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Commentary

US FDA erratic approach to placebo-controlled trials after issuing an emergency use authorization for a COVID-19 vaccine

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Operation Warp Speed has critically impacted the sense of urgency of all stakeholders involved on the development, manufacturing and distribution of COVID-19 vaccines, therapeutics and diagnostics [1]. In these lasts months of rush to develop COVID-19 vaccine candidates, the leadership of the FDA has been critical in setting the requirements that manufacturers should comply with to have their vaccine available through an emergency use authorization (EUA) or a full licensing. This leadership, however, has created a huge issue regarding what should be the attitude of placebo-controlled randomized controlled trials (RCTs) sponsors concerning all participants that were randomized to receive placebo, when a vaccine starts to be deployed.

1. The FDA initial approach

In June, the FDA issued a guidance on how industry should develop COVID-19 vaccine candidates, acknowledging that efficacy phase 3 RCTs should include contingency plans for continued follow up of safety and efficacy in the event that a COVID-19 vaccine becomes available [2]. In this case, the trial sponsor should discuss with the FDA how to address the ethical need to break the blind and offer the available vaccine to placebo recipients. It was clear that the FDA was taking into consideration both ethical and legal requirements. From the ethical perspective, interest of society (scientific knowledge) should never take precedence over the interests of research participants [3]; from the legal perspective, RCTs participants should be aware of any information that could influence their willingness to continue in the trial [4,5]: participants must re-consent to stay in the trial [6].

On October 6 the FDA stated that, following the issuance of an EUA, the sponsor will continue collecting data from the placebo-controlled RCTs "for as long as feasible" [7]. The agency expected that issuing an EUA will not interfere with the conduct of the RCT that will eventually demonstrate efficacy that would drive to the full licensure of the vaccine. Surprisingly, the FDA explicitly considered that the availability of a COVID-19 vaccine under EUA will not impact placebo-controlled RCTs and that these could continue on a blinded fashion [7]. Yet, the agency asked that manufacturers should include strategies to ensure the continuation of RCTs when submitting an EUA, but acknowledged that trial participants could choose to withdraw to receive the available vaccine [7]. Two contradictory statements, as vaccinating those who received placebo forces breaking the blind that could lead, in the worse scenario, to the early termination of the trial as it was started although it could continue as an open-label trial.

2. Clinical trial sponsors raise ethical requirements

On October 15, Pfizer submitted a letter to the FDA commenting on the information provided for the Vaccines and Related Biological Products Advisory Committee (VRBPAC), that was going to be held

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on October 22 [8]. Pfizer and BioNTech correctly believed that they have the ethical responsibility to inform all participants that an emergency authorized vaccine has been issued. Furthermore, in the case Pfizer's vaccine was granted EUA, this company will propose amending the trial protocol to allow cross-over of placebo recipients to the vaccine arm [8]. This issue was discussed at the VRBPAC, and to solve it, the FDA suggested that the vaccine could be made available through an expanded access rather than under an EUA [9]. Yet, it is the manufacturer who decides whether to file an EUA application and its scope (e.g., the population groups included), and the agency who decides whether to approve it or not.

On October 16, Krause and Gruber, two FDA officials, published a reflection on safety and efficacy follow-up issues regarding COVID-19 vaccines under EUA [10]. They were concerned that an EUA will interfere with long-term assessment in ongoing RCTs and claimed that there is the need to continue assessing the vaccine versus placebo "for as long as feasible". They believed that issuing of an EUA does not necessarily imply that the trial must be unblinded to vaccinate those placebo recipients willing to receive the available vaccine; doing so, they admitted, may jeopardize the full licensure of the vaccine. These FDA officials seemed to be suggesting not to offer the available vaccine to those trial participants that received placebo, and that they believed that science – gathering long-term safety and efficacy data– should take preference over the rights of participants, something unacceptable from the legal and ethical perspectives, respectively.

3. The critical points of issuing an EUA

Two are the critical points of issuing an EUA for a COVID-19 vaccine: (a) it could impact all placebo-controlled RCTs on any COVID-19 vaccine candidate; and (b) the key factor being the population groups that will be entitled to be vaccinated.

With regards to the first point, it is not only that the company with a vaccine under an EUA could cross-over placebo recipients to the vaccine arm, but all other companies conducting placebo-controlled RCTs with their own vaccine candidates, should provide the available vaccine to those placebo recipients who request it [11,12]. Concerning the second point if, for instance, only high-risk health workers are included in the EUA, it is likely that RCTs could go on since the number included in trials will likely be limited. If other population groups (eg, elderly) are also included, the situation could dramatically change, since many participants will have to be informed to vaccinate those who want. The issue here will be that, although placebo-controlled RCTs could continue with other population groups, no further double-blind data will be gathered for the elderly. In this situation, scientific knowledge will be correctly aborted for the sake of ethical and legal requirements. The worse situation would be if the EUA includes other additional population groups that could lead to having the majority (if not all) of placebo recipients asking to be vaccinated with the available vaccine: this will likely lead to the early termination of all current phase 3 RCTs with all COVID-19 vaccine candidates as they were conceived and conducted until the deployment of a vaccine. In the USA, the first trials started in Summer 2020. Since it is expected that all Americans will have access to a COVID-19 vaccine no later than April 2021 [13], termination of these trials could happen no later than early Spring 2021, several months before any COVID-19 vaccine candidate trial could had even reached a 12-month follow-up period –the minimum time needed to assess whether the vaccine has or not an effect on the community transmission of SARS-CoV-2 [14].

4. Expanded access as an alternative to EUA

The FDA has managed this critical topic issuing erratic and contradictory statements. It seems that the agency did not realize the serious scientific consequences that the early availability of a COVID-19 vaccine under an EUA could have. Of course, it should be acknowledged that how to address this unprecedented critical situation –a pandemic with thousands of daily deaths and several promising vaccine candidates in the same stage of clinical development– was extremely complex. But a clear and consistent message would have helped a lot to prevent the current confusion, that was clearly showed at the VRBPAC meeting. Meanwhile, it has been suggested that COVID-19 vaccines should not be available under EUAs but through expanded access [15,16].

In an expanded access the protocol should be approved by the relevant IRB, participants must provide informed consent, physicians should report adverse events and the manufacturer should submit safety reports to the FDA [17]. Hence, it is a much more controlled way of administering the vaccine than under an EUA and will restrict its administration to a limited number of individuals.

However, expanded access will not prevent clinical trial participants who received placebo from being vaccinated if they meet the selection criteria of the expanded access protocol. Placebo recipients of RCTs have the same right as all other citizens to be included in an expanded access. Furthermore, placebo recipients of ongoing trials should have readily access to the available vaccine once they are informed by the investigators that the population group to which they belong is being vaccinated.

The issue that an EUA poses may not be fully fixed even with expanded access unless this latter is open only, as it should be expected, to a limited number of very high-risk individuals [15]. Then, following the slow and lengthy procedure of an expanded access tens of thousands of individuals belonging to very high-risk groups will have access to the vaccine, rather than the tens of millions of individuals of all population groups that will be vaccinated in a much shorter period of time under an EUA. To date two companies have expressed their intention to urgently submit to the FDA for EUA; so, they will not pursue the expanded access approach. This latter could only be envisaged in the case the FDA rejects issuing EUAs. This is, however, very unlikely, since most would believe that it is unacceptable from the political and social standpoints.

We have to accept that in few weeks from now, several COVID-19 vaccines will be made available in the USA and many other countries, and that the long-term safety and efficacy effects will not be assessed as should have been expected in a non-pandemic situation. If the FDA would have made clear from the very beginning that issuing an EUA would have jeopardize the conduct of all placebo-controlled RCTs, the society could have openly discussed whether expanded access could be considered the best approach from both the scientific and ethical perspectives. However, it is unclear that a limited access to a vaccine through expanded access would have been acceptable to the public.

Declaration of Competing Interest

The author declare that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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