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7 August 2025
Version 1.0
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Expedited Assessment of Applications for Phase I and Integrated Phase I-II Clinical Trials with Medicinal Products

Introduction

The implementation of the Clinical Trials Regulation ((EU) No 536/2014) introduced new procedures for obtaining approval for clinical trials in the EU. The Clinical Trials Information System was established as the single-entry point for submitting clinical trial applications to regulatory authorities in the EU member states and to facilitate a coordinated assessment. The introduction of CTIS, has required sponsors to adapt to new application processes, and prompted authorities to explore ways to improve the assessment procedures.

One goal of the Danish life science strategy, launched by the Danish government in 2024, is to accelerate assessment to enable faster initiation of clinical trials with medicinal products in Denmark and strengthen early-stage clinical research. This will be achieved by providing either a Request for Information (RFI) or an approval within 14 days of completed validation of a clinical trial application, compared to the standard 45-day timeline. The procedure will be continuously refined - maintaining high standards and ambition - in line with experience gained.

The core process for expedited assessments applies to mononational trials conducted in Denmark. However, upon request it may be possible to apply the expedited process to multinational trials, provided that the sponsor has agreements with the involved member states to comply with the requirements and timelines outlined in this document.

Please note, that the Danish authorities comply with the CT-CURE framework offering extraordinary short assessment timelines in case of public health crisis'. The procedure presented in this document is a separate framework for expedited assessment which may be applicable when CT-CURE is not.

The Scope of the Expedited Assessment Procedure

Generally, both the validation and assessment phase of the application process has been shortened in this expedited assessment procedure. There are no changes to the requirements for applications or the documents to be submitted in connection with clinical trial applications. For general requirements for clinical trial applications, please refer to our guidance available on the Danish Medicines Agency webpage and the Danish MREC webpage.

There are, however, requirements that must be met for a clinical trial application to be eligible for the expedited assessment procedure. Requirements are as follows:

- The expedited assessment procedure is only applicable for applications which contain both Part I and Part II.
- Only phase I and integrated phase I-II clinical trial applications are eligible for expedited assessment.
- Master protocols or complex clinical trials may be eligible for expedited assessment, provided that no more than one investigational medicinal product does not have marketing authorisation at the time of submission.
- For *mononational* clinical trials applications, prior notification and/or agreement is not required with the Danish Medicines Agency and the Danish Medical Research Ethics Committees. For these applications, the request for expedited assessment must be clearly stated at the beginning of the application cover letter.

- For *multinational* clinical trial applications, prior notification and agreement is required with the Danish Medicines Agency and the Danish Medical Research Ethics Committees by sending an email addressed to kf@dkma.dk and kontakt@dvmk.dk. The request will be reviewed based on the role of Denmark as either Reporting Member State (RMS) or Member State Concerned (MSC) and available resources. It is a prerequisite for expedited assessment that the sponsor has established agreements in advance with all other EU Member States involved in the clinical trial application, covering both Part I and Part II.

- The expedited assessment procedure cannot be combined with the coordinated application process for combined CTR-IVDR studies in Denmark.

In addition to the requirements above, sponsors should carefully consider the following procedural aspects when planning to submit a clinical trial application under the expedited assessment procedure:

- The feasibility of the expedited assessment procedure relies on the submission of high-quality application dossiers that meet all applicable requirements, e.g. that the protocol fulfils the requirements of the CTR and that national requirements are met (either in the protocol or in Part II).

- Although the CTR permits a 50-day extension of the assessment phase for clinical trials involving advanced therapeutic medicinal products, this provision is, as a general rule, not applied in Denmark.

- CTIS has a built-in winter clock stop functionality where no evaluation of a clinical trial application is performed. During this period, it is not possible to accommodate any request for expedited assessment. Similarly, a summer clock stop is introduced for the expedited assessment why the procedure is not applicable during week 29-31.

- For all steps of the expedited assessment procedure and timelines in CTIS, the term “day(s)” refers to calendar days. If the calculation of a due date falls on a public holiday or a weekend day, the due date will automatically be extended to the next business day. The provision of due dates in this expedited assessment procedure follows the existing technical behaviour in CTIS.

Please note that the above list of procedural aspects is additions to the usual requirements sponsors must comply with when submitting a clinical trial application to CTIS.

Validation Phase

Once a clinical trial application is submitted, the validation phase begins. Please refer to Figure 1 below for an overview of the validation phase under the expedited assessment procedure.

On day 7 after the application submission date, there are two possible outcomes: 1) the application is declared valid and proceeds to the assessment phase, denoted T0; or 2) an RFI is sent to the sponsor to resolve validation issues.

If a validation RFI is sent on day 7, the validation phase continues. The sponsor will then receive a validation RFI with a deadline for submitting a response on day 12 (giving sponsor 5 days to respond). Following submission of the RFI response, authorities have five days to assess the response, with the last day considered T0, regardless of the outcome (the application is valid and the assessment phase starts; or the application is not valid and is rejected).

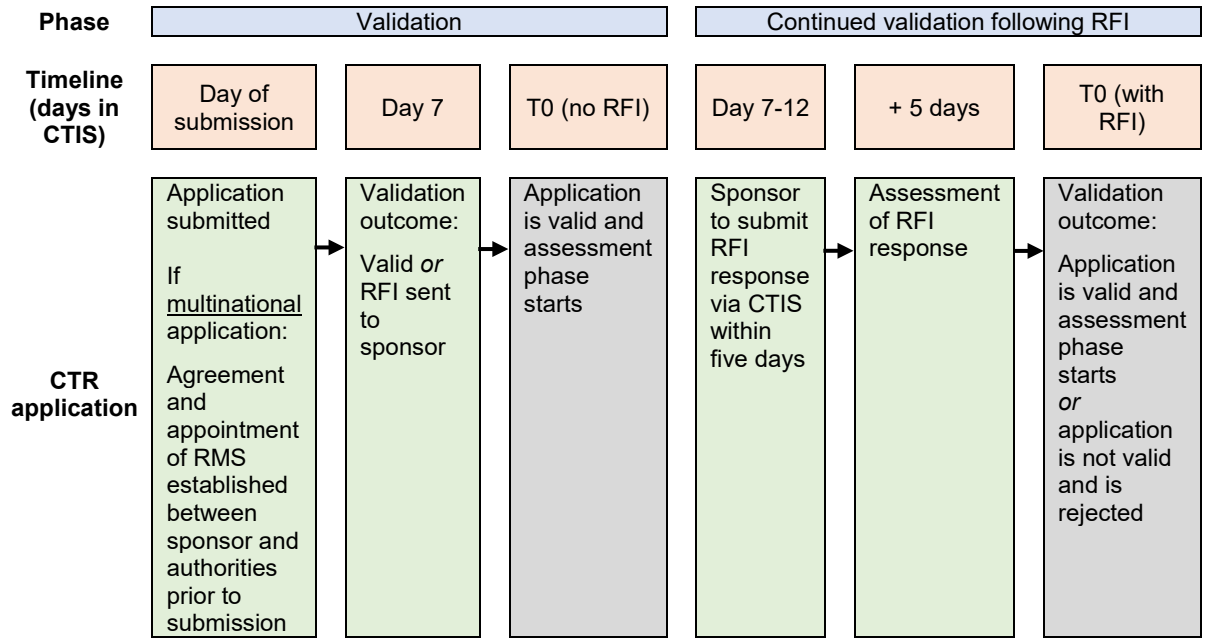

Figure 1 Overview of the validation phase under the expedited assessment procedure

Assessment Phase

Once an application is declared valid, it proceeds to the assessment phase. Please refer to Figure 2 and Figure 3 below for an overview of the assessment phase under the expedited assessment procedure, depending on whether the application is mono- or multinational.

Mononational applications

For mononational applications, the initial assessment ends 14 days after T0, i.e. 14 days after the application is declared valid. On day 14 after the validation date, there are two possible outcomes: 1) the application is approved (both Part I and Part II) or 2) an RFI is sent to the sponsor to resolve assessment issues (either in Part I, Part II or both).

If an RFI is sent on day 14, the assessment phase continues. The sponsor will then receive an RFI (either in Part I, Part II or both) with a deadline for submitting a response on day 26 (giving sponsor 12 days to respond). Following submission of the RFI response, authorities have 10 days to assess the response with two possible outcomes: 1) the application is approved (both Part I and Part II) or 2) a second RFI is sent to the sponsor to resolve remaining assessment issues (either in Part I, Part II or both).

If sponsor has submitted an insufficient RFI response (either in Part I, Part II or both), a second RFI will be issued on day 36 to allow the sponsor to resolve the remaining issues. The deadline for submitting the second RFI response is day 41 (giving sponsor 5 days to respond). Once the sponsor has submitted a response to the second RFI, the authorities have five days to assess this with two possible outcomes: 1) the application is approved (both Part I and Part II) or 2) the application is not acceptable (either Part I, Part II or both) and is rejected.

Exceptionally, an application may be approved with conditions if the clinical trials overall risk-benefit profile is positive despite remaining deficiencies. The clinical trial can be initiated as soon as there is an approval/decision in CTIS, and the required changes can be implemented immediately in the trial dossier without prior authorisation. However, the dossier is expected to be updated in line with the condition at the time of the first application for substantial modification.

Multinational applications

For multinational applications, the assessment phase under the expedited assessment procedure follows a similar logic as for mono-national applications. The only difference is the involvement of other

member states in the assessment phase of Part I, which extends the overall timeline for the assessment phase.

The RMS shares their initial assessment with the other member states in CTIS on day 14. Input from the remaining member states is received in CTIS on day 21 and is subsequently consolidated into one RFI by the RMS, which is sent to the sponsor on day 26. The subsequent timeline after sending the RFI to the sponsor as described for mono-national applications remains unchanged.

Decision

Following the timelines in Figure 2 for mono-national applications, sponsors can expect a decision (approval/rejection) on the clinical trial application on day 14, day 36, or day 46, depending on the course of the review. For multinational applications, and as outlined in Figure 3, a Part I conclusion and a Part II conclusion can be expected on day 21, day 48 or day 58, depending on the course of the review.

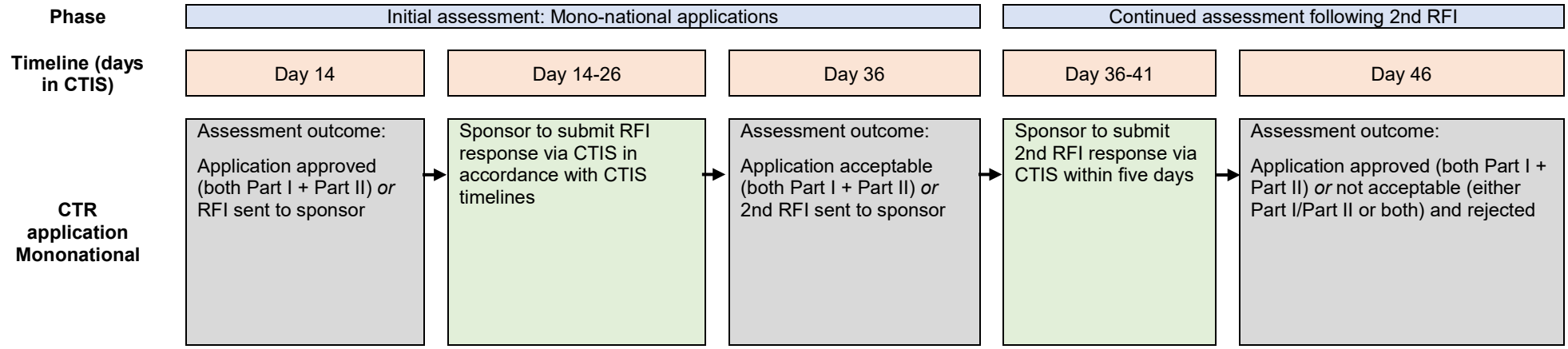

Figure 2 Overview of the assessment phase for mono-national applications under the expedited assessment procedure

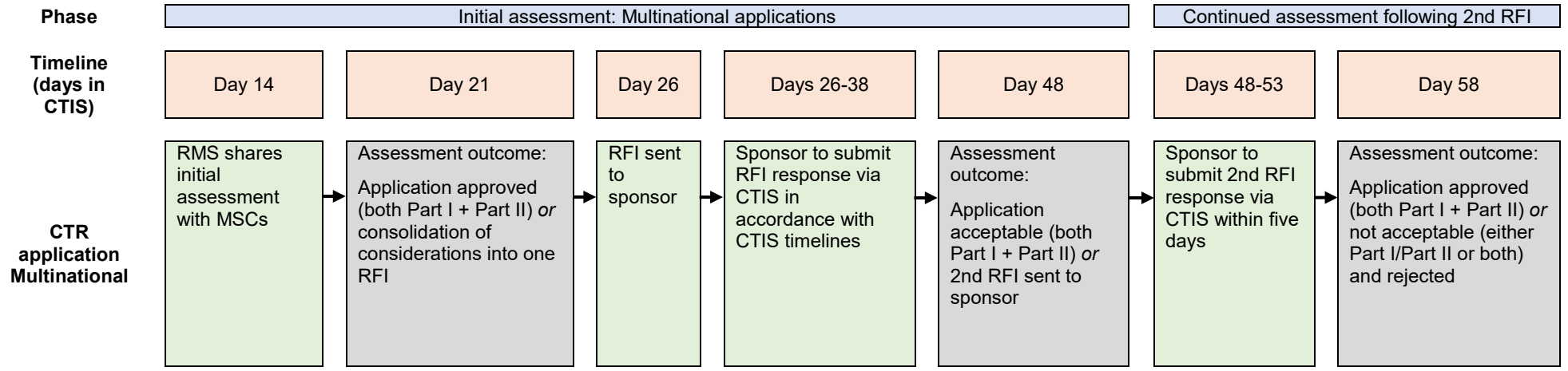

Figure 3 Overview of the assessment phase for multinational applications under the expedited assessment procedure