

Report from the Field

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Abbreviations:

AMC, Advanced Market Commitment; CEPI, Coalition for Epidemic Preparedness Innovations; COVID-19, Coronavirus Disease; CTD, Common Technical Document; DPM, Directorate of Pharmacy and Medicines; EMA, European Medicines Agency; EUA, Emergency Use Authorization; EPAM, Exceptional Provisional Authorization of Marketing; FDA, Food and Drug Administration; GAVI, Global Alliance for Vaccine; LNCM, National Drug Control Laboratory; MA, Marketing Authorization; MOH, Ministry of Health; RWD, Real-world Evidence; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SC, Specialized Committee; WHO, World Health Organization

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COVID-19 Vaccines and Roles of the Health Regulatory Authority in Tunisia

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Abstract

Given the unstoppable spread of coronavirus disease (COVID-19), the development of a vaccine was needed to contain the pandemic. In such a situation of global emergency, regulatory authorities ensured timely, safe, and equitable access to the vaccine.

This article aims to outline the roles of the Tunisian regulatory authority, the Directorate of Pharmacy and Medicines (DPM) at the Ministry of Health, in registration and procurement of the COVID-19 vaccine.

Requirement to grant the Exceptional Provisional Authorizations of Marketing (EPAM) for COVID-19 vaccines was 27 days versus 869 days for conventional marketing authorizations (MAs). The DPM has optimized its activity through: early dialogue with manufacturers, online submission, the use of distance communication technologies. It has demonstrated unprecedented flexibility through the continuous and rolling review approach.

Regulatory authorities in Tunisia and around the world have partnered with manufacturers to speed up administrative procedures while ensuring the quality, safety, and efficacy of vaccines.

On December 31, 2019, an outbreak of pneumonia, described at the time as viral in nature and of unknown cause, occurred in the city of Wuhan (Hubei Province, China).¹ On January 9, 2020, biological investigations showed the presence of a new coronavirus, 2019-nCoV.² This severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is considered to be the causative agent of a new respiratory infectious disease called *coronavirus disease* (COVID-19).³

Despite all the measures taken to stop this global crisis, the virus has continued to spread, causing unprecedented human and economic damage. Faced with this situation, the development of a vaccine has become a universal emergency in order to take over the economy and allow humanity to regain a normal life. Pharmaceutical companies around the world were racing to develop a vaccine against COVID-19.

The main objective of this paper is to describe the role of the Ministry of Health (MOH) through the Directorate of Pharmacy and Medicine (DPM) in the vaccine registration and procurement process. The measures undertaken to grant the exceptional provisional authorization of marketing (EPAM) will be specifically explored.

Narrative

Preassessment

As of July 2020, an ad hoc committee, tasked to assess the vaccines, began an early and ongoing dialogue with vaccine developers who passed to phase III of their clinical trials.⁴ It is noteworthy that the first contact was made with the Pfizer laboratory on July 18, 2020, even before the start of the phase III clinical trials of their vaccine (July 27, 2020), followed by the Gamaleya laboratory (sputnik V vaccine) on August 14, 2020. Since then, several meetings have taken place with other manufacturers.

The World Health Organization (WHO) officially transmitted the call for applications to the MOH on October 30, 2020, for the COVAX facility (a coordinated initiative by the Global Alliance for Vaccines [GAVI], the Coalition for Epidemic Preparedness Innovations [CEPI], and 4 WHO) to support the research, development, and manufacture of a broad range of COVID-19 candidate vaccines, and to ensure rapid, fair, and equitable access to these vaccines for populations around the world. On December 7, 2020, Tunisia submitted its application for the advanced market commitment (AMC) COVAX and it was approved on December 11, 2020.

Table 1. Time required for quality evaluation and granting exceptional provisional marketing authorizations

N°	Vaccine	Country	First MA in the world	Date of submission of the file by the laboratory in Tunisia	Duration of the quality evaluation (Days)	Date of EPAM	Time required for granting EPAM (Days)
1	Pfizer-BioNTech COVID-19 Vaccine	USA	11/12/2020	09/12/2020	28	11/01/2021	34
2	Sputnik V	Russia	11/08/2020	13/01/2021	17	30/01/2020	18
3	COVID-19 Vaccine AstraZeneca	United Kingdom	31/12/2020	22/02/2021	3	26/02/2021	5
4	Sinovac-CoronaVac	China	03/02/2021	27/01/2021	36	04/03/2021	37
6	Comirnaty *	Europe	21/12/2020	22/02/2021	–	17/03/2021	24
5	Janssen COVID-19 Vaccine	USA	27/02/2021	19/03/2021	15	07/04/2021	20
7	MODERNA	USA	18/12/2020	03/05/2021	30	25/06/2021	54

* it is the same quality file as Pfizer-BioNTech COVID-19 Vaccine.

Assessment

The case of the anti-COVID-19 vaccines appears well in a decree of the Tunisian legislation, which stipulates that for “drugs which have an urgent character or present a major therapeutic interest or a major interest for the public health and in the event of absence of sufficient scientific hindsight,” the granting of an EPAM is justified.⁵

All the steps of the conventional registration procedure of human drugs in Tunisia were followed with some exceptional measures taken to accelerate the process of granting the EPAM.

In fact, the files have been submitted online, without prior appointment, and with a lighter administrative module.

The DPM has adopted the rolling review procedure by processing the data submitted by manufacturers in real time. The preclinical and clinical data were evaluated by the Specialized Committee (SC) on Antibiotics, Antifungals, Antiparasitics and Biological Drugs (serums, vaccines, and blood derivatives), which was reinforced by external experts from different specialties (virology, toxicology, immunology, and geriatrics) who were invited to evaluate the files and present their reports on the meeting of the CS. This committee met each time the report of the National Drug Control Laboratory (LNCM) evaluation of the quality module was available. Thus, several meetings were held in a few months, whereas the usual frequency of meetings is once a year. The documentary evaluation of the quality file was done by the LNCM and required an exceptional mobilization of human resources, which shortened their evaluation time from 782 days to 21 days (Table 1).

It took an average of 27 days to grant the EPAM for COVID-19 vaccines, versus an average of 869 days calculated for all conventional vaccines previously authorized in Tunisia (see Table 1).

Other Roles Performed by the Regulatory Authority

Vaccine procurement has been achieved both through participation in initiatives such as COVAX and through bilateral agreements with manufacturers.

Special efforts were also made to raise funds for the purchase of vaccines. For example, negotiations with the World Bank resulted in an additional US \$100 million in funding for the COVID-19

Response Project in Tunisia to ensure equitable and affordable access to vaccines throughout the country.⁶

Moreover, the DPM played a very important role in managing the involvement of pharmacies in the deployment of the immunization campaign and also in the negotiations of a possible collaboration between vaccine manufacturers and the Tunisian pharmaceutical industries to promote a local production of the vaccine. Additionally, being a WHO collaborating center for drug registration and regulation since May 17, 1998,⁷ the DPM, through its experts, has been requested by the WHO and various working groups at the global level to contribute to international efforts in the fight against COVID-19.

Discussion

COVID-19 had enormous health, psychological, and economic repercussions on all humanity. Consequently, in the face of overwhelmed health care systems and inefficient preventive measures (lockdown, barrier measures, cessation of schooling, travel restrictions, etc.), an effective vaccine against SARS-CoV-2 was the most promising way to overcome this pandemic and reduce its burden.

This has been a real challenge for drug regulatory authorities. In Tunisia, the DPM worked to accelerate the process of granting EPAM, while respecting its usual procedure for evaluating vaccines. A similar approach was followed by the Food and Drug Administration (FDA) by granting the Emergency Use Authorization (EUA) for Vaccines anti-COVID-19. Similarly, the FDA confirmed that efforts to speed vaccine development to address the ongoing COVID-19 pandemic have not sacrificed scientific standards, integrity of the vaccine review process, or safety.⁸ This was possible by adopting new approaches in the working methodology such as solicitation of vaccine producers (from July 2020) even before submission of their MA application. Flexibility in terms of receipt of dossiers by using online submission and without prior appointment, which was the case in the main regions of the world, industry, and regulatory bodies, now uses electronic submissions based on a common technical document (CTD).⁹ A “fast track” procedure has been adopted for the evaluation of applications. For this purpose, the DPM has used the concept of the rolling review, which is an ad hoc procedure also

used by the European Medicines Agency (EMA) in this emergency context to allow continuous evaluation of data as soon as they become available.¹⁰

The active collaboration established between the DPM, LNCM, and experts from various specialties has significantly shortened the time needed to obtain the EPAM compared to a conventional MA by 869 days to 27 days. This unprecedented speed in the regulatory processing of COVID-19 vaccines has been seen in most authorities around the world. For example, the EMA's standard time for evaluating a drug is a maximum of 210 active days. However, fast-tracking of COVID-19 applications has reduced the evaluation time to less than 150 active days.¹⁰

Although the Tunisian regulatory authority and all of its collaborators demonstrated remarkable efficiency during the COVID-19 crisis, certain limitations can be attributed to this experience. Indeed, the DPM carried out the full evaluation of all authorized vaccines, whereas communication and sharing of evaluation data with other authorities could have further facilitated and accelerated regulatory reviews and ensured more rapid access to the vaccine. Thus, the COVID-19 pandemic highlighted the urgent need for streamlined regulatory approval processes—which can be achieved in part through regulatory convergence and cooperation—both to accelerate availability of COVID-19 vaccines, treatments, and diagnostics and to maintain the availability of the existing medical products unrelated to COVID-19.¹¹

As these authorizations were granted in an emergency context and in the absence of sufficient scientific hindsight, the DPM continues to closely monitor the results of clinical trials not completed at the time of the evaluation and requires continued submission of clinical data by holders of EPAM. This is also the case for the EMA and FDA, which have required manufacturers with EUAs to continue their clinical trials and provide additional information on the safety and efficacy of authorized vaccines.

Conclusion

Despite all the human and economic damage, it is undeniable that the COVID-19 pandemic has revolutionized the pharmaceutical industry in terms of research and development as well as regulatory evaluation. In the face of the health emergency, the regulatory authorities have proven their ability to adapt to the pressure of the crisis by optimizing their procedures and adopting new, much more efficient and effective working methodologies. Hopefully, these accelerated procedures will be maintained in the post-pandemic era, especially for products with therapeutic value no less important than COVID-19. Another aspect of drug development

that has become necessary is post-marketing evaluation. Thus, several studies on empirical or real-world evidence (RWE) will have to be carried out on the various vaccines authorized and used.

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