Center for Biologics Evaluation and Research's (CBER)

Vaccines and Related Biological Products Advisory Committee (VRBPAC)

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Written Comments of Lynda Dee, submitted October 15, 2020

Risk versus Benefit and Community Mistrust

We all know what a risk/benefit ratio analysis is. It is the business of the FDA to apply risk versus benefit principles to every drug, biologic or device before FDA approval or authorization is granted, including Emergency Use Authorization (EUA). The EUA standard for approval is much less stringent than the Agency's full approval standards. Nevertheless, there should be clear and compelling evidence in the case of vaccines because they are administered to healthy people with no other alternatives, and thus require a much higher standard of probable safety and efficacy demonstrated in at least one well-designed clinical trial that demonstrates that the benefit outweighs the risk by establishing safety and efficacy in a clear and compelling manner. (Federal Food, Drug & Cosmetic Act, 21 USC, 360bbb-3, Section 564 and FDA Guidance for Industry 2017).

Alarmingly, the AstraZeneca (AZ) Phase 3 AZD1222 COVID-19 vaccine trial was halted on September 8, 2020, as a result of a participant developing transverse myelitis which may have resulted from AZD1222 use. Transverse myelitis is a serious autoimmune condition that may take years to resolve, and may result from a post-vaccine autoimmune phenomenon during which the body's immune system mistakenly attacks its own tissue. Although AZD1222 trials have been reopened in the UK, Brazil, South Africa, India and Japan, they remain paused in the US. According to STAT News, The Johnson & Johnson (J&J) 60,000 person Phase 3 vaccine trial was mysteriously halted on October 12, 2020 due to "an unexplained illness in a study participant." These forebodings should convince us that the remaining Phase 3 vaccine trials clearly need to continue in order to obtain more safety data before the FDA begins its independent vaccine data review process, and before any EUA and/or any other licensure is granted.

Even though there is a great need for a COVID-19 preventative vaccine, this need is outweighed by the need to be sure we first do no serious harm, and that we do not essentially destroy the future COVID-19 vaccine effort. The AZ and J&J vaccine signals are stark warnings, and the exact reason why we conduct clinical trials.

The White House's vaccine effort has proceeded at "warp speed". While the HIV community has done much to expedite the conduct of clinical trials and the overall drug development process, divergence from well-established norms should be based on reputable science and biostatistics, not politics. From a community perspective, a very different sort of risk/benefit analysis is occurring here. The instant question for this long-time AIDS activist is the risk and benefit for whom. The general public and other stakeholders are shouldering all the risk while the Administration is attempting to reap all the benefit for re-election purposes.

FDA Commissioner Stephen Hahn has publicly stated the minimum efficacy point must be at least 50%. Estimates indicate that studies with an n of 30,000 could possibly predict 50% efficacy with only 150 endpoints, 100 in the placebo arm and 50 in the treatment arm.[1] While this very limited number of endpoints may possibly be acceptable from an efficacy perspective, it is not sufficient to determine vaccine safety, and will not justify any DSMB stopping a trial before it is completed without additional safety data. Adequate safety cannot be assessed from efficacy events alone. We do not want a repeat of the 1976 swine flu disaster. The swine flu vaccine was rushed to market without adequate safety data, and was later linked to hundreds of cases of paralyzing Guillain-Barre syndrome.

Further, although half of the COVID-19 cases in the United States (US) are among people of color, non-white people represent only 15% of the trial participants in the Phase 3 COVID-19 vaccine trials.[2] Without more data from communities of color, we may never know if any of the current Phase 3 COVID-19 vaccines are safe and effective in ethnic and racial minorities. This is an untenable situation as people of color are not only disproportionately infected with COVID-19 with a three times greater infection rate than whites, they also suffer disparate outcomes, resulting in serious morbidity and mortality two times higher than that of whites and Asians as a result of co-morbidities linked to poverty and unequal healthcare.[3]

There is a great deal of deep distrust and lack of confidence about vaccines and clinical trials generally in the US. This mistrust is particularly evident in the African-American community that has a long standing, agonizing memory of the unethical Tuskegee Syphilis Study. We desperately need sufficient data in people of color, older peoples and pregnant women as well as people with other co-morbidities such as HIV, HBV and HCV to ensure that we know how these vaccines work in this these populations. It is important to note that people with HIV were initially excluded from two of the four current Phase 3 vaccine trials. The exclusion was reversed only because of the rapid response and fierce advocacy on the part of the HIV community.

Recent polling tells us that public apprehension in the COVID-19 arena has reached significant new highs. An NPR, PBS News Hour/Marist poll conducted August 3-11, 2020, revealed that 35% of Americans are suspicious of the Administration's push to speed up COVID-19 vaccine development. A USA Today/Suffolk poll conducted the week of September 1, 2020, disclosed that 2/3 of Americans will not take any COVID-19 vaccine when it initially becomes available. One in four in this survey said they would never take a COVID-19 vaccine. According to the polls, much trepidation has been caused by names like "Operation Warp Speed" and the White House's politicization of vaccine development which is viewed as a re-election maneuver.

The transverse myelitis case is a clear signal of a possible very serious risk related to AZD1222 which shares a platform with other non-Phase 3 COVID-19 candidates. If the current Phase 3 COVID-19 vaccine trials are stopped early and transverse myelitis or other unknown safety issues surrounding the J&J trial or other vaccine trials are later linked to vaccine use, the entire vaccine effort may very well fall into even more churning chaos, the operative description for everything the current Administration touches. If such issues arise, it will only further erode public trust. As a result, we may never be able to determine if any current or future vaccines are safe and effective in preventing COVID-19 if people are no longer willing to enroll in vaccine trials because of suspicion and skepticism.

Because of mounting mistrust, many imminent researchers have called for the Phase 3 vaccine trials to be completed, and the data be made publicly available for review before any FDA EUA. Even nine vaccine manufacturers, "AstraZeneca, GlaxoSmithKline, Johnson & Johnson, Moderna, Novavax, Pfizer and BioNTech, Sanof" have signed an extraordinary letter, pledging "not to seek regulatory approval before safety and efficacy of their experimental coronavirus vaccine has been established in Phase 3 clinical trials, an extraordinary effort to bolster public faith in a vaccine amid President Trump's public rush to introduce a vaccine before Election Day." "The statement left open the door for partial data from the massive Phase 3 vaccine trials…being used to seek emergency-use authorization."[4] Moreover, Albert Bouria, Pfizer's Chief Operating Officer has said that Pfizer's Phase 3 COVID-19 vaccine trial could have sufficient events to establish efficacy by the end of October 2020.[5]

Widespread chaos has blanketed many Health and Human Services (HHS) agencies as a result of political pressure from the Administration. The FDA, the nation's world renowned gold standard gatekeeper of independent data review for safety and efficacy for experimental interventions, has already given EUA to many numerous SARS-CoV-2 antibody tests that were allowed to be marketed without any FDA review, only to be withdrawn as a result of NIH testing after immense pressure from the scientific and

patient communities. Nevertheless, HHS ruled that the NIH had no authority to review the antibody tests and restored EUA status to many useless antibody tests.

Hydroxychloroquine (HCQ) received EUA after being touted by the President as a cure for COVID-19 without any evidence whatsoever, only to have it withdrawn after every single NIH trial had to be stopped by DSMBs for non-efficacy. What a waste of time and energy as well as precious human and financial resources!

Convalescent plasma (CP) received EUA before the FDA's review was complete in an unbelievable maneuver by the Administration one day before the start of the Republican National Convention in an end run around the FDA amid a huge efficacy controversy in the field. Commissioner Hahn had a new version of the data daily. First he stated that CP was 35% effective. Then, he had to walk that back.[6] The situation at the FDA has been pure pandemonium, caused by flagrant meddling by the Administration for obvious political purposes. We may now never know if CP is effective against COVID-19. The President is now calling for a Regeneron EUA, claiming it is a cure! Regeneron Pharmaceuticals has already submitted an EUA application!

Commissioner Stephen Hahn has also stated publicly that the FDA could consider EUA for a COVID-19 vaccine before the Phase 3 trials are completed.[7] These tensions seemed to have been overshadowed by other recent events. But on October 5, 2020, the White House initially blocked the new stricter FDA proposed EUA Guidelines for COVID-19 vaccines, championed by Commissioner Hahn who is now apparently fully supporting career FDA scientists on a number of controversial issues. Amazingly, the FDA courageously circumvented the Administration by publishing the new FDA Guidelines. This action was met widespread acceptance from both the scientific community and industry. The Federal Office of Management and Budget (OMB) approved the new Guidelines on October 6, 2020! The FDA should be applauded for this incredible tactical maneuver. Kudos to the Agency!!!

Arguably, worst of all, the CDC, which started this clown car chaos with their ineffective COVID-19 diagnostic test and anemic Guidances, not the least of which are the lily livered Guidances for meat packers and their recent irrational testing Guidance which flies in the face of established science regarding the highly contagious nature of asymptomatic COVID-19. CDC Director Robert Redfield, MD also contacted the states via letter on August 27, 2020, attempting to prepare for coronavirus vaccine distribution by November 1, 2020, and indicating that the CDC has contracted with McKesson Corporation to distribute COVID-19 vaccines through various entities, including state and local health departments. Redfield stated "the CDC 'urgently requests' your assistance in expediting applications for these distribution facilities and, if necessary, asks that you consider waiving requirements that would prevent these facilities from becoming fully operational by November 1, 2020."[8] Only the NIH, so well represented by Anthony Fauci, MD has consistently maintained its integrity.

Is this Administration capable of successfully distributing the necessary doses the AZ, Moderna and Pfizer vaccines that all require the administration of two doses weeks apart? The AZ and Moderna vaccines need to be stored at below 20 degrees Celsius. The Pfizer vaccine needs to be stored at below 70 degrees Celsius! We all remember the distribution debacle when this Administration tried to distribute some 32,000 doses of Gilead's remdesivir to only seven US states.[9] Will they be able to distribute even 100,000 million vaccine doses that need such freezer capacity as well as vials and other necessary administration equipment anywhere near the November 1, 2020 in time for the election? I think not!

As we know, the presidential election occurs on November 3, 2020. Certainly there is enough evidence for a jury to find beyond a reasonable doubt that authorizing an EUA before vaccine trial data are sufficiently analyzed and VRBPAC reviewed is clearly an election maneuver, and that the White House is politicizing the vaccine approval process for its own benefit, without the least bit of care or concern for public health and safety. The Administration is responsible for the US being the country with the most COVID-19 cases in the entire world, over 8,000,000, and over 220,000 deaths, both rising daily as well as

a COVID-19 devastated economy. There is no end in sight, and no solutions to the US COVID-19 crisis without maintaining rigorous scientific integrity across the board.

As I initially wrote these comments which have been repeatedly revised and supplemented as a result of many recent events, the thought of the havoc being reeked upon marginalized and undermined HHS agencies literally brought tears to my eyes. I have been an AIDS activist for over 33 years, lost my son to Sudden Infant Death Syndrome in 1985, my husband to AIDS in 1987, my father to Alzheimer's Disease in 1989, survived cancer in 1996, and was cured of HCV in 2012. I have personally learned the hard way that evidence based medicine is the only reliable way to treat and eventually eradicate diseases. Having worked closely with NIH and FDA for many years, including being a community representative on three FDA CDER Antiviral Advisory Committees, my heart was breaking over the reckless repudiation of science, well-established clinical trial processes and public health policies as well as the shameless outright destruction of the FDA's credibility as a result of White House pressure. The relief I experienced after the OMB approved the new COVID-19 Guidelines was tremendous!

Nevertheless, the highly politicized current climate is a clear and present danger to the ultimate vaccine effort. We all know that the White House is capable of drastically changing its position at the drop of a hat. Further, the potentially serious signal raised by the recent potential transverse myelitis autoimmune AZD1222 case and the mysterious J&J case remind us of what could happen if the FDA is derelict in its duty of clearly establishing the safety of COVID-19 vaccines. Many members of the public will be reassured about the safety and efficacy of any vaccine candidate authorized and/or licensed pursuant to stringent VRBPAC guidelines. At this critical juncture, the VRBPAC may be the last official bastion of independent US scientific experts able to help prevent the foolhardy politicization of science, and ensure public protection against authorization and/or licensure of COVID-19 vaccines without proven safety and efficacy. Thus, I urge the VRBPAC to advance the Agency's bravery and determination by considering the following.

Recommendations regarding the data necessary for the development, authorization and/or licensure of vaccines to prevent COVID-19:

1. Provide stringent recommendations to address uniform standards for assays and other essential research tools and metrics so we are all speaking the same language.
2. Acknowledge that only an authorized DSMB is permitted to stop current Phase 3 COVID-19 vaccine trials before they are completed, that all trial results must be independently reviewed by career FDA professionals and that although not required, VRBPAC review should occur before EUA and/or licensure for every vaccine candidate in order to foster scientific integrity and promote public trust at this critical juncture.
3. Require that in all future COVID-19 vaccine trials, a significant number of older adults and people of color are included and stratified in order to permit a safety and efficacy sub-analysis for these populations as well as their co-morbidities. If there are insufficient numbers in current Phase 3 trials to permit such a sub-analysis, describe potential safety and efficacy signals that would justify EUA in these especially vulnerable populations, require Post-Marketing studies that will establish safety and efficacy in these populations.
4. Recommend that adequately funded government and industry Community Advisory Boards (CABs) constituted with COVID-19 survivors and advocates be established immediately to foster education and inclusion of vulnerable populations in future vaccine trials.
5. Recommend that all COVID-19 vaccine trials include people with controlled HIV, HBV and HCV, and a clear pathway for inclusion of women of child-bearing age and pregnant women, including a final study report or timeline for completion for a Developmental and Reproductive Toxicology (DART) study.
6. Require that at least 100 primary endpoints occur to establish efficacy, 75 COVID-19 infection events in the placebo arm, and no more than 25 cases of COVID-19 in the treatment arm, and recommend a standard number of severe COVID-19 events in the both the placebo versus

vaccine arms to ascertain enhanced disease generally as well as vaccine associated enhanced respiratory disease.

7. Require that at least 3,000 participants be followed for at least three months after the requisite number of vaccine doses are administered in order to provide the time necessary to capture most serious adverse events and events of special interest.
8. Recommend that all current Phase 3 participants be followed for at least five years after trial completion to establish vaccine durability and long-term safety, utilizing all required pharmacovigilance metrics, including a minimum of deaths, hospitalizations and serious or clinically significant adverse events.
9. Provide required safety and efficacy pathways/standards for both EUA versus Biologic License Application (BLA) approvals.
10. Approve the most recent FDA proposed Guidelines for EUA of COVID-19 vaccines regarding Chemistry, Manufacturing and Control Information Guidelines in Appendix II of Briefing Document for this meeting, or in the alternative, approve all the recommendations set forth in the new stricter FDA Guidelines.

Thank you for your dedication, committed service and your consideration of my comments.

[1]COVID-19 vaccine by Nov. 1: Scientists call for full release of data before distribution; NYT, Erika Edwards, 9/3-4/2020.

[2]More People Of Color Needed In COVID-19 Vaccine Trials, NPR Weekend Edition, Lulu Garcia-Navarro, 8/23/2020.

[3]The Color of Coronavirus: COVID-19 Deaths by Race and Ethnicity in the U.S; APM Research Staff, 8/18-20.

[4]Vaccine CEOs issue safety pledge amid Trump's quest for pre-election approval; WAPO, Christopher Rowland, 9/8/20.

[5]Pfizer CEO: We'll Know By October Whether Covid-19 Vaccine Works; Forbes, Bruce Japsen, 8/6/20; Fox Business; Daniella Genovese, 9/8/20.

[6] Trump Pressed for Plasma Therapy. Officials Worry, Is an Unvetted Vaccine Next?: NYT, Sharon LaFraniere, Noah Weiland, Michael D. Shear

[7]FDA leader says agency could consider authorization for Covid-19 vaccine before Phase 3 trials are complete, Financial Times & CNN, Jamie Gumbrecht-Profile-Image, 8/30/20.

[8]CDC Tells States: Be Ready to Distribute Vaccines on Nov. 1, apnews and NYT, 9/2/2020.

[9]Trump officials' dysfunction harms delivery of coronavirus drug; Axious, Jonathan Swan, 5/8/20.

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