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Inisght Brief

Companion Diagnostics: Regulatory Strategies for MedTech Innovators

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Introduction

In November 2023, the FDA approved PD-L1 IHC 22C3 pharmDx, an assay used to assess PD-L1 expression. The diagnostic assay helps identify patients most likely to benefit from pembrolizumab (KEYTRUDA), a cancer immunotherapy designed for patients with high levels of PD-L1. Without the companion diagnostic (CDx), oncologists would have to rely on less accurate methods to determine which medication to prescribe, perhaps to the detriment of patient outcomes.

Immunotherapies and other personalized medicines depend on diagnostics like the PD-L1 test to help detect biomarkers related to drug safety and efficacy. To date, the FDA has approved 170 companion diagnostics (CDx)[1], beginning with the HER2 assay for Herceptin® (trastuzumab) in 1998.[2] Genentech developed the HER2 assay in parallel with its phase 3 clinical trial for trastuzumab.

The HER2 assay showed how the pharmaceutical industry could benefit from CDx. Tests that identify patients most likely to benefit—or those most at risk of serious adverse reactions—enable oncologists to prescribe an appropriate treatment without the frustrating trial and error methodology. In clinical trials, a biomarker-based approach that incorporates CDx may save time and cost through leaner clinical trials that have a higher probability of success.[3]

As more CDx emerged, the FDA and other regulatory bodies developed guidance to help companies develop safe, effective tests. Development of a therapy and CDx in tandem accelerates time to submission and approval, which means patients receive access to promising treatments sooner.

Here, we describe the process for obtaining regulatory approval or clearance for a CDx in the United States. We'll also touch on how processes differ in the EU, where CDx regulation falls under the In Vitro Diagnostic Regulation (IVDR).

Assay progression

	Pre-clinical	Clinical	Cleared/approved
Assay stage	Prototype	Clinical Trial Assay (CTA)	Companion Diagnostic (CDx)
Activities	Feasibility exploratory	Clinical studies validation	Post market
Testing location	Research lab	CLIA certified lab	CLIA certified lab
Component labeling	Research Use Only (RUO)	Investigational use only (IUO)	21 CFR 809.10(a)(2) Intended Use w/Therapeutic.
FDA interaction	Q-Sub or pre-IDE study risk determination	**Possible IDE**	510(k)/*de novo*/HDE/PMA 21 CFR Part 803

CDx regulatory pathways

Because CDx safety and efficacy is unknown prior to clinical trials, and because the diagnostic is essential for the drug or biologic to meet labeled safety and effectiveness claims, the FDA recommends a joint development process.[4] The FDA assesses CDx safety and effectiveness through premarket review and clearance or approval.

PRECLINICAL

During preclinical biologic development, researchers may use a prototype biomarker for feasibility or exploratory analysis. Biomarkers may be used in preclinical safety assessments, in identifying mechanism of action, or in helping with dose selection.

Biomarker testing takes place in a research lab. The test would be labeled "For Research Use Only." Interaction with the FDA typically takes place via the Q-Submission Program.

CLINICAL

The clinical phase is where the clinical validation studies occur. At this stage, the assay is identified as a clinical trial assay (CTA). There are many reasons to use a CTA—not all are for the clinical validation of an eventual CDx. CTAs have no impact on treatment decisions and may not become a companion diagnostic. For CDx clinical validation, the CTA is used to support a primary endpoint, or to inform patient selection and/or treatment decisions. In some cases, the assay becomes a CDx intended to be used to improve safety and efficacy of the therapeutic.

IVD clinical studies that do not require invasive sampling and do not impact patient treatment decisions may be exempt from the Investigational Device Exemption (IDE) requirements. However, if the IVD is intended for use in a clinical investigation subject to 21 CFR part 812, it should be labeled for "Investigational Use Only." The IVD may be subject to design controls under 21 CFR 820.30. Testing must take place in a CLIA-certified lab.

CLEARED/APPROVED

For FDA clearance or approval, a 510(k), a De Novo classification, a Humanitarian Device Exemption, or a Premarket Approval (PMA) application will be required. In addition, the device will need to comply with 809.10 labeling requirements, which includes labeling that indicates that the IVD is intended to be used with the corresponding therapeutic.

IDE requirements and risk assessment

IDE requirements depend on the level of risk associated with the CDx. It's up to the diagnostic developer, aka the clinical trial sponsor, to assess the risk the diagnostic presents to patients—whether clinical trial participants or the biologic's intended patient population. Common questions used to assess risk include:

- What is the procedural risk?
- Are the samples collected analyzed prospectively or retrospectively using surplus samples?
- Is the sampling required invasive or noninvasive?
- Does diagnostic direct the treatment of subjects enrolled in the therapeutic clinical trial?
- Is the diagnostic used to screen patients or to assign them to treatment arms?

Diagnostics used in preclinical research typically do not pose risk and are therefore exempt from IDE requirements. CTAs that pose a nonsignificant risk must follow abbreviated IDE requirements.

CTAs used to direct treatment are considered significant-risk devices and will require IDE approval. CTAs used to enroll subjects into a clinical trial of a biologic, assign subjects to different treatment arms, or to select a particular therapeutic dose are also considered significant risk. Sponsors must receive an approved IDE before beginning the trial.[5]

CDx regulation: 510(k) or PMA?

Risk level, as well as available controls to mitigate risk, determine whether a CDx will require either a 510(k) or PMA. However, historical trends indicate most are Class III devices, with a few exceptions. This indicates that many products require a PMA, a process that is significantly more rigorous than the process for 510(k) clearance. Among the products currently available in the U.S., only two have received 510(k) clearance or granted De Novo classification.

The ratio may change moving forward. In January 2024, the FDA announced an intent to initiate a reclassification process for most high-risk in-vitro diagnostics, including CDx assays.[6]

Reclassification would allow test manufacturers to seek marketing clearance through the 510(k) pathway rather than the PMA. The agency believes reclassification will encourage further development of these tests, which could increase competition and improve patient access.

The risk-based approach will continue, which includes determining whether a new IVD could be designated Class II with special controls through the De Novo Classification pathway instead of Class III with PMA.

The decision coincides with the FDA's move to regulate lab-developed tests (LDTs) as IVDs. Reclassifying means less devices subject to PMA, which helps lessen the regulatory burden for both test developers and regulatory authorities.

What's different in the EU

The EU is the second-largest pharmaceutical market in the world, making it a natural part of global regulatory strategy.[7] CDx are regulated under Regulation (EU) IVDR 2017/746.

Both the U.S. and EU define CDx similarly. CDx are intended to identify patients who are most likely to benefit from the therapeutic product. They may also identify patients likely to be at risk for serious adverse reactions as a result of treatment with the therapeutic.

However, the FDA provides additional context to its definition. This encompasses devices that monitor responses to therapeutics for the purpose of adjusting treatment, as well as those that assist in identifying patient populations for whom the therapeutic product has been studied and determined to be safe and effective.

Both regulatory authorities use a risk classification system, and both encourage parallel development. The FDA classifies CDx as either Class II (moderate to high risk) or Class III (high risk). IVDR classifies diagnostics into four risk classes. CDx fall into Class C.

IVDR requires more rigorous post-market oversight compared to the FDA's post-market requirements. IVDR also carries specific requirements for technical documentation, performance evaluation, and clinical evidence. Identify and engage with a notified body early in development for guidance on IVDR documentation.

An essential companion for biologics development

Development of more complex biomarkers paves the way for more effective targeted therapies. With CDx, companies developing immunotherapies and other biologics will benefit from more efficient clinical trials, while physicians will be able to prescribe the most precise, effective treatment.

Early engagement with regulators will ensure your study designs are aligned with the product's intended use. It will also help set expectations, paving the way for a smoother submission process.

Partnering with IQVIA further accelerates time to market. We develop global CDx regulatory strategies that align with current regulations and guidelines while supporting regulatory interactions and submissions.

By tapping into IQVIA's real-world data, CDx sponsors can identify even more biomarkers and targets of interest. Our end-to-end solutions cover activities from discovery through regulatory approval and post-market surveillance.

References

1. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). U.S. Food and Drug Administration. May 1, 2024. https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools#Group_Labeling

2. Scheerens H, Malong A, Bassett K, et al. Current Status of Companion and Complementary Diagnostics: Strategic Considerations for Development and Launch. Clin Transl Sci. 2017;10(2):84-92. doi:10.1111/cts.12455

3. Ansari M. The Regulation of Companion Diagnostics: A Global Perspective. Ther Innov Regul Sci. 2013;47(4):405-415. doi:10.1177/2168479013492734

4. In Vitro Companion Diagnostic Devices—Guidance for Industry and Food and Drug Administration Staff. Guidance Document, U.S. Food and Drug Administration, August 6, 2014.

5. Principles for Codevelopment of an In Vitro Companion Diagnostic] Device with a Therapeutic Product. Guidance Document, U.S. Food and Drug Administration, July 15, 2016. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/principles-codevelopment-in-vitro-companion-diagnostic-device-therapeutic-product

6. CDRH Announces Intent to Initiate the Reclassification Process for Most High Risk IVDs. Press release, January 31, 2024. https://www.fda.gov/medical-devices/medical-devices-news-and-events/cdrh-announces-intent-initiate-reclassification-process-most-high-risk-ivds

7. The Pharmaceutical Industry in Figures. European Federation of Pharmaceutical Industries and Associations, Key Data, 2022. https://www.efpia.eu/media/637143/the-pharmaceutical-industry-in-figures-2022.pdf

Additional resources

- In Vitro Companion Diagnostic Devices—Guidance for Industry and Food and Drug Administration Staff (August 6, 2014)
- Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product—Draft Guidance for Industry and Food and Drug Administration Staff (July 15, 2016)
- Investigational IVDs Used in Clinical Investigations of Therapeutic Products—Draft Guidance for Industry, Food and Drug Administration Staff, Sponsors, and Institutional Review Boards (December 18, 2017)
- Distribution of In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only—Guidance for Industry and Food and Drug Administration Staff (November 25, 2013)
- Significant Risk and Nonsignificant Risk Medical Device Studies—Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors (January 2006)
- Studies Using Leftover, Deidentified Human Specimens Require IRB Review – Letter to Industry (October 18, 2021)
- Consolidated text: Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices (March 2023)

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