Regulatory Pathways in the US and EU

PMC Virtual Tutorial
12 September 2023

Agenda

1. **Fundamentals: Regulation of clinical lab tests in the US**
   a) Key agencies / stakeholders and regulations
   b) PMA, 510k, de novo definitions, including CDx
   c) IVD and LDT pathways

2. **US market entry considerations**

3. **Fundamentals: Regulation of clinical lab tests in the EU**
   a) IVDR overview including agencies / stakeholders and regulations including timelines
   b) In-house tests
   c) Companion diagnostics

4. **Testing in clinical trials**
   a) IVDR compliance requirements for tests in clinical trials
   b) Compliance requirements and implications: Testing EU trial samples in US

5. **Summary and Q&A**

Fundamentals: Regulation of clinical lab tests in the US

Fundamentals: Key U.S. regulatory authorities & stakeholders

Regulatory Body	Role	Primary authority/standard
FDA (Food & Drug Administration)	Develops & implements federal regulations and guidelines for IVD tests	*Federal Food Drug & Cosmetic Act* **(FD&C Act);** IVD tests must be ***safe and effective*** for the claimed intended use
CMS (Centers for Medicare & Medicaid Services)	(1) Regulates labs that perform testing on human specimens and report patient-specific results for use in clinical diagnosis, prevention, treatment, or assessment	*(1) Clinical Laboratory Improvement Amendments* **(CLIA)** - Ensure **accurate and reliable** clinical test results; excludes research use
	(2) Establishes clinical laboratory tests coverage/payment policies for the Medicare and Medicaid programs	(2) Tests must be **reasonable and necessary** for clinical care

Fundamentals: Key U.S. regulatory authorities & stakeholders

Regulatory Body	Role	Primary authority/standard
State Agencies (SAs) 	Oversee lab licensing, process CLIA applications & maintain records	In addition to federal requirements, federal regulations, some state health departments have their own requirements
FTC (Federal Trade Commission) 	Investigates deceptive advertising practices and enforces consumer protection laws	*Federal Trade Commission Act* (**FTC Act) –** advertising/scientific claims about clinical tests must be ***truthful and not misleading***
3rd Party Accreditors (CAP; Joint Commission) 	Offer accreditation and conduct peer inspections for clinical laboratories.	Under CLIA, CMS may deem 3rd parties for inspections in lieu of CMS.

Fundamentals: 2 pathways in U.S. for commercial (clinical use) diagnostics

	Laboratory Developed Test ("LDT")	In Vitro Diagnostic Device ("IVD")
Setting	• Designed, developed and furnished by a single high complexity CLIA certified laboratory • Generally, does NOT require FDA clearance/approval	• "Manufactured" and distributed as "kit" to multiple CLIA labs or furnished as a "single-site IVD" • Generally, requires FDA clearance/approval
Intended Use/ Indications for Use	• Indications are not restricted by FDA (must be *truthful and not misleading* as per FTC) • Must establish test performance characteristics under CLIA (limited validation data)	• Indications are limited to FDA cleared/approved labeling • Each indication requires comprehensive validation data to assure reasonable "safety & effectiveness"
Quality Systems	• CLIA certification required; CAP accreditation is typical • Design control & ISO certification NOT required • NOT subject to FDA inspections	• Product /components must be developed under QSR (FDA quality systems regulations including ISO 13485) • Subject to FDA inspections

FDA Submission	• Generally, LDTs are under FDA "enforcement discretion" (see FDA ProCode QQS)
	• However, NOT "exempt" from FDA oversight - as a subset/type of IVD medical device, FDA submission could be required to continue offering the test
	• *LDTs with FDA clearance/approval are called "single-site IVD" medical devices*
		• Must submit comprehensive "valid scientific evidence"
		• FDA submission must include evidence of:
		  • Design control from sample collection to result
		  • Software design control and validation
		  • Performance data (analytical and clinical validity)
		• *Clinical utility/outcomes and cost data NOT required or reviewed by FDA*

Fundamentals: FDA pathways in U.S. are risk-based per *Intended Use*

Regulatory Pathway	Risk Assessment*	Requirements
PMA ("premarket application")	High (Class 3)	Intended use already classified as high risk/Class 3, or an IVD with no legally marketed predicate • New devices with novel intended use and/or technology are, automatically by default, classified as Class III, but may be "down" classified to Class 2; *requires valid scientific evidence*
De Novo ("request for classification")	Moderate (Class 2)	New device with novel intended use and/or technology with risks lower than Class III (moderate risk) • *Risk assessment*: Could special controls mitigate risks? Yes = de novo /moderate risk classification (class 2)
510(k) ("pre-market notification")	Moderate (Class 2)	"Class 2" IVD with a legally marketed predicate • Must be "substantially equivalent" to its predicate (same Intended Use; limited differences in technological characteristics)
Registration & Listing ("510(k) Exempt")	Low (Class 1)	Most Class 1 (and some Class 2) IVD devices do NOT require FDA submission. Must meet general controls (including quality systems regulations) unless Intended Use is specifically exempted
IDE (Investigational Device Exemption)	Significant Risk(SR) vs Non-Significant Risk (NSR)	Clinical Trial Assays (CTAs) and clinical studies determined to be a "significant risk" must have an IDE in addition to IRB oversight. For "non-significant risk" studies the IRB acts in place of the IDE.

FDA's primary risk consideration is the risk to human health from false results!

Fundamentals: Regulatory requirements for Clinical Trial Assays (CTA) in the U.S.

Pathway	Investigational Use Only (IUO) – Non-Significant Risk (NSR)	Investigational Use Only (IUO) – Significant Risk (SR)
Intended use settings	• CLIA certified lab	• CLIA certified lab
Patient-specific results report	Report labeled as "For Investigational Use Only"	Report labeled as "For Investigational Use Only"
Regulatory requirements	• IRB oversight • May be single site assay or kit distributed to multiple labs • Abbreviated IDE requirements (IRB oversight - no FDA submission)	• IRB oversight • IDE submission to FDA ✓Design control procedures ✓Abbr. Manufacturing ✓Software development ✓AV data (accuracy, precision & LOD studies) ✓Prior clinical investigations ✓Clinical study protocol
Typical Pharma requirements for CTA (compared to LDT use only)	• CTAs are used in clinical studies and typically tailored to pharma trial • Diagnostic partner should be prepared to meet additional standards: ✓ Specific turn around times (TAT) ✓ More validation data to pharma's requirements ✓ QMS showing complete system level information (e.g., design control) for pharma audit • IDE requirements for LDTs remain unclear for FDA's new CDx Oncology Pilot Program	

US market entry considerations

U.S. Market Entry: Product comparisons for commercial/clinical tests

LDT	IVD - Single Site	IVD - Distributed	CDx	DTC access
Clinical test designed, developed & performed in a single clinical lab	LDT that has been FDA cleared/approved for use in a single clinical lab	IVD "kit" that has been FDA cleared/approved for distribution to more than one clinical lab	IVD (distributed kit or single-site) that provides information "necessary for the safe & effective use" of corresponding drug/ biologic	IVD (distributed kit or single-site) or LDT sold directly to patients and/or consumers
• Must be CLIA/CAP certified • FDA submission is generally voluntary • Could be subject to (potential) new FDA regulations	• Must be CLIA/CAP certified • Unless exempt, must be FDA cleared/approved • Design controls required • FDA QSR compliant QMS required	• Unless exempt, must be FDA cleared/ approved • Design controls required • FDA QSR compliant QMS required	• "CDx" determination is drug focused - made per FDA-Center for Drug Research and Evaluation (CDER) • LDTs indicated for such CDx –high FDA enforcement risk	• FDA submission required for certain LDT indications (e.g., COVID-19 Dx; PGx) • Typically includes "at home" sample collection • FDA requires additional human factors studies and labeling for IVDs
Invitae *CRC panel*	Myriad *BRCAnalysis CDx*	PGDx *Elio Tissue Complete*	Thermo Fisher *Oncomine Dx*	23andMe *PGS PGx*

INVITAE Myriad genetics PGDx ThermoFisher SCIENTIFIC 23andMe®

U.S. Market Pathways:
2 options for drug response/therapy management indications

"COMPANION DIAGNOSTIC" (CDx)

Device type: **Next generation sequencing oncology panel, somatic or germline detection system**

FDA Product Code ("ProCode"): **PQP**
Risk Classification: **High (Class 3 device)**
Requirement: **PMA submission**

Identification/definition:

- **For professional use only (Rx)**
- **For CDx use** *(i.e.,* test result is determined by FDA to provide information that is *"essential for safe and effective use of a corresponding"* therapeutic product)

Example:
Results of the **Myriad BRACAnalysis CDx** test *"…are used as an aid in identifying ovarian cancer patients with deleterious or suspected deleterious germline BRCA variants eligible for treatment with LynparzaTM (olaparib)."* [PMA Number: P140020]

Myriad genetics

Lynparza® olaparib

"PHARMACOGENETIC TEST "(PGx)

Device type: **direct-to-consumer access pharmacogenomic assessment system**

FDA Product Code ("ProCode"): **QDJ**
Risk Classification: **Moderate (Class 2 device)**
Requirement: **510(k) submission (see 21 CFR 862.3364)**

Identification/definition:

- **For use OTC/DTC***
- **Intended use:** *"……for the purpose of assessing the presence of genetic variants that impact the metabolism, exposure, response, risk of adverse events, dosing, or mechanisms of prescription or over-the-counter medications."*
- **Limitation**: *"…must not include an indication for use in supporting or sustaining human life, being of substantial importance in preventing impairment of human health, or presenting a potential, unreasonable risk of illness or injury."* **(e.g., not for CDx use)**

Example:
Results of the **23anMe Personal Genome Service** (PGS) test Pharmacogen
describe[s] if a person has variants associated with metabolism of some th
does not describe if a person will or will not respond to a particular therape
not describe the association between detected variants and any specific th
Novo Number: DEN180028]

23andMe®

**Over-the-counter/direct-to-consumer access* IVDs do not require prescription/professional authorization).

U.S. Market Entry – Additional Regulatory Considerations in the U.S.

- **Managing Assay Modifications**
  - Predetermined Change Control Plan (“PCCP”) - New FDA regulatory tool for managing ongoing changes to software/assays *without* a new FDA submission
  - FDA guidance available for managing reagent/instrument changes, software updates
  - Evolving policies may enable single-site IVDs avoid serial number controls for instrumentation

- **Potential regulatory changes**
  - New federal legislation - VALID, MCED, CLIA expansion – unlikely to be enacted
  - New FDA regulations – modifications to medical device regulations
    - Explicit FDA regulation of LDTs (proposed and under review at OMB/White House *https://www.reginfo.gov/public/do/eoDetails?rrid=325012*)
    - ISO 13485 harmonization with FDA quality systems regulations (soon to be published as “final” regulations)*

**The extent to which additional FDA QSR requirements remain following harmonization will be determined by the final rule.*

U.S. Market Entry: Use Case Scenario # 1 - LDT

- I am a laboratory located in Europe
- I have a cancer diagnostic assay
- My assay has been self-certified under IVDD and is marketed in the EU countries (under transition period)

I am looking to enter US market as an LDT. What are the regulatory considerations?

The following key requirements should be considered for entering the US market as an LDT (others may apply):

- Establishing CLIA /CAP laboratory
- Transferring the technology and implementing the assay in the Lab
- Validating the test meeting CLIA requirements
- Complying with state specific regulatory requirements
- Investing in implementation of FDA compliant QMS (for data traceability and Pharma collaboration opportunities)

U.S. Market Entry: Use Case Scenario # 2 - Distributed Kit IVD

- I am a laboratory located in Europe
- I have a distributed kit for a cancer diagnostic assay
- I have a CE mark to offer the test in 5 European countries
- I have ISO 13485 certified manufacturing facility

I am looking to distribute my assay in the United states (in all states). What are the regulatory considerations?

The following key requirements should be considered for entering the US market as a distribute kit IVD (others may apply):

- Achieving FDA premarket authorization (unless the device meets exemption requirements)
  - Request for an authorization most likely would need to include clinical validation data on US population
- Completing an FDA inspection of the European manufacturing facility
- Completing establishment registration and device listing
- Identifying a qualified US agent

U.S. Market Entry: Use Case Scenario # 3 - CTA

- I am a laboratory located in Europe
- I have a distributed kit for a cancer diagnostic assay
- I have a CE mark and offer the test in 5 European countries
- I have ISO 13485 certified manufacturing facility

I am looking to partner with pharma for selecting patients for their clinical trials in the US. What are the regulatory considerations?

The following key requirements should be considered for entering the US market as a CTA (others may apply):

- Obtaining IRB approvals for each clinical site
- Determining level of risk for use of the device in every clinical trial
- Obtaining an FDA IDE (if the use of considered as significant risk)
- Preparing for QMS audit from a pharma partner

U.S. Market Entry
Key regulatory considerations for successful test launch in U.S.

	If launching as an LDT / Partner with Pharma for CTA…	If entering the U.S. market with an IVD…
1 **Regulatory strategy**	Mitigate FDA enforcement risk!	Clarify desired intended use/indication (desired "claims") based on gap assessment; consider Breakthrough Designation Request
2 **Regulatory compliance**	FDA and CLIA regulations "co-exist" ✓ CLIA certification is absolutely required if are patient-specific results are reported to anyone ✓ IRB is needed for both significant risk and non-significant risk clinical studies	Identify indications for least burdensome FDA submission, e.g.: ✓ Comprehensive predicate search ✓ Risk assessment focused on risk to the patient/human health from a FALSE RESULT vs benefit to patient/human health ✓ Develop a Predetermined Chance Control Plan (PCCP)
3 **FDA submission**	LDTs as CTAs require risk determination for submission requirements	Confirm adequate data per FDA (analytical and clinical performance data, not clinical utility & cost data)

Fundamentals: Regulation of clinical lab tests in the EU

In Vitro Diagnostic Medical Device Definition

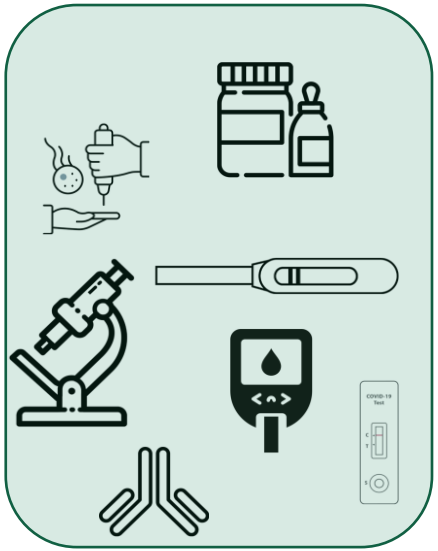
Human Specimen

In Vitro examination

Information

Medical Decision

IVD Medical Device



IVD

IVDR Article 2(2)

Definition of Companion Diagnostic (CDx)

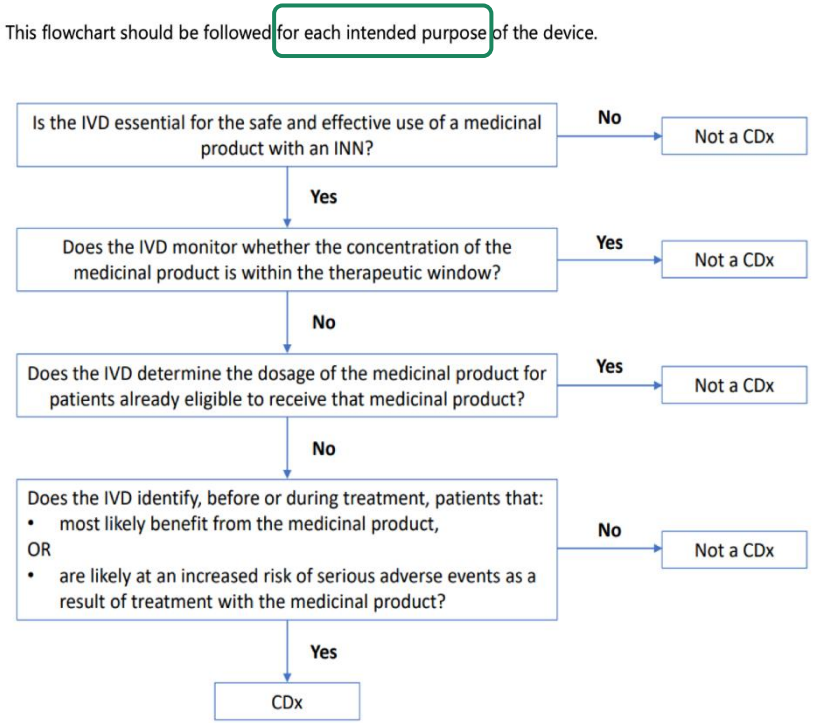
'Companion diagnostic' (CDx) is defined in Article 2.7 IVDR as a device which is essential for the safe and effective use of a corresponding medicinal product to:

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.

General CDx examples (non-exhaustive):

- A device intended to identify a marker (receptor, transporter, other protein-based biomarker or its variant) specifically targeted by the corresponding medicinal product.
- Devices intended to detect antibodies against a specific medicinal product during the course of treatment.
- Devices intended to identify patients who are expected to benefit from treatment with a specific medicinal product, based on the absence of a marker.

Annex II: Flowchart to help determine whether an IVD is a CDx



MDCG 2020-16 rev.2 Guidance on Classification Rules for in vitro Diagnostic Medical Devices under Regulation 2017/746

In Vitro Diagnostic Devices and CE-Marking

In-Vitro Diagnostic Directive

Sets out general rules that are transferred to national law by each member state.

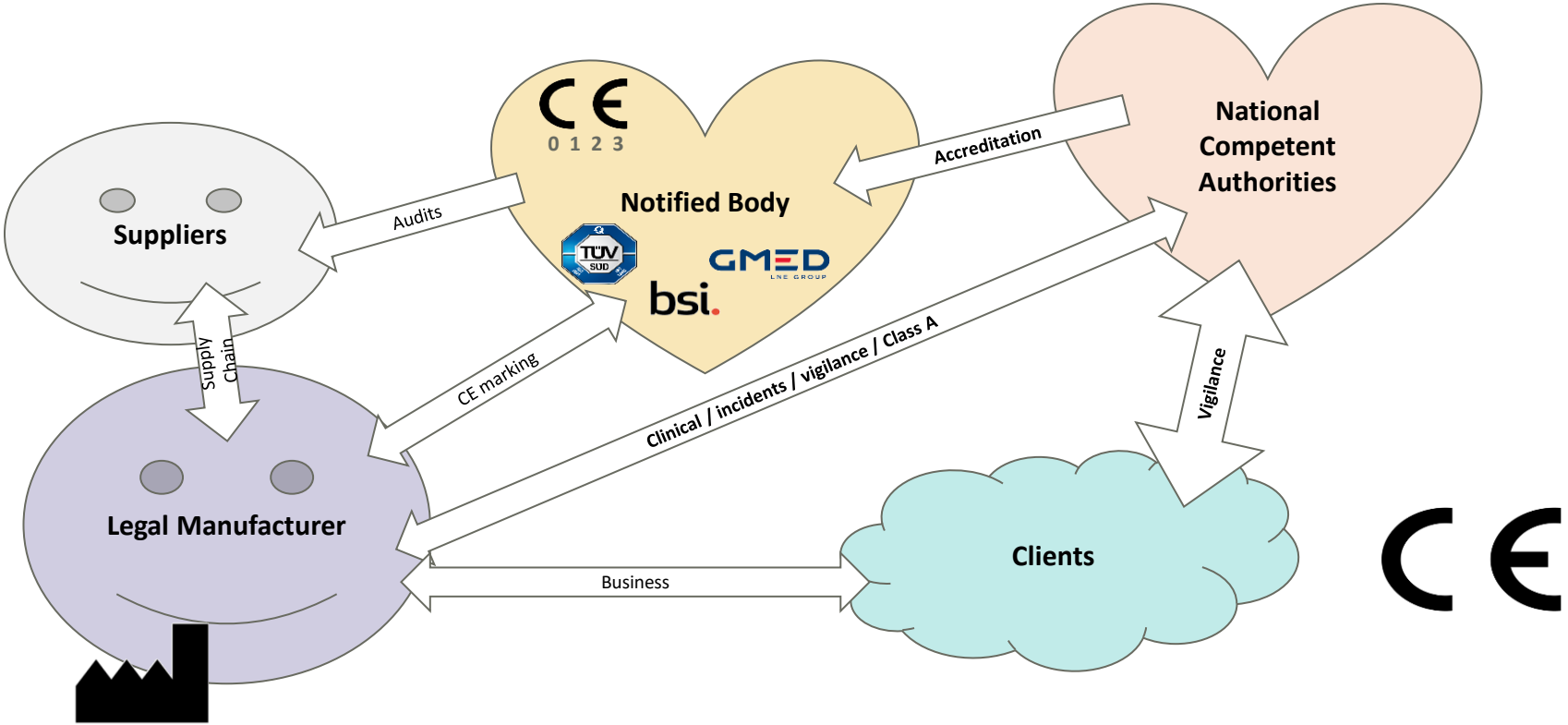
In-Vitro Diagnostic Regulation 2017/746 EC (IVDR)

Directly applicable in all European Member states. Leaves no room for local interpretation.

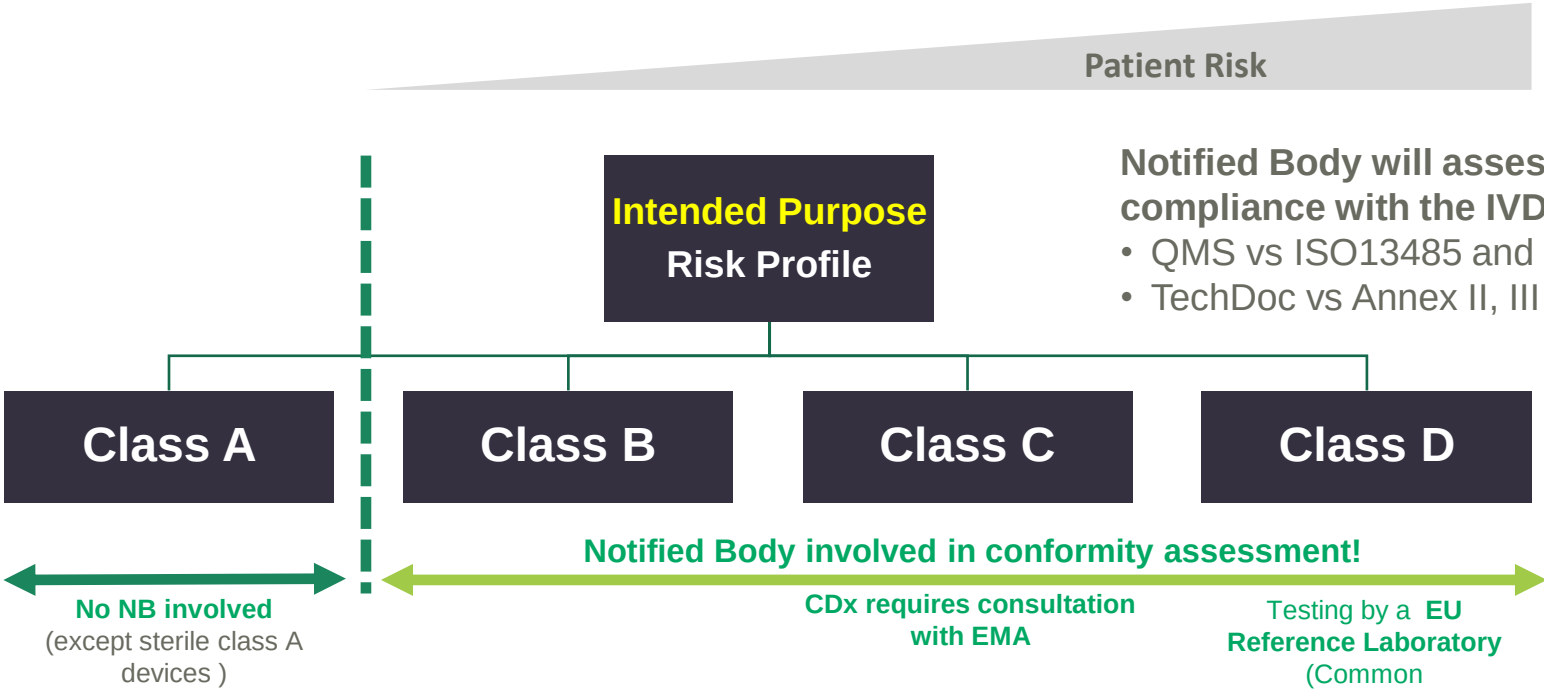
May 26, 2022

- **'Conformity Assessment'** means the process demonstrating whether the requirements of the Regulation relating to a device have been fulfilled

CE Marking: Stakeholders EU

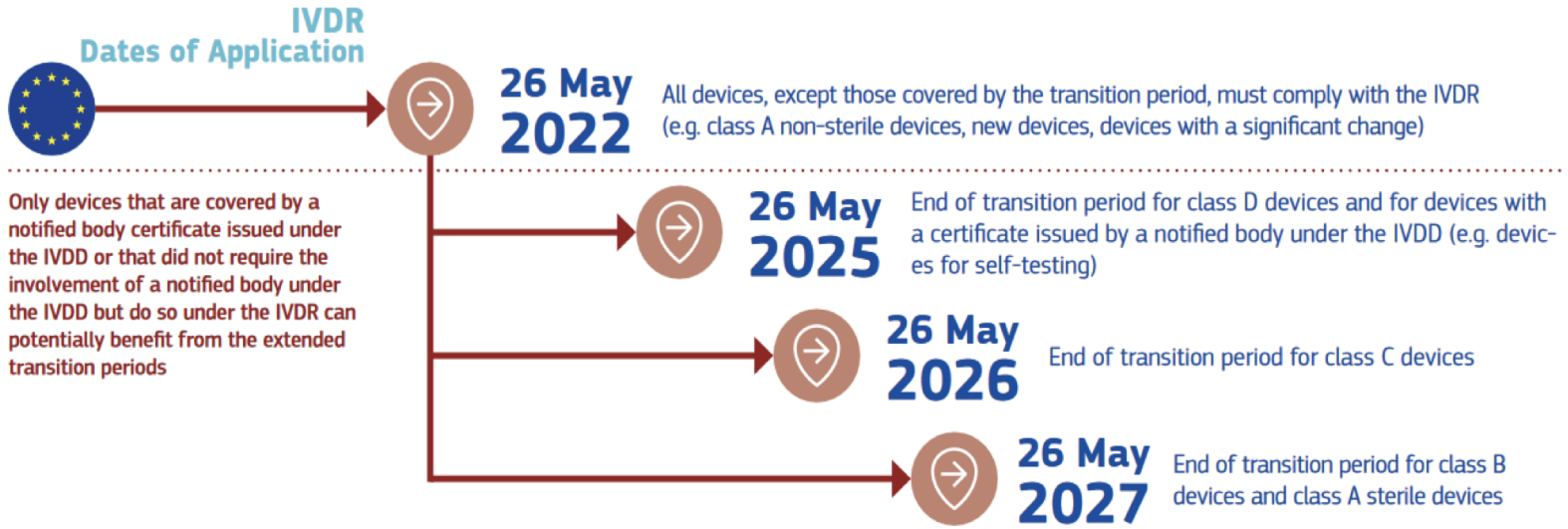


IVD Classification and impact on the Conformity Assessment



MDCG 2021-22 rev.1 Consultation of the expert panel
MDCG 2022-3 Verification of manufactured class D IVDs by NBs
MDCG 2022-2 Application of transitional provisions for certification of class D IVDs according to IVDR

IVDR and New Transition Timelines (Regulation 2022/112)



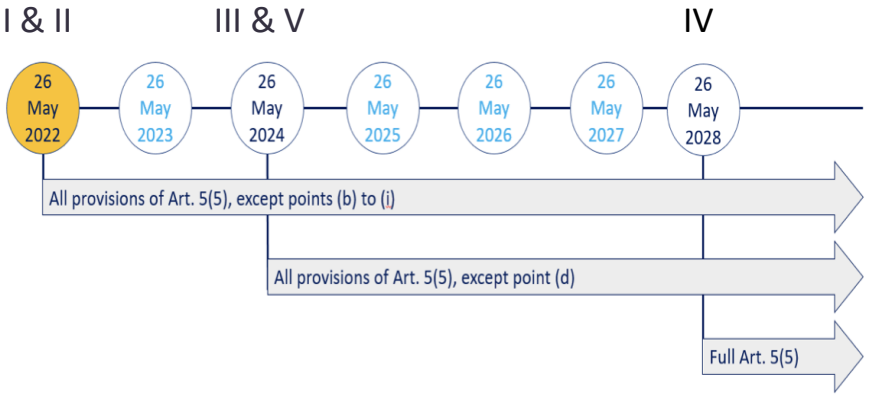
Conditions to be fulfilled to benefit from extended transition period

- Devices continue to comply with previously applicable EU legislation (IVDD)
- No significant changes in design or intended purpose
- Notified body certificate or declaration of conformity drawn up before 26 May 2022

In House - IVDR – Art 5.5 Restriction of application

- **Devices can only be defined as in-house devices if:**
  - Manufacture and use is limited to health institutions established in the EU
  - The devices are not transferred to another legal entity;
  - Manufacture and use of the devices occur under appropriate quality management systems, the compliant with standard EN ISO 15189 or […];
  - Documented justification that the target patient group's specific needs cannot be met, or cannot be met at the appropriate level of performance by an equivalent device available on the market;
  - The health institution provides information upon request on the use of such devices to its competent authority, which shall include a justification of their manufacturing, modification and use;

Timeline for the application of the different provisions of IVDR Article 5(5)



Testing in clinical trials

EU Regulatory status of assays in the context of clinical trials for medicinal products (CTR)

No impact on medical management decisions

Qualification

Information **impacts medical management decisions**

- ✓ Incl/excl criteria
- ✓ Treatment allocation
- ✓ Monitoring safety/efficacy
- ✓ Follow-up

No compliance to IVDR

Compliance to IVDR

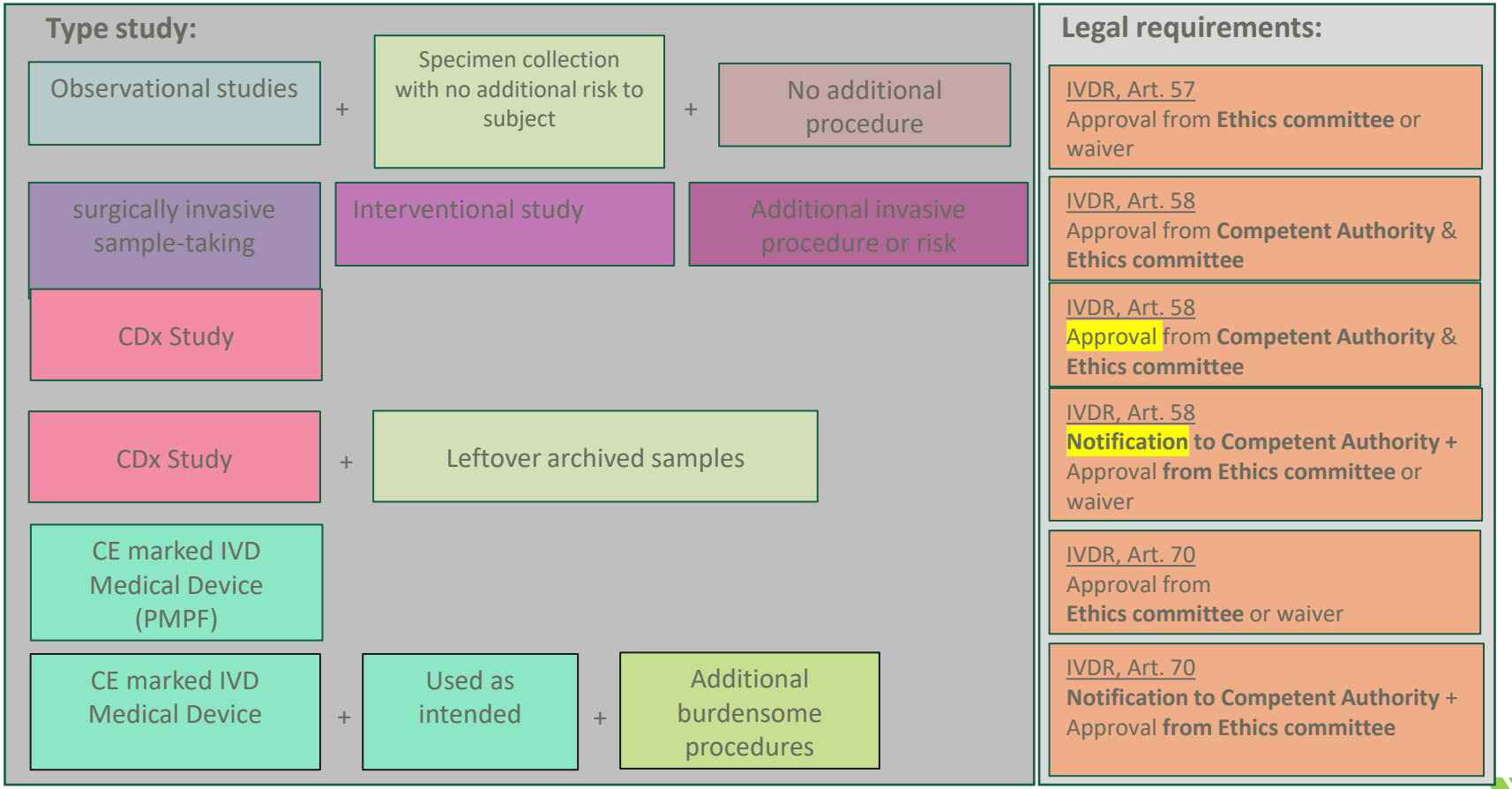
- ✓ CE-marked
- ✓ In-house, Article 5.5
- ✓ Device for performance study

Testing EU trial samples in US

There is no general answer but several considerations:

- ✓ General Data Protection Regulation (**GDPR**)
  - Information provided in the clinical trial application?
  - Information given in the Informed consent?
  - Appropriate safeguards related to data subject rights in place (no approved legal framework EU/US, GDPR compliance)?
- ✓ Compliance **IVDR**
  - Test impacts the medical management decisions? (if yes, need to comply to IVDR)
  - What is the current regulatory status of the device in EU?
  - Applicability of Article 6
- ✓ **National law(s)** related to management of data protection and/or genetic data

Study Submission – EU Regulatory Requirements



IVDR – EU Legal Basis for clinical Performance studies

IVDR, Art. 57: General requirements regarding performance studies

Observational studies + Leftover or archived samples + No additional procedure

- The device for performance study shall comply with the GSPRs apart from the aspects covered by the performance study
- Take every precaution to protect the health and safety of the patient, user and other persons.
- Where appropriate, performance studies shall be performed in circumstances similar to the normal conditions of use of the device.
- Protect rights, safety, dignity and well-being of the study subjects, which shall prevail over all other interests
- Generated data shall be scientifically valid, reliable and robust.
- Shall be conducted in accordance with applicable law on data protection (GDPR).

IVDR – Legal Basis for clinical Performance studies

IVDR, Art. 58: Additional requirements for certain performance studies

surgically invasive sample-taking	Interventional study	Additional invasive procedure or risk

Such studies may be conducted under following conditions:

- Subject to scientific and **ethical review => Ethics committee**
- Subject of an **authorisation by the Member State(s)**
- Sponsor or legal representative **established in the Union**
- Appropriate **protection of vulnerable populations** and subjects (Articles 59 to 64)
- Anticipated **benefits justify the foreseeable risks** and inconveniences
- **Informed consent** is obtained and contact details provided with the => Subject may withdraw at any time
- **Rights of the subject** to physical and mental integrity, to privacy and to the protection of the data
- Study designed to involve **as little pain, discomfort, fear and any other foreseeable risk** as possible
- Medical care provided to the subjects is the responsibility of an appropriately **qualified medical doctor**
- Subject is under **no undue influence**, including that of a financial nature
- **Biological safety** testing has been conducted and **technical safety** proven (taking into consideration the state of the art)
- **Analytical performance** has been demonstrated => for interventional studies also **scientific validity** (for CDx, where the scientific validity is not established, the scientific rationale for the use of the biomarker shall be provided);
- **Investigator shall be qualified professional**
- **Suitable facilities** where the performance study involving subjects is to be conducted
- the requirements of **Annex XIV** are fulfilled => **Study documentation**

Summary and Q&A

Thank you.