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Conditional Approval Procedures for Vaccines in European Union (EU)

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ABSTRACT: Supporting the development and marketing authorisation of safe, effective and high-quality therapeutics and vaccines as soon as possible is one of EMA's top priorities in the COVID-19 public health emergency. The rapid procedures described in the inventory can accelerate every step of a medicine's regulatory pathway and the Agency is fully mobilised to deliver these fast-track assessments in the shortest possible timeframes while ensuring robust scientific opinions are reached.Before a vaccine can be approved in the EU, it has to undergo rigorous testing by its developer and then scientific evaluation by regulatory authorities. These include the European Medicines Agency (EMA) and other regulators in the EU/EEA countries.Coronavirus disease 2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first known case was identified in Wuhan, China, in December 2019.This knowledge accelerated the development of various vaccine platforms during early 2020. The initial focus of SARS-CoV-2 vaccines was on preventing symptomatic, often severe illness.[1]
Twenty vaccines are authorized by at least one national regulatory authority for public use: one DNA vaccine (ZyCoV-D) two RNA vaccines (Pfizer–BioNTech and Moderna), nine conventional inactivated vaccines (BBIBP-CorV, Chinese Academy of Medical Sciences, CoronaVac, Covaxin, CoviVac, COVIran Barakat, Minhai-Kangtai, QazVac, and WIBP-CorV), five viral vector vaccines (Sputnik Light, Sputnik V, Oxford–AstraZeneca, Convidecia, and Janssen), and five protein subunit vaccines (Abdala, EpiVacCorona, MVC-COV1901, Soberana 02, and ZF2001).

Keywords – Fast Track Assessment, European Medicines Agency,COVID-19es in the European Union

I. INTRODUCTION

Vaccination is a simple, safe, and effective way of protecting people against harmful diseases, before they come into contact with them. It uses your body's natural defences to build resistance to specific infections and makes your immune system stronger[2].

Vaccines train your immune system to create antibodies, just as it does when it's exposed to a disease. However, because vaccines contain only killed or weakened forms of germs like viruses or bacteria, they do not cause the disease or put you at risk of its complications

Conditional marketing authorisation, in line with the defined scope and criteria and in the interest of public health, is usually appropriate for products where the benefit-risk balance is such that the immediate availability outweighs the limitations of less comprehensive data than normally required, i.e., medicines with an established potential to address an unmet medical need.

The applicant may present a request for a conditional marketing authorisation at the time of the application for marketing authorisation. A request for conditional marketing authorisation shall be submitted in module 1.5.5 of the EU-CTD.

Covid – 19

Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus.

Most people infected with the COVID-19 virus will experience mild to moderate respiratory illness and recover without requiring special treatment. Older people, and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop serious illness.

The best way to prevent and slow down transmission is to be well informed about the COVID-19 virus, the disease it causes and how it spreads. Protect yourself and others from infection

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by washing your hands or using an alcohol-based rub frequently and not touching your face.

The COVID-19 virus spreads primarily through droplets of saliva or discharge from the nose when an infected person coughs or sneezes, so it's important that you also practice respiratory etiquette (for example, by coughing into a flexed elbow).

Symptoms

COVID-19 affects different people in different ways. Most infected people will develop mild to moderate illness and recover without hospitalization.

Most common symptoms:

- Fever.
- Dry Cough.
- Tiredness.

Less common symptoms:

- Aches And Pains.
- Sore Throat.
- Diarrhoea.
- Conjunctivitis.
- Headache.
- Loss Of Taste or Smell.
- A Rash on Skin, Or Discolouration of Fingers or Toes.

Serious symptoms:

- Difficulty Breathing or Shortness of Breath.
- Chest Pain or Pressure.
- Loss of Speech or Movement.

Seek immediate medical attention if you have serious symptoms. Always call before visiting your doctor or health facility.

People with mild symptoms who are otherwise healthy should manage their symptoms at home.

On average it takes 5–6 days from when someone is infected with the virus for symptoms to show, however it can take up to 14 days.[1]

Scope

Conditional Marketing

Conditional marketing authorisation is a pragmatic tool for the fast-track approval of a medicine that fulfils an unmet medical need. Despite earlier approval, it guarantees that the medicine meets rigorous EU standards for safety, efficacy and quality and that comprehensive data is still generated post-approval.

It offers a robust post-authorisation regulatory framework based on legally binding obligations, safeguards and controls.[3]

These include:

- Full Prescribing Information and Package Leaflet with Detailed Instructions for Safe Use and Conditions for Storage;
- A Robust Risk-Management and Safety Monitoring Plan;
- Manufacturing Controls Including Official Batch Controls for Vaccines, As Required;
- Legally Binding Post-Approval Obligations (I.E. Conditions) For the Marketing Authorisation Holder and A Clear Legal Framework for The Evaluation of Emerging Efficacy and Safety Data;
- APaediatric Investigation Plan.

Products which come under Conditional Marketing

The following categories of products fall within the scope of Commission Regulation according to the provisions of Article 2, and could be potentially be eligible for a conditional marketing authorisation:

1. Medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases;
2. Medicinal products to be used in emergency situations, in response to public health threats duly recognised either by the World Health Organisation or by the Community in the framework of Decision No 2119/98/EC;
3. Medicinal products designated as orphan medicinal products in accordance with Article 3 of Regulation (EC) No 141/2000.

Criteria and Conditions

EMA's CHMP may grant a conditional marketing authorisation for a medicine if it finds that all of the following criteria are met:

- The Benefit-Risk Balance of The Medicine Is Positive;
- It Is Likely That the Applicant Will Be Able to Provide Comprehensive Data Post-Authorisation;
- The Medicine Fulfils an Unmet Medical Need;
- The Benefit of The Medicine's Immediate Availability to Patients Is Greater Than the Risk Inherent in The Fact That Additional Data Are Still Required.
- Conditional Marketing Authorisations Are Valid for One Year and Can Be Renewed Annually.

Once a conditional marketing authorisation has been granted, the marketing authorisation holder must fulfil specific obligations within defined timelines.

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These obligations could include completing ongoing or new studies or collecting additional data to confirm the medicine's benefit-risk balance remains positive.

EMA publishes the conditions of the marketing authorisation in the medicine's European public assessment report.

Conditional marketing authorisations granted

Since 2006, a total of 30 conditional marketing authorisations have been granted. Of these, two have been subsequently withdrawn (both withdrawals concerned pandemic influenza vaccines and both withdrawals were made for commercial reasons), eleven have been converted into marketing authorisations not subject to specific obligations ("standard"/ "full" authorisations) and the remaining are still conditional marketing authorisations. Just over a half of conditional authorisations were in oncology area, followed by almost a third for infectious diseases, the remaining products being for neurology or ophthalmology indications. It is evident that certain therapeutic areas, although being represented in the overall portfolio of centrally authorised products, have not been active or successful in using the conditional authorisation route. These areas include, for example, cardiovascular diseases, endocrinology, respiratory medicine and rheumatology. [4]

Rapid Procedures

EMA rapid procedures can accelerate every step of the regulatory pathway while ensuring that robust evidence on efficacy, safety and quality is generated to support scientific and regulatory decisions.

They are available for initial marketing-authorisation applications for the treatment or prevention of COVID-19, as well as for applications to 'repurpose' medicines already authorised for other conditions, by extending their indications to include COVID-19.

Rolling Review

- EMA's scientific committees - Committee for Medicinal Products for Human Use (CHMP) and Pharmacovigilance Risk Assessment Committee (PRAC) - review data as they become available on a rolling basis. This review is done with the support of the COVID-19 EMA pandemic Task Force (COVID-ETF).
- The review takes place while development is still ongoing
- The COVID-ETF has to agree on the start of a rolling review
- Several rolling review cycles can be carried out during the evaluation of one product while data continue to emerge. The number of cycles depends on the amount to be assessed
- Each cycle is pre-agreed between EMA and the applicant
- The submission for each cycle takes place in eCTD format.
- In addition to the newly available data, each submission normally includes:
- An Application Form
- Module 2 Overview(S)
- Responses To All Outstanding Questions from Previous Review Cycles

During the rolling review, EMA assess whether the data package is complete enough to invite the applicant to submit a formal marketing authorisation application. In these cases, EMA processes the application under a shortened timetable.

The key features of rolling review process are the following:

• Each Rolling Review submission occurs in eCTD format with an application form, a Module 2 overview and responses to a cumulative listing of all outstanding questions from previous review cycles. The contents of each rolling review submission have to be pre-agreed between the applicant and the EMA.

• There can be several Rolling Review cycles with the timelines for assessment and providing questions to the applicant being agreed with Rapporteurs and EMA for each review cycle, based on the contents of the respective submission and the overall time plan for submission of data. Responses to list of questions from previous Rolling Review cycles are ideally to be incorporated into subsequent Rolling Review submissions. While only applications of sufficient maturity are accepted for rolling review, unexpected delays with providing responses to the questions raised or significant delays from the agreed submission schedule may lead to delays in completing the rolling review stage of the application review.[7]

Accelerated Assessment

- Can be considered for medicines and vaccines not undergoing a rolling review
- Requires a complete application to be available at the time of submission (unlike a rolling review)

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- Review is reduced to 150 days (from 210 days) or less after validation of a complete application

Conditional marketing authorisation

- Is a regulatory tool to fast-track medicines for use in emergency situations by granting a marketing authorisation as soon as sufficient data becomes available to demonstrate that the benefits outweigh the risks
- Ensures that the medicine is manufactured and controlled according to high pharmaceutical standards compatible with large scale commercialisation
- Once a it has been granted, companies must provide further data from ongoing or new studies within pre-defined deadlines to confirm that the benefits continue to outweigh the risks
- Is valid for one year and renewable[5]
- Use during COVID-19 pandemic

Use of Conditional Marketing Authorisation Use during COVID-19 pandemic

During the COVID-19 pandemic, the conditional marketing authorisation procedure is being used to expedite the approval of safe and effective COVID-19 treatments and vaccines in the EU.

This is in line with EU legislation which foresees that conditional marketing authorisation is used as the fast-track authorisation during public health emergencies to speed up approval and save lives.

It allows regulators to grant a marketing authorisation as soon as sufficient data becomes available to demonstrate that the medicine's benefits outweigh its risks, with robust safeguards and controls in place post-authorisation.

In a public health emergency, it can also be combined with a rolling review of data during the development of a promising medicine, to further expedite the evaluation.

Conditional marketing authorisation is the most appropriate tool to grant access to COVID-19 vaccines to all EU citizens at the same time and to underpin mass vaccination campaigns.

A conditional marketing authorisation guarantees that the approved vaccine:

meets rigorous EU standards for safety, efficacy and quality is manufactured and controlled in approved, certified facilities in line with high pharmaceutical standards that are compatible with large-scale commercialisation.

Conditional marketing authorisation is a tool that allows regulators to approve a medicine quickly and in a pragmatic manner when there is an urgent need.

A conditional marketing authorisation is different from an emergency use authorisation, which some countries use to permit the temporary use of an unauthorised medicine in an emergency situation. An emergency use authorisation is not a marketing authorisation.

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WHY CONDITIONAL APPROVAL IS THE MOST APPROPRIATE TOOL IN THE EU?

Formal approval of a medicine across the EU: all member states benefit from the joint scientific assessment and approval

• It has all safeguards and controls in place to ensure high level of protection to citizens during a mass vaccination campaign:

• A robust monitoring plan for managing safety

• Clear legal framework for evaluation of emerging efficacy data

• Manufacturing controls including batch controls for vaccines

• Full prescribing information and package leaflet with defined conditions for storage and use of the vaccine

• A plan for use of the vaccine in children

• Additional studies or other data (‘conditions’) that the company is legally obliged to provide with definedtimelines

Monitoring vaccine safety and use in real life

The scientific evaluation needs to show that a vaccine’s benefits in protecting people against diseases are far greater than any potential risk.

Like any medicine, vaccines have benefits and risks. Although highly effective, no vaccine is one hundred per cent effective in preventing disease or one hundred per cent safe in all vaccinated people.

At the time of approval, the main body of evidence for vaccine safety and efficacy comes from large controlled, randomised clinical trials. Selected volunteers are randomly allocated to receive the vaccine being tested and followed up under controlled conditions in line with strict protocols.

After approval, many people will receive the vaccine. Certain rare or very rare side effects

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may only emerge when millions of people are vaccinated. EU law requires that the safety of vaccines is monitored while they are in use in routine clinical practice.

Standard monitoring

The EU has a comprehensive safety monitoring and risk management (pharmacovigilance) system, which ensures measures are in place for:

- providing advice to minimise risk;
- reporting suspected side effects;
- conducting studies after authorisation;
- detecting any potential side effects;
- conducting rigorous scientific assessments of all safety data;
- introducing any necessary mitigating actions early on.

Competent authorities carry out safety and efficacy studies after authorisation and can also require a marketing authorisation holder to carry out such studies as an obligation of the authorisation. Public health authorities responsible for vaccination programmes will also conduct other studies.

Studies collecting effectiveness data give additional information, for example, on long term protection or on the need for and timing of booster doses, to complement the 'efficacy' data obtained in clinical trials before the vaccine was authorised.

COVID-19 Vaccine approval under EUA by FDA

Regarding the CoVID-19 pandemic FDA has requisitioned the sponsors and other bodies to produce vaccines in order to counter the unforeseen emergency. Manufacturers need to submit clinical and non-clinical data with proven patient safety and efficiency of the product that intends to be effective against CoVID-19. In Phase I clinical trials, a vaccine is given to healthy volunteers to determine the safety and identify human immune response to the medication. In Phase II clinical trials, vaccine is administered to hundreds of subjects in a randomized and controlled manner and in this phase common side effects, immune response, and effectiveness of vaccine are observed. In phase 3 clinical trials, vaccines will be administered to a larger population, in this phase immune response to vaccine is compared with those who receive a control (Placebo).

To find safety and effectiveness of the vaccine subjects that were a part of phase III trials will be undersupervision for at least a month post vaccine regimen in order to track serious adverse events, if any.

Even after receiving the approval from EUA, the FDA will expect the sponsor to perform clinical trials and update the safety and efficiency of the product in the market. Data safety Monitoring board will help in assessing the safety of the product and there are some bodies such as Vaccine adverse event reporting system (VAERS), the vaccine safety datalink (VSD), Biologics effectiveness and safety (BEST) and Medicare claims data that help FDA in rapidly determining the safety of the product.[6]

Difference between Accelerated Assessment and Conditional Marketing authorisation

	Accelerated Assessment	Conditional Marketing Authorisation
Eligibility criteria	Medicine is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation	Medicine fulfils unmet medical need • Medicine targets seriously debilitating or life-threatening disease, rare disease or is for use in emergency situations in response to a public health threat • Benefit-risk balance of the product is positive, and benefit to public health of its immediate availability outweigh the risk related to need for additional data • Comprehensive data expected to be provided after authorisation
Benefits	• Faster assessment of marketing authorisation application	• Authorisation can be granted early on the basis of less complete clinical data
Overview of	• More detailed guidance	• Emphasis on importance of

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proposed key changes	on how to justify major public health interest, i.e., fulfilment of unmet medical need • Acknowledgment that comprehensive clinical data may not be available in certain situations, allowing accelerated assessment in the context of a conditional marketing authorisation for example • Optimisation of the assessment timetable by better balancing evaluation phases to reach a CHMP opinion within 150 days after the start of the marketing authorisation application procedure • Intent to request accelerated assessment to be indicated 6-7 months in advance and submission of accelerated assessment request encouraged to take place 2-3 months ahead of marketing authorisation application instead of 10-30 days ahead • Importance of early dialogue with EMA so that accelerated assessment can be planned well ahead of the submission, e.g. by detailed discussion of the data package at pre-submission meetings	planning conditional marketing authorisation prospectively to ensure swift assessment procedure • Emphasis on advantages of engaging in early dialogue with EMA on the development programme, in particular in the context of joint scientific advice with health technology assessment bodies • Clarification of how a positive benefit-risk balance should be substantiated where there are less complete data • Examples and further guidance on the level of evidence that must be provided at the time of authorisation and data that can be provided post-authorisation • Updated guidance on extent and type of data required to be included in annual renewal submissions • Guidance on when a condition could be considered life threatening or seriously debilitating if these effects are in the long-term • Clarification on fulfilment of unmet medical needs, i.e. medicines providing major improvements in patient care over existing therapies can be eligible in certain cases

II. CONCLUSION

Approval of a product with minimal data submitted by the applicant in desperate times and counting on it to fight against the odds is taxing for regulatory bodies. As mentioned earlier, submission of the data to regulatory bodies is very vital and it has to be meticulous as per the guidelines. Advisory bodies do not only assist agencies in the approval process of the vaccines and/or drugs in emergency conditions, but they also aid in development of robust regulatory guidelines for the procedure, termination, import and export of the medications meant to treat emergency conditions.Emergency use authorization of medical products by the regulatory agencies is not a usual procedure; it happens to cope with unanticipated health emergencies affecting a large group of population, these can be because of outbreak agents like virus, bacteria, etc., which can cause contagious diseases. Contagious diseases are classified into an outbreak, epidemic and pandemic disease, based on size and intensity of spread of the disease.

Since introduction of the conditional marketing authorisation route there has been considerable interest among stakeholders, even if it remains just a small fraction of authorisations granted. However, there also appears to be certain reluctance of applicants to request this authorisation type upfront in the submission for the marketing authorisation. The CHMP, however have actively used this tool and considered its application when appropriate, as demonstrated by numerous cases when conditional marketing authorisation was eventually recommended, even though it was not proposed by the applicant in initial submission

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