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EMA initiatives for acceleration of development support and evaluation procedures for COVID-19 treatments and vaccines

The European Medicines Agency (EMA) together with the responsible scientific committees and their working parties, and in collaboration with the European Commission, operates rapid procedures to support the development and evaluation of treatments and vaccines for COVID-19. The EMA emerging health threats plan foresees that detailed procedures are set-up to adapt different types of review activities to the needs of the health threat/crisis situation. Whilst respecting the regulatory requirements and established review principles (e.g. independence of experts), these procedures aim, within timelines that are appropriate for the public health emergency situation, to provide most efficient management of product-review activities leading to scientifically sound and robust outcomes.

The COVID-19 EMA pandemic Task Force (COVID-ETF) coordinates and enables fast regulatory action on the development, authorisation and safety monitoring of treatments and vaccines intended for the treatment and prevention of COVID-19. Working with the best experts from within the EU regulatory network, the COVID-ETF's activities include providing guidance on development plans of COVID-19 medicines when formal scientific advice is not yet feasible, advising the Scientific Advice Working Party (SAWP) and the Committee for Human Medicinal Products (CHMP) on formal scientific advice (rapid or regular – see section 1) and, ultimately, on product-related assessments, including those on a rolling basis. For such formal development support and evaluation activities rapid procedures have been established. These procedures are available for products intended for prevention or treatment of COVID-19, including both new products and products already authorised in other conditions.

This document provides an overview of EMA's rapid formal review procedures related to COVID-19 and is mainly intended as procedural guide for developers. It complements other documents published under the guidance for medicine developers and companies on COVID-19 and the respective guidance provided for regular procedures published on the EMA website for research and development and for marketing authorisation.

EMA's rapid formal review procedures related to COVID-19 are outlined in the following sections:

1. Rapid scientific advice
2. Rapid agreement of a paediatric investigation plan and rapid compliance check
3. Rolling review
4. Marketing authorisation
5. Extension of indication and extension of marketing authorisation
6. Compassionate Use
7. Other considerations

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1. Rapid scientific advice

Rapid scientific advice is provided in support of evidence generation planning for treatments and vaccines for COVID-19. It is an *ad hoc* procedure which follows the general principles of the regular scientific advice but with adaptations to facilitate acceleration. The advice will be adopted by the CHMP, but the process will also involve the COVID-ETF.

Since assessment standards will need to be maintained, the level of expedition in providing the scientific advice will depend on the number and complexity of the requests and on the availability of resources in the public health threat situation of COVID-19. The rapid scientific advice process will not be applicable to all scientific advice requests related to an emerging public health threat and regular scientific advice procedures will continue to be used as well.

The key features of rapid scientific advice are the following:

- There are **no pre-specified submission deadlines** for developers to submit their submission dossier.
- There is flexibility regarding the **type and extent of the briefing dossier**, which needs to be discussed on a case-by-case basis.
- This scientific advice is **free of charge** in accordance with the EMA Executive Director Decision (EMA/134143/2020).
- The total review time from the start to the final advice letter is **reduced to 20 days**, compared to the regular 40/70 days timeframe. This is achieved through accelerating all milestone stages of the process (validation, assessment report circulation, peer review, adoption). Depending on the nature of the request the timelines could be shortened even further.

The scope and general principles of rapid scientific advice are the same as of regular scientific advice. Any scientific advice is not a pre-assessment of data but rather supports prospective evidence planning. The European regulatory system will make every effort to assist the development of the products by providing relevant rapid feedback. Importantly, the scientific robustness of the advice remains ensured through the involvement of the SAWP and the CHMP, enriched with additional expertise particularly through the COVID-ETF. The final advice is always adopted by CHMP.

To plan for such rapid scientific advice, developers should make the initial contact through the 2019-ncov@ema.europa.eu mailbox in order to allow review of suitability and maturity of the planned request for the rapid scientific advice procedure. Once agreed, a project manager will be allocated and the request should be sent through the usual work flow for scientific advice (see scientific advice). Additional guidance and support will be provided by EMA's scientific advice office. In case of preliminary development plans, not yet suitable for formal rapid scientific advice, early guidance will be provided by EMA and the COVID-ETF instead.

2. Rapid agreement of a paediatric investigation plan and rapid compliance check

Applications for agreement of a paediatric investigation plans (PIP), deferrals or waivers for treatments and vaccines for COVID-19 will be reviewed in expedited manner, taking into account applicable legislative requirements. The compliance checks will also be expedited. On the basis of the regular processes, a rapid and flexible approach will be identified for each case, whilst preserving the scientific robustness of the outcome.

The Paediatric Committee (PDCO) is responsible for the scientific assessment of such applications and the COVID-ETF provides scientific input. The received applications for products intended for prevention or treatment of COVID-19 will be prioritised in their need for acceleration, considering in each case the immediate progress with the development (e.g. initiation of clinical trials in the paediatric population) or the upcoming submission of a marketing authorisation application.

The key features of rapid PIP and compliance checks are the following:

- There are **no pre-specified submission deadlines** for developers to submit their submission dossier.
- There is the possibility of a **focused scientific documentation** to be provided by the developer, which needs to be discussed on a case-by-case basis.
- The total evaluation time for a paediatric investigation plan (including waiver or deferral) from the start to the adopted PDCO opinion will be reduced to a **minimum of 20 days**, compared to normally up to 120 days active review time. This is achieved through accelerating all milestone stages of the process (validation, summary report preparation, peer review, committee discussion, adoption). The exact timelines will depend on the complexity of the PIP, as well as on the preparedness by the sponsor to respond to questions during the evaluation. Following PDCO opinion, the EMA decision will be adopted within 2 days, compared to the usual 10 days.
- Given that paediatric development needs to be seen from a global perspective, it is foreseen to discuss the plan with **international regulators** during the evaluation. Sponsors are invited to consider outreach to other regulators (e.g. FDA) in parallel to facilitate such exchange.
- The timelines for a **compliance check** in advance of a marketing authorisation application will be defined in accordance with the urgency and can be reduced to 4 days if necessary. However, in case of non-compliance by the sponsor, these timelines might not be met. Developers are highly recommended to prepare early for such interaction.

To enable such acceleration, it is of utmost importance that the sponsor is well prepared and the proposed plan is mature. Specifically, also in the current situation, applicants are strongly advised to consider the paediatric requirements early in development and to contact the EMA well in advance of submission to prevent any possible delays. A pre-submission interaction is highly recommended. Submission of applications should follow the usual procedures (see paediatric medicines), unless stated otherwise in this guidance (e.g. concerning submission deadlines). Additional guidance and support will be provided by the EMA paediatric medicines office.

3. Rolling review

Rolling Review is an *ad hoc* procedure used in an emergency context to allow EMA to continuously assess the data for an upcoming highly promising application as they become available, i.e. preceding the formal submission of a complete application for a new marketing authorisation (or for an extension of indication in case of authorised medicines). Through this process, EMA will be able to complete the review of marketing authorisation application dossier earlier while ensuring robust scientific opinions. Such rolling reviews are conducted under the EMA emerging health threats plan and starting them requires specific agreement by the COVID-ETF, which also acts as forum for discussion on the rolling data assessment. As for other procedures, the rolling review assessment is performed by the Rapporteur and Co-rapporteur teams and the outcomes are adopted by the CHMP.

The key features of rolling review 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.
- There can be **several Rolling Review cycles** with each cycle normally requiring a **two-week review**, depending on amount of data. Responses to list of questions from previous Rolling Review cycles are to be incorporated into subsequent Rolling Review submissions.

Following the rolling review, once the CHMP considers that the data package is sufficiently complete to proceed to formal regulatory submission, submission by the company of the formal marketing authorisation application or extension of indication is expected, which, after validation, will be processed under a shortened timetable (see section 4 and 5). The duration of the procedure will depend on the amount of data not yet assessed as part of rolling review cycles.

To plan for such Rolling Review, developers should make the initial contact through the 2019-ncov@ema.europa.eu mailbox in order to allow review of suitability and maturity of the planned submission for appointment of Rapporteurs for potential rolling review [1]. Once agreed[2], an EMA product lead will be allocated, who will provide guidance and support throughout the procedure.

4. Marketing authorisation

Applications for a marketing authorisation for products intended for prevention or treatment of COVID-19 will be treated in an expedited manner. The applicants are advised to contact EMA via email to 2019-ncov@ema.europa.eu early in the development to discuss scientific and regulatory aspects of their planned application.

Following or in parallel with confirmation of the eligibility to centralised procedure, the applicants may also ask to appoint rapporteurs for a potential rolling review. Such requests should be addressed to 2019-ncov@ema.europa.eu and will be reviewed by the COVID-ETF. The EMA Product Lead will also be appointed at the same time. Once the Rapporteurs and the EMA Product Lead are appointed, the applicant may request a pre-submission meeting to present their development and submission plans and discuss potential use of rolling review (as described in section 3). Use of a rolling review is expected to lead to finalisation of the marketing authorisation procedure much earlier than with other types of review.

Should the applicant not wish to use rolling review or in case the application has not been accepted for such review, the applicant may still apply for accelerated assessment. In such case, the review of the application is started only after validation of a complete application, but the maximum active review time is reduced from 210 to 150 days, which in practice may even be shorter.

In addition to the above listed options, should the applicants consider that shortening of procedural timelines would have important public health impact in dealing with COVID-19 pandemic in another context (e.g. a need is identified during a clock-stop of an ongoing procedure), they are encouraged to contact their EMA Product Lead and provide a description of the expected public health impact and explain how accelerating the assessment would support dealing with COVID-19 pandemic, with a view to agree a shorter review timetable *ad hoc* (see section 5).

[1] If considerable amount of data becomes available on products intended for prevention or treatment of COVID-19 after appointment of rapporteurs but before an agreement on rolling review is reached, it may still be possible to arrange sharing this data informally with EMA and the rapporteurs to facilitate familiarisation with the data and preparations for upcoming assessment.
[2] The eligibility of the product for centralised procedure also needs to be confirmed, but can be done independently, in advance of Rapporteur appointment.

EMA will also accelerate the linguistic review process for products intended for prevention or treatment of COVID-19 and will work closely with the European Commission, keeping them informed about such applications, to facilitate the acceleration of the decision-making process.

5. Extension of indication and extension of marketing authorisation

The above mentioned support measures are also available for already authorised products that are being developed (repurposed) for treatment or prevention of COVID-19. Marketing authorisation holders (MAHs) are encouraged to share early information about their planned development for COVID-19 with the EMA (the appointed Product Lead) and the Rapporteurs. They can make use of rapid scientific advice (see section 1) and rapid agreement of a PIP or its modification (see section 2). Should the data on new development become available stepwise (rather than from completion of a single pivotal study), the MAHs may consider applying for a rolling review (see section 3). Alternatively, the MAHs are encouraged to contact their EMA Product Lead and provide a description of how a shorter review timetable for the procedure concerned is expected to have an important public health impact and would support dealing with COVID-19 pandemic. Such possible shortening of procedure timelines will be considered by EMA and COVID-ETF, as appropriate.

EMA will also substantially accelerate the linguistic review process for procedures related to COVID-19 and will closely work with the European Commission, keeping them informed about such applications, to facilitate the acceleration of the decision-making process.

6. Compassionate Use

Certain unauthorised medicinal products may be made available at national level through compassionate use programmes, even more in an emergency context, in order to facilitate the availability to patients of new treatment options that are under development.

While coordination and implementation of a compassionate use programme remain competence of a Member State, EMA can provide through the CHMP recommendations for a "group of patients' on a medicinal product eligible to the centralised procedure, in order to favour a common approach across Member States

Applicants cannot submit directly to the EMA a request for a CHMP opinion on a compassionate use and should instead contact National Competent Authorities for any proposals to offer a compassionate use programme.

However, developers of products for treatment or prevention of COVID-19 are encouraged to contact EMA via email to 2019-ncov@ema.europa.eu and in this context provide also information on compassionate use applications underway at national level. National Competent Authorities should inform EMA if they are making a product available to a group of patients for compassionate use. A CHMP opinion on a compassionate use can only be initiated by the CHMP based on request from a National Competent Authority.

Upon initiation of such procedures, applicants should be ready to submit their available data. The CHMP can accelerate the procedure and issue an opinion in a short timeframe, depending on the urgency of the situation and the amount of data available.

The CHMP opinion on compassionate use will be updated on a regular basis as more data become available (e.g. new safety data).

7. Other considerations

The Priority medicines (PRIME) scheme could be considered by developers to receive enhanced support for the development of treatments or vaccines for COVID-19. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines. Through such enhanced development support it is envisaged that the evidence generation is optimised, which should also facilitate accelerated assessment at the time of application for a marketing authorisation. In the context of COVID-19 the scheme is predominantly suitable for treatments and vaccines in earlier stages of development. Other options described in this document, including rapid scientific advice and rolling review, are expected to remain the main tools for acceleration of procedures in the context of COVID-19 pandemic.

Applications for orphan designation for treatment (or prevention) of COVID-19 are not expected due to the high number of cases of infections in the EU and worldwide. Therefore, no specific consideration is provided in this document regarding rapid reviews of orphan designations. Developers should contact the Orphan Medicines office, in case they wish to discuss specific proposals.

The detailed description of rapid procedures for further post-authorisation activities will be considered once the first COVID-19 treatments or vaccines have been authorised.