MEDTECH & PHARMA
PLATFORM

Position Paper

Best Practice Recommendations for Transitioning from In-House Assays to CE-Marked IVDs and Companion Diagnostics in EU Medicinal-Product Development

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Abstract

The development of targeted therapies increasingly depends on biomarker assays and, in some cases, companion diagnostics (CDx) that identify patients most likely to benefit from treatment or those at increased risk of serious adverse reactions. In the European Union, this creates a practical and regulatory interface between medicinal-product development and the In Vitro Diagnostic Medical Devices Regulation (IVDR). Under the current framework, assays used in clinical trials may fall under IVDR if they are used for medical purposes such as patient selection, treatment allocation, or monitoring. In such cases, the assay must either be CE marked for the intended purpose, qualify as an in-house IVD under Article 5(5), or be used as a device for performance study in compliance with the relevant IVDR route. MDCG 2022-10 confirms that combined drug-diagnostic studies may be subject to both the Clinical Trials Regulation (CTR) and the IVDR and also clarifies that there is currently no dedicated harmonised EU procedure for combined trials. EMA, meanwhile, recommends that biomarker assay and CDx development be planned as early as possible, with particular attention to analytical validity, clinical relevance, cut-off justification, assay-version management, and concordance where more than one assay is used. The COMBINE pilot and the Commission proposal of 16 December 2025 may improve the future framework, but they do not replace current obligations. This paper proposes a practical best-practice approach for pharmaceutical and diagnostic developers planning the transition from in-house or early-stage assays to CE-marked IVDs or CDx in the EU. [1-6]

Keywords: companion diagnostic (CDx); IVDR; CTR; biomarker assay; performance study; in-house IVD; Article 5(5); precision medicine

1. Introduction

Precision medicine increasingly relies on biomarker-directed development strategies in which the assay is not a peripheral laboratory tool but a core part of the evidence package supporting a medicinal product. This is particularly true where the assay determines patient eligibility, identifies a biomarker-defined population, or supports treatment decisions during a clinical trial. EMA's FAQ on companion diagnostics emphasizes that, within the current regulatory framework, a CDx is a device essential for the safe and effective use of a corresponding medicinal product, and that the reliability and suitability of the assay used in pivotal trials contribute directly to the robustness of the medicinal-product data and the overall benefit-risk assessment. [3]

In parallel, MDCG 2022-10 clarifies that an assay used in a medicinal-product clinical trial may fall under IVDR when it has a medical purpose in that trial, for example when it guides patient-management decisions or follow-up. Not all assays used in trials are IVDs, but those that meet the definition of an IVD are subject to IVDR, and the sponsor may assume manufacturer responsibilities depending on the intended use assigned in the protocol. This makes assay choice, analytical

performance, cut-off rationale, laboratory model, and assay-version control central regulatory issues rather than secondary operational details. [1]

The EU framework is also evolving. MDCG 2022-10 states that there is currently no dedicated harmonised EU procedure for combined trials, and sponsors are encouraged to consult national guidance and competent authorities. To address this gap, the European Commission, participating Member States, and EMA launched the first phase of the COMBINE Project 1 pilot on 13 June 2025 for a limited number of combined studies involving a clinical trial of a medicinal product and a simultaneous IVD performance study run by the same sponsor. Separately, the Commission published a proposal on 16 December 2025 to simplify MDR/IVDR rules, including proposals relevant to in-house IVDs, combined studies, companion diagnostics, and orphan devices. These developments are important, but they should be described as pilot or proposed reform rather than current law. [1,4-6]

2. Current EU Regulatory Context

Under the current IVDR/CTR interface, assays used in medicinal-product clinical trials must be assessed according to their actual role in the study. MDCG 2022-10 explains that an IVD used in a clinical trial must either have CE marking for the intended purpose, qualify as an in-house IVD, or be a device for performance study under IVDR. The same guidance also states that use of a CE-marked IVD outside its prescribed intended purpose is not covered by the CE marking and renders the device a non-CE-marked IVD in the context of that clinical trial. [1]

Where a non-CE-marked IVD is used for a medical purpose in a clinical trial, MDCG 2022-10 states that the device must either be an in-house IVD or a device for performance study; it is not acceptable to use an investigational IVD without evaluating its performance. The guidance further warns that if performance data are generated outside a performance study, those data may later be insufficient for a future performance evaluation, and additional studies may be needed. This is a key practical reason to align the drug-development and device-development strategies early. [1]

MDCG 2025-5 reinforces the current framework for performance studies. It states that performance studies meeting the criteria in IVDR Article 58(1) must, in addition to Article 57 and Annex XIII, be designed, authorised, conducted, recorded, and reported in accordance with Articles 58 to 77 and Annex XIV. It also states that each performance-study application under Article 66(1) must be accompanied by the documentation referred to in Sections 2 and 3 of Annex XIII and in Annex XIV. [2]

3. In-House Assays and Article 5(5)

In-house assays remain important in medicinal-product development, particularly in early-phase studies, rare diseases, and rapidly evolving biomarker programmes. MDCG 2022-10 confirms that in-house IVDs may still be used in clinical trials, provided the Article 5(5) conditions are met. The guidance also makes clear that the in-house concept applies to the device itself: it must be manufactured and used within the responsible health institution, and it cannot be transferred to another legal entity. Samples may travel to a core laboratory, but the device must remain within the responsible health institution. [1]

MDCG 2023-1 is central to the sustainability of in-house use. It explains that the health institution must justify that the target patient group's specific needs cannot be met, or cannot be met at the appropriate level of performance, by an equivalent CE-marked device available on the market.

That justification must be reviewed and updated over time. Importantly, MDCG 2023-1 states that the subsequent availability of an equivalent CE-marked device does not invalidate the initial justification retrospectively. However, if the CE-marked device proves to be at least equivalent and to meet the target patient group's specific needs at the appropriate level of performance, a transition process toward use of the CE-marked device should start. [7]

A further constrain specific to in-house IVDs is that in contrast to an assay conducted as part of a performance evaluation, all applicable General Safety and Performance Requirements (GSPRs) set out in Annex I IVDR must be fulfilled before any patient samples are tested. This requirement presents practical challenges and necessitates a well defined strategy with respect to the intended purpose of the in house IVD: In particular, clinical performance data sufficient to support a full companion diagnostic intended purpose - such as the identification of patients eligible for a dedicated treatment - are typically not available at this stage. Conversely, where the intended purpose is defined in overly generic terms, competent authorities may question whether it adequately covers the specific use of the in house test within the clinical drug trial concerned.

This interpretation is consistent with MDCG 2025-5, which clarifies that the requirement to submit a performance study application may also apply to in-house IVDs where the test is used under an intended purpose for which compliance with the applicable GSPRs has not yet been demonstrated.

This is more nuanced than the common shorthand that the Article 5(5) exemption is "lost" automatically once a CE-marked equivalent appears. The current position is better understood as an ongoing justification-and-review obligation, with the potential need for transition where a suitable equivalent becomes available. For sponsors, this means that in-house use may be a legitimate early-stage strategy, but it is not a stable default for large-scale, multi-site, or late-stage programmes that may ultimately support a CDx claim. [1,7]

The Commission proposal of 16 December 2025 would, if adopted, change this landscape. The proposal states that, under the IVDR, the condition that there is no equivalent device on the market would be removed for in-house IVDs. It also states that central laboratories manufacturing and using tests exclusively for clinical trials would be added to the scope of the in-house device exemption. Those points are highly relevant for future planning, but they are not yet operative law. [5]

4. Transition Planning from In-House Assay to CE-Marked IVD or CDx

The transition from an in-house assay to a CE-marked IVD or CDx is best understood as a staged, lifecycle-dependent process rather than a single milestone. EMA states that, as a general principle, the strategy for development of a biomarker assay for defining patients' eligibility should be scientifically sound and planned as early as possible, with the aim of co-development alongside the medicinal product. EMA also advises applicants to plan biomarker assay/CDx development as early as possible during drug development to enable timely access to new medicines. [3]

A frequently overlooked issue in the transition from an in-house test to a CE-marked IVD or CDx concerns the scope of informed consent and the future usability of residual specimens and

associated data. In practice, data generated with the in-house IVD, as well as leftover biological samples collected during the clinical study, may later be useful to support future assay development, validation, bridging activities, or regulatory submissions for a CE-marked IVD or CDx. Therefore, the informed consent form, protocol, and related sample/data governance framework should be reviewed early to confirm that such future use is permitted.

Where leftover samples or associated data may be needed for future studies, the informed consent form should include a clear but general statement allowing the storage and future use of residual specimens and related coded or pseudonymised data. This wording should be broad enough to cover future research and development activities related to biomarker assays, IVDs, or companion diagnostics, including future studies supporting CDx development, without including overly technical detail that may be difficult to justify or approve at the time of initial consent.

The transition should be planned before pivotal assay-dependent evidence generation. In many programmes this will occur during or by Phase 2 because cut-off selection, enrichment strategy, and trial architecture often solidify at that stage. The true regulatory concern is not the nominal phase label but whether the assay used in pivotal evidence generation is adequately validated for the intended context and whether any later assay changes can be bridged without undermining the interpretability of the clinical dataset. [3]

Accordingly, transition planning should address not only the technical and regulatory pathway for the assay, but also whether the clinical samples and associated data can be used later to support the future CE-marked IVD or CDx development programme. Early alignment of assay strategy, consent language, data governance, sample retention, and bridging plans reduces the risk that valuable evidence cannot be re-used for regulatory purposes.

EMA further expects applicants to identify whether the medicinal product is to be used with a CDx within the meaning of IVDR Article 2(7). If the candidate CDx has not yet been CE marked or submitted for conformity assessment, preliminary information on the possible CDx should still be provided with anticipated timelines for conformity assessment. EMA also states that the dossier should specify which assay version was used in the pivotal trial, identify the testing laboratories, demonstrate their adequate accreditation, and discuss the scientific rationale for biomarker selection together with the analytical and clinical validation strategy. [3]

This creates a direct bridge between the device strategy and the medicinal-product dossier. EMA is explicit that there is no legal requirement for medicinal-product evaluation and device certification to take place in parallel, and there are therefore no mandatory simultaneous review periods. At the same time, EMA recommends early interaction between the NCA or EMA and the relevant notified body to enable timely patient access. In practice, the best approach is therefore not strict synchronisation, but coordinated planning of evidence generation, conformity assessment, and submission timelines. [3]

5. Performance Studies and Combined Studies

Where the assay used in a clinical trial does not have CE marking for that specific intended purpose, sponsors need a deliberate device evidence strategy. MDCG 2022-10 states that, if the assay qualifies as an IVD with a medical purpose in the trial, the sponsor should assess whether a performance-study route applies and should identify the device appropriately in the CTA cover

letter and protocol. MDCG 2025-5 adds that each performance-study application must include the documentation referred to in Sections 2 and 3 of Annex XIII and in Annex XIV, while also noting that the performance evaluation plan is not itself required to be included in the application, although it may be useful and can be requested by the competent authority. [1,2]

The practical difficulty is that the current EU system still creates substantial duplication and timing risk. MDCG 2022-10 states that there is no dedicated procedure foreseen in the Regulations and that currently no harmonised procedure is in place for combined trials. The COMBINE analysis phase then documented a high degree of heterogeneity in Member State practice, based on responses from 24 of 28 competent authorities. The same report notes stakeholder estimates that, for 849 expected clinical-trial submissions over three years, between 1,992 and 3,275 performance-study submissions might be required under the current system, and that the average time from submission to approval for a performance study was seen as 137 days with a range of 45-267 days. The report also notes that these stakeholder analyses were conducted without authority input or verification. [1,4]

The COMBINE programme is the main current EU attempt to address this problem. The European Commission's COMBINE pages state that the programme completed its first phase with publication of the analysis report in May 2024 and moved into a second phase organised as a programme of projects. Project 1 explores an "all-in-one" coordinated assessment procedure. The first pilot phase launched on 13 June 2025 and accepts a limited number of combined-study applications involving a clinical trial of a medicinal product and a simultaneous interventional performance study of an IVD or CDx run by the same sponsor. The sponsor guide further states that Phase 1 eligibility includes a multinational clinical trial with at least three participating Member States, one sponsor for both the clinical trial and the performance study, and defined endpoints for the IVD, while standard document formats and the underlying legal requirements still apply. [4]

The Commission proposal of 16 December 2025 goes further than the pilot. It proposes new Article 75a IVDR for performance studies in combined studies and states that, for combined studies, the sponsor may submit a single application triggering coordinated assessment in accordance with the CTR as amended by the Biotech Act. The same proposal states that consultation of a medicinal-products authority should only be necessary regarding novel companion diagnostics. These are potentially important reforms, but they remain proposals and should not be described as operative law in current manuscripts or submission strategies. [5]

6. Rare-Disease and Orphan-Context Considerations

Rare-disease programmes intensify the usual challenges of assay and CDx development. Small patient populations, compressed development timelines, and hybrid or seamless phase structures can increase reliance on in-house or prototype assays in early and even potentially pivotal settings. This does not remove the need for a robust device strategy; rather, it makes early planning more important because any later transition or assay change may be difficult to bridge convincingly in a small dataset. EMA's general expectations on early planning, validation, assay-version control, and concordance remain relevant in rare-disease settings even where standard validation paradigms are harder to apply. [3]

It is also important to distinguish medicinal-product orphan designation from device concepts. MDCG 2024-10 is an MDR guidance on orphan medical devices and expressly states that in vitro diagnostic medical devices are outside its scope. It may nevertheless be informative as an example of proportionate evidence thinking for small patient populations. However, orphan designation in the EU remains a medicinal-product concept; there is no current formal orphan designation for CDx or other IVDs under the IVDR. The Commission proposal of 16 December 2025 would, if adopted, introduce specific provisions for orphan devices, but those measures remain prospective only. [8]

The Commission proposal of 16 December 2025 would, if adopted, introduce a dedicated orphan-device pathway, including provisions for devices placed on the market or put into service as orphan devices without a valid certificate under specified conditions and with expert-panel oversight. Until such changes are enacted, the best-practice position is to rely on the current framework, use proportionate evidence strategies where justified, and explicitly distinguish between current orphan-device guidance and proposed future orphan-device legislation. [5,8]

7. Best Practice Recommendations

The recommendations below synthesise the current IVDR, CTR-interface guidance, EMA CDx expectations, COMBINE materials, and the December 2025 proposal. They are intended as practical risk-management tools for sponsors and diagnostic developers under the current framework, while also flagging likely areas of future change. [1-8]

7.1. For Pharma Developers

The transition from an in-house assay to a CE-marked IVD or CDx is a staged, lifecycle-dependent process at the interface of medicinal-product and device regulation. EMA recommends that biomarker assay/CDx development be planned as early as possible and that co-development of the biomarker assay/CDx and the drug candidate be pursued where relevant. While in-house assays may be pragmatic in early development, their use as interventional tests in clinical trials can create later regulatory complexity, including limitations linked to use within one legal entity, challenges in multi-site comparability, the need to maintain and periodically review the Article 5(5) justification, and the potential need for concordance or bridging studies if assay versions change over the course of development.

Where the assay used in early clinical trials differs materially from the assay used in later trials, or from the final CDx submitted for conformity assessment, regulators may expect bridging evidence to demonstrate concordance, analytical validity, and clinical relevance. For that reason, transition should be planned before pivotal assay-dependent evidence generation. In many development programmes this will occur during or by Phase 2, but this is not a fixed regulatory deadline.

During MAA preparation, sponsors should identify the regulatory status of the assay used in pivotal studies and provide appropriate information on assay version, laboratories, accreditation, analytical validation, clinical validation, and cut-off justification. If the candidate CDx has not yet been CE marked or submitted for conformity assessment, preliminary CDx information and anticipated conformity-assessment timelines should still be included in the application. Early coordination between the pharmaceutical sponsor, the diagnostic manufacturer, the notified

body, and the relevant medicinal-product authorities remains critical to minimise regulatory risk and protect the interpretability of pivotal data.

The table below uses a conventional Phase 1 to Phase 3 model for simplicity. In orphan and other rare-disease programmes, phases may overlap or be compressed, and Phase I/II data may sometimes contribute to pivotal evidence. On the medicinal-product side, orphan designation may be relevant where applicable. On the device side, MDCG 2024-10 is an MDR guidance on orphan medical devices and is not directly applicable to IVDs/CDx, but it illustrates the EU direction of travel toward proportionate evidence strategies in small populations. The Commission proposal of 16 December 2025 would, if adopted, introduce a dedicated orphan-device pathway. Those proposed measures are not yet current law.

Table 1: ***Strategic Transition from In-House Assay to CE-Marked Companion Diagnostic (Pharma Perspective)***

Development Stage	Assay Status & Use	Regulatory Status Trigger	Key Transition Risks	Downstream Regulatory Consequences	Evidence & Documentation Implications	Strategic Recommendation
Discovery / Preclinical	Exploratory assay (RUO or in-house); no patient management decisions	None if not used to guide clinical decisions	Premature platform lock-in	Limited scalability for later development	Analytical feasibility data only	Define long-term CDx strategy early; preserve flexibility
Phase 1 (Early Clinical Trials)	In-house assay used for patient stratification, allocation, or monitoring	Becomes regulated IVD if used as interventional test (MDCG 2022-10)	Implicit IVDR obligations; unclear manufacturer responsibility	Potential IVDR performance-study requirements; sponsor/manufacturer responsibilities may need clarification	Initial analytical validation; intended use clarity	Clearly define assay role; assess whether long-term CE-marked pathway is anticipated
Phase 2 (Biomarker Refinement & Cut-Off Determination)	Continued in-house use; cut-off development ongoing	Maintains IVD status if guiding decisions	Late transition increases bridging burden; data variability risk	Bridging studies likely if assay changes; regulatory scrutiny intensifies	Emerging clinical validity; cut-off justification; cross-site consistency documentation	Plan transition before pivotal assay-dependent evidence generation; in many programmes this occurs during or by Phase 2, but this is not a fixed regulatory deadline
Multi-Site Development	Potential use of different in-house assays at different sites	Use of multiple assay versions or laboratories within the same development programme	Uncertainty in cross-site or cross-version comparability	Heterogeneity may impair interpretation of pivotal data	Concordance or bridging data may be needed	Prefer central testing where feasible; otherwise prospectively manage comparability and concordance
Pre-Pivotal / Phase 3	Assay generates benefit–risk evidence	Final marketed CDx must align with pivotal data	Concordance failure between early and late assay versions	Concordance or bridging evidence may be needed to demonstrate analytical and clinical consistency	Robust analytical and clinical validation data	Lock the assay version as early as feasible before pivotal evidence generation; if changes are unavoidable, generate concordance or bridging evidence
Availability of CE-Marked Equivalent	Market introduction of	Availability of an equivalent CE-marked	Need to reassess ongoing reliance on the Article 5(5)	Current Article 5(5) justification must be reviewed and updated;	Documented market review; updated justification; transition	Monitor market developments and periodically review the

Development Stage	Assay Status & Use	Regulatory Status Trigger	Key Transition Risks	Downstream Regulatory Consequences	Evidence & Documentation Implications	Strategic Recommendation
	equivalent CE-marked IVD/CDx	IVD/CDx on the market	justification; potential operational disruption if transition is delayed	transition may be required if the CE-marked device is at least equivalent and meets the target patient group's specific needs at the appropriate level of performance	plan and, where relevant, bridging or concordance strategy	Article 5(5) justification; plan transition where appropriate
Pre-MAA Phase	CDx version defined; CE marking ongoing or pending	MAA must integrate CDx validation evidence	Misalignment between CE marking and MAA timelines	Potential MAA delay; increased regulatory queries	Comprehensive analytical & clinical validation; lab accreditation; missing data handling	Coordinate CE-marking and MAA timelines pragmatically; where CE marking is not yet in place, provide preliminary CDx information and anticipated conformity-assessment timelines in the MAA
Marketing & Post-Authorisation	CE-marked CDx in use	IVDR post-market obligations apply	Performance drift; lifecycle misalignment	Vigilance and PMPF requirements	Ongoing performance monitoring documentation	Maintain alignment between CDx performance and product label

7.2. For Diagnostic developers

The regulatory pathway for companion diagnostics under the IVDR requires lifecycle planning from early classification through performance evaluation, conformity assessment, consultation with the relevant medicinal-products authority, and post-market follow-up. CDx manufacturers must navigate multiple interfaces, including notified bodies, national competent authorities, and, where relevant, the EMA. Under the current framework, combined drug–diagnostic studies may still require parallel CTR and IVDR pathways, depending on the study design and the regulatory status of the assay. In parallel, the COMBINE pilot explores voluntary coordinated assessment, while the Commission proposal of 16 December 2025 would, if adopted, establish a formal single-application route for certain combined studies. Given that CDx validation can directly influence the benefit–risk assessment of the associated medicinal product, early coordination remains essential, but CE marking and marketing authorisation should not be described as subject to a legal requirement for simultaneous review.

Table 2: ***Regulatory Pathway for Companion Diagnostics Under the IVDR: From Development to CE Marking and Clinical Integration***

Regulatory Phase	Legal Basis	Core Requirements	Authority Involved	Timeline Considerations	Key Risks	Strategic Recommendations
Device Classification	IVDR Annex VIII	Classification as Class C (high-risk CDx)	Manufacturer determination (subject to NB confirmation)	Early in development	Underestimating regulatory burden	Plan for class C CDx notified-body conformity assessment under the applicable IVDR route from the outset (Annex IX or, alternatively, Annex X coupled with Annex XI)
Conformity Assessment (Pre-Market)	Article 48(1); Article 48(7); Annex IX	QMS assessment; Technical documentation review; Performance Evaluation Plan (PEP) and Performance Evaluation Report (PER)	Notified Body	Dependent on NB capacity	NB bottlenecks; documentation gaps	Engage NB early; ensure documentation maturity before submission
Performance Evaluation	Annex XIII; Annex XIV where performance studies are required.	Demonstration of scientific validity, analytical performance, and clinical performance; compliance with Annex I GSPR	Manufacturer + NB review	Ongoing throughout development	Insufficient clinical validation data	Coordinate CE-marking and MAA timelines pragmatically; there is no legal requirement for simultaneous review, but early planning is recommended.
Mandatory Consultation with Medicinal Product Authority	Article 48(7); Annex IX Section 5.2 or Annex X Section 3(k), as applicable	Assessment of CDx suitability for associated medicinal product	EMA (for centrally authorised products) or relevant authority	60 days (extendable once; plan up to 120 days)	Timeline misalignment; duplicative review	Coordinate CE-marking and MAA timelines pragmatically; there is no legal requirement for simultaneous review, but early planning is recommended
Non-CE-Marked CDx in Clinical Trials	IVDR Chapter VI; Articles 57–77	Performance-study application or other applicable IVDR route, depending on study type, intended purpose, and risk.	Member State competent authorities; coordinating Member State where the coordinated assessment procedure applies	Depends on the applicable Article 58/70 route and, where relevant, coordinated-assessment arrangements	Parallel CTR + IVDR submissions	Coordinate early with NCAs; anticipate dual submissions

Regulatory Phase	Legal Basis	Core Requirements	Authority Involved	Timeline Considerations	Key Risks	Strategic Recommendations
Combined Drug–CDx Clinical Trials	Current IVDR + CTR framework; COMBINE pilot and proposed Article 75a relevant prospectively only	Under current law, parallel CTA and performance-study application may still be required, depending on study design and device status	Concerned Member States under current law; EMA separately where medicinal-product advice or later CDx consultation is relevant	Dependent on national coordination, study design, and pilot eligibility	Administrative duplication; inconsistent timelines; divergence across frameworks	Engage NCAs early; assess eligibility for the COMBINE pilot where relevant; monitor the legislative reform separately from current compliance obligations.
Use Outside Intended Purpose	Article 16(1)	Sponsor assumes manufacturer obligations	Sponsor + NB oversight	Immediate upon off-label use	Expanded compliance exposure	Avoid unnecessary off-label use in trials; if off-label use is intended, define the regulatory status and responsibilities explicitly
CE Marking & Declaration of Conformity	Article 17; Article 48	EU Declaration of Conformity; affixing CE mark	Manufacturer + NB	After successful conformity and consultation	Market access delay if documentation incomplete	Ensure CE marking readiness aligned with product launch
Interface with Marketing Authorisation Application	Pharmaceutical legislation + IVDR interface	Provide CDx validation data in MAA (assay version, labs, cut-off, validation strategy)	EMA or relevant national medicinal-products authority, depending on the authorisation route	During MAA review	Regulatory queries; benefit–risk challenge	Provide transparent validation strategy and preliminary CDx information where CE marking is ongoing or pending.
Post-Market Obligations	Articles 78–81 and 82–87 IVDR; Annex XIII Part B (PMPF)	Post-market surveillance system, PMS plan, PSUR (for class C/D as applicable), vigilance reporting, trend reporting, and PMPF as appropriate	Manufacturer, notified body, and competent authorities	Continuous	Performance drift; real-world variability	Implement robust lifecycle monitoring, PMPF, vigilance, and traceability systems

7.3. Cross-cutting recommendations

The transition from an in-house assay to a CE-marked companion diagnostic (CDx) is shaped not only by procedural compliance requirements, but also by broader structural and strategic factors. Regulatory fragmentation between pharmaceutical and device frameworks requires deliberate coordination to avoid misaligned timelines and duplicated assessments. Maintaining evidence continuity across development phases is essential to minimise bridging study requirements and protect the integrity of pivotal data.

In rare disease settings, proportional and risk-based validation approaches may be necessary due to limited patient populations, while ensuring patient safety through strengthened post-market monitoring. The sustainability of in-house testing under Article 5(5) must also be monitored, particularly if CE-marked equivalents become available. Finally, combined drug–diagnostic development continues to face procedural complexity under parallel regulatory frameworks, underscoring the importance of early regulatory engagement and coordinated strategy.

Table 3: ***Cross-Cutting Strategic Considerations in CDx Transition***

Strategic Domain	Structural Driver	Core Regulatory Risk	Impact on Transition	Strategic Response
Regulatory Fragmentation	Separation of pharmaceutical and device frameworks (EMA vs NB under IVDR)	Misaligned timelines; duplicated queries; procedural delays	CE marking and MAA progression may diverge	Early tripartite coordination (sponsor–manufacturer–NB); coordinated development planning
Evidence Continuity	Evolution of assay versions across development phases	Bridging study requirements; data variability; benefit–risk uncertainty	Increased evidentiary burden; potential delay in approval	Lock the assay as early as feasible before pivotal evidence generation; plan concordance strategy early.
Rare Disease Context	Small patient populations; limited datasets	Insufficient statistical power for traditional validation paradigms	Risk of non-acceptance of evidence; feasibility challenges	Apply proportionate, risk-based validation; justify evidentiary limitations explicitly; strengthen follow-up where appropriate; leverage ERNs where useful.
Article 5(5) Sustainability	Availability of equivalent CE-marked devices	Need to review and update the Article 5(5) justification in light of potentially equivalent CE-marked alternatives	Potential need to transition where an equivalent CE-marked device meets the target patient group's specific needs at the appropriate level of performance	Monitor market landscape, document periodic review of the justification, and prepare transition and bridging plans where relevant
Combined Drug–CDx Development	Parallel CTR and IVDR frameworks under current law	Administrative duplication, regulatory uncertainty, and	Increased operational complexity in combined clinical	Engage NCAs early; comply with current parallel pathways where applicable; assess

Strategic Domain	Structural Driver	Core Regulatory Risk	Impact on Transition	Strategic Response
		inconsistent timelines across frameworks and Member States	studies and potential delays in evidence generation	COMBINE pilot opportunities; monitor the proposed reform separately from current obligations
Post-Market Governance	Continuous performance monitoring obligations	Performance drift; real-world variability	Ongoing regulatory exposure beyond CE marking	Implement robust PMPF, vigilance, and real-world evidence systems

8. Conclusion

The current EU framework does not prohibit the use of in-house or early-stage assays in medicinal-product development, but it makes their use highly context dependent. Once an assay is used for a medical purpose in a clinical trial, especially for patient eligibility, allocation, or monitoring, it may trigger IVDR obligations that must be managed in parallel with the CTR. Under current law, sponsors should not assume a harmonised EU route for combined studies, should not assume that Article 5(5) falls away automatically when a CE-marked alternative appears, and should not present future legislative reforms as though they were already in force. The most defensible current strategy is to treat the diagnostic workstream as integral to development from the outset, plan transition before pivotal assay-dependent evidence generation, manage assay changes with concordance and bridging evidence where needed, and coordinate early across sponsor, diagnostic manufacturer, notified body, and medicinal-products authorities. That approach is the most robust under today's framework and remains compatible with likely future simplifications if the COMBINE pilot and the December 2025 legislative proposal ultimately lead to lasting reform.

9. References

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The Medtech & Pharma Platform Association (MPP) brings together companies from the pharmaceutical, medtech, diagnostic and tech sectors and provides opportunities to exchange knowledge and to collaborate in technology and regulatory areas related to combined products.

The MPP's objectives are:

- To enhance synergies between the pharma, medtech, diagnostic and tech industries,
- To establish new collaboration models to ensure and accelerate market access for safe and innovative treatment options,
- To work toward the development of a balanced and proportionate regulatory and policy framework for combined products including connected combined products.