TRENDS-in-MEDICINE

BULLETIN: UPDATE ON CORONAVIRUS 9/5

THE INDUSTRY PERSPECTIVE

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by Lynne Peterson

Be careful, be safe, and be well…but still enjoy the Labor Day weekend.

For the second time this year – and perhaps only the second time ever – the chief executive officers (CEOs) of five major pharmaceutical companies jointly held a press conference, sponsored and moderated by the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA). Once again, the topic was Covid-19, with the main focus on therapeutics, though vaccines were also discussed by the heads of Gilead Sciences, Lilly, Merck MSD, Pfizer, and Roche.

Background

There currently are more than 300 Covid-19 treatments – repurposed and novel – in development, with 22 leading IFPMA members involved in 81 clinical trials. The main treatments being used are antivirals, antibodies, convalescent plasma, and anti-inflammatories. So far, there is no "magic bullet" to treat/cure Covid-19 patients. Two repurposed drugs have been tested and have not worked: hydroxychloroquine and Roche's Actemra (tocilizumab), an anti-IL-6. One repurposed drug has been proven effective: dexamethasone.

Thomas Cueni, director general of IFPMA, said, "We have come quite a long way [in 7 months]. Some hopes were dashed. Some hopes were fulfilled…What we learned is we are still in a learning curve. Most likely there will not be a single effective treatment…We will need different treatments for different patient groups for different stages."

Highlights

- **Collaboration** among pharmas is at an unprecedented level as is the speed with which pharmas are moving. That collaboration is not just on drug/vaccine development but also manufacturing/production. Pfizer and Roche, in particular, have offered their production capacity to others.
- **Regulatory agencies** are working remarkably fast, but speakers insisted the regulators are not cutting corners or sacrificing science or safety.
- **Antivirals – Gilead's remdesivir** – Gilead expects full FDA approval of remdesivir "in the coming months." Merck MSD expects to start a pivotal trial of its antiviral later this month or in early October.
- **Antibody treatments** – Lilly, Merck MSD, and Pfizer all have antibodies in development that could be stand-alone or combination therapies. Lilly is likely to have data first, perhaps within a few weeks, in Covid-19 patients not hospitalized. However, scale-up of antibody production is "very difficult."
- **Combination therapies** – Roche and Gilead have both shifted to studying combinations – Gilead for add-ons to remdesivir, and Roche for add-ons to Actemra and with Regeneron Pharmaceuticals on a two-antibody cocktail.

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Vaccines

- Pfizer has already enrolled 23,000 patients and expects to reach its goal of 30,000 patients "within days." By the end of October, Pfizer expects to know if its 2-dose vaccine works or not. If the data are positive, Pfizer thinks an emergency use authorization (EUA) by the FDA could be appropriate.
- The industry is committed to data transparency and insisted they would not cut corners, but industry does have concerns about the anti-vaccine movement in general.

THE INDUSTRY PERSPECTIVE

LILLY

David Ricks, Lilly's chairman/CEO, who is also president of IFPMA, said Lilly is looking at collaborations, adding, "The speed with which we are moving is truly unprecedented…We are collaborating with two biotechs on neutralizing antibodies…and within a few weeks we will have pretty good data in ambulatory setting in people infected but not hospitalized…with the goal to reduce hospitalization."

He said Lilly is also looking at neutralizing antibodies in nursing homes where an infected staff member or patient means the risk of infecting others is very high and mortality is significant, "What we want to do is treat patients with an antibody, a passive immunization approach. The other approach is in the hospital, and we are working with the NIH [the National Institutes of Health] on their hospitalization study, a platform study."

MERCK MSD

Merck has an antiviral candidate that is the result of a cross sector collaboration. Kenneth Frazier, chairman of the board/CEO said, "I think collaboration will be the solution…We are going to need great cooperation…We are moving with the most urgency."

Merck is collaborating with Ridgeback Biotherapeutics on MK-4482 (EIDD-2801), an investigational orally-available antiviral agent, and Frazier said there are three different programs on this in the U.S. and the U.K. He said the studies will be (at least initially) in pre-hospitalization outpatient patients, but there will be a separate study for hospitalized patients to see if it can prevent hospitalization.

PFIZER

Albert Bourla, DVM, PhD, chairman/CEO, stressed his company's end-to-end capabilities and said Pfizer "jumped immediately" into research once the virus sequence was announced. He said they had looked at antivirals before, particularly during the 2003 SARS outbreak, and "pretty soon identified a few that were promising [for Covid-19]…and then ended with one we think has promise."

- **Pfizer's lead antiviral.** "It has a different mechanism from remdesivir. It could be an alternative for people who don't respond to remdesivir or in combination. Right now it is in a clinical trial."
- **Status of vaccine with BioNTech.** Dr. Bourla said, "It is in a very advanced stage. Right now, yesterday [September 2], we had 23,000 enrolled, and a significant number of them are already starting to get the second dose…We expect by the end of October to have enough events to say if the product works or not."

ROCHE

CEO Severin Schwan, PhD, who is also vice president of IFPMA, said Roche is not giving up, even though Actemra monotherapy was unsuccessful.

- **The failure of Actemra.** "The idea with Actemra was that for severe Covid-19 pneumonia patients who often suffer from an overactive immune system that Actemra could help dampen the immune response and, therefore, improve the chances for those severely sick Covid-19 patients. We had a lot of anecdotes around that…so we started a very robust clinical trial, and unfortunately the trial did not read out positively…Unfortunately, Actemra on its own did not help severely sick patients. We are now working on combinations with other medicines…including a test with remdesivir."

- **Combinations.** Roche is collaborating with Regeneron on antibody treatments – a cocktail of two antibodies. Dr. Schwan said, "The hypothesis is that if people get infected, you develop antibodies after some time, and that antibody would then take care of the virus. We call them neutralizing antibodies…The problem is some patients do not develop antibodies in the first place or neutralizing antibodies are only at a very late stage…The idea is to give those patients antibodies immediately after diagnosis, especially higher risk patients, and hope to help them…Another study is running to give it prophylactically to people highly exposed."

GILEAD SCIENCES' Veklury (remdesivir)

Daniel O'Day, chairman of the board/CEO, said:

- **Status of remdesivir.** Remdesivir was the result of "decades of investment in research…one of a number of mechanisms we believe will have an impact. Remdesivir inhibits the ability of the virus to replicate…It is now approved in >50 countries."
- **Recruitment.** O'Day said recruiting patients for the ongoing clinical trials is "going very fast." In addition to the three published trials – where the patients are continuing to be followed – he said there are 36 additional remdesivir trials ongoing.
- **Combinations.** He said the focus has shifted to combination therapies, "Now that we know it has such impact as a stand-alone agent, we have collaborated with companies here today to see if we can have a combination approach to have a stronger, more durable effect…As in HIV and HCV where we have seen that when you combine an antiviral with other antivirals or other mechanisms, you can have an even greater impact, so we are looking at remdesivir in combination."
- **Formulations.** Currently, remdesivir is IV, but Gilead is working on an inhaled formulation. O'Day said it is "not a compound suitable for pills because of how it is metabolized in the body, quickly through the liver."

The IFPMA perspective

Cueni said, "What we heard from the CEOs was a remarkable alignment in terms of commitment to randomized trials to the highest standards of regulatory science. It has been amazing how regulatory agencies – the EMA [European Medicines Agency], FDA, and others – have adapted to speed up without compromising quality. This is a period where an extraordinary amount of transparency is required. Occasionally, your expectation is not met, but industry is committed. We are all concerned about the anti-vaccine movement…The companies are also concerned about access and scaling up…Pfizer was one of the first to share its manufacturing capacity…I was asked at the time if they were serious or if it was lip service, but we see it is serious."

REPORTER QUESTIONS

Roche – manufacturing

Roche's Actemra didn't work out, but did Roche put a lot of thinking into production and planning and into the collaboration with Regeneron and how to manufacture that treatment?

Roche's Dr. Schwan said:

- With antibodies "the manufacturing capacity is the major limitation. Worldwide, it is very difficult to scale up manufacturing capacity for antibodies, so for Roche, which has one of the biggest capacities for antibodies, a drive in our collaboration has been to help make the necessary production capacities available if one of those antibody treatments really works. Just imagine what a tragedy it would be if every company sat on their own manufacturing capacity, and one company finds a breakthrough therapy but is not able to produce it."
- "The collaboration within the industry is unprecedented…We are competitors and would not give away manufacturing capacity, but in this situation we are looking at [collaboration]…If an antibody cocktail will work, we can increase capacities 3-4-fold by bringing in our capacities. And if it doesn't work, then, of course, we will immediately look for a collaboration with other players who are bringing such opportunities to patients, and we will come in and help with our capacity."

Asked about the fact that this anti-IL-6 continues to be prescribed in India, where there is a supply shortage, and whether Roche reduced production or supply to India, Roche's Dr. Schwan said, "There is sufficient supply globally to provide it for its main indication, rheumatic arthritis…We can supply it worldwide…Overall there is enough supply."

Lilly – regulators

Asked how they are working with regulators, Lilly's Ricks said:

- "This industry and our company has no intention of pursuing a product that doesn't meet the standards of safety and efficacy… We will publish all our data, subject it to scientific scrutiny, and expect regulators to follow standard procedures."
- "What we are seeing is good engagement with the FDA, the EMA, etc…Typically, if you want to meet with the FDA [it takes months] to get the data, submit complex documents…In this environment, all this is happening within one week…Both industry and regulators get credit for adapting."

Gilead's remdesivir

- **Demand.** *Asked how Gilead expects to meet the demand for this antiviral*, Gilead's O'Day said:
  - "We will be in a position to meet demand by next month. There is nothing that is business as usual in terms of the industry response to Covid-19."
  - "Remdesivir is a very complex manufacturing small molecule…In January it took 12 months with >36 chemical steps, some that can't be done in parallel…We started supply in January at 5,000 treatment courses. We expect to have that at more than 2 million by the end of this year…We broke down barriers. Thanks to the creativity of our scientists, we took a 12-month cycle time down to 6 months. It is difficult to compress that further because chemical steps need time to happen."
  - "We can't do it alone. We reached out to partners and suppliers. Pfizer is one of our more than 30 partners supporting us in one of the critical stages, and that allowed us to ramp up… Based on our view of epidemiology today, we will be in a position starting next month to meet real-time demand and will have the ability to expand beyond 2 million doses in 2021."
- **Pricing.** Gilead's O'Day said, "We all understand our responsibility here to patients and society…We donated our entire supply chain through the end of June to make sure price and access discussions were off the table…And then, once we better understood the clinical data, we decided to price well below the value and strike a balance between pricing at a level that meets the lowest spending power of developed countries while being sure we can invest in R&D for this and future pandemics…As with HIV and HCV, we immediately went to licensing remdesivir to 9 generic manufacturers to sell it in 127 countries…The technology transfers to them is complete, and manufacturing supply is building up there."
- **Distribution.**
  - *Asked about the U.S. buying the bulk of the remdesivir supply*, O'Day said, "We are a global company focused on global supply… As we started to have increased supply over the summer, we had discussions with the U.S. government and agreed to supply a significant supply to the U.S. At that time, it was some of the highest epidemic in the world…and at the same time over the summer months we have been working with companies, following the science and epidemiology. We will be guided by where the disease is and by public health officials."
  - *Asked about Spain running out of remdesivir, voluntary licensing, and when the remdesivir license will be published*, Gilead's O'Day said:
    - ✓ "We will do everything we can to make sure we can produce as much remdesivir as possible and get it to patients. What we need is a coordinated global supply chain…The concept of licensing to everyone will not get more remdesivir. It is a complex [manufacturing] process…And that is the approach we took with expanding our supply chain…We have partners from Europe, North America, Asia, and we used the best of the best, combined with voluntarily licensing to generic manufacturers. The chemicals needed to make [remdesivir] are put to use more efficiently that way.
    - ✓ "On Spain, we understand we are not yet in a position to meet demand in every corner of the world…We expanded capacity…and there will be exponential growth…We are working to allocate [remdesivir] outside the U.S. based on epidemiology, which is an imperfect process…We have an agreement with the European Commission to supply remdesivir,

starting in September, and it will be up to the European Commission to allocate it within the EU…We want to make sure you don't have it sitting in hospitals where the disease is not spreading."

- **FDA approval.** *Asked when full approval for remdesivir is expected in the U.S. and elsewhere*, Gilead's O'Day said, "In the U.S. we have completed all the requirements for the FDA to review it for full approval, and we expect that in the coming months. In the EU, we have conditional approval. And in more than 50 countries around the world, including Japan, it is already approved. Approvals are moving very rapidly based on the strength of the data."

Merck MSD's antiviral, MK-4482

How is the trial of Merck MSD's antiviral progressing? Merck MSD's Frazier said, "We are evaluating it in a Phase II trial…We expect to start a pivotal trial later this month or early next month…We continue to be optimistic."

Asked how they will make sure the treatment gets to those who really need them, Merck MSD's Frazier said, "Covid-19 shines a light on health disparities within and between countries…A core priority of our company is advancing health equity…global access…and vulnerable communities."

Pfizer and BioNTech's mRNA vaccine, BNT-162

Asked how recruitment is going in its vaccine trial, how soon a U.S. authorization is likely in the U.S and elsewhere, and the likely durability, Pfizer's Dr. Bourla said:

- "Recruitment is progressing…125 sites are recruiting, mainly in the U.S. and Brazil…We already have 23,000 patients [as of September 2], and we expect 30,000 in a few days…The results depend on how severe the disease is where they are vaccinated. We selected places with a high disease rate…We expect to know that in October."
- On when it will be authorized – "If we have a successful Phase III trial, it is a setting that will be good enough for regulatory authorities, maybe before final approval."
- On durability – "I don't think we know if the people will have immunity that lasts for life, for 5 years, or a year…It could be parts of the population will need recurrent vaccinating, maybe annually or maybe every few years…We plan to follow our 30,000 patients for at least two years, so we will know if there will be a need for revaccination because either durability is not that strong or the virus mutates…The good news is with our mRNA technology, if there is a need, you can vaccinate as many times as you need."

General vaccine confidence

Asked whether, when there is a vaccine, how companies will assure patients of the safety, given the compressed timeline:

- Merck MSD's Frazier: "We all understand the need to move with urgency, but we will not sacrifice safety under any set of circumstances. We will not submit for an EUA or more general approval any vaccine candidate before we have a quantum of proof in Phase III studies that allows us to make a reasonable statement of the safety and efficacy of that vaccine."
- Pfizer's Dr. Bourla: "I echo Merck. We understand people are skeptical because there is so much politicization of the science…So many people feel that, for political gains, vaccines will be [pushed]…Political pressure is irrelevant…We will never ourselves submit for authorization or approval any vaccine before we feel it is safe and effective…Pfizer has a 170-year history, and I don't intend to ruin that reputation. We will not cut corners. Our Phase III study will be the only thing that says it is safe and effective…Without the results of the Phase III, we will not submit."
- IFPMA: "That is the IFPMA position, too."

Asked if an FDA advisory committee will be need for any vaccine EUA:

- Pfizer's Dr. Bourla said, "I would be supportive to use an advisory committee because we need this extra transparency."
- Merck MSD's Frazier said, "I think the key to all science is transparency…With the concern about vaccine safety, I think it is particularly important that the data or application for an EUA is fully available, public, gets reviewed not only by the FDA or any advisory committee but is available so the scientific community can pour through it and assure the public it has been looked at carefully and it is appropriate for use in a number of patients."

Vaccines and Covax

Covax is a global initiative – lead by the Coalition for Epidemic Preparedness Innovations (CEPI), Gavi, the Vaccine Alliance, and the World Health Organization (WHO) – aimed at ensuring Covid-19 vaccines are available worldwide once they are approved. Currently, 9 Covid-19 vaccines are in the Covax portfolio, with another 9 under consideration. The U.S. has opted not to participate, but Japan, the U.K., Germany, and many other countries are participating.

Asked why industry is not collaborating with Covax, IFPMA's Cueni said, "This has come up in the past. It is the responsibility of companies to ensure the quality of their product, and there you want some control. There is a lot of collaboration and an amazing number of licensing agreements."

Asked if Pfizer made any commitment on dose guarantees to Covax, Pfizer's Dr. Bourla said, "We are in very intense discussions with Gavi, but there is no conclusion."

Asked with pandemic affecting huge populations, what steps industry is taking to scale down costs, Cueni said, "India is one of the countries with some of the biggest manufacturing capacity…I expect India to join Covax…We need solidarity between high, mid, and low income countries…I am optimistic…that it will meet the two *billion* dose target next year…It already has Japan, the European Union, and the U.K. The U.S. does not want to join, so it is mixed news…But, at the end of the day, the manufacturers are clearly committed…No one sees this as business as usual."

Merck MSD's vaccines

Asked if there are any animal data on its vaccines, Merck MSD's Frazier said, "We are working on two separate vaccine platforms… The first is a vaccine related to our Ebola vaccine. We are also working on a vaccine that uses a measles virus vector as a platform. Both are going forward. We expect larger trials of the measles vaccine fairly soon, and the other later this year. When we have clinically meaningful data, we will share it."

Convalescent plasma

Asked for their opinion on the EUA for convalescent plasma and whether the data were strong enough for an EUA, Merck MSD's Frazier said, "I haven't studied the data myself. I know there is a controversy, but I would rely on medical voices…One of the problems we have is too many commentators on science without the people with the correct science background being heard." Gilead's O'Day said, "I wouldn't speculate on someone else's EUA, but having received one with remdesivir, I want to assure people it was a very thorough vetting process from my own experience working with an EUA."