Emergency use authorization (EUA), conditional marketing authorization (CMA), and the precautionary principle at the time of COVID-19 pandemic

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Accepted: 15 July 2021 / Published online: 27 July 2021
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To the Editor

Coronavirus Disease 2019 (COVID-19) is the most dramatic pandemic of the new millennium and extraordinary vaccination campaigns to reduce the death burden and to prevent the collapse of sanitary and socio-economic systems are needed around the globe [1–4]. Historically, the words ‘vaccination’ and ‘vaccine’ derived from *Variolae vaccinae*, a Latin expression to denote cowpox devised by Dr. Edward Jenner, MD, FRS, FRCPE (May 17, 1749, Berkeley, Gloucestershire—January 26, 1823, Berkeley, Gloucestershire). Jenner pioneered the world’s first vaccine against smallpox and universally he is known as the father of immunology. As often said, his contributions have saved more lives than the work of any other human being. In the years following Jenner’s breakthroughs, vaccines and national policies of compulsory vaccination have become among the most important achievements of the mankind. Nevertheless, vaccine hesitancy has recently gained ground due to the possible adverse reactions to vaccines in healthy subjects. The World Health Organization has identified vaccine hesitancy as one of the top ten threats to health globally [5].

During the ongoing COVID-19 pandemic, the urgent need to stop the rising death trend and the saturation of hospital services, and to revive a restriction-free economy, has prompted global regulatory agencies to authorize specific vaccines for emergency use, the so-called ‘emergency use authorization’ (EUA). For

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conditional marketing, there is a different form of provisional authorization called ‘conditional marketing authorization’ (CMA).

What do EUA and CMA really mean? EUA does not represent approval of a drug or device in the full statutory meaning of the term, but instead authorizes use of an unapproved product, or an unapproved use of an approved product, during a declared state of emergency [6]. Authorities designed EUA to quickly respond to public health threats, such as bioterrorism. An EUA terminates once the state of emergency is over or when a product or an unapproved use is approved through normal channels.

A product can be considered for EUA if it is reasonable to believe that it may be effective to prevent, diagnose, or treat serious or life-threatening diseases or conditions caused by one or more chemical, biological, radiological, or nuclear agents. The “may be effective” standard for EUA requires a lower level of evidence than the “effectiveness” standard adopted by regulatory agencies for product approvals. The latter results from a benefit/risk analysis based on the totality of the scientific evidence available, by virtue of which is reasonable to believe that the product may be effective for the specified purpose and that its benefits outweigh the inherent risks.

In contrast, CMA is a pragmatic tool for the fast-track conditional approval of a medicine to address an unmet medical need. Its purpose is to make an innovative drug immediately available to target a seriously debilitating, rare or life-threatening disease devoid of any treatment, to provide patients with a major therapeutic advantage over existing treatments, or to save as many lives as possible in course of public health emergencies—such as a new pandemic [7]. Approval is granted on the condition that an applicant company will supply additional information after the drug placing on the market. CMA guarantees that the medicine meets sufficient standards for safety, efficacy and quality; that is, that the benefit/risk balance is favorable. But, comprehensive data are still required post-approval, unlike after a normal marketing authorization where all data are submitted before authorization is granted.

As soon as enough data have been gathered to show the drug’s benefit/risk balance remains definitively positive, the company is expected to make a formal application; in this way, the medicine can be authorized for human use without reservations.

However, in epistemology, philosophy and law, application of the ‘precautionary principle’ (PP) represents a prudential approach to innovations with potential for causing harm, when extensive scientific knowledge on the matter is lacking [8]. It emphasizes caution in advance, pausing, reflection and review before leaping into significant innovations. Critics argue that PP is vague, self-canceling, an obstacle to scientific progress, and, apparently, in contrast with the Popperian criterion of falsifiability [9]. Public health authorities interrupted use of the AstraZeneca COVID-19 vaccine (trade name: Vaxzevria®) for some days in many European countries following notifications of serious adverse events, in particular those from the Paul Ehrlich-Institut, the German Federal Institute for Vaccines and Biomedicines [10]. Subsequently, after about two months from the CMA for COVID-19 Vaccine AstraZeneca [11], the European Medicines Agency updated the product information in the midst of vaccination campaign, as follows:

“thrombosis with thrombocytopenia syndrome (TTS), in some cases accompanied by bleeding, has been observed very rarely following vaccination with Vaxzevria®. This includes severe cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. Some cases had a fatal outcome. The majority of these cases occurred within the first three weeks following vaccination and occurred mostly in women under 60 years of age” [12].

On 1 April 2021, the Italian Government made mandatory COVID-19 vaccination with CMA vaccines for all health care workers and pharmacists, in the absence of proven clinical problems. Otherwise, these workers are to be demoted or suspended from service until fulfillment of the vaccination obligation. The Italian ruling endures until 31 December 2021 [13]. However, Resolution 2361 by Parliamentary Assembly of the Council of Europe states:

“the vaccination is not mandatory and no one is politically, socially, or otherwise pressured to get themselves vaccinated, if they do not wish to do so themselves; ... no one is discriminated against for not having been vaccinated, due to possible health risks or not wanting to be vaccinated” [14].

On 7 April 2021, the Italian Ministry of Health issued a circular recommending preferential use of Vaxzevria® in people over 60 years of age, in agreement with other nations of the European Union [15]. After a week, the Danish Health Authority and the Norwegian Institute of Public Health definitively opted to continue their vaccination program against COVID-19 without Vaxzevria® [16, 17].

Therefore, a question spontaneously arises: to overcome the widespread vaccine hesitancy in the public interest during a new pandemic, is it ethically correct to strongly encourage, oblige, or recommend mass vaccinations in healthy people with unapproved vaccines or conditionally approved ones to prevent a disease with a mean lethality rate below 5%, like COVID-19? Is this more ethical than waiting, as a precaution, for eventual full approval? Would this latter approach better guarantee the health of millions of human beings?

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Roncati L, Corsi L. Nucleoside-modified messenger RNA COVID-19 vaccine platform. *J Med Virol.* 2021;93:4054–7.
2. Roncati L, Vadalà M, Corazzari V, Palmieri B. COVID-19 vaccine and boosted immunity: nothing ad interim to do? *Vaccine.* 2020;38:7581–4.
3. Roncati L, Gallo G, Manenti A, Palmieri B. Renin-angiotensin system: the unexpected flaw inside the human immune system revealed by SARS-CoV-2. *Med Hypotheses.* 2020;140:109686.

4. Roncati L, Palmieri B. What about the original antigenic sin of the humans versus SARS-CoV-2? *Med Hypotheses*. 2020;142:109824.
5. World Health Organization. Ten threats to global health in 2019. 2019. <https://web.archive.org/web/20190627025209/www.who.int/emergencies/ten-threats-to-global-health-in-2019>.
6. Rizk JG, Forthal DN, Kalantar-Zadeh K, Mehra MR, Lavie CJ, Rizk Y, Pfeiffer JP, Lewin JC. Expanded Access Programs, compassionate drug use, and Emergency Use Authorizations during the COVID-19 pandemic. *Drug Discov Today*. 2021;26:593–603.
7. Cavaleri M, Enzmann H, Straus S, Cooke E. The European Medicines Agency's EU conditional marketing authorisations for COVID-19 vaccines. *Lancet*. 2021;397:355–7.
8. Hanna TP, Evans GA, Booth CM. Cancer, COVID-19 and the precautionary principle: prioritizing treatment during a global pandemic. *Nat Rev Clin Oncol*. 2020;17:268–70.
9. Robergs RA. Lessons from Popper for science, paradigm shifts, scientific revolutions and exercise physiology. *BMJ Open Sport Exerc Med*. 2017;3:e000226.
10. Paul-Ehrlich-Institut. Occurrence of cerebral venous thrombosis after vaccination with COVID-19 Vaccine AstraZeneca. 2021. <https://www.pei.de/EN/newsroom/hp-news/2021/210322-occurrence-cerebral-venous-thrombosis-vaccination-covid-19-astrazeneca.html?sessionId=BD748C0A0C7B10E2AE157320ABF20BA3.intranet231?nn=164440>.
11. European Medicines Agency. EMA recommends COVID-19 Vaccine AstraZeneca for authorisation in the EU. 2021. <https://www.ema.europa.eu/en/news/ema-recommends-covid-19-vaccine-astrazeneca-authorisation-eu>.
12. European Medicines Agency. Annex I—Summary of product characteristics. 2021. https://www.ema.europa.eu/en/documents/product-information/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-product-information_en.pdf.
13. Gazzetta Ufficiale della Repubblica Italiana. Misure urgenti per il contenimento dell'epidemia da COVID-19, in materia di vaccinazioni anti SARS-CoV-2, di giustizia e di concorsi pubblici. 2021. <https://www.gazzettaufficiale.it/eli/gu/2021/04/01/79/sg/pdf>.
14. Parliamentary Assembly of the Council of Europe. Covid-19 vaccines: ethical, legal and practical considerations. 2021. <https://pace.coe.int/en/files/29004/html>.
15. Ministero della Salute. Vaccino Vaxzevria (precedentemente denominato COVID-19 Vaccine AstraZeneca). Aggiornamento raccomandazioni. 2021. <https://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2021&codLeg=79629&parte=1%20&serie=null>.
16. Danish Health Authority. Denmark continues its vaccine rollout without the COVID-19 vaccine from AstraZeneca. 2021. <https://www.sst.dk/en/english/news/2021/denmark-continues-its-vaccine-rollout-without-the-covid-19-vaccine-from-astrazeneca>.
17. Norwegian Institute of Public Health. Norwegian Institute of Public Health's recommendation about AstraZeneca vaccine. 2021. <https://www.fhi.no/en/news/2021/astrazeneca-vaccine-removed-from-coronavirus-immunisation-programme-in-norw/>

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