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Guidance for the Coordinated Application Process for Combined Studies in Denmark

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Introduction

In 2021 and 2022, three significant regulations came into force: The Clinical Trials Regulation (CTR)[1], the Medical Devices Regulation (MDR)[2] and the In Vitro Diagnostic Medical Devices Regulation (IVDR)[3].These regulations introduced new requirements for obtaining approval for clinical trials, clinical investigations of medical devices and performance studies. According to CTR, applications for clinical trials must now be submitted through an IT system, the Clinical Trials Information System (CTIS), facilitating a coordinated assessment among EU member states. For clinical investigation of medical devices and certain performance studies of in vitro diagnostic medical devices, sponsors must now obtain an approval from both Danish Medicines Agency (DKMA) and the Danish Medical Research Ethics Committees (MREC). Authorization under IVDR and MDR is not yet coordinated among EU member states.

The new requirements under CTR and IVDR can especially pose challenges for the clinical trials where a performance study of an in vitro diagnostic device (IVD) is conducted simultaneously. For these combined studies sponsors must obtain authorization for both the clinical trial of the medicinal product and for the performance study of the IVD before the clinical trial can commence. An ongoing EU project, the "COMBINE" project[4], coordinated by DKMA, is addressing these challenges on EU level.

To strengthen the interface between clinical trials and medical devices in Denmark, sponsors of combined studies now have the opportunity to apply under a national coordinated process with DKMA and VMK. This national coordinated process aims to improve the quality and streamline the approval procedure for combined studies, ensure that sponsors receive simultaneous decisions on both the clinical trial under CTR and the performance study under IVDR. This also enables parallel alignment of documents in both application processes. The coordinated process further ensures that the applications are assessed simultaneously and by the same ethics committee at MREC, and that the clinical assessment at DKMA is coordinated across the responsible sections.

The national coordinated application process is possible either when Denmark is involved in a mononational or multinational clinical trial in CTIS. In Denmark, the authorities will, as outlined in this document, coordinate the process between the application for the clinical trial in CTIS (CTR application) and the application for the performance study (IVDR application), irrespective of whether Denmark is the Reference Member State (RMS) or Member State Concerned (MSC) in CTIS. However, please note that there will be differences in the timelines and how the IVDR application is coordinated depending on whether Denmark is RMS or MSC in the clinical trial in CTIS. the It will be prioritized to express willingness to act as RMS under CTR for combined studies if the sponsor proposes Denmark as RMS.

Sponsors should be particularly aware of the following requirements for the coordinated process:

- Submission of the IVDR application to DKMA and MREC can be made up to 5 days before, but no later than the submission of the CTR application via CTIS.

- Validation and assessment of the IVDR application at DKMA and MREC occur in parallel with the validation and assessment of the CTR application, and follow CTIS deadlines. This means that deadlines for submitting response to the request for information (RFI) in CTIS apply to both the IVDR and CTR applications.

- Sponsors must submit simultaneously their RFI responses for both the IVDR and CTR applications.

[1] Clinical Trials Regulation (EU) No 536/2014
[2] Medical Device Regulation (EU) 2017/745
[3] In Vitro Diagnostic Regulation (EU) 2017/746
[4] More information on 'COMBINE' at EU Commission webpage: Combined studies - European Commission (europa.eu)

- The decision on the IVDR application is always made shortly before the decision on the CTR application.

Further instructions on the national coordinated process and sponsor requirements can be found in the subsequent sections of this guidance and in Figure 1.

For general requirements for the application on clinical trial, a reference is made to information about CTR available on the DKMA webpage, and for the application on performance evaluation study, a reference is made to IVDR and information available on the DKMA webpage and MREC guidance

Parallel Submission of IVDR Application and CTR Application

Sponsors should be aware of the following when using the national coordinated application process:

- Sponsors can submit the IVDR application to DKMA and MREC **up to 5 days before** but no later than the CTR application in CTIS.
- The performance study is applied for as before by submitting a joint email (e.g. via Eudralink) to DKMA (med-device@dkma.dk) and MREC (dketik@dketik.dk).
- The clinical trial is applied for through CTIS. It is a requirement that Part I and Part II of the clinical trial application will be submitted simultaneously in CTIS.

The cover letter for both the IVDR and CTR application should include the following:

- Notification of that this application concerns a 'combined study' and reference to the EU CT number for the clinical trial in CTIS and the EUDAMED2 CIV-ID number, if already allocated by an IVD authority for the IVD study.
- Confirmation of simultaneous submission (though IVDR application up to 5 days before CTR application).
- Statement that sponsor wants to make use of the coordinated process, including the sponsor's acceptance that the process, including deadlines for responding to RFI, follows the deadlines applicable to the CTR application as stated in CTIS.
- A list of the documents submitted that are identical in the IVDR and CTR applications (including version and date).

Parallel Validation of IVDR Application and CTR Application

Validation of the IVDR application at DKMA and MREC, and the CTR application in CTIS, occur in parallel in the coordinated process.

Sponsors should be aware that responses to validation for both the IVDR application and CTR application follow the deadlines applicable to the CTR application in CTIS. Therefore, the sponsor's deadline for responding to RFI for the IVDR application will be based on the applicable deadlines for the sponsor's CTR application in CTIS. This also means that sponsors must submit RFI responses for both the IVDR and CTR applications simultaneously. Thus, both the IVDR and CTR applications can be declared valid simultaneously, within the applicable timelines in CTIS, with the same day 0 as the start of the assessment phase. A coordinated process requires both applications to be declared valid.

If the sponsor does not respond simultaneously to RFI during the validation of the IVDR and CTR applications, the coordinated process cannot be completed. The same applies if the sponsor receives an

administrative RFI for one of the applications. The administrative RFI will be sent to the sponsor to ensure the parallel process in cases where there is RFI only for one of the applications. The administrative RFI must also be answered within the CTIS deadline.

- Responses to RFI during the validation phase for the IVDR application are submitted via email to DKMA and MREC by e-mail.
- Responses to RFI during the validation phase for the CTR application are submitted via CTIS.
- Requested documents are sent by email or placed in CTIS as appropriate.

Parallel Assessment of IVDR Application and CTR Application

Assessment of the IVDR application at DKMA and MREC occurs in parallel with the assessment of the CTR application. In a coordinated process, it will be the same ethics committee at MREC that assesses both IVDR and CTR application. Likewise, at DKMA, the clinical assessment of the applications is coordinated across the responsible sections.

The assessment of the applications begins day 0, i.e., the day the applications are declared valid.

Sponsors should be aware that deadlines for the CTR application in CTIS will define the sponsor's deadline for responding to RFI for the IVDR application, meaning that the RFI response deadline in CTIS for the CTR application will apply to both applications. **For a coordinated process to be carried out, the sponsor's response to RFI must be submitted simultaneously for the IVDR and CTR applications**. The same applies if the sponsor receives an administrative RFI for one of the applications. The administrative RFI can be sent to the sponsor to ensure the parallel process in cases where there is RFI only for one of the applications. The administrative RFI must also be answered within the CTIS deadline.

- Responses to RFI during the assessment phase for the IVDR application are submitted via e-mail to DKMA and MREC.
- Responses to RFI during the assessment phase for the CTR application are submitted via CTIS.
- Requested documents are sent by email or placed in CTIS as appropriate. It is the sponsor's responsibility to ensure that all documents in CTIS are updated in accordance with RFI for both the IVDR and CTR applications.

Decision for IVDR Application in a National Coordinated Process with CTR Application

After submitting responses, sponsors can expect a decision on the IVDR application from DKMA, including MREC opinion, no later than day 45, followed by a decision on the CTR application. In other words, with a coordinated process, the decision on IVDR application will always be made shortly before the decision on the clinical trial application.

The decision on the clinical trial application follows the applicable deadlines in CTIS.

Figure 1 The process timeline overview