Pink Sheet

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COVID-19 UPDATE

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VIRTUAL ADVISORY COMMITTEES ARE COMING:
US FDA Panels Will Be Smaller, More Focused

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The US Food & Drug Administration is moving ahead with plans to host virtual advisory committee meetings as the agency continues to respond to the need for social distancing during the COVID-19 crisis, Office of New Drug Director Peter Stein said in an interview with the *Pink Sheet*.

The decision to move ahead with virtual advisory committees will build on FDA's increasing experience with online hosting of large internal meetings – such as the Center for Drug Evaluation & Research's Medical Policy Council – and after discussion with division directors and FDA's advisory committee staff on the need and practicalities associated with such an endeavor. *(Also see "US FDA Exploring Virtual Advisory Cmtes.; Might Sponsors Want To Wait For In-Person Meetings?" - Pink Sheet, 1 Apr, 2020.)*

The virtual meetings will be held only for product applications with near-term PDUFA deadlines, and will be markedly different in the typical size and scope: they will involve fewer members, and the discussion will be focused on a targeted set of issues on which FDA needs the most advice. No virtual meetings have been scheduled, and while Stein declined to name the applications under consideration, any meetings that have not already been canceled are likely candidates.

Stein was careful in his phrasing, noting that FDA is still discussing which meetings to make virtual, but it is clear the agency is in active planning mode. "We are going forward with some of the ones that have been scheduled. We've canceled some, and we've canceled some public workshops – those kinds of things that aren't on a timeline, we've canceled. But I think the advisory committees that are related to PDUFA goals, where we do need to advisory committee … it's doable."

"We'll take it one at a time, and look at it, and discuss it. I had an earlier discussion with one of the division directors about exactly this, and we decided we'd try and go ahead and try to have a focused discussion. I think it will work out. We'll get experience as we get the first ones under our belt. But I'm hoping they will be productive and able to answer the questions that we have," he said.

CANDIDATES FOR VIRTUAL MEETINGS

Stein's comments amplify those made by CDER Director Janet Woodcock in an earlier podcast interview. In that interview, two weeks prior to this interview with Stein, Woodcock said FDA was considering virtual advisory committees, but made no commitment about whether the agency would move forward.

As with most news during COVID-19, that sentiment has shifted in the two weeks since, with FDA now actively considering the practicalities of virtual meetings. *(Also see "CDER's Woodcock On COVID-19: Missed User Fees Unlikely, But Some Work Will Be 'Set Aside'" - Pink Sheet, 31 Mar, 2020.)*

Early in the COVID-19 pandemic, CDER canceled or postponed all scheduled in-person advisory committee meetings through

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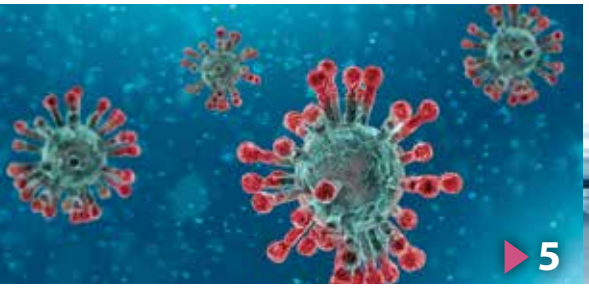

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China Approves First Coronavirus Drugs, Rushes Two Vaccine Trials

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A coronavirus vaccine race is on in China with three domestic developers leading the charge, while traditional medicines are pioneering the drug race after the first official approvals of treatments for COVID-19.

AstraZeneca/MSD's Koselugo Among 14 New Hopefuls At EMA

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New drugs from Eli Lilly, Pfizer, Janssen, GSK, Arvelle, BioCryst, Diurnal and Myovant are also among the latest products the European Medicines Agency is evaluating for potential pan-EU approval.

Delayed Advisory Committees Need Not Worry Sponsors Too Much

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US FDA advisory committee meetings held in close proximity to user fee goal dates are approved at a similar rate to all products reviewed by the advisory panels, according to a *Pink Sheet* analysis of drug and biologic advisory committees since 2015.

How To Implement A Whistleblowing Corporate Policy In The UK

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In the second of his two articles on the whistleblowing landscape, Sean Curran explains global best practices and the practical steps that companies in the UK can take to make sure that whistleblowing claims are handled responsibly and effectively.

inside:

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April, including GlaxoSmithKline PLC's Trelegy for COPD and Eli Lilly & Co.'s flortaucipir F18 Alzheimer's imaging drug. A third meeting, Intercept Pharmaceuticals Inc.'s Ocaliva for NASH, has been delayed to 9 June, according to the sponsor, although that data has not been announced by FDA.

Intercept's Ocaliva would appear to be a prime candidate for a virtual meeting, as would DBV Technologies SA's peanut allergy patch Viaskin Peanut. That meeting was originally scheduled for 15 May but has been postponed due to questions about efficacy. It is also possible that the Trelegy advisory committee could be resurrected as a virtual meeting.

Stein says that while he was initially skeptical of FDA's ability to host productive advisory committee meetings on a virtual platform, he has been pleasantly surprised with the agency's use of technology to convene internal meetings, including those of the Medical Policy Council. Given the success of those meetings, which involve 15 high-level staff, plus review teams with applications under discussion, Stein thinks FDA can host a productive advisory committee meeting.

At the Medical Policy Council meetings, "we have robust discussions that are very organized," he said. "We have a chat room, we can see who wants to raise their hand to ask a question or comment. We can use WebEx to look at the slides and presentations. It's actually worked out pretty well. I will say, after the first one, where there was a little bit of a learning curve, they've gone very well. We've been able to get good input to the teams, make decisions, make recommendations."

"So I am confident, with more planning then we might need to do ordinarily, I think we will be able to have successful advisory committees."

IRONING OUT MEETING LOGISTICS

Stein outlined two major considerations in hosting virtual advisory committee meetings. The first is technical: "We need to make sure that technically, the platform is robust. The last thing that we need is to put everyone together for a meeting and have something go out. There's going to have to be a lot of work" by CDER's Division of Advisory Committee and Consultant Management. "I know that they've been giving a lot of thought to this. But at a high level, the technical piece is critical."

The second piece is organizational, given the number of parties presenting and asking questions. A clear and open discussion – with fewer, more targeted questions to the committee – will be critical factors in ensuring productive meetings. That will require extra preparation (or perhaps, in some cases, a different) committee chair to ensure all members are heard and that any views and opinions are understood by all.

Stein acknowledged the importance of the chair in a successful virtual meeting. "It's really critical that the chair be able to make sure we know who's speaking…so that we can be very clear about what we're hearing and from whom we're hearing it...so that we can do this is a careful way."

"The presentations aren't going to be the challenge – that's pretty straightforward," he said. "It's the discussion that is going to require great focus and organization, and making sure we know who is speaking, give them a chance to speak, use ways that we have, like the 'raise your hand' option so we know they want to comment." And perhaps more so than is needed in on-site meetings, "the chair is going to have to go around purposefully to each member and ask if they have comments."

The topics for discussion will also be narrowed to the critical issues on which FDA needs advice, Stein said. "We may have two safety questions that we really want answered, and we may say, 'let's narrow the discussion to those questions' and make sure the discussion is rich in that area, recognizing that some things we might have discussed that aren't as critical concerns of ours with regard to understanding the data, those thing we might not focus on as much."

The challenge for the committee chair and FDA officials will be herding what is sometimes a meandering and wide-ranging discussion into something that is much more targeted. That could require extra training of committee members by the advisory committee staff.

A tighter, more focused discussion also could mean that the meetings are shorter, and perhaps follow the half-day sessions typical followed by the Oncologic Drug Advisory Committee.

SMALLER COMMITTEES, FEWER MEMBERS

Stein also noted that advisory committees will likely involve fewer members – and certainly not the dual committees often used to discuss safety issues with applications. That most often happens when the therapeutic advisory committee is paired with the Drug Safety and Risk Management Advisory Committee (as is often the case with opioid product reviews).

"We did have a meeting planned that had two different advisory committees coming together, and with a relatively complex set of issues that were quite diverse, and we canceled that, thinking that, first of all, it was something that we could cancel, because it was something that was important, but making sure it was a productive discussion was even more important," Stein said. That meeting was still in the planning stages and not formally announced by FDA.

"Where there are advisory committees related to products that have PDUFA timelines, we certainly will try to go ahead with those, hopefully, they will be ones that are smaller – not two different advisory committees put together," he said.

"It's going to require some work, but I don't think that we have to cancel all of them. We can go ahead and do ones that are more focused and where we don't have a huge number of committee members put together from two different advisory committees."

Stein also acknowledged that applications with more complex issues may need to be postponed. "Is it possible that because of the complexity of some of the issues and the extent of the size of some of the advisory committees that we may end up delaying some of them? It's possible. But I think we are planning on going ahead with the ones that I'm aware of that are upcoming."

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EU Moves To Ease Regulatory Burden On Pharma

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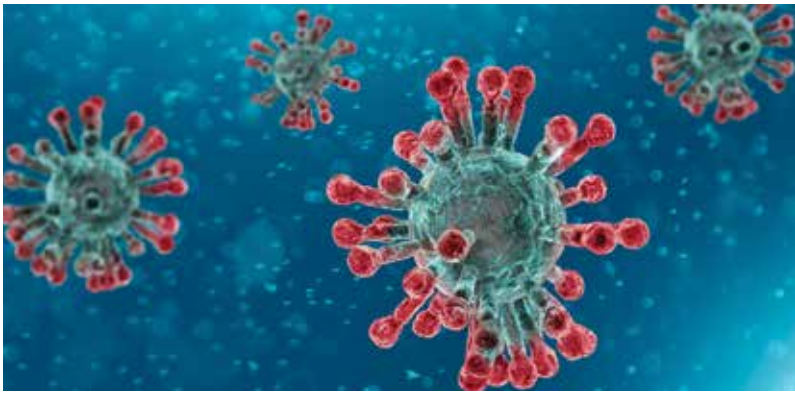

A new pan-EU guideline has been issued to offer regulatory flexibilities to drug companies during the COVID-19 pandemic. In addition, authorities have agreed on an EU-wide approach to collect information on and monitor convalescent plasma transfusion, which has emerged as a potentially promising therapy for COVID-19.

The guideline on regulatory flexibilities was jointly developed by the European Medicines Agency, the European Commission and the EU Heads of Medicines Agencies to address some of the constraints drug companies may be facing within the context of the COVID-19 pandemic.

In the guideline, the regulators have outlined their expectations of marketing authorization holders (MAHs) and areas where regulatory flexibility is possible. Some of the new measures introduced in the guideline, such as an exceptional change management process, are reserved for crucial medicines for use in COVID-19 patients.

The guideline covers various areas of drug regulation including marketing authorizations and related regulatory procedures, manufacturing and import of active pharmaceutical ingredients and finished products, quality variations. It also covers requirements for labeling and packaging and flexibility to facilitate the movement of medicinal products within the EU to address potential shortages.

Among other things, the guideline introduces the concept of an exceptional change management process (ECMP) that companies can use to reduce the risk of shortages or disruption of supply following manufacturing and/or supply problems in relation to crucial COVID-19 medicines.

The ECMP will permit companies to swiftly implement changes to suppliers and/or manufacturing/control sites necessary to reduce the risks of shortages under certain conditions intended to ensure the quality of the medicinal product, while deferring the full assessment of the variation.

The ECMP allows companies to exceptionally source starting materials, reagents, intermediates or active substances from suppliers not specifically mentioned in the marketing authorization if it is necessary to prevent/mitigate shortages of supplies in the EU. Likewise, it permits companies to use manufacturing sites or sites responsible for quality control that are not specifically mentioned in the marketing authorization.

The guideline clarifies that the ECMP cannot be applied to changes classified as extensions of the marketing authorization. The process is reserved for changes that companies may have to introduce to address supply chain/manufacturing challenges as a result of the COVID-19 pandemic to ensure continuity of supplies. Some of the other flexibilities discussed in the guideline relate to:

- **Quality variations** – In cases where companies find it difficult to perform the quality controls specified in the marketing authorization (eg, due to significant increase of manufacturing capacity to meet the demands of EU patients or other circumstances related to the COVID-19 pandemic), they should contact the concerned competent authority to submit an adapted control scheme based on a risk-based approach.
- **Product information and labeling** – During the COVID-19 pandemic, EU member states may grant full or partial exemptions to certain labeling and packaging requirements to address severe drug shortages. For example, member states may accept that the product information for medicines marketed in their territory may not be translated into the relevant official language. Moreover, it may be acceptable that national specific information does not appear on the packaging/labeling, or that the presentation differs from the presentations authorized in the member state where the product is marketed.
- **Renewals** – Companies finding it difficult to apply for the renewal of their initial marketing authorization within the specified deadline are being urged to contact the EMA (for centrally-authorized products) or the reference member state (for products authorized under Europe's mutual recognition/decentralized procedures) with a justified request to postpone the submission of the complete dossier to a later point in time.
- **Sunset clause** – The sunset clause is a legal provision which states that the marketing authorization of a medicine will cease to be valid if the medicine is not placed on the market within three years of the authorization being granted or if the medicine is removed from the market for three consecutive years. Companies can request an exemption here in view of exceptional circumstances and on public health grounds. For centrally authorized products, the commission may accept sunset clause requests that refer to the pandemic as a reason without the need for any further justification. For nationally authorized products, such requests would have to be submitted to the concerned competent authority and these would be dealt with according to the national rules considering the pandemic situation.

The regulatory flexibilities guideline will remain valid until further notice and will be updated to address new questions and to adjust its content as the pandemic situation evolves.

PLASMA TRANSFUSION

Among various treatments being developed for COVID-19, plasma transfusion has emerged as a potentially promising therapy patients that can be made widely available at a relatively short notice.

The commission, in collaboration with the European Centre for Disease Prevention and Control, has issued guidance to facilitate a common approach across member states regarding the donation, collection, testing, processing, storage, distribution and monitoring of convalescent plasma for the treatment of COVID-19 patients. The guideline has been endorsed by EU member state competent authorities for blood and blood components.

It supports a coordinated and effective approach to the collection of convalescent plasma across the EU for the possible treatment of acutely ill patients (or patients at risk of becoming acutely ill) with the plasma within observational studies or randomized and case-controlled clinical trials, and in the longer term, for the development of immune globulin concentrates by industry.

In addition to the guideline, the European Blood Alliance is building an open-access database to collect information on donations and patient outcomes. The EBA's database, which is expected to become functional later this month, will be open to all EU/EEA blood establishments that wish to participate. It will gather data from monitored use, as well as from randomized clinical trials, and will consolidate EU evidence on the safety and effectiveness of this therapy.

In the US, the Food and Drug Administration has also issued guidance on the administration and study of investigational convalescent plasma collected from individuals who have recovered from COVID-19. The FDA has also tied up with the American Red Cross to help seek patients who have fully recovered from COVID-19 to sign up to donate plasma to help current COVID-19 patients. *(Also see "Coronavirus Update: Searching For A Treatment" - Pink Sheet, 9 Apr, 2020.)(Also see "Coronavirus Update: FDA Fast-Tracks Blood Plasma Trials, Novavax Closes In On Vaccine Start" - Scrip, 9 Apr, 2020.)*

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New China Drug Regulation Legalizes Emergency Approval Mechanism

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China's National Medical Products Administration (NMPA) issued a new Drug Registration Regulation (DRR) on 30 March that will take effect from July and incorporates several provisions which underline the regulatory agency's main priorities.

One is a special review and approval mechanism that can be initiated in a public health crisis and under which the NMPA can grant special approvals to drugs that are in urgent need. It can also specify certain geographic regions and time frame for the use of products approved under the special pathway, if required by the disease control needs.

The new mechanism, which is somewhat akin to the emergency use authorization system in the US, should improve current approval pathways, which have been criticized for being too rushed, with no conditions attached to products developed specifically for the coronavirus outbreak.

In a move to promote the use of generics and help bring down overall medical costs, the new regulation requires publishing a list similar to the Orange Book in the US, containing information such as generic names, active ingredients, dosage forms, product specifications and marketing authorization holders.

Notably, the list of generic drugs that have passed bioequivalence testing in China won't contain any originator or data exclusivity-related information, law firm Sidley Austin observed in a note to clients. Citing such intellectual protection issues as being beyond the NMPA's authority, the regulator left out such provisions as patent linkage and data protection in the updated DRR, added the legal experts.

Also notable is new "basket review" system, meaning that NMPA reviewers will now review finished products, active ingredients, excipients and packaging related to the same product.

FOUR FAST-TRACK REVIEW PATHWAYS

The DRR also clarifies the types of products for which fast-track review pathways can be applied.

1. Breakthrough therapies. This allows sponsors to file an approval application during clinical trials for innovative drugs for life-threatening diseases;

2. Special pathway for public crisis use. Drugs eligible for conditional approvals or considered breakthrough therapies will be eligible for priority review, with shortened approval timelines and more flexibility in providing supplementary information during the review process.

3. Drugs eligible for conditional approval.

4. Drugs eligible for priority review. This will be granted to certain eligible products such as orphan drugs and innovative oncology drugs.

"Compared with the previous DRR, the new regulation reflects a more dynamic, interactive, risk-based approach the NMPA intends to take in overseeing clinical trials," noted Lei Li and Chen Yang of Sidley Austin, citing adverse event report obligations for marketing authorization holders and post-marketing surveillance requirements.

Data integrity is another emphasis. The NMPA requires authorization holders to be held accountable for conducting clinical studies in compliance with good clinical practice and good manufacturing practice, and will take a risk-based approach to pre-market GCP/GMP compliance.

HUMIRA BIOSIMILAR GUIDELINES

The NMPA's Center for Drug Evaluation has also issued a draft guidance for industry in a bid to encourage the development of biosimilar versions of AbbVie Inc.'s blockbuster antibody Humira (adalimumab). The guidance outlines wide-ranging issues such as how to perform pharmacokinetic comparisons in healthy subjects and how to assess clinical effectiveness in patients.

So far, several companies in China are in the race to develop their versions of the global top-selling treatment for rheumatoid arthritis in the domestic market, including Fosun subsidiary Shanghai Henlius Biotech Inc. and Bio-Thera Solutions, which was first to win an approval for its biosimilar Humira in China late last year.

Henlius is also looking to go beyond China's domestic market and to sell biosimilars to emerging Eastern European markets including Poland.

Through the guidance for industry, the NMPA hopes to encourage more companies to leap into the fray, despite a single-digit market share for biologics (as opposed to other standard drugs) to treat immunology conditions such as rheumatoid arthritis. In the draft guidance, the agency lays out specifics such as criteria for selecting study subjects for trials, disease activity levels eligible for participation and dosing regimens.

The agency is gathering feedback on the draft throughout April.

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Gilead's Compassionate Use Data Promising, But Imminent COVID-19 Treatment Shift Unlikely

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Promising data on Gilead Sciences Inc.'s experimental antiviral remdesivir given as compassionate use to more than 50 hospitalized COVID-19 patients is unlikely to change current clinical trials or clinical care.

That's largely due to the limitations of the uncontrolled data in a disease where most patients will improve over time, along with the rapid conclusion expected of already ongoing studies that were designed to assess efficacy and safety.

Gilead expects to have preliminary data of a Phase III study of remdesivir in severe patients later in this month. In May, it expects data from its Phase III study of patients with moderate COIVD-19, and initial data from a trial run by the US National Institutes of Health.

Still, the Gilead data published Friday in the New England Journal of Medicine was met with enthusiasm by some. Former FDA Commissioner Scott Gottlieb suggested it could potentially be used to help expedite the drug's regulatory filings.

"There's latitude to consider an emergency use authorization or accelerated approval" for remdesivir to broaden access now, once NIH's adaptive trial of the drug is fully enrolled, Gottlieb tweeted, particularly if ongoing trials support the benefit believed to be seen in compassionate use. He said the NIH trial could be used as a confirmatory study for the EUA or accelerated approval.

The compassionate use data showed that 36 of 53 or 68% of patients who received the drug had an improvement in the category of oxygen support compared to eight, or 15% who showed worsening over a median 18 days of follow up. By the most recent follow-up nearly half, or 25 of the 53 patients had been discharged from the hospital, including 24% who had been on ventilators

The company looked at patients who received the drug under compassionate use from 25 January through 7 March. While 61 patients got the drug during that period, eight were excluded because

they did not have clinical data for at least one subsequent day. Patients were supposed to receive a 200mg dose of the drug intravenously on day 1 followed by 100mg daily for 9 days, though only 75% received all 10 days of treatment.

Gilead said the comparison of their patient cohort to contemporaneous cohorts from literature suggest the drug may have produced clinical benefit though it acknowledged that the "lack of a randomized control group … precludes definitive conclusions."

> IDSA will not make any formalized recommendations on remdesivir for COVID-19 until "the entire body of evidence," particularly randomized controlled trials, is available.

Besides the lack of randomization and a control group, the small size, short follow up and missing data are drawbacks, the company acknowledged. Other factors that could have contributed to the differences in patient outcomes in the study include the differences in supportive care received by patients and different thresholds for hospitalization.

'IT DIDN'T MOVE THE NEEDLE': SELF-RESOLVING INFECTIONS NEED COMPARATORS

"To me, it didn't move the needle in terms of saying, you know, this is gonna work or not," Rajesh Gandhi, an infectious disease physician at Massachusetts General Hospital and professor of medicine at Harvard, told the *Pink Sheet*. "Without a comparison group I can't say whether 68% of people who didn't get remdesivir would have improved. Because the majority of people with COVID-19 do recover. So that is the issue."

Gandhi, a fellow of the Infectious Diseases Society of America and chair-elect of the HIV Medicine Association, said that there have been some cases like with hepatitis C where single arm studies have been interpretable. That was because drugs were showing cure rates of 90% or more in a chronic infection. But "a self-resolving" infection needs a comparison, he said.

Gilead also didn't look at surrogate markers of viral load in the compassionate use patients, Gandhi said. If they had collected viral load data and patients viral load went down over the course of treatment that "would be an indicator the drug is doing what we think it's doing."

TREATMENT GUIDELINES SKIP REMDESIVIR

Gandhi helped write IDSA's guidelines on the treatment and management of COVID-19 patients, which was published Sunday. The guidelines mention remdesivir and the NEJM data in a section on treatments undergoing evaluation, but IDSA said it won't make any formalized recommendations on the drug for COVID-19 until "the entire body of evidence," particularly randomized controlled trials, are available.

In comparison, IDSA does make formal recommendations on other drugs for which randomized controlled trials in COVID-19 patients have not been completed. In these cases, IDSA's preference was almost always that patients receive the medicines as part of clinical trials.

The big distinction between drugs that were mentioned in the recommendations section is that they are all already FDA approved for other uses and can be prescribed by physicians off-label, which is why the guideline committee wanted to highlight the available evidence for those medicines, Gandhi said.

SKEPTICISM AND OPTIMISM AS GILEAD ADDS PATIENTS TO TRIALS

Investors were excited about the compassionate use data but also cautious.

"Don't jump the gun," Geoffrey Porges of SVB Leerink wrote in a Friday investor note, which also warns about uncontrolled data in a self-resolving disease. The risks that the data Gilead reported are non-valid or non-repeatable "are heightened in a disease in which the natural history for most actively treated patient is to improve and recover."

Still Porges believes the drug will likely be the first treatment approved for COVID-19, saying SVB Leerink is "more encouraged" about the upcoming trial results after the NEJM data. He expects a conditional approval as soon as mid-May and at the latest Memorial Day.

Wolfe BioPharma's Tim Anderson said when comparing the NEJM reported results to other studies they offer "encouraging signs that remdesivir may be having a positive clinical effect (of unclear magnitude)." But commercial prospects for the drug may still be limited, he added, saying he believes the company may give away much if not all of the drug in 2020 for humanitarian and political reasons.

The NEJM study offered a boost for Gilead after some skepticism earlier in the week about its decision to increase enrollment in two key Phase III open-label trials. Its Phase III study in moderate patients will enroll 1,600 patients, up from 600, and its study in severe patients will enroll 2,400, up from 400. This led to speculation the drug may not be a clear home run.

Porges noted that the "thrust" of the drug trials have been shifted from severe to moderate patients, and suggested this accounts for the company's decision last week to increase recruitment. Moderate patients do better on standard treatment so more patients will be required to demonstrate a meaningful treatment effect, he said. He also said the expansion was likely due to the need for more safety data.

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Inspections Prompt EU Advice On Validating Computerized Clinical Trial Systems

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The European Medicines Agency has expressed concern over recent inspection findings where clinical trial sponsors were unable to demonstrate how they qualified/validated the computerized systems that are used for managing trial data.

The inspection findings have prompted the EMA to issue a notice to trial sponsors on the topic, which clarifies that failure to document and demonstrate the validated state of a computerized system could pose a risk to data integrity, reliability and robustness.

This in turn could result in good clinical practice (GCP) inspectors recommending that the affected trial data – depending on its criticality – should not be used within the context of a marketing authorization application.

The EMA's notice lists common inspection findings related to qualification and validation of computerized systems by trial sponsors and offers advice on how these issues should be addressed. A common finding, for example, relates to the lack of documentation or access to documentation of qualification activities.

As sponsors usually purchase computerized systems used in clinical trials from a vendor, it is likely that qualification activities would either be performed by the vendor or by the sponsor or it may be a shared effort. Irrespective of who performs these activities, the notice states that sponsors should be able to provide the GCP inspectors with access to documentation on the qualification and validation of the computerized systems.

While sponsors can rely on the qualification documentation provided by the vendor, they may also have to undertake additional qualification and validation activities based on a documented risk assessment, the EMA had explained in an earlier guideline. *(Also see "EMA Clarifies Sponsor's Role In Validating Electronic Systems Used In Clinical Trials" - Pink Sheet, 24 May, 2018.)*

Another key inspection finding in this area relates to insufficient contractual arrangements between the sponsor and vendor regarding qualification and validation. The EMA's GCP Inspectors Working Group (IWG) has issued related guidance on the pitfalls that sponsors should be aware of regarding contractual arrangements with vendors of electronic systems used in trials.

In its guideline, the IWG suggests that the sponsor should amend any contract with vendors to ensure availability of qualification documentation. If a vendor is unwilling to amend the contract, then the sponsor would be responsible for demonstrating that the system concerned is in a validated and qualified state. For this, the sponsor would have to requalify the computerized system on the basis of its own and of the vendor's system requirement specifications.

The EMA's notice to sponsors makes it clear that if appropriate contracts cannot be put in place with a vendor, then computerized systems from such a vendor should not be used in clinical trials. This is irrespective of the number of other sponsors making use of, or having used the vendor's system, and the number of years such a system has been on the market, the notice adds.

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US FDA Is Pulled Into Zofran Product Liability Litigation

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While the US Food and Drug Administration's actions on drugs are typically cited in product liability litigation, the agency does not play a direct role in these cases. But through the filing of a citizen petition, GlaxoSmithKline PLC has drawn the agency into multidistrict litigation alleging GSK failed to warn of the risk of birth defects with use of its antiemetic Zofran (ondansetron) during pregnancy.

The 1 November citizen petition led FDA to hold separate "listening meetings" with GSK and members of the plaintiffs' steering committee to hear their views on what impact FDA's response to the

petition would have on preemption law and the filing of similar petitions in other cases. Massachusetts US District Judge F. Dennis Saylor IV also sent a letter to FDA Chief Counsel Stacy Cline Amin asking the agency to respond to the petition "as expeditiously as possible."

The first bellwether trial had been scheduled to begin on 13 January. But Saylor said in his 13 December letter that the citizen petition "could potentially affect the resolution of the preemption dispute, and therefore the outcome of the entire litigation," and both parties had therefore sought to postpone the trial at least several months. A new trial date was set for 4 May but has been pushed back indefinitely.

Amin sent a 23 January letter in response, telling Saylor that "the agency is diligently examining the issues raised by the citizen petition and is working to respond to that petition as quickly as feasible."

There are more than 400 individual lawsuits against GSK in the MDL proceeding, which has been underway since 2015. In April 2017, the judge denied defendants' motion to dismiss fraud-based claims. *(Also see "Product Liability Litigation Playbook: Pros And Cons For Pharma" - Pink Sheet, 24 Sep, 2017.)*

WAS FDA GIVEN THE COMPLETE PICTURE?

FDA approved Zofran in 1991 for prevention of nausea and vomiting induced by chemotherapy or radiation therapy and postoperatic nausea and vomiting. It has been used off-label for nausea and vomiting in pregnancy. Plaintiffs contend that GSK was required under state laws to provide a warning about ingesting Zofran during pregnancy. GSK argues that state-law-failure-to-warn claims are preempted by federal law.

Judge Saylor notes that GSK has requested summary judgment in its favor as to all cases on the basis of federal preemption. The motion is based, in substantial part, on the fact that the FDA did not require substantial labeling changes in response to a 2013 citizen petition by an individual asking the agency to provide pregnancy warnings in the label, or when Novartis AG (which acquired rights to Zofran in 2015) proposed an update to the label to advise against use of Zofran during pregnancy and to warn of potential risks to a developing fetus.

The plaintiffs allege that GSK improperly withheld certain information from FDA concerning the dangers of ingesting Zofran during pregnancy at the time of its initial approvals and afterward.

GSK's citizen petition requests that FDA review four categories of information concerning the use of Zofran in pregnancy and "either refrain from taking action to alter Zofran's pregnancy-related labeling or take action to alter the labeling in light of these four categories of information, as the agency deems appropriate."

The petition says plaintiffs claim that GSK failed to fully inform FDA of these four categories of information, which they contend would have caused FDA to change Zofran's pregnancy labeling.

The categories of information include: three animal reproductive toxicity studies performed to seek approval of Zofran in Japan; information regarding the potential of ondansetron to inhibit hERG ion channels; allegations that GSK's coding of similar adverse events would dilute the total number of cardiac birth defects; and GSK's assessment of and alleged involvement in a 2004 epidemiological study.

GSK also submitted exhibits with the petition, which it contends include all the information that plaintiffs allege was wrongfully withheld.

> The petition has given both parties an opportunity to talk directly with FDA, a very unusual event in litigation. And the documentation provides a rare look at their behind-the-scenes maneuvers.

PETITION OPENS DOOR TO FDA DISCUSSIONS

The petition has given both parties an opportunity to talk directly with FDA, a very unusual event in litigation. And the agency's documentation of the meetings and correspondence provides a rare look at their behind-the-scenes maneuvers.

Chief Counsel Amin declined a request by the MDL plaintiffs' steering committee to be deposed about her knowledge of communications between GSK and FDA regarding the citizen petition. But in a 23 January letter to attorneys on both sides, she said FDA regulations specify that in reviewing a citizen petition, the agency may meet with interested parties and grant meeting requests in limited circumstances.

Before meeting with the litigants, FDA's Sara Beardsley, senior advisor to FDA' chief counsel, had a phone conversation with GSK counsel Amy Saharia and Sarah Harris of Williams & Connolly on 8 November, during which they explained why they filed the petition and the preemption issues that had been raised in the Zofran litigation.

In a 24 January memorandum about the call, Beardsley said Saharia told her that the litigation is unlike many product liability cases because there was no recall of Zofran, and no warnings related to the risks in question have been added to the drug's labeling. Saharia also said that the case is the first significant decision on preemption since the US Supreme Court's ruling last year in Merck Sharpe & Dohme Corp. v. Albrecht, which found that judges, not juries, should decide if FDA would have rejected a drug manufacturer's request to add a warning to its labeling. *(Also see "Product Liability: Discussions With FDA Remain Key In Defeating State Tort Suits" - Pink Sheet, 20 May, 2019.)*

"Ms. Saharia expressed the view that the case could have an outsized influence on how other courts decide preemption in light of *Albrecht*," the memorandum states. "In her view, the outcome of the case could have an impact on FDA for two reasons. First, she said Plaintiffs' view of materiality could mean that FDA would be flooded with information by new drug application (NDA) holders. Second, she stated that Plaintiffs' theory requires judges to second-guess FDA's prior position, which GSK views as an attack on FDA's authority. Finally, she noted that including a warning under state

law that is not required by FDA could mislead the public."

In addition, the memorandum says that Ms. Saharia noted that the petition was novel and that GSK does not envision doing this often. "She stated her view that this situation was unique because FDA had actually rejected the warnings in the past. She stated that GSK would not have filed the petition if they thought they did something wrong, and that GSK wants FDA's views on this question," the memorandum says.

MEETINGS WITH FDA

FDA Chief Counsel Amin, Beardsley and seven other FDA officials subsequently met with GSK representatives and their outside counsel at FDA's headquarters on 5 March. They included GSK's senior counsel Bridget Lankford, chief medical officer Sabine Luik, Brennan Torregrossa, senior VP, head of regulatory and quality of global litigation, scientist Patrick Wier and Saharia.

FDA's memorandum of meeting minutes says Torregrossa noted why GSK's petition is unique, Luik and Wier presented scientific information, and Saharia summarized the preemption issues and explained why GSK believes that FDA should respond to the petition on its merits.

The same agency officials held a Zoom video call with six members of the plaintiffs' steering committee on 30 March. They included Louis Bograd of Motley Rice, Thomas Ayala of Grant & Eisenhofer, and Robert Jenner of Jenner Law.

The meeting minutes of that call note that Amin sought their views on the impact of FDA's response to the petition on preemption law and the volume of similar citizen petitions that might be submitted in the context of other cases. The attorneys gave presentations on the legal and scientific issues in the litigation.

PLAINTIFFS ALLEGE 'SECRETIVE LOBBYING' OF FDA

Plaintiffs' attorneys have objected to GSK's discussions with FDA. They filed a motion for the court to sanction GSK, claiming the company was lobbying FDA to issue a decision in its favor.

"At the very time it was asking both this Court to consider the preemption question and the FDA to consider its Citizen Petition that goes directly to the questions of preemption, GSK was secretly meeting and lobbying the FDA between at least October 2019 and November 8, 2019 to prime the agency to rule favorably on its petition," a 5 February memorandum in support of the motion states.

In a filing opposing the motion for sanctions, GSK said there was nothing inappropriate about its counsel's interactions with FDA.

"Despite GSK's multiple attempts to clear Plaintiffs' counsel's misperceptions about GSK's contacts with FDA regarding its Citizen Petition, Plaintiffs continue to choose conspiracy theories and conjecture over fact," the filing states.

GSK says a lawyer from Williams & Connolly called Amin on 28 October to notify the Office of Chief Counsel "as a courtesy" that GSK intended to file the citizen petition and lawyers spoke by phone on 8 November with FDA's Beardsley, who indicated that the petition had been received.

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SUPPLY CHAIN TRUCE IN COVID-19: Will It Carry Over When Rx Price Debate Resumes?

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There is nothing like a common enemy to bring feuding parties back together.

The outbreak of COVID-19 appears to be having that effect on the key stakeholders in the prescription drug supply chain. The global outbreak has prompted all the key trade associations representing every component of the supply chain to band together to try to anticipate, mitigate and address potential shortages or other disruptions to access to medicines in the US.

That unity was demonstrated in a March 26 letter to Vice President Pence (head of the White House coronavirus task force) and congressional leaders from both parties. The letter was signed by trade associations representing manufacturers (Pharmaceutical Research and Manufacturers of America, Association for Accessible Medicines), payers (America's Health Insurance Plans, Blue Cross Blue Shield Association), pharmacy (National Association of Chain Drug Stores, Academy of Managed Care Pharmacy), pharmacy benefit managers (Pharmaceutical Care Management Association) and specialty distributors (National Association of Specialty Pharmacy).

The letter specifically asked the federal leaders to focus more attention on issues that could lead to shortages amid the COVID-19 outbreak, ranging from spikes in demand for drugs "identified as potential treatment for COVID-19," to the increased transportation costs for some pharmaceuticals that used to be shipped routinely

as freight on passenger airlines. *(Also see "AAM Urges Trump Not To Destabilize Supply Chain" - Generics Bulletin, 2 Apr, 2020.)*

The letter also delicately sought to stop two steps initiated by President Trump. First, "all of our industries are concerned that a reported 'Buy America' Executive Order under consideration by the White House could have an immediate and detrimental impact on the ability of Americans who rely on federally funded health programs to access their medicines."

Second, they urged the promulgation of national treatment guidelines to help identify and manage appropriate use of potential COVID-19 therapies – and "to ensure that patients who have been on therapies for FDA-approved indications prior to the spread of COVID-19 still have appropriate access." *(Also see "Biopharma, Payers Seek National Guidelines For Prescribing Potential COVID-19 Drugs" - Pink Sheet, 1 Apr, 2020.)*

Unstated in the letter is the primary case example: hydroxychloroquine, which is now in short supply for use by lupus patients and in other rheumatology settings thanks to demand as a potential treatment for coronavirus. "Our industries pledge to continue to work collaboratively with each other and with the FDA and other federal, state, and local officials to keep the prescription drug supply chain functioning well as we confront this unprecedented health system challenge," the letter concludes.

That is a comforting message of unity amid crisis, to be sure. But in the broader context of the finger-pointing that has defined the relationship among the signatories amid the debate over specialty drug pricing, it is truly remarkable.

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To put it mildly, it has been a long time since the associations for brand name and generic drugs, PBM and retail pharmacy, payers and specialty distributors have been able to agree on anything one-to-one – much less all together. And while it is certainly easier to come together in a crisis when everyone is desperate for solutions (and no one is worried too much about who has to pay for it), this must have been a particularly delicate letter to negotiate. After all, the only reason anyone is talking about a "Buy American" order – and a very big reason why everyone is talking about hydroxychloroquine – is because of the messaging directly from President Trump. *(Also see "Off-Label Promoter In Chief: President Trump Pushes COVID-19 Therapy" - Pink Sheet, 23 Mar, 2020.)*

A simple way to translate the letter, in fact, is a plea to Pence, Senate Majority Leader Mitch McConnell and House Minority Leader Kevin McCarthy to try to rein the president in. Doing so in a public document, one that also directly addresses House Speaker Pelosi and Senate Democratic leader Schumer, takes no small amount of courage – at least as courage is measured in the world of trade association leadership.

The COVID-19 outbreak has already brought an abrupt end to any near-term push to complete work on major drug pricing legislation this year. The truce within the supply chain could go a long way to determining whether that effort resumes – and, if it does, what direction it takes – once the crisis is finally over.

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DRUG COVERAGE IN THE PANDEMIC:

US Payers Shift Focus From Costs To Access, For Now

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US payers are concentrating on ensuring access to health care during the COVID-19 pandemic, which has led them to relax, postpone or waive some formulary and coverage policies to avoid disruptions in patient access to prescription drugs.

Most pharmacy benefit managers have temporarily waived early medication refill limits, particularly for chronic use drugs, to accommodate patients who are staying at home to avoid exposure to the coronavirus, according to a 6 April report by Milliman pharmacy benefit consultants. The report is based on information from the three leading PBMs, Express Scripts Holding Co., CVS Health Corp. and OptumRx Inc., and a number of mid-sized PBMs.

> **"We have this continuing unsustainability of the high and ever rising prices for medications that will still be there" after the pandemic. "From the employer plan perspective that's still an issue."**
> **– Business Group On Health official**

The concession is in line with a provision in recently-enacted COVID-19 aid legislation, which also allows early refills in Medicare Part D. *(Also see "Part D Plans Would Need To Cover COVID-19 Drugs Without Cost Sharing Under House Bill" - Pink Sheet, 24 Mar, 2020.)*

Many PBMs have also decided to extend previously approved prior authorizations to reduce the administrative burden on providers to renew PAs, the report notes. UnitedHealthCare says in a recent "frequently asked questions"

There's an increasing recognition that policies around at-home administration of drugs typically dosed in a physician's office should be relaxed to ensure continuity of care, including for chemotherapy.

notice to brokers that it will extend prior authorizations scheduled to expire during April for 90 days.

Some PBMs are allowing temporary overrides for non-preferred drugs, allowing members to pay lower, preferred drug copays, in certain situations, the reports says. The overrides are enacted if the preferred drug is out of stock and the member has an immediate need for the prescription. "This could cause plan costs to increase due to increased utilization of non-preferred drugs compared to preferred drugs, the latter of which typically carry larger rebates to help control costs," the report observes.

Payers are also adjusting formulary exclusions to avoid patient disruption. Express Scripts will implement its mid-year formulary exclusions as planned but will also grandfather members who are already taking an excluded drug, a spokesperson for the company said. UnitedHealthcare will postpone exclusions for some respiratory and diabetes drugs from 1 May to 1 July to alleviate disruption. These concessions could also lead to lost rebates.

Payer concerns with access have taken priority over a focus on lowering drug costs, which can offer a benefit to biopharma. But the respite won't last forever and may even lead to increased cost pressures on manufacturers down the road, according to reimbursement and health care policy experts.

"Every health plan that I talk to, every payer, is focused now on ensuring their members have access to care, whether it's for COVID, which they're spending a tremendous amount of time on, as well as continuation of care … particularly for those who needs access to care because of their chronic condition or their access to medication," Real Endpoints executive VP and chief clinical officer Jane Barlow said in an interview.

There's an increasing recognition that policies around at-home administration of drugs typically dosed in a physician's office should be relaxed to ensure continuity of care, including for chemotherapy, she pointed out. "So this is a really critical time and that's where payers' heads are." Real Endpoints is an information and data/analytics company focused on drug reimbursement, pricing and market access.

Along the same lines, the Centers for Medicare and Medicaid Services recently moved to address access to physician-administered drugs with a rule allowing Medicare coverage for Part B drugs administered at home. *(Also see "Part B Drugs At Home: Medicare Policy Responds To COVID-Driven Access Concerns" - Pink Sheet, 5 Apr, 2020.)*

DRUG MANAGEMENT PROGRAMS MAY BE POSTPONED

Barlow suggested that because the COVID-19 outbreak is happening at a time that plans are typically finishing up their formularies and plan designs for 2021, they may decide to postpone implementation of new cost management programs to a later year.

Medicare formularies and bids are generally due in the May /June time period, she noted. And "most payers are on a cycle where they would have open enrollment in the fall time period, which means they would have to have everything agreed to, signed up and ready to go around July 1."

The pandemic "is going to cause disruption in a lot of that work and my anticipation is that payers may put off some things that they would already otherwise have done because change, on top of everything that's going on now, is going to be disruptive."

However, Barlow said, things will be different longer term, when costs from the pandemic catch up with payers. Real Endpoints CEO Jeff Berkowitz agreed. "One of the repercussions of all the extraordinary expense that is going to be diverted to other areas is that it's going to put additional pressure on pharma companies coming from payers," he predicted.

"That pricing pressure is going to start to get more acute on drugs where it normally wasn't acute just because there are so many cost pressures in the system," he added. Berkowitz suggested treatments for non-alcoholic steatohepatitis and some of the higher priced drugs for orphan drug disease would be among those targeted.

Some payers are also expecting that the costs associated with the pandemic may hamper development of reimbursement solutions for regenerative therapies. *(Also see "COVID-19 Economic Fallout May Delay Cell And Gene Therapy Reimbursement Solutions" - Pink Sheet, 7 Apr, 2020.)*

Business Group on Health VP public policy Steve Wojcik suggested the pandemic's net cost to payers is not yet clear. The Business Group on Health (formerly known as the National Business Group on Health), advocates on health care policy for large employers.

"There are some unknowns about how things shake out" for payers, Wojcik said. COVID-19 "is going to put upward pressure on health plan expenses but the decline in elective and routine care is going to have, at least temporarily, a downward impact."

Nevertheless, "there will still be a need for affordable sustainable pricing for prescription drugs overall," he maintained. "We have this continuing unsustainability of the high and ever rising prices for medications that will still be there. From the employer plan perspective that's still an issue."

PUTTING THE GENIE BACK IN THE BOTTLE

Cooperation between members of the drug supply chain during the pandemic has been impressive but it also begs the question of why the same approach couldn't be applied to tackling widespread chronic conditions, Real Endpoints' Berkowitz pointed out.

"We're hearing … it's going to be a little hard to put the genie back in the bottle," he noted. "I completely understand the desire to fix this [crisis] and the spirit of comaraderie between all of the associated pieces of the health care delivery system. But you sort of wonder, if you can waive copays and testing charges for this particular issue, how do you go back to normal where you're not doing that for diabetes, respiratory [illness] or cardiovascular disease?"

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NOTE: The FDA is not expected to announce new advisory committee meetings during its current freeze on in-person meetings due to the COVID-19 pandemic.

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