IVDR in Clinical Trials

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AMDM Focus Meeting 2022-10-20

This presentation is intended for educational purposes and the opinions expressed in this presentation are my own and do not reflect those of Janssen or Johnson & Johnson

agenda

Introduction

The date of application for the IVDR (2017/746) was May 26, 2022

We are now almost 5 months into the new regulation including “Clinical Trials” or “Performance Studies”

Just as in the US, a diagnostic with medical objective when used on subjects from the Union (27 member EU states or European Economic Area) must be either:

- A performance study device (equivalent to IUO in US)
- A CE marked or IVD device (equivalent to IVD in US)
- An in-house device (from a lab within the Union as defined in the regulation, like an LDT in US terms, but not the same)

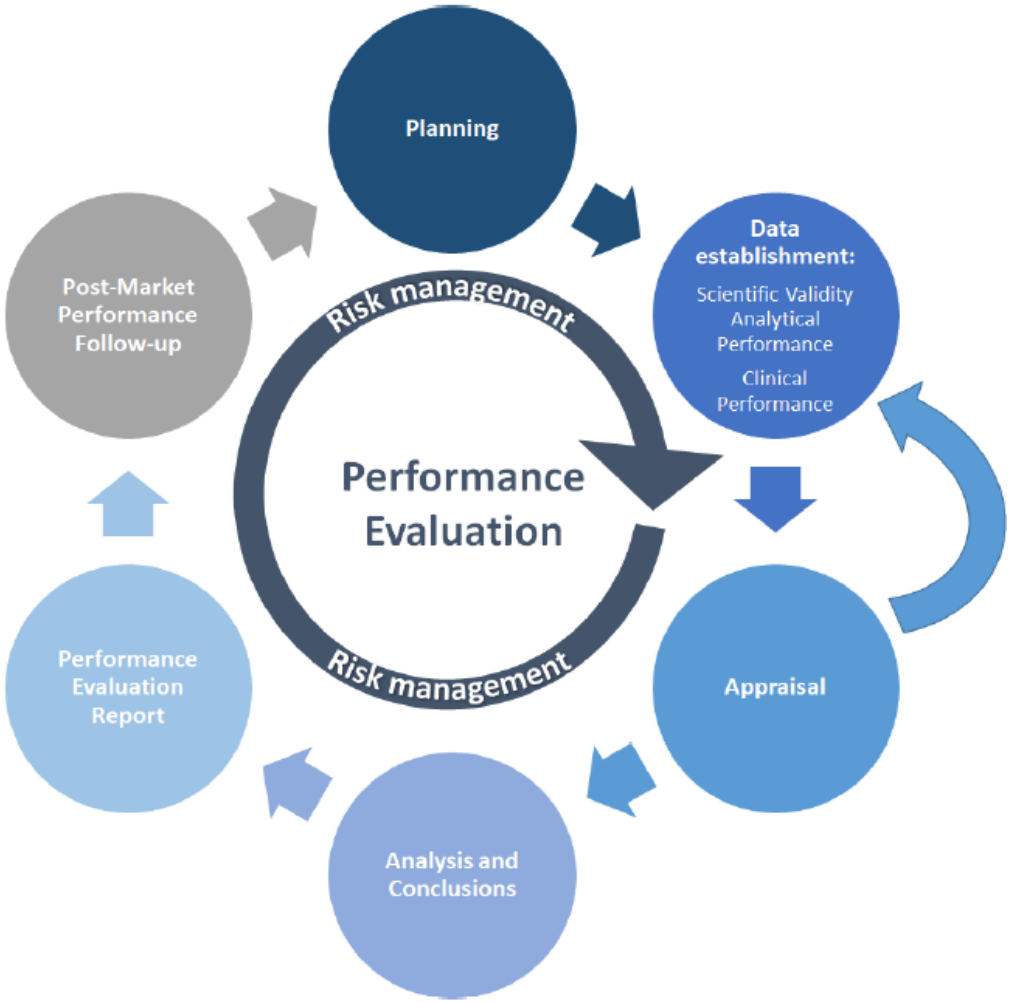
Performance study data is an important aspect of an IVDR dossier.

Clinical Performance

- The manufacturer shall specify and justify the level of the clinical evidence necessary to demonstrate conformity with the relevant GSPR.
- To that end, manufacturers shall plan, conduct and document a performance evaluation in accordance with Article 56 and with Part A of Annex XIII.
- The clinical evidence shall support the intended purpose of the device as stated by the manufacturer and be based on a continuous process of performance evaluation, following a performance evaluation plan.
- All aspects of clinical performance studies will be conducted in accordance with recognized ethical principles.

MDCG 2022-2: Clinical Evidence IVD

Figure 1. Overview of the Performance Evaluation process



Clinical Performance IVD – Chapter VI MDCG 2022-2

The clinical performance aims to demonstrate that the IVD can achieve clinically relevant outputs through predictable and reliable use by the intended user(s). The manufacturer should demonstrate that the IVD has been tested for the intended use(s), target population(s), use condition(s), operating- and use environment(s) and with all the intended user group(s). Indicators of clinical performance vary and depend strongly on the intended purpose and performance claims.

It is important that aspects of clinical performance are assessed in terms of their statistical relevance, e.g. inclusion of confidence interval(s) and interpretation of the impact on robustness of the result with regards to the intended purpose. Where due to specific device characteristics demonstration of conformity with GSPRs based on clinical data is not deemed appropriate, a performance evaluation is still required and a justification shall be provided and documented in the PEP and the corresponding PER.

Clinical Performance Data

- Potential sources of clinical performance data:
  - Data from scientific peer-reviewed literature
  - Data from published experience gained by routine diagnostic testing
  - Data from clinical performance studies (clinical trials)
  - Other sources of clinical performance data

MDCG 2022-2

Guidance on general principles of clinical evidence for *In Vitro* Diagnostic medical devices (IVDs)

Clinical performance can be characterised by the demonstration and evaluation of applicable aspects of clinical performance for the device in question, such as (non-exhaustive):

- diagnostic sensitivity,
- diagnostic specificity,
- positive predictive value,
- negative predictive value,
- number needed to treat/diagnose (average number of patients that need to be treated/diagnosed in order to have an impact on one person),
- number needed to harm/misdiagnose (number of patients that need to be diagnosed/ treated in order have an adverse effect on one patient),
- positive likelihood ratio,
- negative likelihood ratio,
- odds ratio,
- usability /user interface.

Clinical Performance Studies Art. 57-58

Clinical performance studies conducted under the IVDD should be considered as 'other sources of clinical performance data' per Annex XIII 1.2.3 as they wouldn't meet the requirements of Annex XIII 2.3.[14]. It should be noted that an assessment of quality and completeness of the data is essential to identify any potential gaps. This data should be supported by either literature and/or data from published experience gained by routine diagnostic testing.

It must be noted additional requirements must be met by the manufacturer for certain performance studies, such as studies which require 'surgically invasive sample-taking only for the purpose of the performance study', that are 'interventional clinical performance studies' or which 'involve additional invasive procedures or other risks for the subjects of the studies'.[15]

Important References

Reference to Standards

Corrigendum to 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

(Official Journal of the European Union L 117 of 5 May 2017)

1. On page 183, Recital (66)

for:

'(66) The rules on performance studies should be in line with well-established international guidance in this field, such as the international standard ISO 14155:2011 on good clinical practice for clinical investigations of medical devices for human subjects, so as to make it easier for the results of performance studies …',

read:

'(66) The rules on performance studies should be in line with well-established international guidance in this field, such as the international standard ISO 20916 on clinical performance studies using specimens from human subjects, currently under development, so as to make it easier for the results of performance studies …'.

2. On page 198, Article 10(14)

- ISO14155:2011 Good Clinical Practice for clinical investigations

Clinical investigation of medical devices for human subjects — Good clinical practice

- ISO 20916 on Clinical Performance Studies using specimens from human subjects

In vitro diagnostic medical devices — Clinical performance studies using specimens from human subjects — Good study practice

Guidance Documents MDCG (IVDR)

Reference	Title	Publication
MDCG 2022-15	Guidance on appropriate surveillance regarding the transitional provisions under Article 110 of the IVDR with regard to devices covered by certificates according to the IVDD	Sept 2022
MDCG 2021-22 rev.1	Clarification on “first certification for that type of device” and corresponding procedures to be followed by notified bodies, in context of the consultation of the expert panel referred to in Article 48(6) of Regulation (EU) 2017/746	Sept 2022
MDCG 2022-10	Q&A on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR) and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR)	May 2022
MDCG 2022-9	Summary of safety and performance template	May 2022
MDCG 2022-8	Regulation (EU) 2017/746 - application of IVDR requirements to ‘legacy devices’ and to devices placed on the market prior to 26 May 2022 in accordance with Directive 98/79/EC	May 2022
MDCG 2022-6	Guidance on significant changes regarding the transitional provision under Article 110(3) of the IVDR	May 2022
MDCG 2022-3	Verification of manufactured class D IVDs by notified bodies	Feb 2022
MDCG 2022-12	Guidance on harmonised administrative practices and alternative technical solutions until Eudamed is fully functional (for Regulation (EU) 2017/746 on in vitro diagnostic medical devices)	July 2022
MDCG 2022-2	Guidance on general principles of clinical evidence for In Vitro Diagnostic medical devices (IVDs)	Jan 2022
MDCG 2021-4	Application of transitional provisions for certification of class D in vitro diagnostic medical devices according to Regulation (EU) 2017/746	April 2021
MDCG 2020-16 Rev.1	Guidance on Classification Rules for in vitro Diagnostic Medical Devices under Regulation (EU) 2017/746	Jan 2022

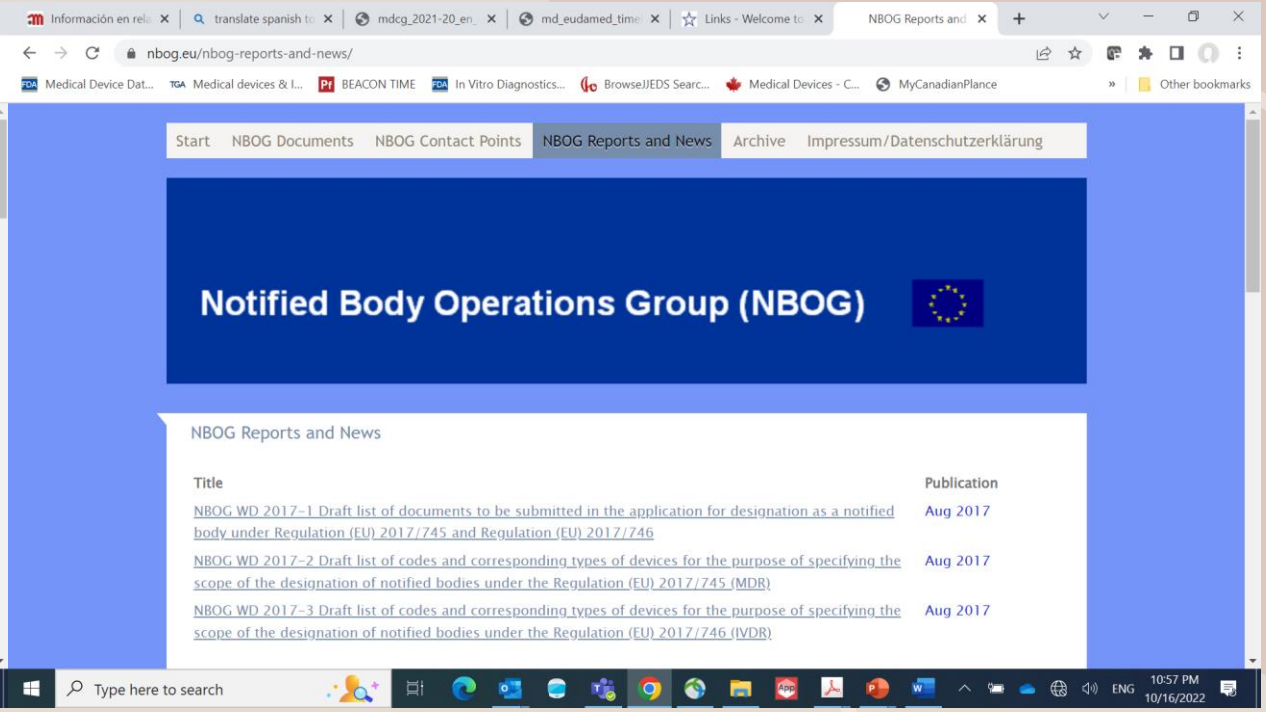
Guidance Documents (MDR)

Reference	Title	Publication
MDCG 2021-28	Substantial modification of clinical investigation under Medical Device Regulation (MDR)	Dec 2021
MDCG 2021-20	Instructions for generating CIV-ID for MDR Clinical Investigations (union wide Single ID#)	July 2021
MDCG 2021-8	Clinical investigation application/notification documents (MDR)	May 2021
MDCG 2021-6	Regulation (EU) 2017/745 (MDR) – Questions & Answers regarding clinical investigation	April 2021
MDCG 2020-13	Clinical evaluation assessment report template (MDR)	July 2020
MDCG 2020-10/1 MDCG 2020-10/2	Guidance on safety reporting in clinical investigations (MDR) Appendix: Clinical investigation summary safety report form (MDR)	May 2020 May 2020
MDCG 2020-8	Guidance on PMCF evaluation report template (MDR)	April 2020
MDCG 2020-7	Guidance on PMCF plan template (MDR)	April 2020
MDCG 2020-6	Guidance on sufficient clinical evidence for legacy devices (MDR) Background note on the relationship between MDCG 2020-6 and MEDDEV 2.7/1 rev.4 on clinical evaluation	April 2020
MDCG 2020-5	Guidance on clinical evaluation – Equivalence (MDR)	April 2020
MDCG 2019-9 -Rev.1	Summary of safety and clinical performance (MDR)	March 2022

Notified Body Documents (NBOG)

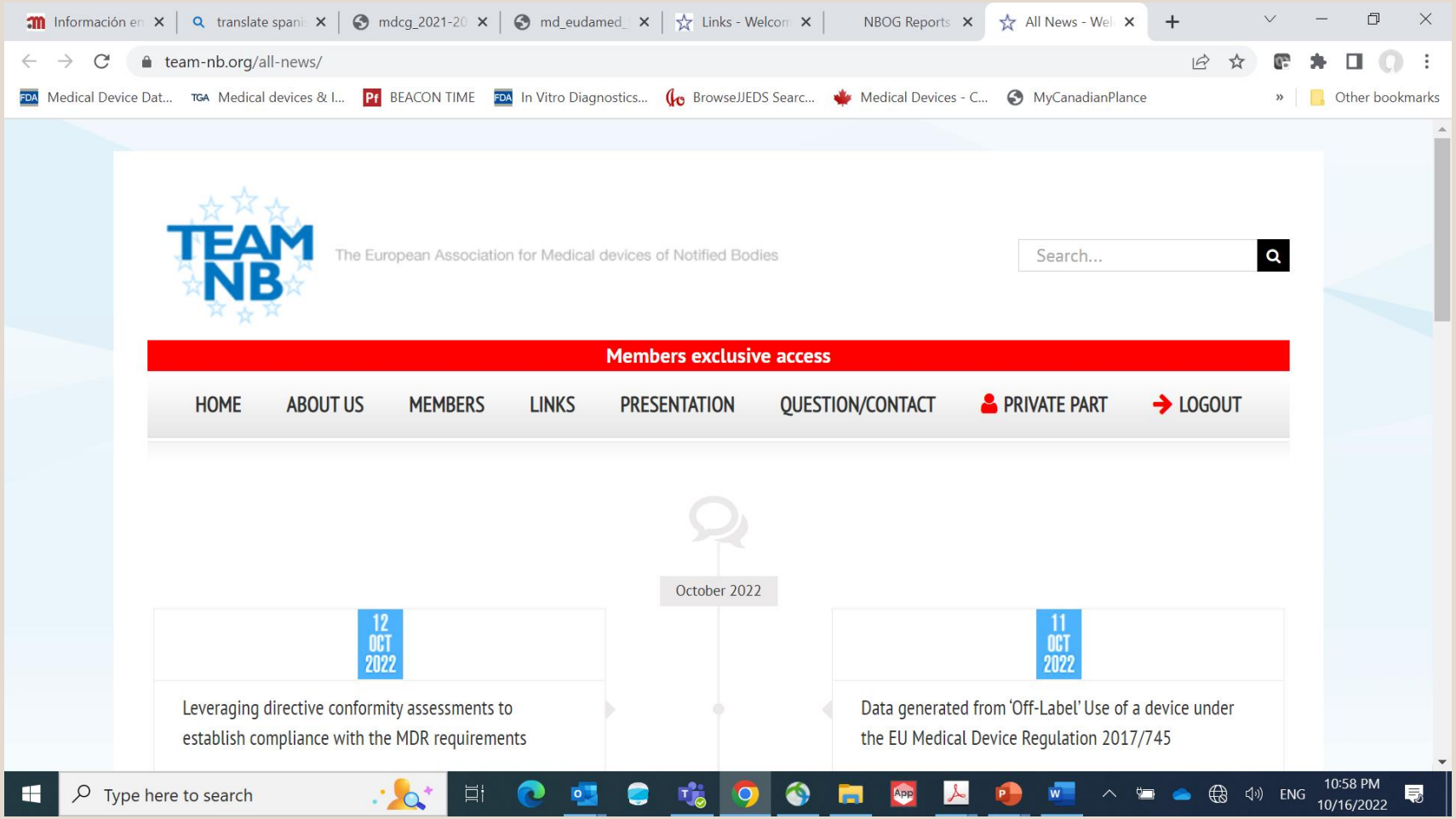
https://www.nbog.eu/nbog-documents/

https://www.nbog.eu/nbog-reports-and-news/

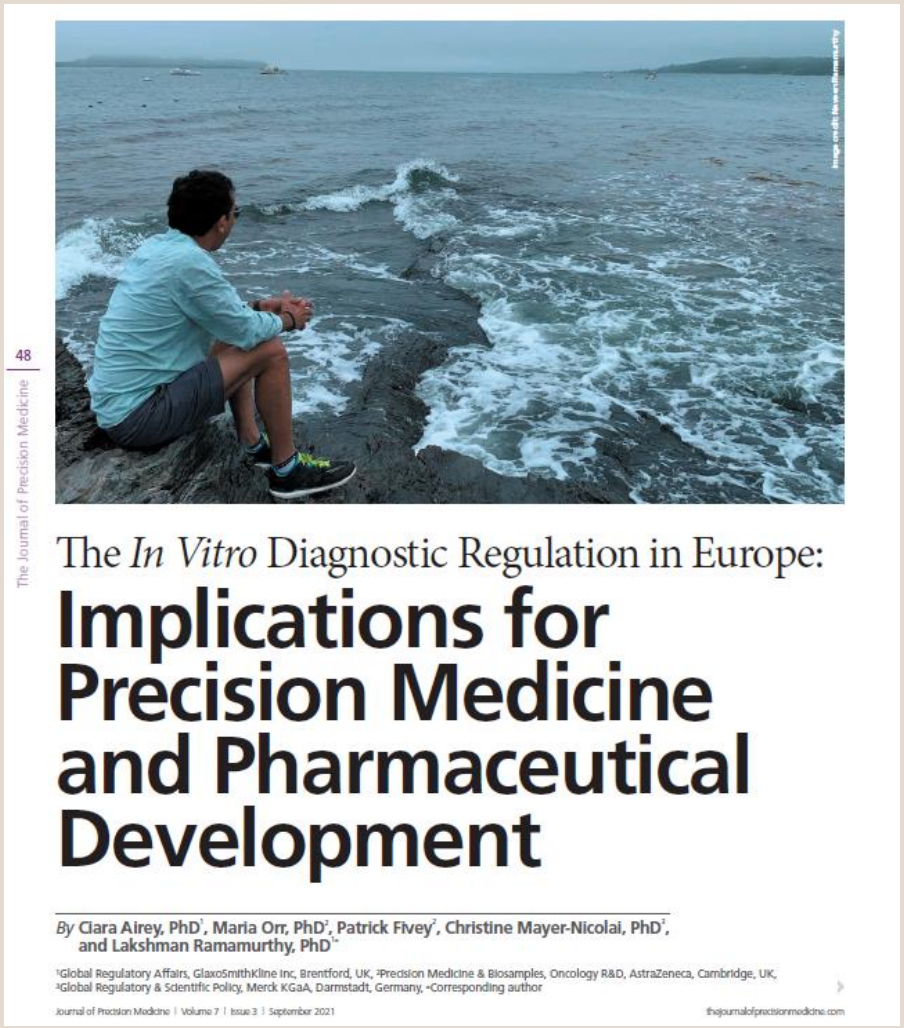


Team NB (Notified Body) Papers

- https://www.team-nb.org/all-news/



MedTech Europe & Other Resources



https://www.medtecheurope.org/resource-library/

Definitions - Article 2

(7) ‘companion diagnostic’ means a device which is essential for the safe and effective use of a corresponding medicinal product to:

(a) identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or

(b) 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;

(46) ‘interventional clinical performance study’ means a clinical performance study where the test results may influence patient management decisions and/or may be used to guide treatment;

By definition, companion diagnostic performance studies (result of test guides selection or exclusion of patients who will receive an investigational medicinal product) are an **interventional clinical performance study**.

Article 58: Authorization or Notification

Article 58

Additional requirements for certain performance studies

1. Any performance study:

(a) in which surgically invasive sample-taking is done only for the purpose of the performance study;

(b) that is an interventional clinical performance study as defined in point (46) of Article 2; or

(c) where the conduct of the study involves additional invasive procedures or other risks for the subjects of the studies,

shall, in addition to meeting the requirements set out in Article 57 and Annex XIII, be designed, authorised, conducted, recorded and reported in accordance with this Article and Articles 59 to 77 and Annex XIV.

2. Performance studies involving companion diagnostics shall be subject to the same requirements as the performance studies listed in paragraph 1. This does not apply to performance studies involving companion diagnostics using only left-over samples. Such studies shall however be notified to the competent authority.

3. Performance studies shall be subject to scientific and ethical review. The ethical review shall be performed by an ethics committee in accordance with national law. Member States shall ensure that the procedures for review by ethics committees are compatible with the procedures set out in this Regulation for the assessment of the application for authorisation of a performance study. At least one lay person shall participate in the ethical review.

- If Sponsor is not in Union,
- Then a natural or legal person established in the Union must be appointed and utilized as their legal representative
- All communications will be with the Legal Representative of the Sponsor in this case.

- Article 59: Informed Consent
- Article 60: Performance Studies on Incapacitated Subjects
- Article 61: Performance Studies on Minors
- Article 62: Performance Studies on Pregnant or Breastfeeding Women
- Article 63: Additional National Measures
- Article 64: Performance Studies in Emergency Situations
- Article 65: Damage Compensation
- Article 66: Application for Performance Studies

8. Where appropriate, the facilities where the performance study involving subjects is to be conducted shall be suitable for the performance study and shall be similar to the facilities where the device is intended to be used.

Draft Clinical Trial Application Docs

Section 5: National information

5.1 Study site information

Please provide the list of sites taking part in the study performance

Name of institution	Site address	Investigator attached to tl

Email:

Contact person of the sponsor

First name:	
Last name:	
Telephone number:	
Email:	

DRAFT Forms (A through G), Part A has 21 pages to complete

○ First submission at the national level (EEA)

In this case, please provide the p

○ Resubmission

Please provide the PS-ID if alr

1.5 Participating countries within the

Select the participating countries for the performance study

2.8 Scope of the investigational device

2.8.1 Combined investigation Medical Device/*In Vitro* Diagnostic Medical Device?

○ Yes ○ No

If yes, please provide the related identification number of the clinical study.

2.8.2 Is the application submitted in parallel with an application for a clinical trial on medicinal products

○ Yes ○ No

If yes, please provide the EU Clinical Trial Number:

2.9 Coordinating investigator

First name:

Last name:

Address	Street name:	Street number:
	Postal code:	City:
	Country: Australia	

Telephone number:

Email:

Documents Required marked with X

Document or Item for Dx Partner for Performance Study Device (investigational)	Submitted with CPS Application
Annex XIII Documents	
Performance Evaluation Plan (PEP)*	
Scientific Validity Report (SVR)	X
Analytical performance documentation or Analytical Performance Report (APR)	X
Clinical Performance Report (CPR)*	
Performance Evaluation Report (PER)*	
Clinical Performance Study Plan (CPSP)	X
Evidence of qualified investigator(s)	X
Instructions for Use	X
CPS Monitoring Plan (may be incorporated into the CPSP)	X
CPS Data Management Plan (may be incorporated into the CPSP)	X
Statements or declarations of compliance with recognized and applicable ethical principles	X
Patient Information Sheet (not required for studies using only left-over samples) see Annex XIII, 2.3.2u	X
Informed Consent forms (not required for studies using only left-over samples)	X
Procedures for safety recording and reporting (may be incorporated into the CPSP)	X
Procedures for subject follow up (may be incorporated into the CPSP; not required for studies using only left-over samples)	X
Procedures for communicating study results to subjects (may be incorporated into the CPSP; not required for studies using only left-over samples)	X
Policy for establishing the CPS report and publishing results (may be incorporated into the CPSP; not required for studies using only left-over samples)	X
Clinical Performance Study Report (CPSR)*	
Post Market Performance Follow-up Plan (PMPFP)*	
Annex XIV Documents	
Signed statement declaring compliance with GSPRs, except for those being evaluated as part of CPS	X
Investigator Brochure	X
GSPR checklist mapping evidence of demonstration that these were met	X
Evidence supporting demonstration of meeting GSPRs (available for CA review upon request)	X
Opinions from Ethics Committee reviews	X
Proof of insurance for Article 65 (damage suffered by a subject for each country where study is conducted) – for example insurance certificate or schedule	X
Description of how subject personal data are protected and held confidential	X
Other Documents	
Post Market Surveillance Plan (PMS Plan or PMSP)*	
Summary of Safety and Performance (SSP)*	

Just as US FDA expects an IDE for certain studies, European Commission and National Competent Authorities expect to **review and authorize** certain diagnostic studies (i.e. as defined in Article 58 and Article 70).

These submissions for clinical trial authorization to use the performance study device require inclusion of DATA to support use of the product in the study for the intended use population.

Some docs you may not realize (XIV)

- Sponsor shall ensure an agreement is in place to ensure that any serious adverse events or any other event as referred to in Article 76(2) are reported by the investigator or investigators to the sponsor in a timely manner
- Record retention period: at least 10 years after the clinical performance study with the device in question has ended, or, in the event that the device is subsequently placed on the market, for at least 10 years after the last device has been placed on the market.
- Proof of insurance cover or indemnification of subjects in case of injury, pursuant to Article 65 and the corresponding national law.
- Description of the arrangements to comply with the applicable rules on the protection and confidentiality of personal data, in particular:
  - organisational and technical arrangements that will be implemented to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and personal data processed;
  - a description of measures that will be implemented to ensure confidentiality of records and personal data of subjects;
  - a description of measures that will be implemented in case of a data security breach in order to mitigate the possible adverse effects.
- A signed statement by the natural or legal person responsible for the manufacture of the device for performance study that the device in question conforms to the general safety and performance requirements laid down in Annex I apart from the aspects covered by the clinical performance study and that, with regard to those aspects, every precaution has been taken to protect the health and safety of the subject.
- Summary of the benefit-risk analysis and the risk management, including information regarding known or foreseeable risks and warnings

Result of Clinical Trial Application

7. The sponsor may start the performance study in the following circumstances:

(a) in the case of performance studies carried out pursuant to point (a) of Article 58(1) and where the specimen collection does not represent a major clinical risk to the subject of the study, unless otherwise stated by national law, immediately after the validation date of application described in paragraph 5 of this Article, provided that a negative opinion which is valid for the entire Member State, under national law, has not been issued by an ethics committee in the Member State concerned in respect of the performance study;

(b) in the case of performance studies carried out pursuant to points (b) and (c) of Article 58(1) and Article 58(2) or performance studies other than those referred to in point (a) of this paragraph, as soon as the Member State concerned has notified the sponsor of its authorisation and provided that a negative opinion which is valid for the entire Member State, under national law, has not been issued by an ethics committee in the Member State concerned in respect of the performance study. The Member State shall notify the sponsor of the authorisation within 45 days of the validation date of the application referred to in paragraph 5. The Member State may extend this period by a further 20 days for the purpose of consulting with experts.

Example Review Times (Authorization)

Country	CPS (CTA) Review Duration Anticipated	Ethics Review Duration Anticipated
Belgium	55 days (additional 20 days could be added)	EC review combined with CTA review
Czech Republic	60 days	60 days
France	60 days	45-60 days
Germany	55 days (additional 20 days could be added)	EC approval required prior to submitting CPS clinical trial application to CA
Hungary	75 days	EC review combined with CTA review
Italy	15-35 days (additional 20 days could be added)	No timeline specified in National Law
Netherlands	56 days	EC review combined with CTA review
Portugal	30 days	EC review combined with CTA review
Poland	60 days	45 days
Spain	45 days	60 days

Review Time (Notification)

- Member States have **10 days from the receipt of the application** dossier to notify the sponsor that the application is:
  a) within the scope of the IVDR regulations, and
  b) is considered to be a complete application.

- **If the sponsor is not notified by the Member State by day 10, the sponsor may consider their application to be within the scope of the IVDR regulations and complete**. Whichever is the case, the 'validation date' of the application is either the date on which the sponsor is notified by the Member State that their study is within the IVDR scope and is complete, or the last day of the designated waiting period if the sponsor does not get a response from the Member State.
- Worst case is 10 days past the date the Member State receives the application to be able to consider the study application as 'valid'.

References: IVDR 2017/746, Article 66(1) and 66(5).

Article 70 (PMPF)

Performance studies regarding devices bearing the CE marking

1. Where a performance study is to be conducted to further assess, within the scope of its intended purpose, a device which already bears the CE marking in accordance with Article 18(1) ('PMPF study'), and where the performance study would involve submitting subjects to procedures additional to those performed under the normal conditions of use of the device and those additional procedures are invasive or burdensome, the sponsor shall notify the Member States concerned at least 30 days prior to its commencement by means of the electronic system referred to in Article 69. The sponsor shall include the documentation referred to in Section 2 of Part A of Annex XIII and in Annex XIV. Points (b) to (l) and (p) of Article 58(5), and Articles 71, 72 and 73 Article 76(5) and the relevant provisions of Annexes XIII and XIV shall apply to PMPF studies.

2. Where a performance study is to be conducted to assess, outside the scope of its intended purpose, a device which already bears the CE marking in accordance with Article 18(1), Articles 58 to 77 shall apply.

- Annex I: GSPR (General Safety & Performance Requirements)
- Annex XIII: Performance Evaluation, Performance Studies & Post market Performance Follow-Up
- Annex XIV: Interventional Clinical Performance Studies & Certain Other Studies
- Are you planning a Significant Modification to Study?

What to Do?

What to Do

1. Determine if study requires authorization or notification before it can begin
2. Follow IVDR, GCP, ISO Standards, and relevant MDCG Documents
   - Annex I General Safety & Performance Requirements
   - Annex XIII
   - Annex XIV
   - AE (PS) and Vigilance Reporting (PMPF)
3. Generate Documents Needed: Study Protocol, Investigator Brochure, Instructions for Use, Informed Consent Form, Product Labels etc.
4. Determine Clinical Trial Sites (and countries), investigator agreements, CVs, install performance evaluation study device(s), train site operator(s)
5. File - Obtain Country Authorization(s) or File Notifications & Obtain Country & Site Ethics Approval(s)
6. Execute Study (Study & Site Monitoring, Update Risk, AE)
7. Report

Determine Study Requirements

- Does this clinical study on human subjects require an authorization or notification before it can start?
  - Is it a performance study device?
  - Will the data from the study be needed to support a device dossier?
  - Is it a CE marked device that has been significantly changed for use in the study?
  - Is it a CE marked device that is used on label in the study?
  - Is it an interventional clinical performance study?
    - Are you using prospectively collected samples?
    - Are you using banked specimens?
  - Is the collection of samples from the human subject for testing with the performance study device surgically invasive?
  - Is the collection of samples from the human subject for testing invasive and

- Is the study a pre-market study or a post market performance follow-up study?

EUDAMED Timeline

EUDAMED Time line

The European Commission planning – June 2022

Q4 2023	Q1-Q2 2024	Q2 2024	Q2 2024	Q4 2024	Q2 2026
End of the EUDAMED MVP[1] development for all six modules	Independent **Audit**	Audit results presented to the Medical Devices Coordination Group (MDCG)	EUDAMED has achieved full functionality following the outcome of the Audit. **Publication of a Commission notice** in the *Official Journal of the European Union* **(OJEU)** The full EUDAMED system (all 6 modules) is released.	End of 6 months transitional period after publication of the notice in the OJEU The use of **EUDAMED** becomes **mandatory** as regards obligations and requirements related to **Actors, Vigilance, Clinical Investigation & Performance Studies and Market Surveillance modules**	End of 24 months transitional period after publication of the notice in the OJEU The use of **EUDAMED** becomes **mandatory** as regards obligations and requirements related to **UDI/Device and NB & Certificate modules**

[1] EUDAMED Minimum Viable Product (MVP) means that the system developed implements at least the minimum Medical Devices Regulations requirements and allows competent authorities and all stakeholders to comply with their legal obligations.

EUDAMED Playground Module CPS

- Due to technical reasons, we are forced to postpone the *Playground – release 3.2* that was scheduled for 10/13/2022.
- At the moment, there is no specific date available for the coming release therefore we will return with an email to inform you about the final date and any other changes, if applicable.
- We apologize for any inconveniences generated and we thank you for your continuous support and interest in testing Eudamed.

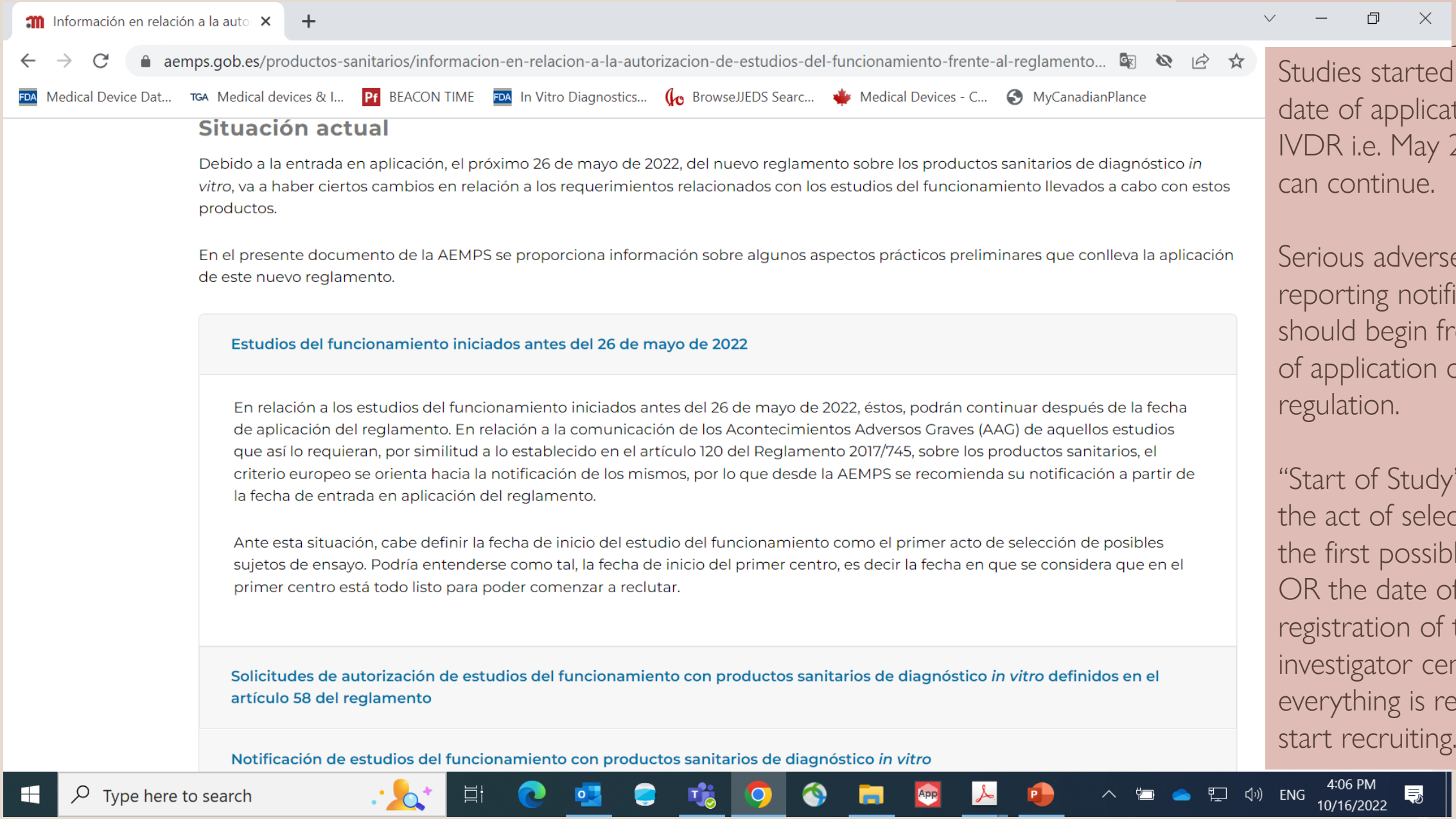
In Absence of EUDAMED

MDCG 2022-12

Guidance on harmonised administrative practices and alternative technical solutions until Eudamed is fully functional (for Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices)

July 2022

Example Spain (AEMPS)



Studies started before date of application of the IVDR i.e. May 26, 2022 can continue.

Serious adverse event reporting notification should begin from date of application of the regulation.

"Start of Study" means the act of selection of the first possible subject OR the date of registration of the first investigator center where everything is ready to start recruiting.

Example – Spain continued

- **For new clinical studies that require authorization per Article 58**(1), i.e. for example samples where surgically invasive sampling is carried out solely for the purpose of the study, and where the collection of samples does not pose a significant clinical risk to the subject.
- The **evaluation period will be 45 days**, from the date of validation, for all products. This will be reflected in new legislation to be published at national level.
- In Spain, a favorable opinion issued by a Research Ethics Committee of Medicines (CEIm) will be required, as well as the agreement of the management of the participating centers for the initiation of the same.
- The new royal decree on in vitro diagnostic medical devices, which is currently under development, will require certain documentation to be submitted at least in Spanish. However, in order to facilitate and promote research in Spain, and provided that the CEIm has no objection in this regard, the study plan of the operation and the researcher's manual, could be accepted in English.
- **For clinical studies that require notification** per Article 70(1) for example or per Article 58(2) for example (diagnostic tests for therapeutic selection using only surplus samples), until the future European EUDAMED database is available, these will be notified through the NEOPS platform.

If this was a CDx Study? Suggestions

- The diagnostic manufacturer of CDx is a Performance Study Sponsor for their 'clinical performance study' device that is used within the investigational medicinal product study protocol of the pharma company.
- The diagnostic manufacturer would have a 'Study Protocol' for the diagnostic testing
- If using prospective sample collection in the 'interventional' study, then the diagnostic manufacturer must obtain authorization to use the performance study device.
- The diagnostic manufacturer would have to obtain Ethics approvals to use the performance study device in the device study protocol
- The diagnostic manufacturer would cross reference the medicinal product study protocol reference number (CTIS or EUDRACT), and pharma company will cross-reference the SIN (study ID number) from EUDAMED or individual competent authority authorization(s)

Considerations for CDx studies

- Will require either authorization (prospective sample collection for performance study device) or notification (use of surplus leftover specimens for CDx study)
- Informed consent (and any updates)
- Study Monitoring
- Investigator Brochure (study test sites)
- What information needs to go to study sites where sample is being collected?
- Adverse Event Tracking and Serious Adverse Event Reporting
- List of participating investigator(s), site(s), countries, planned first patient in (FPI) dates
- Investigator Agreement(s)
- Clear communication (routine meetings) and written agreement between Pharma Company and Diagnostic Manufacturer.
- Process for 'escalation' discussions (Steering Committee) i.e. via senior management of both companies

Summary

The intended use of the product drives the evidence needed to support the dossier.

Certain types of studies require clinical trial authorization or clinical trial notification before they can be executed.

The CPSP and CPSR are only one part of the overall Clinical Evidence picture!

Plan early, document clearly to support the intended use of your product and align timelines for Companion Diagnostics (interventional) Clinical Performance Studies

thank you

plan for clinical study

PLAN	Risk assessment, scientific validity, analytical validity, QMS, SVR, AVR, Responsibilities, PEP
DOCUMENT	**Protocol (CPSP)**, Informed Consent, Labels, Brochures, CVs, Agreements etc.
FILE	Coordinate **applications (Authorization/Notification/Ethics)**
EXECUTE	Studies and monitoring using **superior methodologies**
REPORT	AE, PSUR, **Clinical Study Report**

Understand timeline

SEP 20XX
Plan

NOV 20XX
Document

JAN 20XX
File CTA / CTN, Ethics Review Board etc.

MAR 20XX
Execute Clinical Study

MAY 20XX
Report

Clinical Performance Report

The amount and quality of data collected should allow the manufacturer to make a qualified assessment whether the IVD will achieve the intended clinical benefit(s) and safety, when used as intended by the manufacturer. The data and conclusions drawn from this assessment constitute the clinical evidence and should take into account the following considerations:

- the intended users,
- the state-of-the-art,
- the nature, severity and the evolution of the condition being diagnosed or treated,
- the adequacy of the estimation of associated risk for each identified hazard,
- the number and severity of adverse events,
- the availability of alternative diagnostic devices and current standard of care.

- Does the data support the intended purpose, intended users indications, device specifications, target groups, clinical claims and the relevant general safety and performance requirements?
- Has the novelty and level of innovation/history on the market been evaluated and considered?
- Have the risks been identified, mitigated and the effectiveness of the risk control measures been verified?
- Have for example environmental conditions, interference factors, exogenous factors and endogenous factors been evaluated?
- Has the quality of literature retrieved and reviewed been evaluated and has a rationale for the selection process been provided?

Clinical report

- Has there been a sufficient number of observations to draw scientifically valid conclusions?
- Have any limitations within the observations been appropriately justified?
- Was the statistical approach including sample size appropriate to reach a scientifically valid conclusion?
- Have the scientific validity, analytical and clinical performances been demonstrated?
- Is data from performance studies or other sources sufficient to verify the safety and performance, including clinical benefits (where applicable) of the device when used as intended with respect to the state-of-the-art?
- Does the design and results of the performance studies support the clinical evidence?
- Have all deviations from and all planned changes to the performance evaluation plan been justified?
- Has the relevance of the information of the performance evaluation been assessed and documented?
- Has the contribution of each data set to the performance evaluation been weighted according to systematic criteria?
- Is the data set appropriate and takes into account the state-of-the-art of the device?
- Is all supporting data fully traceable, documented and is integrity assured?
- Were all ethical, legal and regulatory considerations/ requirements taken into account?
- Have all omissions been clearly outlined and justified?

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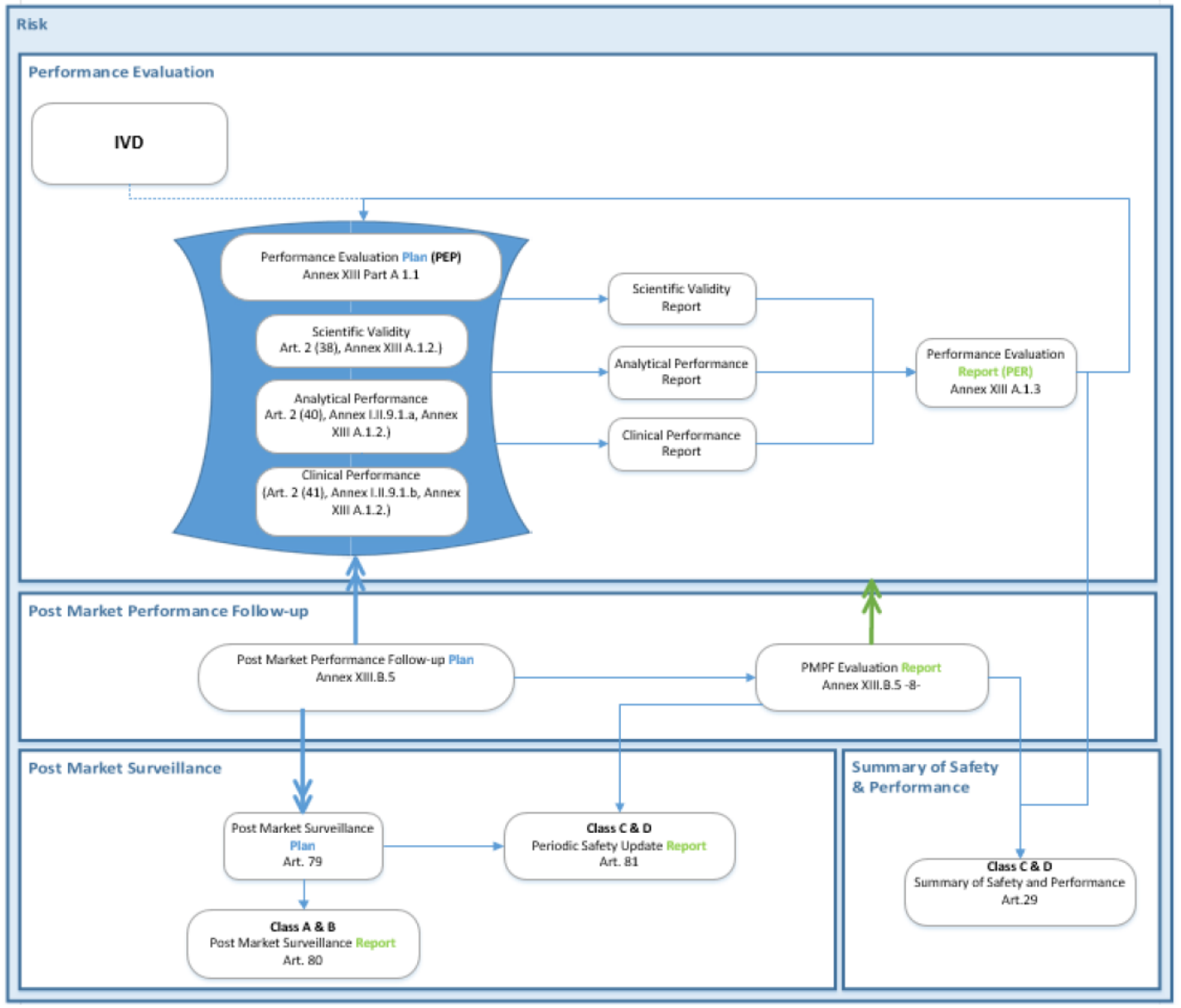
Figure 2

Figure 2 Continuous performance evaluation process including flow of plans and reports.
The blue double arrows denote where plans are linked namely that the post market surveillance plan should include PMPF plan (Annex III 1b), and that the performance evaluation plan shall include PMPF planning (Annex XIII part A 1.1). A green double arrow is used to demonstrate that the PMPF report feeds back into the PE process. (Annex XIII part B.7). The blue frame indicates risk management and continuous performance evaluation process inter-dependency.



Definitions from Article 2 (2017/746)

(42) ‘performance study’ means a study undertaken to establish or confirm the analytical or clinical performance of a device;

(43) ‘performance study plan’ means a document that describes the rationale, objectives, design methodology, monitoring, statistical considerations, organisation and conduct of a performance study;

(44) ‘performance evaluation’ means an assessment and analysis of data to establish or verify the scientific validity, the analytical and, where applicable, the clinical performance of a device;

(45) ‘device for performance study’ means a device intended by the manufacturer to be used in a performance study. A device intended to be used for research purposes, without any medical objective, shall not be deemed to be a device for performance study;

(47) ‘subject’ means an individual who participates in a performance study and whose specimen(s) undergo *in vitro* examination by a device for performance study and/or by a device used for control purposes;

(57) ‘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;

(58) ‘informed consent’ means a subject's free and voluntary expression of his or her willingness to participate in a particular performance study, after having been informed of all aspects of the performance study that are relevant to the subject's decision to participate or, in the case of minors and of incapacitated subjects, an authorisation or agreement from their legally designated representative to include them in the performance study;

(59) ‘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 this Regulation, taking into account the views of laypersons, in particular patients or patients' organisations;

Out of Scope Products MDCG 2022-2

It is important to remind that per Article 1(3) of the IVDR, the following products are not considered IVDs and are henceforth out of scope of this guidance:

a) products for general laboratory use or research-use only products, unless such products, in view of their characteristics, are specifically intended by their manufacturer to be used for in vitro diagnostic examination;
b) invasive sampling products or products which are directly applied to the human body for the purpose of obtaining a specimen;
c) internationally certified reference materials;
d) materials used for external quality assessment scheme.