IVDR: Supporting Companion Diagnostic Clinical Trials

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Companion Diagnostics (CDx) Definition

FDA: a medical device, often an in vitro diagnostic (IVD), which provides information that is *essential for the safe and effective use of a corresponding drug* or biological product.

- identify patients who are most likely to benefit from a particular therapeutic product,
- identify patients likely to be at increased risk for serious side effects as a result of treatment with a particular therapeutic product; or
- monitor response to treatment with a particular therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness.

Article 2 (7) IVDR: 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;

Differences in CDx Definitions

FDA vs IVDR

	Identify patients to benefit from treatment	Identify patients at increased risk for adverse events as a result of treatment	Establish the dosage of drug for patients already eligible to receive drug	Monitor result to treatment to ensure concentration of drug in therapeutic window
FDA	☑	☑	☑	X
IVDR	☑	☑	X	X

The similarities and difference between the FDA and IVDR definitions of a CDx are important to note while building a strategy for bringing a CDx to the EU/US market

Impact to Starting a Study: Transition from IVDD to IVDR

Historically under IVDD (98/79/EC) (07Dec1998 to 25May2022)

- The manufacturer (or authorized representative) was required to issue a Declaration of Manufacturer to the IVDD Annex VIII
- Notification process, not a formal review or approval
- Some countries had additional national requirements

Currently under IVDR (EU) 2017/746

(26 May 2022-)

- Higher bar for documentation and evidence in the clinical performance study authorization submission package that is reviewed
- Subject to a formal ethical and scientific review by each participating member state (includes clinical enrollment and testing sites)
- Article 56 PLUS requirements per Article 58 apply. Some countries have additional national requirements.

Impact of IVDR Requirements on Co-Development

Both Clinical Trial Regulation (CTR) and IVDR requirements must be met

Co-Developed: Device is developed in a clinical development program together with the concerned medicinal product, either in view of an initial marketing authorization or a change of the indication. This can mean that the **device was developed in the framework of a pivotal clinical trial with the concerned medicinal product** or of a bridging study assessing the concordance of the CDx and the device used in the pivotal clinical trial of the corresponding medicinal product

Follow-on: Device that seeks the same indication in its intended use as the co-developed CDx. Follow-on CDx targets same biomarker but is not developed in parallel with the clinical development program of the medicinal product and is not necessarily based on the same technology as original CDx.

Legacy : The device is already marketed under Directive 98/79/EC on in vitro diagnostic medical devices (IVDD) and requires a re-classification as Companion Diagnostics under EU Regulation 2017/746 on in vitro diagnostic medical devices (IVDR).

**Note: Legacy CE marked CDx can stay on the market under IVDD until May 2026 unless there is a significant change to the product.*

Combined trial

Per MDCG 2022-10: A combined trial is a simultaneous investigation of a medicinal product (clinical trial authorised under the Clinical Trial Regulation) and an IVD (clinical performance study).

The combined trial is **subject to requirements of both** the clinical trial legislation (CTR when this applies) and the IVD legislation (IVDR when this applies).

Definitions modified from: https://www.ema.europa.eu/en/documents/scientific-guideline/guidance-procedural-aspects-consultation-european-medicines-agency-notified-body-companion_en.pdf.
*Medical Device Coordination Group (MDCG) Guidance on Significant Changes Regarding the Transitional Provision under article 110(3) of the IVDR (MDCG 2022-6) provides guidance regarding significant/non-significant changes.

Performance Studies Involving Companion Diagnostics

Considerations

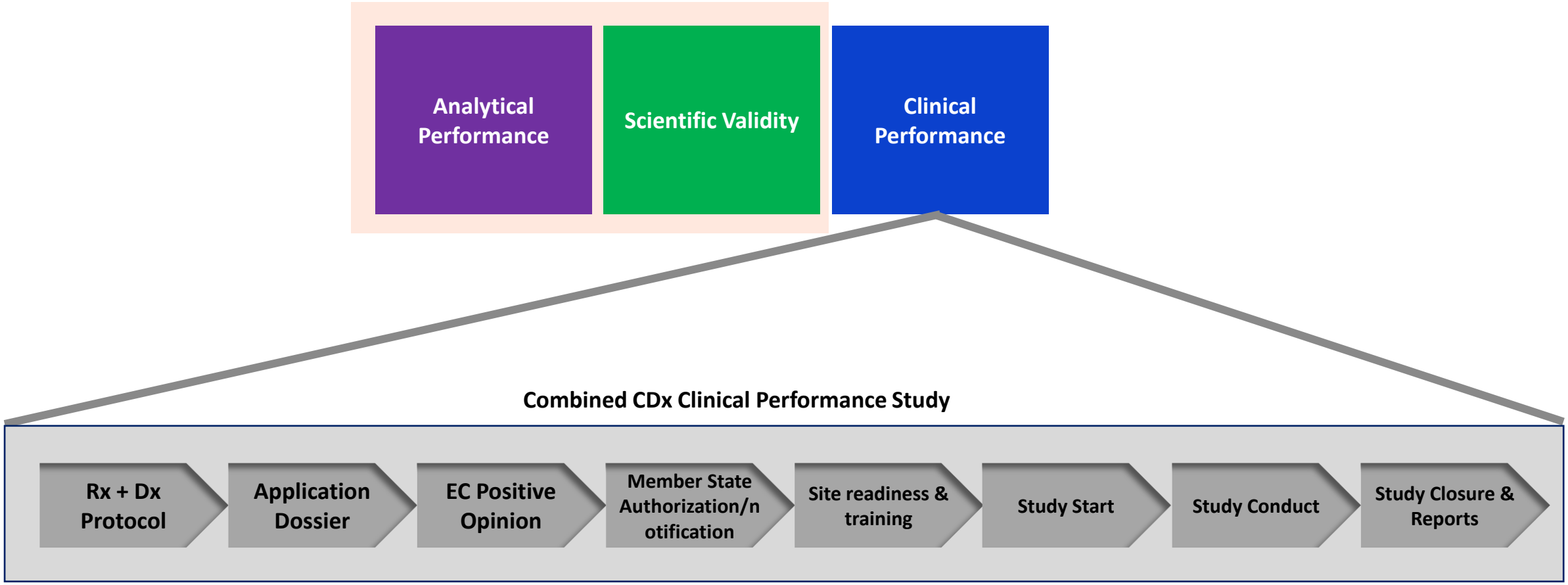
- For legacy claims, new clinical performance studies may not be required
- For new studies, the study design, patient treatment decisions, and samples types to be tested must be assessed
- Some studies may not meet the criteria outlined in IVDR Article 58 and therefore may not require authorization or notification such as research studies that do not have a medial objective or plans for CDx filing
- Registration intent does not dictate whether or not clinical performance applications are required
- US-based risk classifications (i.e. “significant risk” or “non-significant risk”) are irrelevant to clinical performance requirements under IVDR
- Study classifications and the requirements may be interpreted differently between member states, thus each state may need to be consulted individually
- Without notification or authorization data may not be able to be used to support CDx registration claims

Preparing a Robust Application Dossier

Plan Early

- Align early on roles and responsibilities associated with sponsorship, documentation required from each party, communication and response plan for EC and Member States requests for information
- Be aware of country specific requirements, for example some countries require periodic safety reports, translation of documents into the local language, or ink signatures
- Assemble the analytical performance data and scientific validity necessary to support initiation of clinical performance study design
- Ensure core documents (e.g. CPSP, IB, ICF) fulfill each and every requirement specified in the IVDR/ISO 20916; include justifications for non-relevant requirements

Evidence Required Prior to Initiating a Clinical Performance Study



IVDR Clinical Evidence Components

Elements to support clinical performance study authorization* and registration

Analytical Performance

- Demonstration that the device correctly detects or measures the analyte, IVDR Article 2, (40)

- Indicators of analytical performance are typically similar or identical across IVD devices, including CDx devices
- Performance characteristics should take into account the generally acknowledged state of the art
- The manufacturer should set pre-defined acceptance criteria
- The manufacturer should provide justifications when typical indicators are not required or applicable
- Level of data to start a study may not be the same as what is used to register a device

*Refer to IVDR Article 56 and with Part A of Annex XIII and Article 58 with Annex XIV

Analytical Performance Characteristics (Indicator) of a CDx

Characteristic/Indicator*	Applicable to the CDx (yes/no)	If no, Justification	Data necessary for study authorization (yes/no)	If no, justification
Analytical sensitivity (limit of detection)				
Analytical specificity including endogenous interference, exogenous interference and cross-reactions				
Trueness (bias)				
Precision (repeatability and reproducibility)				
Accuracy (resulting from trueness and precision)				
Limits of detection and quantitation				
Measuring range, linearity				
Cut-off				
Criteria for specimen collection and handling				

Relevant characteristics depend upon the device type

*IVDR, Annex I, Chapter II, 9.1b

IVDR Clinical Evidence Components

Elements to support clinical performance study authorization* and registration

Scientific Validity

- Medicinal therapy performance in the population identified by the CDx;
- If not established, provide the scientific rationale for the use of the biomarker shall be provided (IVDR Article 58, 5(n))

- The strength and robustness of available evidence may rely upon the availability of clinical data associated with the corresponding medicinal product and/or the availability of similar or equivalent CDx devices
- Scientific rationale may include estimates of biomarker prevalence in the target population, association of the biomarker with the disease or condition, mechanistic and/or pre-clinical studies supporting an interaction between the therapeutic and the biomarker

*Refer to IVDR Article 56 and with Part A of Annex XIII and Article 58 with Annex XIV

IVDR Clinical Evidence Components

Elements to support clinical performance study plan and registration

Clinical Performance (PLAN)

- Therapy prediction/selection based on outcome measures of efficacy and safety e.g. response rate, progression free survival, overall survival

- Clinical Performance Studies should be designed to demonstrate the device can meet the intended purpose/use
- For co-development studies, pre-defined clinical efficacy (and safety) endpoints should be specified for the sub-population identified by the CDx (prediction) or the population selected by the CDx
- For bridging studies, efficacy and concordance estimates or their confidence bounds are assumed to be the subject of the individual Health Authority review

*Refer to IVDR Article 56 and with Part A of Annex XIII and Article 58 with Annex XIV, Clinical Evidence Requirements under the EU In Vitro Diagnostics Regulation (IVDR) , MedTech Europe, https://www.medtecheurope.org/wp-content/uploads/2020/05/clinical-evidence-requirements-ivdr-ebook-v3-medtech-europe-2023.pdf.

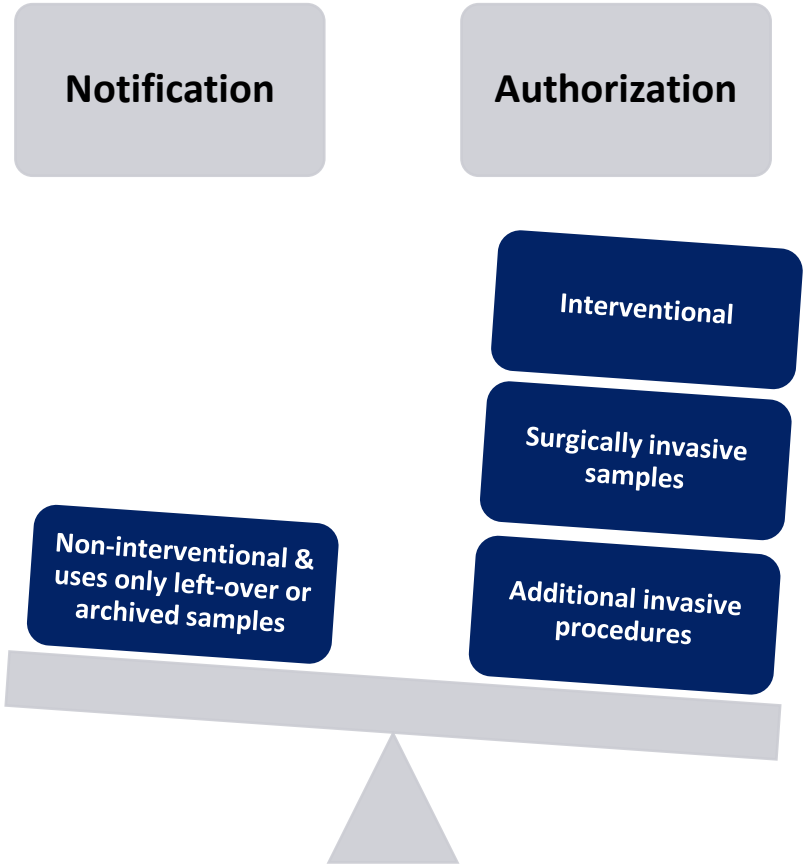
Clinical Performance Characteristics (Indicator) of a CDx

The CDx performance is assessed in the context of the corresponding therapy with regards to the efficacy and safety of the therapeutic

Because a CDx is not diagnosing a disease or health condition, a justification for why typical clinical performance characteristics are not assessed may be required

Characteristic/Indicator	Applicable (Yes/No)	If no, justification
Diagnostic Sensitivity	No	Outcome measures (efficacy and safety) will serve as the basis for determining whether the CDx can identify patients who are likely to benefit from the corresponding medicinal therapy. Although the characteristics listed may be calculated, there are no established criteria or thresholds to assess the clinically meaningfulness of these performance measures in the CDx predictive/selective setting
Diagnostic Specificity	No	
Positive Predictive Value	No	
Negative Predictive Value	No	
Likelihood Ratio	No	
Expected Values	No	

Requirements for Certain Performance Studies; Application for Authorization or Notification



Modified excerpts from Article 58; additional requirements for certain performance studies

- Any performance study:

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

  (b) that is an i**nterventional** clinical performance study as defined in point (46) of Article 2 (where the test result may influence patient management and/or be used to guide treatment); 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, authorized, conducted, recorded and reported in accordance with [Article 58] and Articles 59 to 77 and **Annex XIV***.

- Performance studies involving companion diagnostics shall be subject to the same requirements as the performance studies listed above. 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. (If the study using left-over samples also includes patient management decisions (is interventional), it will still require a full application for authorization from each participating member state.

Examples of Which CDx Studies May Require Notification vs Authorization

- Example situations where notification may be appropriate include

All-comer trial design using only left-over/archived samples

Bridging studies involving re-testing clinical samples that are left-over/archived, to show that results with the candidate IVD CDx are very similar to those with the test that was used in the clinical trial

Analytical method comparison using commercial samples to support a follow-on CDx claim

- Example situations where authorization may be appropriate include

Biomarker positive selection design

All-Comer Trial or biomarker stratification design requiring surgically invasive samples for the purpose of testing with the CDx

Performance Study Application Review and Authorization by Member States

1

- Obtain a study application number. Until European database on medical devices (EUDAMED) is fully functional, a national trial number may be generated for each member state unless indicated otherwise

2

Submit to the Ethics Committees (EC) in all participating member states for an opinion on study conduct.

Note: Most countries typically expect sequential review, but some allow parallel reviews

3

- If the EC opinion is favorable then the **application is submitted** to the competent authorities for their approval/authorization

Some states allow for staggered reviews of Clinical Trial Regulation (CTR) and IVDR applications while others require parallel submissions

Overview of Application Contents (Annex XIV) – Part 1/2

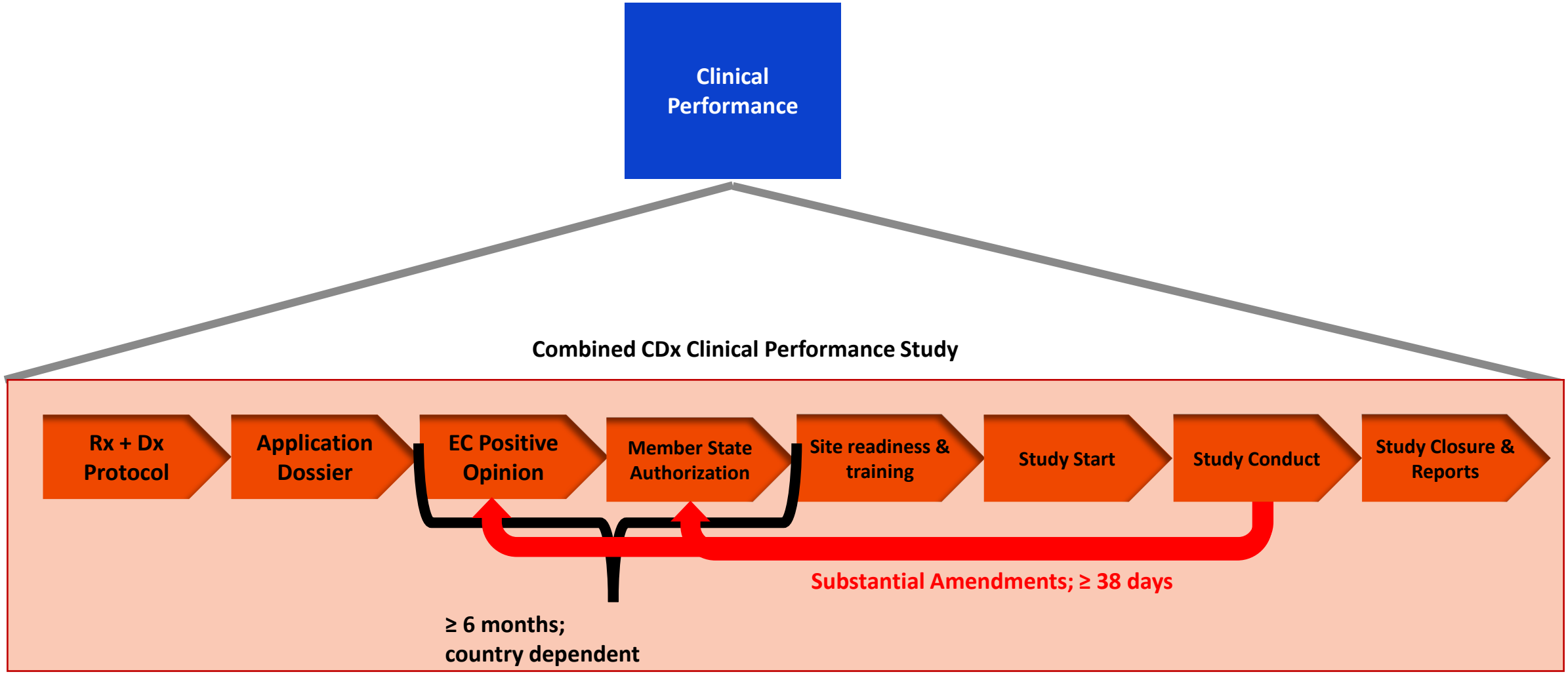
Required Documents	Additional Notes
Cover Letter	
Application Form	See MDCG 2022-19, Performance study application/notification documents under Regulation (EU) 2017/746
Supporting Documents to be attached	
Diagnostic Investigator's Brochure	Prepared in accordance with ISO 20916:2019 and IVDR Annex XIV – includes, but is not limited to, benefit/risk assessment and summary of analytical performance data
Clinical Performance Study Plan (CPSP)* *Note that CPSP is not the same as a Performance Evaluation Plan (PEP). Per MDCG 2022-19, a PEP must also be submitted	• Prepared in accordance with ISO 20916:2019 and IVDR Annex XIII (Section 2 and 3) • Other documents considered essential for conduct of the study can be provided separately from the CPSP (as applicable): ▪ Data Management Plan ▪ Data Monitoring Plan ▪ List of Investigators (Dx and Rx) ▪ Safety reporting plan ▪ Method Sheets ▪ Lab/Operations Manuals Note – Investigators (both Dx and Rx) must acknowledge their willingness to participate in the clinical performance study, and must be trained on performance study conduct

Overview of Application Contents (Annex XIV) – Part 2/2

Required Documents	Additional Notes
Signed Statement of Manufacturer	Statement stating 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 [...]."
Evidence of the positive opinion (approval) by Ethics Committee (EC)	EC that reviews the IVDR application in the participating member state
Proof of insurance coverage	Insurance specific to diagnostic testing procedure – may be in addition to the insurance that covers the investigation of the medicinal product in a CDx study, per Article 65 and national law
Informed consent form(s)	Must include description of the device and associated risks to patients in accordance with ISO 20916:2019
Description of procedures to comply with the application rules on the protection and confidentiality and personal data	Cite relevant sections in Rx and Dx protocols, or other data protection document as applicable
Full details of available technical documentation shall be submitted to the CA upon request	For example: detailed risk analysis/management, or specific test reports may be requested

- See MDCG 2022-19, Performance study application/notification documents under Regulation (EU) 2017/746

Timeline Considerations for Clinical Performance Studies



IVDR – Notified Body Conformity Assessment

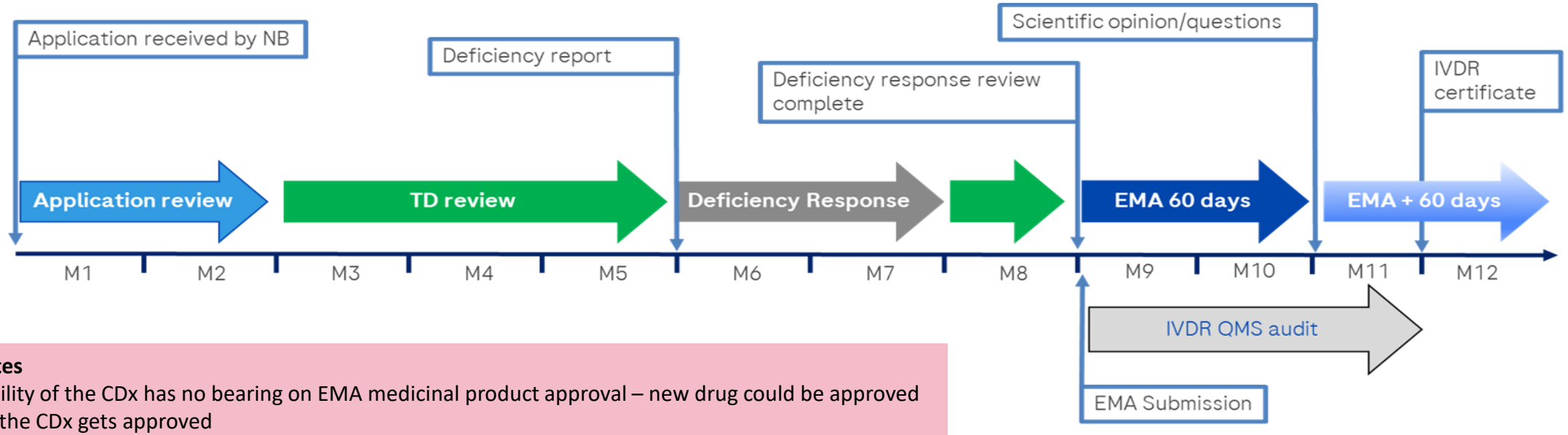
- Under IVDR Directive, 98/79/EC, companion diagnostics was one of the IVD categories that could be placed on the EU market by the manufacturer without Notified Body involvement
- Under IVDR, Companion Diagnostics are classified as Class C and need to undergo a Notified Body conformity assessment
- The Notified Body is required to consult the respective Competent Authority (CA) for medicinal products according to the 2001/83/EC directive or the European Medicines Agency (EMA)

21 December 2022

Notified Body TÜV SÜD Product Service GmbH is happy to announce the issue of the world's first CDx certificate in accordance with the EU Regulation on in vitro diagnostic medical devices, IVDR (EU) 2017/746. The CDx is a cancer biomarker assay used to identify patients who are most likely to benefit from a specific therapeutic treatment. The CDx is used in the oncology care pathway and is manufactured by Roche Diagnostics GmbH.

Notified Body Review Process

Example Timeline



Process Notes

- Availability of the CDx has no bearing on EMA medicinal product approval – new drug could be approved before the CDx gets approved
- Medicinal product can have an accelerated timeline (conditional marketing authorization), while there is no such process defined under IVDR for a CDx
- NBs and EMA operate independently
- The NB reviewer is not able to consult during review process
- EMA provides an opinion on the suitability of the CDx with the concerned medicinal product(s)
- NB has final Certification Decision
- No option for parallel submissions or modular submissions
- No option for class claims

CHMP = Committee for Medicinal Products for Human Use
EMA = European Medicines Agency
NB = Notified Body
QMS = Quality Management System
TD= Technical Documentation

https://www.ema.europa.eu/en/documents/scientific-guideline/guidance-procedural-aspects-consultation-european-medicines-agency-notified-body-companion_en.pdf

Summary: Impact of IVDR on Clinical Trial Conduct and Product Registration

- **Current Negative Impact**
  - **European Federation of Pharmaceutical Industries and Associations (efpia) Survey Results***
    - **Challenges:**
      - Process is not consistent across Member States
      - Inconsistent interpretations of which studies require performance study applications
      - Application documentation is not consistent across Member States
    - **Consequences:**
      - Delayed clinical study initiation (43% of companies estimated 6-12 months delay, currently)
      - Reduction in access to clinical trials for European patients
      - Delayed access to novel therapies for European patients

Long-term Benefit

- Increased regulatory oversight helps to ensure more robust evidence is available to support product registration and post-market performance
- Risk based approach focuses on patient safety

*https://efpia.eu/media/677143/efpia_ivdr-survey-slides.pdf

Resources

- 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), https://health.ec.europa.eu/system/files/2022-05/mdcg_2022-10_en.pdf
- MDCG 2022-19, Performance study application/notification documents under Regulation (EU) 2017/746, https://health.ec.europa.eu/system/files/2023-01/mdcg_2022-19_en.pdf
- Clinical Evidence Requirements under the EU In Vitro Diagnostics Regulation (IVDR) , MedTech Europe, https://www.medtecheurope.org/wp-content/uploads/2020/05/clinical-evidence-requirements-ivdr-ebook-v3-medtech-europe-2023.pdf

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