therapy Yescarta (axicabtagene ciloleucel) "where the full price is set based on the actual benefit that the drug is delivering to patients," said Confalone. "This is done through assessment of real-world evidence through a registry that's been put in place to allow us and the authorities [to know] what is the actual benefit delivered."

Asked if such an approach could be used in the U.S., Bagchi replied, "I don't see why not. I know and I understand that when it comes to our outcomes-based agreements, our risk-sharing agreements, the United States has been behind many of the other countries." However, in the U.S., Novartis has outcomes-based deals in place for its CAR-T therapy, Kymriah (tisagenlecleucel). If there is a response within 30 days, "only then billing and payment happen. If the response is not there, the billing doesn't happen, and there is no payment." The company has similar deals in other countries such as Germany. "The landscape is evolving," he observed. "These are certainly at the forefront, but expect more to come."

Ultimately, all health care industry stakeholders need "to get behind new ways of valuing health care," said Schroter. "That means patients, physicians, policy makers, payers, pharma and others need to change their habits. We can do it. We all have learned that lesson during COVID."

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by Angela Maas

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