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CRISIS PRACTICE

Coronavirus

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Accelerated Covid-19 Vaccine Clinical Trials

Liability exposure and shields for vaccine developers

As the number of COVID-19 cases continues to rise every day, efforts to develop vaccines across the globe have hit record speeds. In the U.S., the U.S. Food and Drug Administration ("FDA") has opened the door for accelerated development and testing of investigational vaccines. While companies involved with these accelerated clinical trials may be concerned about exposing themselves to liability as a result, federal legislation is likely to offer broad protection. Companies should also consider taking additional steps to further buttress these legislative protections.

Federal acceleration of COVID-19 vaccine development

To accelerate COVID-19 vaccine development, as well as treatments, the National Institutes of Health ("NIH") and Foundation for the NIH ("FNIH") recently announced the new Accelerating COVID-19 Therapeutic Interventions and Vaccines ("ACTIV") partnership between regulatory agencies – NIH, HHS Office of the Assistant Secretary for Preparedness and Response, FDA, Centers for Disease Control and Prevention ("CDC"), and the European Medicines Agency ("EMA") – and 16 biopharmaceutical companies, several of which are already actively engaged in vaccine development against the SARS-CoV-2 virus.[1] Pertinent to vaccines, ACTIV will rapidly prioritize vaccine candidates and advance development by collaboration on critical vaccine science; development and use of master clinical trial protocols to enable rapid collection of clinical data on immune responses to candidate vaccines; and engagement with regulators for "surrogate" endpoints for clinical evaluation. At this time, it is not clear if the acceleration of vaccine development may include flexibility or "partial waiver" of certain regulatory requirements.

Premarket clinical vaccine development. In the U.S., clinical testing of an investigational vaccine requires conduct of the studies under an FDA-approved Investigational New Drug Application ("IND"), including full compliance with all legal requirements for the protection of human subjects.[2] A marketing application with the data is then submitted to the Center for Biologics Evaluation and Research ("CBER") and, if the application is acceptable, the vaccine is licensed for distribution in interstate commerce under a Biologics License Application ("BLA"). Following pre-clinical development of the potential construct of the vaccine that is intended to incite an immune response by the recipient, including animal testing, clinical testing of a vaccine candidate under an FDA-approved IND generally follows the following sequence: phase 1 testing of safety, dose-finding, and immunogenicity in a very small number of healthy adults; phase 2 testing of safety and dose ranges in hundreds of volunteers, including expansion of subject age; and phase 3 testing in thousands of volunteers to determine if the vaccine actually lowers the rate of infection compared with a control group and obtain additional safety information to provide adequate product labeling, including disclosure of potential risks and benefits. In the context of the current COVID-19 pandemic, Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases, recently cautioned that even accelerated vaccine development would take at least a "year to year and a half."[3] Following this announcement, several vaccine experts objected that this was not realistic, may compromise safety, and noted that vaccine development typically takes over 10 years.[4] In a publicly transmitted Senate Health Committee hearing on May 12, 2020, Dr. Fauci updated his prediction and noted that the time course of moving vaccine development into phase 1 human testing was occurring more rapidly than he previously estimated.[5]

Multiple shots on goal. According to the World Health Organization, over 100 potential COVID-19 vaccines are in development around the world. Currently, several U.S. and foreign companies have launched, or are about to launch, phase 1 clinical safety trials of vaccines targeted against SARS-CoV-2 virus.[6] In this race, the University of Oxford Jenner Institute announced that it initiated human testing of a COVID-19 vaccine on April 23rd and intends to dose 10 healthy volunteers and then recruit up to 1102 subjects;[7] human testing began following testing of a single dose in six monkeys that resisted infection after exposure to the virus.[8] As another example of accelerated COVID-19 vaccine development, Pfizer and BioNTech just announced completion of dosing of the first subject cohort in Germany and initiation of phase 1 dosing in the U.S. and emphasized the "less than four-month timeframe" for the transition from pre-clinical studies to human testing.[9] On May 7th, Moderna Therapeutics announced that it intends to accelerate development by initiating a phase 2 trial while its phase 1 trial, which is being conducted by the National Institute of Allergy and Infectious Diseases, is still ongoing.[10]

Unique challenges of vaccine trials for COVID-19: Potential implications for liability

Clinical development of all vaccines differs from therapeutic drugs and biologics because testing is done in healthy volunteers rather than patients. Thus, demonstration of safety is paramount. Further, prior to clinical testing in healthy volunteers, there is usually extensive testing of safety in non-human primates. In addition, the transition from animal studies to the progression from phase 1 through phase 3 clinical testing is usually sequential and cautious because of prior historical experience of unanticipated safety issues during vaccine development as well as the need to identify negative occurrences such as "immune enhancement" where the vaccine actually weakens the individual's response to the infectious virus and increases the risk of infection. Potential adverse "immune enhancement" is a particular safety concern for development of a COVID-19 vaccine.[11] In the acceleration of vaccine development for COVID-19, there are also potential safety risks related to shortening and overlapping the safety evaluation processes that are usually sequential, including very rapid exposure to large populations of healthy people and contemporaneous testing in animals. In addition, several of the vaccines in development are based on the delivery of synthetic RNA or DNA genetic sequences, which are based on the RNA genetic code of the SARS-CoV-2 virus, for

uptake inside the human subject's own cells to produce "SARS-CoV-2-like" proteins to trigger the body's immune response. This type of vaccine construct, in which a synthetic genetic sequence must be taken up inside the healthy volunteers' cells to trigger the immune response, has not been previously tested in humans and shown to be safe either short-term or long-term. In addition, for a virus as dangerous as SARS-CoV-2, it is generally viewed as unethical to artificially challenge healthy volunteers with the active virus to see if an effective immune response occurs. To determine if the vaccine is effective, it must be trialed on humans during a natural outbreak of the virus. When vaccines for SARS were under development, they were ultimately put on hold because the SARS epidemic had subsided, preventing demonstration of benefit. Thus, for current vaccine development to prevent COVID-19 infection, there is also the risk that normal volunteers may develop serious injuries without any later demonstration of efficacy (benefit) of the vaccine.

Potential avenues for protection from liability

THE VACCINE ACT

As the race to develop vaccine candidates to stem the tide of the SARS-CoV-2 virus progresses, countless companies will begin recruiting healthy volunteers to participate in clinical trials. While the focus will certainly be on the safety of those volunteers and the scientific outcomes of the trials, companies should also keep in mind ways to protect against potential liability that may arise because of the accelerated development timetable. Given its nearly 35-year history, many may be familiar with the protections afforded to vaccine manufacturers under the "Vaccine Act." However, developers and manufacturers of COVID-19 vaccines cannot count on those liability protections.

Congress enacted the Vaccine Act, formally known as the National Childhood Vaccine Injury Act of 1986,[12] in part to address increasing litigation and litigation costs relating to vaccine-related injuries that were disincentivizing manufacturers from the development of new vaccines. To serve this goal and allow for no-fault compensation to injured parties, the Vaccine Act created the National Vaccine Injury Compensation Program ("VICP") through which those injured parties can be compensated for injures recognized to be caused by covered vaccines and listed on the Vaccine Injury Table (the "VICP Table").[13] Vaccine manufacturers, in turn, are not parties to VICP claims and are able to avoid liability and damages.[14]

While the same policy reasons behind the Vaccine Act and VICP may resonate in today's COVID-19 world, as the name suggests, the focus of the Vaccine Act protections is vaccines primarily administered to children.[15] As a result, the VICP Table currently includes vaccines such as measles, mumps, and rubella ("MMR"); polio; diphtheria, tetanus, and acellular pertussis (*e.g.*, "DTaP"); and seasonal influenza vaccines.[16] While the Secretary of HHS may amend the VICP Table, following notice and comment, to include new vaccines, that authority is limited to those vaccines that are recommended by CDC for routine administration to children and pregnant women. At this stage, it is unclear whether CDC ultimately will characterize COVID-19 vaccines as recommended for routine administration to children or pregnant women.[17] In light of the novelty of the virus and the many unknowns surrounding a vaccine, even if COVID-19 vaccines are added to the VICP Table, that amendment may be years in the future and, thus, would not afford protections to developers and manufacturers engaging in accelerated clinical trials now.[18]

THE PREP ACT AND THE COVID-19 DECLARATION

While the Vaccine Act will not shield COVID-19 vaccine manufacturers, the Public Readiness and Emergency Preparedness Act ("PREP Act") can provide protection from liability.[19] Under the PREP Act, the Secretary of Health and Human Services ("HHS") may issue a Declaration immunizing certain entities from liability for claims arising from

the "manufacture, distribution, administration, or use of medical countermeasures" used to respond to a public health emergency. On March 17, 2020, the Secretary issued the Declaration Under the Public Readiness and Emergency Preparedness Act for Medical Countermeasures Against COVID-19 ("Declaration").

PREP Act's coverage of investigational vaccines. The Declaration and the PREP Act shield developers and manufacturers from liability arising from the use of "covered countermeasures." These "covered countermeasures" must be approved or cleared by FDA, the object of an investigational exemption under sections 505(i) or 520(g) of the Food, Drug and Cosmetic Act ("FDCA"), or authorized for emergency use pursuant to an Emergency Use Authorization under sections 564, 564A, or 564B of the FDCA. The Declaration explicitly lists vaccines as a covered countermeasure. As discussed, all entities seeking to develop and produce a COVID-19 vaccine must first submit an IND application prior to initiating clinical trials. While not binding law, an Advisory Opinion published by HHS to accompany the Declaration states that, consistent with the PREP Act, a COVID-19 vaccine "used under . . . an [IND] application" is a covered countermeasure and, thus, within the scope of PREP Act immunity. Furthermore, the PREP Act covers injuries arising from clinical testing of investigational vaccines as well as injuries arising from the ordinary post-trial administration of vaccines to the public.[20]

Scope of PREP Act tort immunity. Under the PREP Act, a plaintiff may succeed in a suit for personal injury or property damage against a covered manufacturer or developer arising from the use of a covered countermeasure only if the plaintiff can prove by clear and convincing evidence that the manufacturer or developer engaged in willful misconduct resulting in death or serious injury. Furthermore, plaintiffs are subject to a higher pleading standard and, crucially, cannot bring suit unless and until the Secretary or the Attorney General have initiated an enforcement action regarding the act or omission at issue and that has resulted in a final outcome of criminal conviction, injunction, civil monetary payment, a product recall, or some other "covered remedy."[21]

Similar to the Vaccine Act, the PREP Act authorizes the establishment of a mechanism for compensation for those who suffer serious injury or death directly caused by covered countermeasures,[22] through the Countermeasures Injury Compensation Program ("CICP"). The PREP Act requires the Secretary to establish procedures for compensation through the CICP after issuing a Declaration. The Secretary has yet to release an interim rule regarding these procedures, though the Declaration states that the CICP will compensate certain individuals, suggesting that such a rule could be on the way. Like the VICP Table, CICP Injury Tables identify covered countermeasures and the injuries or conditions for which compensation is available based on a rebuttable presumption of causation. Because causation is presumed, however, covered injuries or conditions are only those for which there is "compelling, reliable, valid, medical and scientific evidence."[23] Individuals who suffer serious injury or death directly caused by administration or use of a COVID-19 vaccine may qualify for compensation under the CICP, provided the injury is listed in the Injury Tables. However, a plaintiff will waive a tort claim for the injury in either federal or state court if he accepts compensation from the CICP.[24]

In light of the accelerated manner in which vaccine development is progressing, an important open question is whether manufacturers and developers would be shielded by the PREP Act for potential liability arising out of a failure of the investigational vaccine to immunize an individual and prevent COVID-19 infection. While ineffectiveness of a covered countermeasure is not a "covered injury" compensable through the CICP,[25] the PREP Act's definition of "covered injury" is likely broader. The PREP Act broadly states that its immunity applies to "any claim for loss that has a causal relationship with the administration to or use by an individual of a covered countermeasure."[26] Furthermore, when parents sued a hospital because their daughter was vaccinated without their consent, the Eastern District of Missouri found that this alleged injury fell under the PREP Act.[27] If being vaccinated without consent is an injury within the scope of the PREP Act, then it is likely that ineffectiveness of a vaccine would also be a covered injury.

For a more in-depth discussion of the scope of immunity under the PREP Act, see Tort Immunity under PREP Act and COVID-19 Response Declaration.

Steps COVID-19 vaccine developers can take to limit liability

With the above issues in mind, developers and manufacturers should consider taking the following steps to shield themselves from liability, particularly to avoid any claim of "willful misconduct," as they continue their efforts to make COVID-19 vaccines widely available:

- Manufacturers should make sure they are meticulously following the requirements of the PREP Act and Declaration. For example, manufacturers should not move forward with clinical trials until FDA has approved their IND applications. Furthermore, while the PREP Act provides broad immunity, manufacturers must be mindful of the fact that they will not be immunized for willful misconduct.
- Informed consent documents, as well as clinical trial contracts between the manufacturer and clinical site, should specify that investigational vaccines fall under the purview of the PREP Act and, thus, manufacturers and developers will legally not be liable for injuries that might arise from the clinical trial, including the ineffectiveness of the vaccine, absent evidence of willful misconduct. Furthermore, these documents should inform trial participants of the likely future availability of the CICP as a source of compensation for serious injuries that could be suffered as a result of an investigational COVID-19 vaccine.
- Companies should also consider including a statement in their informed consent documents explaining the accelerated nature of the clinical trial and noting the potential additional risks inherent to the abbreviated timeline. For example, human trials may be proceeding without the benefit of data normally gathered from animal studies, or phase 1 and phase 2 human trials may be moving forward on overlapping tracks rather than sequentially. Companies should be transparent about any such deviations from the typical vaccine development process.
- Informed consent documents and related recruitment materials should be as fulsome as possible in terms of possible side effects or adverse events. For example, in the mandatory disclosure in the consent form of *reasonably foreseeable risks*,[28] manufacturers should add warnings about the fact that the investigational vaccine might weaken the patient's response to the SARS-CoV-2 virus (*i.e.*, the potential for immune enhancement of the likelihood of infection). Informed consent documents should also be updated timely with additional safety information as it emerges in the developing science. Manufacturers and developers should ensure prompt IRB/ethics committee review of updated informed consent documents and determine if re-consent of enrolled subjects is required.
- Sponsors of clinical trials of biological products, including vaccines, are legally required to register these "applicable clinical trials" on ClinicalTrials.gov and, at a specified later date, submit information on results, adverse events, and deaths regardless of whether or not the product is later approved or licensed by FDA.[29] Manufacturers conducting clinical trials of COVID-19 vaccines should be aware that the disclosure of results, adverse events, and deaths includes the study protocol and all IRB-approved revisions, which will then be readily available for public scrutiny.

As the legal and practical issues related to 2019 Novel Coronavirus (COVID-19) continue to evolve, King & Spalding's Crisis Practice Coronavirus Task Force brings experience and judgment to help the c-suite, legal team

and the Board address mounting business and legal issues. Our clients benefit from the experience of our Crisis Practice lawyers who have deep experience leveraging the firm's resources around the globe to routinely assist clients in incident response planning and live crisis management situations. We are also able to leverage relationships with premier global duty of care and crisis communications advisors to help our clients stay in front of today's unprecedented and rapidly unfolding developments. Additionally, as a national leader in pharmaceutical and medical device law, King & Spalding is uniquely positioned to guide its clients through the evolving landscape of pharmaceutical and medical device law in the coming months.

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[1] April 17, 2020. HHS NIH News Release. "NIH to launch public-private partnership to speed COVID-19 vaccine and treatment options." Accessed at https://www.nih.gov/news-events/news-releases/nih-launch-public-private-partnership-speed-covid-19-vaccine-treatment-options.
[2] See 21 C.F.R. pts. 50, 56, & 312.
[3] March 25, 2020. White House Daily Briefing.
[4] April 1, 2020. Business Insider. "Fauci said it will take 12 to 18 months to get a coronavirus vaccine in the US. Experts say a quick approval could be risky."
[5] May 12, 2020. Public hearing of the U.S. Senate Health, Education, Labor, and Pensions Committee.
[6] April 29, 2020. Politico. 'The drugs and treatments that could stop Covid-19." Among companies that have launched or are preparing to launch phase 1 vaccine studies are Moderna, for which the U.S. Biomedical Advanced Research and Development Authority (BARDA) has pledged up to $483 million to accelerate the vaccine development; Johnson & Johnson, in collaboration with BARDA and Beth Israel Deaconess Medical Center; Pfizer in collaboration with the German company BioNTech; Sanofi in collaboration with GlaxoSmithKline; and CanSino Biologics and Beijing Institute of Biotechnology. Accessed at https://www.politico.com/news/2020/04/27/tracking-the-hunt-for-coronavirus-drugs-and-vaccines-211416.
[7] April 23, 2020. University of Oxford News & Events. "Oxford COVID-19 vaccine begins human trial stage." Accessed at http://www.ox.ac.uk/news/2020-04-23-oxford-covid-19-vaccine-begins-human-trial-stage
[8] April 30, 2020. The New York Times. "In Race for a Coronavirus Vaccine, an Oxford Group Leaps Ahead." Accessed at https://nyti.ms/3cWsEf9.
[9] May 5, 2020. Press release. "Pfizer and BioNTech Dose First Participants in the U.S. as Part of Global COVID-19 mRNA Vaccine Development Program. Accessed at https://www.pfizer.com/news/press-release/press-release-detail/pfizer_and_biontech_dose_first_participants_in_the_u_s_as_part_of_global_covid_19_mrna_vaccine_development_program.
[10] May 7, 2020. Barron's. "Moderna Speeds Up Timeline for COVID-19 Vaccine, Gets All-Clear for Phase 2 Trial." Accessed at https://www.barrons.com/articles/moderna-coronavirus-vaccine-covid-19-phase-2-approval-fda-51588857786
[11] March 18, 2020. "Summary of FDA & EMA Global Regulators Meeting on Data Requirements Supporting First-in-Human Clinical Trials with SARS-CoV-2 Vaccines." Accessed at https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/summary-fda-ema-global-regulators-meeting-data-requirements-supporting-first-human-clinical-trials
[12] 42 U.S.C. §§ 300aa-1 *et seq*.

[13] The VICP Table provides a list of covered vaccines and associated injuries for which there is a rebuttable presumption that the vaccine caused the injury. 42 C.F.R. § 100.3.
[14] The VICP is funded via a $0.75 excess tax imposed on each dose of covered vaccines.
[15] The 21st Century Cures Act, enacted in December 2016, amended the Vaccine Act to expand coverage beyond just childhood vaccines to also include vaccines recommended by CDC for routine administration during pregnancy. *See* Pub. L. 114-255 §3093(c)(1).
[16] 42 C.F.R. § 100.3.
[17] For example, while seasonal influenza vaccines are included on the VICP Table, the 2009 pandemic H1N1 influenza ("swine flu") vaccine is not. Instead, those injured by the H1N1 vaccine may receive compensation through the Countermeasures Injury Compensation Program ("CICP"), discussed below.
[18] However, if COVID-19 vaccines ultimately are added to the VICP Table, investigational vaccines distributed under an IND would also be covered.
[19] Declaration Under the Public Readiness and Emergency Preparedness Act for Medical Countermeasures Against COVID-19, 85 Fed. Reg. 15,198 (eff. Feb. 4, 2020, pub. Mar. 17, 2020).
[20] *See* 42 U.S.C. §§ 247d-6d(c)(5) (PREP Act immunity "applies to any claim for loss that has a causal relationship with the administration to or use by an individual of a covered countermeasure, including a causal relationship with the design, development, ***clinical testing or investigation***, manufacture, labeling, distribution, formulation, packaging, marketing, promotion, sale, purchase, donation, dispensing, prescribing, administration, licensing, or use of such countermeasure.") (emphasis added).
[21] *See* 42 U.S.C. §§ 247d-6d(c)(5).
[22] *See* 42 C.F.R. § 110.20(a); 110.3(g)(1), (z).
[23] *See* 42 C.F.R. § 110.20(b). Individuals with injuries not listed in the Injury Tables may still pursue claims under the CICP but must prove causation by compelling, reliable, valid, medical and scientific evidence. *See* 42 C.F.R. § 110.20(c).
[24] U.S. Dep't of Health & Human Servs. PREP Act Q&As. Accessed at https://www.phe.gov/Preparedness/legal/prepact/Pages/prepqa.aspx.
[25] 42 C.F.R. § 110.20(d).
[26] 42 U.S.C. § 247d-6d(a)(2)(B).
[27] *Kehler v. Hood*, 2012 WL 1945952 (E.D. Mo. 2012).
[28] 21 C.F.R. § 50.25(a)(2).
[29] 45 C.F.R. pt. 11.