Guidance for Application/Notification for Performance Studies under Regulation (EU) 2017/746 on In-vitro Diagnostics

1. Introduction

The guidance described in this document is based on the principles outlined in the In Vitro Diagnostics Regulation (EU) 2017/746 (IVDR), concerning Performance Studies in Articles 57 to 77 and Annex XIII and XIV. This document is a guidance to the local form *MT-MDF16 Performance Study – Application/Notification form under the In-Vitro Diagnostic Regulation (EU) 2017/746*.

To obtain an authorisation from the Malta Medicines Authority, the sponsor, or its legal representative in cases where the sponsor is not established in the Union, shall submit an application to the Authority. The application should be accompanied by the request to the relevant Ethics Committee/s in Malta.

Before the submission of an application or notification, the Malta Medicines Authority strongly recommends that the applicant arranges a pre-submission meeting with the Authority, to discuss the performance study and obtain further information from the Medical Devices review team on the requirements for authorisation. Reference should be made to *MT-MDF14 Application for Pre-Submission Meeting Request for Clinical Investigations/Performance Studies* and *GL-MDF17 Guidance for Application for Pre-Submission Meeting Request. for Clinical Investigations/Performance Studies.*

If a sponsor intends to introduce modifications to an authorised performance study, reference should be made to *GL-MDF16 Guidance for Notification for Modification of Performance Studies under the Regulation (EU) 2017/746* available on the Malta Medicines Authority website https://medicinesauthority.gov.mt, under the section for medical devices.

The mandatory use of the European databank platform as a registration system will start when the Clinical Investigation and Performance Studies (CIPS) module on EUDAMED has been declared fully functional, in accordance with Article 73 of the Medical Device Regulation.

2. Scope

This document has been prepared to guide applicants when submitting forms related to performance studies to be carried out in Malta, to ensure that In-Vitro Diagnostic Regulation requirements and expectations are fulfilled.

The sponsor is encouraged to refer to the latest version of International Standard ISO 20916 - Clinical performance studies using specimens from human subjects.

3. Terms, definitions & abbreviations

Authorised Representative
Authorised representative means any natural or legal person established within the Union who has received and accepted a written mandate from a manufacturer, located outside the Union, to act on the manufacturer's behalf in relation to specified tasks with regard to the latter's obligations under this Regulation. [Regulation (EU) 2017/746 Article 2(25)]

Companion Diagnostic
A companion diagnostic is a device which is essential for the safe and effective use of a corresponding medicinal product to either identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product, or to identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product. [Regulation (EU) 2017/746 Article 2(7)]

Ethics Committee
Ethics committee means an independent body established in a Member State in accordance with the law of that Member State and empowered to give opinions for the purposes of the In Vitro Diagnostics Regulation, taking into account the views of laypersons, in particular patients or patients' organisations. [Regulation (EU) 2017/746 Article 2(59)]

Ethics Committee/s in Malta
Health Ethics Committee; Research Ethics Committee.

In vitro diagnostic medical device
In vitro diagnostic medical device means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used *in vitro* for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:
(a) concerning a physiological or pathological process or state;
(b) concerning congenital physical or mental impairments;
(c) concerning the predisposition to a medical condition or a disease;
(d) to determine the safety and compatibility with potential recipients;
(e) to predict treatment response or reactions;
(f) to define or monitoring therapeutic measures.
Specimen receptacles shall also be deemed to be *in vitro* diagnostic medical devices.
[Regulation (EU) 2017/746 Article 2(2)]

Leftover samples
Leftover samples are samples resulting from the remnants of specimens taken for purposes of standard of care (ISO 20916 In vitro diagnostic medical devices — Clinical performance studies using specimens from human subjects)

Legal Representative
Where the sponsor of a performance study is not established in the Union, that sponsor shall ensure that a natural or legal person is established in the Union as its legal representative.

Such legal representative shall be responsible for ensuring compliance with the sponsor's obligations pursuant to the IVDR and shall be the addressee for all communications with the sponsor provided for in this Regulation. Any communication with that legal representative shall be deemed to be a communication with the sponsor. [Regulation (EU) 2017/746 Article 58(4)]

Manufacturer
Manufacturer means a natural or legal person who manufactures or fully refurbishes a device or has a device designed, manufactured or fully refurbished, and markets that device under its name or trademark. [Regulation (EU) 2017/746 Article 2(23)]

Performance Study
A performance study is defined by the In Vitro Diagnostics Regulation (IVDR) as a study undertaken to establish or confirm the analytical or clinical performance of a device. [Regulation (EU) 2017/746 Article 2(42)]

Sponsor
Sponsor means any individual, company, institution or organisation which takes responsibility for the initiation, for the management and setting up of the financing of the performance study. [Regulation (EU) 2017/746 Article 2(57)]

Abbreviations

EUDAMED	European Database on Medical Devices
MDCG	Medical Device Coordination Group
IVDR	Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro Diagnostic Medical Devices and Repealing Directive 98/79/EC and Commission Decision 2010/227/EU
IVD	In vitro diagnostic
MMA	Malta Medicines Authority
N/A	Not applicable
PMPF	Post-Market Performance Follow-up

4.1 Types of performance studies

Different types of performance studies are subject to the respective requirements, relevant to the IVDR as described in Table 1 For all performance studies, the documentation submitted to the Malta Medicines Authority must be identical to the documentation sent to the Ethics Committee/s in Malta.
Reference is made to *MDCG 2022-19 Performance study application/notification documents under Regulation (EU) 2017/746* and to the Malta application form *MT-MDF16 Performance Study – Application/Notification form under the In-Vitro Diagnostic Regulation (EU) 2017/746.*

Type of Performance Study	**Relevant IVDR Articles & Annexes**	**EU Forms**	**Malta Forms**
Performance studies of non-CE marked devices including companion diagnostics using only left-over samples	Article 58; Annex XIII and XIV	Performance study - application/notification form under In Vitro Diagnostic Medical Devices Regulation (IVDR) as per MDCG 2022-19	MT-MDF16
Performance studies of a device bearing the CE marking, to be used outside its intended purpose	Article 70(2); Annex XIII and XIV		
PMPF study, where the study would involve submitting subjects to procedures additional to those performed under the normal conditions of use and these procedures are invasive or burdensome	Article 70(1); Annex XIII and XIV		

Table 1: Performance studies regulatory pathways

4.2 Documentation required

For performance studies to be conducted in Malta, it is the responsibility of the sponsor of the performance study to complete and submit all requested forms and supporting documentation to the Malta Medicines Authority, in accordance with Annex XIV of the IVDR and this document. The relevant EU and local forms for different types of performance studies are listed in Table 1.

4.3 General details related to Application

4.3.1 Application Form Title

The application form related to this guidance document is *MT-MDF16 – Performance Study – Application/Notification form under the In-Vitro Diagnostic Regulation (EU) 2017/746*, which may be accessed from the Malta Medicines Authority website https://medicinesauthority.gov.mt, under the section for medical devices.

4.3.2 Application Format

MT-MDF16 Application Form is in a fillable pdf format. Form should be filled in electronically using the shaded areas. Handwritten forms may not be accepted if writing is considered illegible.
Forms should be signed and submitted as a scanned copy or as a signed pdf file.

4.3.3 Official Languages

The official languages in Malta are Maltese and English. All application forms and supporting documentation must be completed in either Maltese or English.

4.4 Filling in the Application Form

All sections must be completed. The application form is divided as follows:

- Section A – Application Introduction and Applicant Details
- Section B – Sponsor Contact Details
- Section C –Legal Representative Contact Details
- Section D – Manufacturer and Authorised Representative Contact Details
- Section E – Notified Body Contact Details
- Section F – Investigator Contact Details
- Section G – Information on the Device
- Section H –Performance Study Title
- Section I – Application / Notification Form (EU)
- Section J – Details of Payment
- Section K– Data Protection Consent Statement
- Malta Medicines Authority Declaration for Form Submission

4.4.1 Section A: Application Introduction

Section A is divided into two sections:

Section A.1 Date of application and applicant contact details
The individual completing the application shall provide the following information: Date of the application, applicant's name, surname, email address and contact number.

Section A.2 Applicant
The applicant making the request, whether the sponsor or the Authorised Representative, must be selected. If the applicant is the sponsor, Section B must be filled in. If the applicant is the Legal Representative (when the Sponsor is outside the Union), section C must be filled in. It is the responsibility of the applicant to update the Authority of any changes in the details of the application.

4.4.2 Section B: Sponsor Contact Details

The details of the sponsor should be included in this section. If the organisation is registered with the Authority, quote the reference number.

4.4.3 Section C: Legal Representative Contact Details

A Legal Representative is required when the sponsor is located outside the Union. The details of the Legal Representative should be included in this section. If the organisation is registered with the Authority, quote the reference number.

4.4.4 Section D: Manufacturer and Authorised Representative Contact Details

The organisation making the request, whether the manufacturer or the Authorised Representative, must be selected. If the organisation is the manufacturer, section D.1 must be filled in. If the organisation is the Authorised Representative (when the manufacturer is located outside the Union), section D.2 must be filled in. Local organisations should be registered with the Authority and the reference number must be quoted in this section.

4.4.5 Section E: Notified Body Contact Details

The Identification Numbers of the Notified Body or Notified Bodies involved, are given in this section.

4.4.6 Section F: Investigator Contact Details

The contact details of the investigator are to be provided. The following information is requested: Name, telephone number, job title, email address and healthcare institution details.

4.4.7 Section G: Information on the Device

The details of the device are to be provided. The following information is requested: Generic name, trade name, model, device intended purpose, classification and to specify whether device is CE marked.

4.4.8 Section H: Performance Study Title

The full title of the performance study and any other title/s utilised, are given in this section.

4.4.9 Section I: Application / notification form (EU) including documents

The applicant is required to submit an application/notification to the Malta Medicines Authority, accompanied by the documentation referred to in Chapter II of Annex XIV of the IVDR.

For this section, refer to the *MDCG 2022-19 guidance Performance study application/notification documents under Regulation (EU) 2017/746.* The attachments of this document provide the following templates, which must all be submitted:

- Performance study – application/notification form under Regulation (EU) 2017/746 on in vitro diagnostic medical devices
- Performance study supporting documents – Appendix of documents to attach

- Checklist of general safety and performance requirements, standards, common specifications and scientific opinions
- Acknowledged application request submitted to the Ethics Committee/s in Malta

4.4.10 Section J: Details of payment

Reference should be made to the *GL-MDF07 Guidance on fees in relation to Medical Devices* available on the Malta Medicines Authority website https://medicinesauthority.gov.mt, under the section for medical devices.

The applicant is requested to attach **Proof of Payment.** This document will be verified by the Finance & Corporate Services Unit at the Malta Medicines Authority, confirming receipt of funds.

4.4.11 Section K: Data Protection Consent Statement

Applicant shall confirm consent, by ticking the box in this section, to the processing of personal data by the Malta Medicines Authority and understands that this data shall be processed in accordance with the General Data Protection Regulation (GDPR).

4.4.12 Malta Medicines Authority Declaration for Form Submission

Applicant shall sign the Malta Medicines Authority declaration that all the information submitted within this application form is correct and complete.

4.5 Letter of Authorisation Validity

The start of a study must take place within two years of the date of approval of your study.

4.6 Timeframes

Timeframes for the processing of applications are stipulated by the IVDR. Refer to Table 2 for a summary of the timeframes required for the processing of the application by the Malta Medicines Authority and the timeframes for the sponsor to respond to the Malta Medicines Authority, should the Authority require any further information or clarification. Such requests will be communicated to the applicant.

The clock is stopped when the applicant is requested to send additional information or comments and restarted upon receipt of responses and review resumes. If further queries arise or responses are not satisfactory, the applicant is informed and clock stops/starts accordingly, with the cycle repeating itself.

	Process Stage	**Responsibility**	**Timeframe**	**Extension of Timeframe**
Review Stages IVDR - Article 58 & Article 70(2)	Review by MMA	MMA Reviewer	Reviewer to notify sponsor within 15 days of the receipt of the application	N/A
	Comments and/or additional information requested by MMA	Sponsor	Sponsor to reply within 10 days of the request for additional information / comments	Can be extended by a further period of 20 days
	Receipt of comments / additional information sent by the sponsor	MMA Reviewer	Reviewer to Notify sponsor within10 days of the receipt of request for comments / additional information	N/A
Assessment Stage IVDR - Article 66(7)b	Assessment of documentation by the MMA	MMA Reviewer	Within 45 days of the review date	Can be extended by a further period of 20 days if experts need to be consulted
PMPF study IVDR - Article 70(1)	Review and assessment of the notification by the MMA	MMA Reviewer	Within 30 days of the commencement of the performance study	N/A

Table 2: Timeframes stipulated by the IVDR for the different stages in the processing of application forms

The Malta Medicines Authority requests the sponsor of performance studies of companion diagnostics where only left-over samples are used, to notify the Authority 30 days before the start of the study.

4.7 Refusal of Authorisation of a Performance Study

The Malta Medicines Authority may refuse to authorise the initiation of the performance study. The reasons for its rejection shall be provided to the sponsor via a written communication.

4.8 Initiation of a performance study

Ethics committee approval is not mandatory before the application submission to the Malta Medicines Authority. The applicant must provide the Authority as per section 5.2.4, the acknowledged application request submitted to the Ethics Committee/s in Malta, as part of the documentation submitted with *MT-MDF16*. The performance study can only commence once the sponsor receives the Letter of Authorisation from the Malta Medicines Authority by email. Before starting the performance study, the sponsor should provide a positive decision of the Ethics Committee/s to the Malta Medicines Authority and should also notify the Authority of the commencement date. The description of the 'Commencement date' should be defined in the Performance Study Plan.

4.9 End of a performance study in Malta

The sponsor is expected to report to the Malta Medicines Authority the termination of the performance study within 15 calendar days of the end the performance study in Malta. If the performance study is also conducted in other Member States, the sponsor shall also notify all the Member States in which it was conducted, when it has been completed in all the Member States. This notification shall be made within 15 days of the end of the performance study in the last Member state. If the performance study is still ongoing in one or more third countries when the end of the performance study in the EU is reported, the sponsor should inform the concerned Member States of the expected end of performance study globally if this does not coincide with the end of study in the EU. Sponsors are encouraged to notify the Member States concerned to confirm the actual end of study globally, once reached.

In accordance with the IVDR, the sponsor is responsible for submitting a Performance Study Report within one year of the end of the performance study, irrespective of the outcome. If the performance study has been temporarily suspended or terminated early, the Performance Study Report must be sent within 3 months, unless it is restarted within 3 months of the temporary halt. In such cases, the sponsor does not have to submit a report until the performance study has been completed. The final performance study report should include details regarding the temporary halt.

4.10 Reporting of adverse events

Refer to *GL-MDC01 Guidance on reporting of adverse events in clinical investigations and performance studies.*

4.11 Contact details for further information

All filled in forms and accompanying documents should be submitted by email to mdforms.medicinesauthority@gov.mt

5. References

Malta Medicines Authority - Medical Devices
https://medicinesauthority.gov.mt/medicaldevices?l=1

GL-MDF07 Guidance on fees in relation to Medical Devices

GL-MDF16 Guidance for Notification for Modification of Performance Studies under the Regulation (EU) 2017/746

GL-MDF17 Guidance for Application for Pre-Submission Meeting Request

GL-MDC01 Guidance on reporting of adverse events in clinical investigations and performance studies

Cap 458 Act no VII of 2020, An Act to amend the Medicines Act
https://legislation.mt/eli/act/2020/7/eng

S.L. 458.59 Medical Devices and In-Vitro Diagnostic Medical Devices Provision On The Maltese Market Regulations https://legislation.mt/eli/sl/458.59/eng

EU legislations- Medical Devices and In-Vitro Diagnostic Medical Devices https://health.ec.europa.eu/medical-devices-sector/new-regulations_en

MDCG 2022-19 Performance study application/notification documents under Regulation (EU) 2017/746 Guidance - MDCG endorsed documents and other guidance (europa.eu)

ISO 20916 - Clinical performance studies using specimens from human subjects – Good study practice

Signatures on file

List of Appendices

N/A