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Acceleration of regulatory procedures during public health emergencies

Annex 1 of the EMA Health Threats Plan

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 tackling public health emergencies. 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. EMA ETF coordinates and enables fast regulatory action on the development, authorisation and safety monitoring of treatments and vaccines intended for tackling the public health emergency.

This document provides an overview of EMA's rapid formal review procedures in response to public health emergencies. Outside public health emergency context, acceleration of procedures remains possible (e.g. based on shortened procedural timetable agreed with the Rapporteurs and respective scientific body) on case-by-case basis in exceptional cases, when EMA considers that acceleration of the procedure will help to tackle an important public health threat.

For accelerated procedures that are expected to be used extensively, upon declaration of a public health emergency more detailed acceleration process descriptions (e.g. as standard operating procedures or working instructions) may be developed or updated based on those used during a past public health emergency, for internal use by the EMA.

1. Rapid scientific advice

Rapid scientific advice is provided in support of evidence generation planning for treatments and vaccines tackling the public health emergency and has been formally established with Regulation (EU) 2022/123, building on the experience gained during the COVID-19 pandemic. It follows the general principles of the regular scientific advice but with adaptations to facilitate acceleration. The coordinators for the scientific advice are members of the ETF, including also EMA staff. Each advice is discussed and agreed by the ETF on the basis of the coordinator's report and adopted by the CHMP.

The rapid scientific advice process is not mandatory and regular scientific advice procedures may continue to be used as well.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

The key features of rapid scientific advice during public health emergencies 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 on clinical trials and clinical trial protocols is **free of charge** in accordance with Regulation (EU) 2022/123. In some cases an EMA Executive Director Decision may be adopted on potential additional fee waivers for pharmaceutical quality and non-clinical aspects.
- Where scientific advice is accelerated, 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 (assessment report circulation, peer review, adoption). In addition to the formal assessment procedure, also the validation process preceding it is accelerated. 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 medicines 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 specific experts and the CHMP, which can be enriched with additional expertise through the ETF where necessary. The final advice is always adopted by CHMP.

To plan for such rapid scientific advice, developers should make the initial contact through the pheearlyinteractions@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 EMA website page on scientific advice). Additional guidance and support on the submission will be provided by the EMA Scientific Advice Office. In case of preliminary development plans, not yet suitable for formal scientific advice, early guidance will be provided by the EMA Department of Public Health Threats and the 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 tackling the public health emergency are being reviewed in an expedited manner, taking into account applicable legislative requirements. The compliance checks are also being 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 ETF provides scientific input. The received applications for products intended for tackling a public health emergency are prioritised based on 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 EMA website page on paediatric medicines), unless stated otherwise in this document (e.g. concerning submission deadlines). Additional guidance and support will be provided to the applicants by the EMA paediatric medicines office.

3. Rolling review

Rolling Review is an *ad hoc* procedure used in a public health emergency context to allow EMA to continuously assess the data on a rolling basis for an upcoming highly promising application as they become available during the development, 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 is able to complete the review of marketing authorisation application dossier earlier while ensuring robust scientific opinions.

Acceptance for a rolling review

Starting a rolling review requires specific prior agreement by the ETF. Use of a rolling review can only be agreed for products the meet the following criteria (rolling review acceptance criteria):

a. that are of strategic importance in the context of the public health emergency and are likely to contribute substantially to addressing it,

b. The exceptional acceleration of the review is proportionate to the severity of the emergency and the availability of assessment resources;

c. for which there is clear pharmacological plausibility and the proof of concept has been established based on clinical data,

d. for which no blocking issues have been identified that would *prima facie* prevent possible positive outcome of the review in a timely manner;

e. for which the dossier, manufacturing, quality control (incl. OMCL testing, if applicable) and supply chain plans are sufficiently mature so that complete application for a (conditional) marketing authorisation can be expected no later than within approximately 4 months from the start of rolling review;

f. for which it is feasible to conduct the required inspections.

To plan for such Rolling Review, developers should make the initial contact through the pheearlyinteractions@ema.europa.eu mailbox in order to allow review of suitability and maturity of the planned submission for appointment of EMA product team for potential rolling review. For this purpose the developer should, together with or following their request for eligibility to the centralised procedure, provide the following information:

- A justification for the assessment of the product via a rapid procedure;
- Data supporting the proposed role of the product in the public health emergency setting;
- Data (including clinical data) supporting the proof of concept;
- A summary of the product's clinical development status and plans for further studies;
- The status of the product's paediatric investigation plan;
- Study protocol(s);
- A high-level plan with a timetable for submitting the different rolling review and marketing authorisation application data packages and other required documentation for the application (incl. a table including submission timeline of all eCTD sections), with justification of their suitability for a prompt assessment;
- A description of the proposed manufacturing process (including status/expected timelines for provision of batch analysis, quality control method, process validation and stability data) and information to demonstrate manufacturing and quality control readiness (incl. for OMCL testing, if applicable) and assurance of the supply chain.

Based on the above information EMA will establish whether the product in the current setting is **likely** to fulfil the rolling review criteria, in which case the EMA product team will be appointed to assess the maturity and completeness of the file as part of its preliminary checks. For this purpose, the developer will be requested to provide additional information enabling EMA to determine:

- the availability of a clear and credible plan, including timelines, for submitting rolling review packages and a (conditional) marketing authorisation application;
- timelines for the availability of pivotal clinical data, based on the status of pivotal clinical trial(s);
- the proposed manufacturing process and supply chain;
- the proposed EU/EEA batch release site(s);
- whether pre-authorisation inspections are required (see Inspections: verifying compliance).

Once the preliminary conclusions support the maturity and completeness of the file, EMA will proceed with appointment of rapporteurs for this upcoming application.

Based on rapporteurs' assessment and on the EMA product team's input on whether the applicant has provided enough information, ETF will conclude whether the criteria for rolling review (see above) are met and the intended application can be accepted for the rolling review, in agreement with the CHMP.

The ETF and the Rapporteurs can at any time request the applicant to provide further data that has been generated on the medicinal product.

In agreement with the CHMP and the Rapporteurs, the ETF can revoke the eligibility of a medicinal product for rolling review at any time, if:

- The medicinal product no longer meets the rolling review acceptance criteria, or
- The data on the medicinal product is not being generated according to plans at the time of granting the rolling review.

The eligibility to rolling review also cedes if the public health emergency status is terminated.

Conduct and outcomes of a rolling review

The ETF also acts as forum for discussion on the rolling data assessment and will advise the CHMP on a recommended course of action. As for other authorisation procedures, the assessment of submissions within rolling review is performed by the Rapporteur and Co-rapporteur teams and the outcomes are adopted by the PRAC and the CHMP[1].

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, responses to a cumulative listing of all outstanding questions from previous review cycles and newly available data. The contents and timing of each rolling review submission have to be pre-agreed between the applicant and the EMA (including Rapporteurs).
- There can be **several Rolling Review cycles** with the timelines for assessment to be 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. As part of the outcome of the assessment of rolling review submission, questions are usually raised to the applicant. Responses to list of questions from previous Rolling Review cycles are ideally to be incorporated into subsequent Rolling Review submissions.

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

If the eligibility to rolling review cedes (see above), no new rolling review cycles are started and the ongoing assessments are normally stopped, but the ETF may exceptionally decide in individual cases, based on the urgency of public health needs and the advancement of the assessment, that assessment of the already started rolling review cycles is to be completed.

[1] In case of advanced therapy medicinal products also by the CAT.

4. Marketing authorisation

Applications for a marketing authorisation for products intended for tackling the public health emergency are often treated in an expedited manner. The applicants are advised to contact EMA via email to pheearlyinteractions@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 EMA Product Lead and EMA product team will be appointed. The EMA Product Lead will liaise with the applicant to understand the proposed submission schedule including the availability of pivotal data. This information will help to estimate the likely start of a possible rolling review (if used) and marketing authorisation application review, so that prospective Rapporteurs have some certainty as regards their resource planning. Once the Rapporteurs 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 for sufficiently mature and well planned applications 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 applicant consider that shortening of procedural timelines would have important public health impact in dealing with the public health emergency 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 the public health emergency, with a view to agree a shorter review timetable *ad hoc* (see section 5).

EMA also accelerates the linguistic review process for products intended for tackling a public health emergency and works 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 tackling the public health emergency. Marketing authorisation holders (MAHs) are encouraged to share early information about their planned development for tackling the public health emergency 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 the public health emergency. Such possible shortening of procedure timelines will be considered by EMA in consultation with the Rapporteurs, the ETF and the CHMP.

EMA also substantially accelerates the linguistic review process for procedures related to public health emergency and works closely with the European Commission, keeping them informed about such applications, to facilitate the acceleration of the decision-making process.

6. Compassionate use and use of unauthorised medicines

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. In the context of a suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation, Member States may also allow the use and distribution of an unauthorised medicinal product in accordance with Article 5(2) of Directive 2001/83/EC.

While coordination and implementation of these exemptions remain competence of a Member State, EMA can provide through the ETF and CHMP an opinion in accordance with article 18(3) and 18(4) of Regulation (EU) 2022/123 on the conditions to be imposed on the use and distribution of the medicinal product concerned as well as on the patients that are targeted. If such opinion is issued, it must be considered by the Member States in their national decisions.

Applicants cannot submit directly to the EMA a request for an ETF and CHMP opinion on a compassionate use or use of unauthorised medicine and should instead contact National Competent Authorities for any proposals to offer a compassionate use programme. However, developers of products for tackling the public health emergency are encouraged to contact EMA via email to PHEearlyinteractions@ema.europa.eu and in this context provide also information on the compassionate use applications underway and unauthorised medicinal product use decisions at national level. National Competent Authorities should also inform EMA if they are making a product available to a group of patients for compassionate use.

An ETF and CHMP opinion on a compassionate use or use of unauthorised medicine can only be initiated upon request from one or more Member States (National Competent Authorities) or the European Commission. The ETF will prepare a recommendation for the CHMP with the support of the CHMP Rapporteurs (if already appointed).

Upon initiation of such procedures, applicants should be ready to submit their available data. The EMA will 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 applicants will be informed about the timetable used for preparing such opinions, which will be developed on a case-by-case basis.

The opinion on compassionate use or use of unauthorised medicine 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 tackling the public health emergency. 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 rapid assessment at the time of application for a marketing authorisation. 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 for medicines tackling the public health emergency are available independently of the PRIME scheme.

Applications for orphan designation for treatment (or prevention) of conditions causing an already occurring public health emergency normally are not expected due to the likely high number of cases 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.

At the request of EMA Executive director or the European Commission EMA may also adopt a scientific opinion under Article 5(3) of the Regulation (EC) No 726/2004 concerning medicines tackling the public health emergency. Timetables applied for such procedures take into account the urgency of the subject matter of the assessment.

The ETF can also consider the need to prepare and publish scientific positions to support the Member States or the relevant European Commission bodies such as Health Emergency Preparedness and Response Authority (HERA) in their decisions to obtain and/or use specific medicines during a declared public health emergency or in preparation for one.

For more detailed advice on use of rapid procedures during a public health emergency for post-authorisation activities, the marketing authorisation holders for relevant treatments or vaccines are advised the contact the respective contact persons in the EMA product team (e.g. the Product Lead or Quality Specialist).