

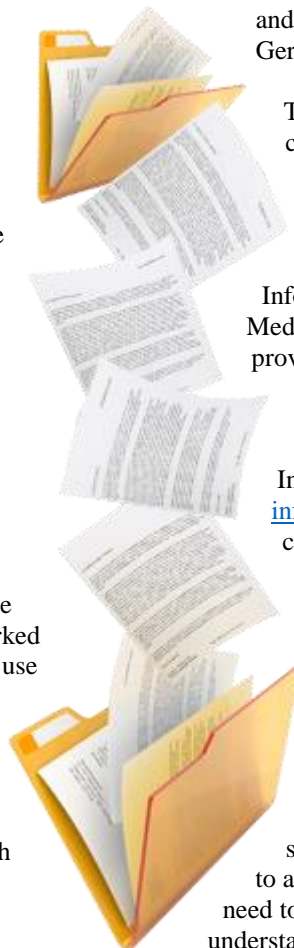
Avoiding delays when conducting medical device clinical or IVD performance evaluation studies in Germany

Germany is a sought-after location for conducting medical device clinical studies and in vitro diagnostic (IVD) performance evaluation studies. This article discusses certain aspects of conducting such studies in Germany, which if not clearly understood, can lead to unnecessary and costly delays.

Clinical study-related regulations and guidance

The Federal Institute for Drugs and Medical Devices (BfArM; Bundesinstitut für Arzneimittel und Medizinprodukte) is the German Competent Authority for medical devices, which is responsible for authorizing and overseeing the conduct of medical device clinical studies and IVD performance evaluation studies in Germany. The law and ordinances applicable to such studies are:

- Act on Medical Devices (MPG; Medizinproduktegesetz), the German medical device law. Requirements for device clinical investigations are in Sections 20 through 23b and the requirements for IVD performance evaluation studies are in Section 24. Sections 20 to 23a do not apply where the clinical study is conducted using CE marked devices, unless the aim of the study is to use the device for a different intended purpose, or additional invasive or other stressful examinations are to be carried out.
- Ordinance on Clinical Investigations with Medical Devices (MPKPV; Verordnung über klinische Prüfung von Medizinprodukten), includes detailed requirements on notification, conduct of medical device clinical and IVD performance studies, and associated timelines.
- Ordinance on the Medical Device Safety Plan (MPSV; Medizinproduktesicherheitsplanverordnung), includes requirements for reporting adverse incidents and serious adverse events (SAEs) occurring during medical device clinical



and IVD performance studies conducted in Germany.

The law and ordinances on medical device clinical studies and IVD performance evaluation studies are available from the BfArM [website](#) in the German language only. However, the website of the German Institute of Medical Documentation and Information [DIMDI; Deutsches Institut für Medizinische Dokumentation und Information] provides a [link](#) to an unofficial translation of the MPG. The role of DIMDI in the application process and SAE reporting is discussed later.

In addition, the BfArM website provides [information and guidance](#) on medical device clinical investigations and IVD performance studies in English, covering the submission of a request for authorization to conduct a study, submission of a request for waiving the authorization of a study, reporting of SAEs, costs in connection with studies, and the BfArM scientific advice process. In addition, responses to [frequently asked questions \(FAQs\)](#) regarding clinical investigations in English are on the site. Even so, if an aspect of the requirements is not clear, to avoid any misunderstandings, companies may need to arrange access to a German speaker who understands regulatory concepts, or work with a translation company that provides services to the medical device sector.

Language may also be an issue during the process of online notification of a medical device clinical study or IVD performance evaluation study to DIMDI, the German organization responsible for this activity, which is discussed below.

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It should be noted that the requirements for notifying and conducting a medical device clinical study or IVD performance evaluation study are addressed to the “sponsor” and not the “manufacturer.” Moreover, the MPG defines “sponsor” (author’s unofficial translation) “as a natural or legal person who assumes responsibility for initiating, organizing and financing a clinical study in humans or performing a performance evaluation study of in vitro diagnostic medical devices.” This means that anyone meeting the definition of “sponsor”, including investigators initiating studies, must meet all applicable clinical study-related laws and regulations in Germany.

IVD performance evaluation studies

In accordance with MPG Section 24, Performance evaluation studies, Sections 20 to 23b of the MPG apply to IVD performance evaluation studies if:

- invasive sampling is conducted either exclusively or to a considerably higher degree to obtain a specimen for the purpose of a performance evaluation of an IVD device, or
- in the context of the performance evaluation study, additional invasive or other stressful examinations are conducted, or
- the results obtained in the context of the performance evaluation are to be used for diagnostic purposes without it being possible to confirm them by means of established procedures.

In the remaining cases, the consent of the person from whom the specimen is to be taken is necessary, in so far as this person’s personal rights or commercial interests are affected.

Process for requesting study authorization

An application for conducting a medical device clinical study or IVD performance evaluation study must be submitted to BfArM using the DIMDI Medical Devices Information System, which is a German internet-based data entry system. To access the system, a user code and password are required; the DIMDI [website](#) provides instructions on how to obtain them. The application process involves the direct entry of data into the online application form and uploading required documents. It is important to note that the entire system is in the German language; however, information in English on the contents of the application form and how to complete it are provided on the DIMDI [website](#). There is also a [link](#) to a page on the clinical study and performance evaluation study application process that includes a [link](#) to an application form in German and English that can be used offline to complete the application form on the DIMDI system, and a [link](#) to a guidance document in English on logging into the system and completing the application form. The information that must be entered into the system to complete the application form can be provided in English.

In addition to completing the DIMDI application form, Section 3 of the MPKPV, specifies the documents that must accompany the application form. These documents can be submitted in German or English unless it is specified that a document must be provided in the German language. The BfArM web [page](#), “Information on submission of a request for authorisation of a clinical trial or a performance evaluation study” lists the documents to be submitted, which include:

- the study protocol or performance evaluation protocol
- investigator’s brochure
- a summary of the main content of the protocol in the German language
- description of the intended medical procedure and examination methods and possible deviations from medical standards
- preclinical assessment
- information on the safe use of the medical device in German
- an evaluation and assessment of the foreseeable risks, disadvantages and stress for the trial subject weighed against the prospective significance of the medical device for medical science and against the anticipated benefit for the trial subjects
- a power of attorney for the representative appointed by the sponsor according to Section 20, sub-section 1, sentence 4, number 1a of the MPG
- descriptions of the procedures for documentation, evaluation, and reporting of SAEs to the competent federal higher authority (i.e., BfArM), and
- other documents.

Power of attorney

The need for a power of attorney under certain circumstances is a special German requirement. That is, the MPG requires that a medical device clinical study or IVD performance evaluation study can be conducted in Germany only if the sponsor or representative of the sponsor has a registered place of business in a Member State of the European Union or in another State that is a signatory to the Agreement on the European Economic Area.

This requirement means that a sponsor located in the United States, Switzerland, Turkey or any other country that is not part of the EU or EEA, must appoint a representative and grant a power of attorney to the representative to notify a clinical investigation intended to be conducted in Germany. It is also important to note that the representative in this context is not the same as the Authorized Representative (AR), although an AR can provide this service.

The [FAQ guidance](#), mentioned previously, includes responses to the questions “Which powers of attorney should be attached to the application?” and “Is it

possible for a sponsor based in Switzerland or Turkey to submit an application.”

Request for waiving authorization

Under MPG Section 20, sub-section 1, sentence 2, BfArM is authorized to waive study authorization of a low risk medical device clinical study or low risk IVD performance evaluation study. The details of the criteria for granting a waiver and the procedures to be followed are specified in Section 7 of the MPKPV. The BfArM [website](#) provides guidance on the criteria for a waiver and additional information in the [FAQ guidance](#) document. A request for such a waiver must be submitted to BfArM electronically using the DIMDI system.

Waivers from the application process are possible for studies involving:

- class I medical devices
- class IIa non-invasive medical devices
- CE-marked medical devices where the study involves additional invasive or otherwise stressful examinations, unless the study concerns a different intended purpose
- IVD devices for which a performance evaluation involves invasive sampling either exclusively or to a considerably higher degree to obtain a specimen for the purpose of the study, or additional invasive or other stressful examinations are conducted as part of the study.

In place of submitting the documents requested for study authorization, the following documents must be attached to the application for the waiver:

- a summary risk assessment
- proof that one of the above-listed criteria has been met, and
- for products that must be sterile when used, proof of validation of the sterilization process used by the manufacturer or information on the preparation and sterilization processes that must be performed by the test site.

Special requirements on SAE reporting

As indicated above, sponsors need to provide descriptions of the procedures for documentation, evaluation, and reporting of SAEs. These procedures must comply with German requirements for reporting SAEs, which exceed those specified in the medical devices Directives and European SAE guideline (MEDDEV 2.7/3). In addition, BfArM requires reporting of adverse events occurring during IVD performance evaluation studies, whereas the IVD Directive (98/79/EC) does not. The BfArM [website](#) provides guidance in English, “Reporting of serious

adverse events (SAEs) in clinical trials or performance evaluation studies for use by sponsors according to Section 3 sub-section 5 of the Ordinance on Medical Devices Vigilance (MPSV)”. The timelines and forms that must be used to report SAEs to BfArM depend upon the presumed cause of the SAE and whether the SAE has occurred in or outside Germany.

The [German SAE Report Form](#) must be used when the SAE occurred in Germany and it cannot be excluded that there is a causal relationship between the SAE and the investigational medical device, a comparator device, a diagnostic or therapeutic procedure performed as part of the clinical study, or other conditions of the study. If the event occurred outside Germany, a Summary Table using the MEDDEV 2.7.3 [reporting form](#), which is an Excel spreadsheet, must be used. In both cases, the SAE must be reported immediately; however, no additional guidance is provided on how to interpret “immediately.” For this reason, we advise and assist sponsors in reporting as soon as practicable, expediting the reporting process as much as possible.

When it is possible to exclude a causal relationship between the SAE and the investigational medical device, a comparator device, a diagnostic or therapeutic procedure performed as part of the clinical study, or other conditions of the study conduct, a Summary Table using the MEDDEV 2.7.3 [reporting form](#) must be used and the reports submitted quarterly.

An [SAE summary evaluation form](#) must be completed for all SAEs regardless of causality or location of occurrence (in or outside Germany) and submitted quarterly. Two additional documents are important for completing the SAE summary evaluation form, which are the [notes](#) on completion of the form and the [complication rates](#) form.

Submission to the Ethics Committee

A favorable opinion from the ethics committee is required before a study can be initiated, including a study that may qualify for a waiver to authorization by BfArM or a post-market study with a CE marked device. Section 22 of the MPG specifies the procedures concerning application to an ethics committee to obtain a favorable opinion on the conduct of a medical device clinical study or IVD performance evaluation study. Additional details are provided in the MPKPV. The DIMDI system is used for such a submission and can be initiated either before or after submission to BfArM. A detailed discussion of these requirements is beyond the scope of this article; however, it is important to clearly understand and follow the requirements laid down in the MPG and the MPKP.