Impact of IVDR on biomarker assessments in Clinical Studies

Examples from Case studies

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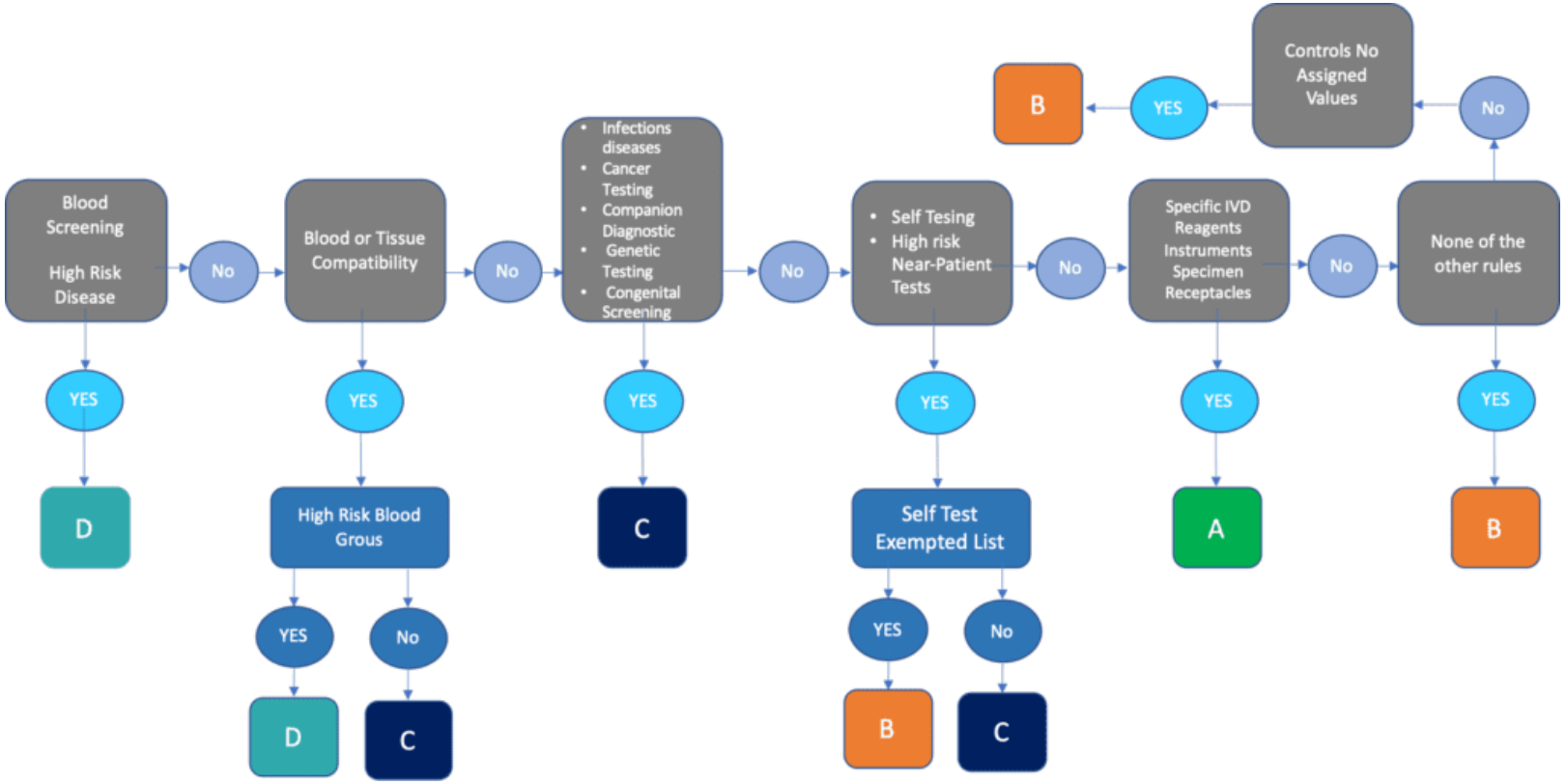
IVDD before IVDR (prior to May 2022)

IVD Medical Devices Classification per IVDD



- ***In vitro diagnostic***" Tests or devices used to detect disease or other conditions that can assist with patient management decisions:

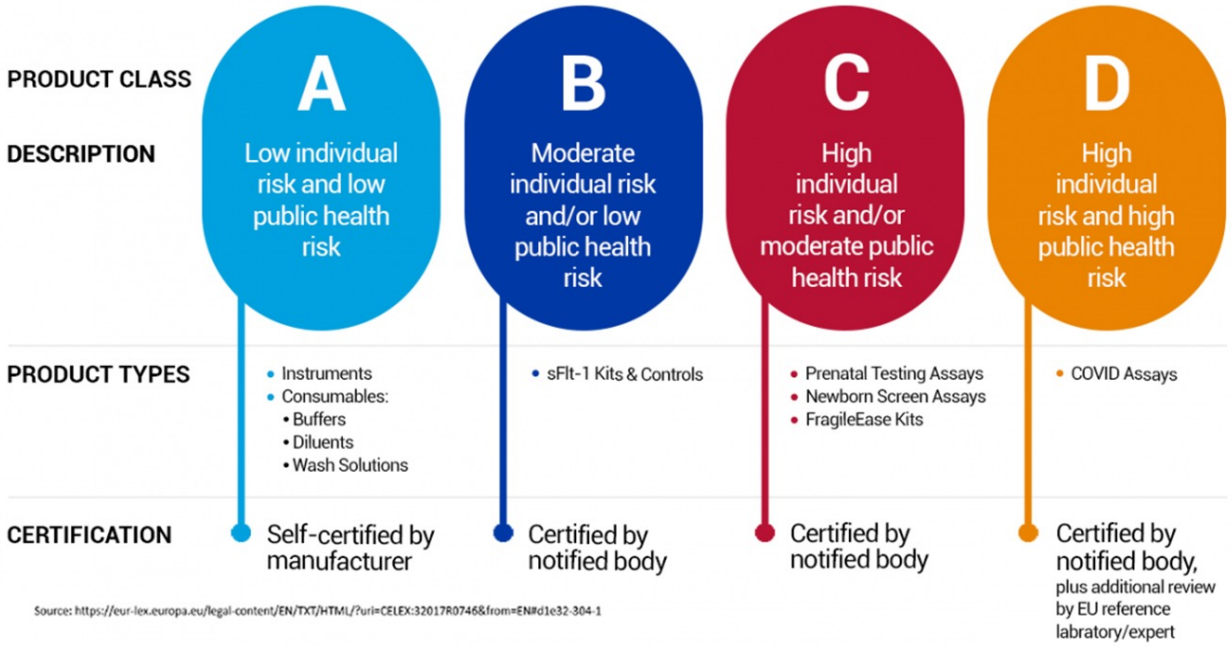
- This can include reagents, calibrators, control materials, specimen, software and related instruments ultimately used for diagnosis, screening, monitoring, predisposition, prognosis, prediction etc.

- Prior to May 2022, **IVDD** (*In vitro* diagnostic Medical Device Directive)

IVDD's regulatory classification was based on which condition or pathogen is diagnosed → different levels of regulatory scrutiny and different standards

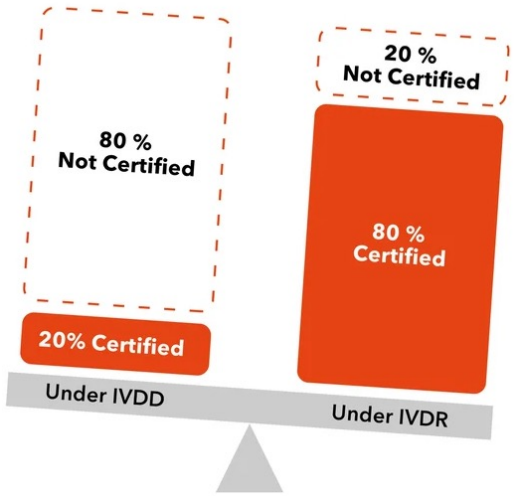
IVDR is risk based instead of list based!

Under the new IVDR regulation, all IVD products must be classified according to a new product classification based on both patient and public health risk.



- **In vitro Diagnostic Regulations (IVDR) introduced in May 2022 to bring positive changes:**
  - Higher quality and safety standards for IVDs
  - Clearer definitions and scope
  - Traceability of development
  - Harmonization across EU - every country before interpreted and implemented IVDD differently

- **Changes under the new system IVDR:**
  - New Classification system for IVD products
  - Need to involve notified bodies



IVDR impact on Clinical Trials

In vitro Diagnostic Regulations (IVDR) introduced in May 2022 requires:

In a Clinical Trial where a Medical device or tests used for a medical purpose – always need the clinical evidence to support the intended purpose

- Certification by a notified body (CE mark)
  or
- A separate Clinical Performance Study application (requires prior regulatory approval)

Clinical Performance studies - This includes assessment and analysis of data to establish or verify scientific validity, analytical performance and clinical performance

- Scientific Validity – association of an analyte with a clinical condition
- Analytical performance – ability of a device to correctly measure the analyte
- Clinical performance – ability of a device to produce results that are correlated to a particular clinical condition to physiological process. Eg, diagnosis – reference ranges etc

Medical purpose – where data is used for patient decisions – eg, data supporting eligibility, patient stratification, treatment assignment decisions or on-trial patient management decisions

Investigational IVDs require Clinical Performance Studies

When a CE marked assay is used outside of it's IFU (Intended purpose) or a LDT (Lab Developed Test) is used → it falls under the category of "***Investigational IVD***"

Investigational IVDs require a separate **Clinical Performance Study approval** (also called device trial) in parallel to the IMP drug trial approval for the same clinical study.

Drug Trial Application	+	Device Trial Application
• Investigational Medicinal Product		• Investigational Device (e.g. IVD for Performance Study)
• Drug protocol		• Clinical Performance Study Plan (CPSP)*
• Drug IB		• Device IB* plus additional device specific documentation
• Drug safety data collection & reporting		• Device safety data collection & reporting
• Patient consent to participate in drug study		• Patient consent to participate in device study
• Clinical trial sites & monitoring		• Device testing sites & monitoring

*For each device in the study; there can be multiple devices in a study. If there are 5 investigational IVDs, this requires 5 clinical performance studies.
Note: Please note that the above lists of trial application activities is not exhaustive.

ISO 20916 : 2019 - is an international standard that provides detailed guidance on Clinical Performance Studies for IVD devices. It defines good study practice for the planning, design, conduct, recording, and reporting of Clinical Performance studies

Considerations in Clinical Studies – when does IVDR apply?

Assay Registration status

- Use of non CE marked test, LDT
- Approved CDx but used with an investigational drug
- **CE marked test but used outside of intended use**

- CE marked assay used within intended use and as per IFU
- A LDT (Lab Developed Test) run in an EU Healthcare Institution compliant with IVDR article 5(5)
- Tests ordered by HCP (Health care professional) as part of SoC (Standard of Care) and not part of Investigational Trial Protocol

Context of Use

- Patient Selection, Screening criteria
- Patient assignment - results used to assign to specific treatment arm
- Eligibility assessment – inclusion/exclusion
- **Prospective patient stratification with capping**
- Confirmatory testing with impact on trial conduct
- **Clinical Endpoint measure that impacts the trial – stopping criteria, individual dose decisions, patient monitoring, patient management**
- Safety assessment – that may lead to treatment discontinuation
- Data is used for analytical or clinical validation of a CDx assay

- Exploratory/Research analysis with no medical objective
- Clinical results not used for patient management decisions (even when reported back to patients or HCPs)
- **Prospective patient stratification with balancing**
- Retrospective stratification in subgroups for analysis

Case Study-1 – Patient stratification – capping or balancing?

Requirements - Even distribution of patients in placebo vs treatment arm based on cell counts (manual procedure performed at site)

- Stratification with balancing objective – to proportionately (not equally) distribute the patients in two arms

Patient stratification prior to randomization with the objective:

- Balancing – even balancing in the treatment arms, for example, with respect to biomarker levels

There is no influence of test result on chance of being treated with investigational drug

- Capping - enrollment in a certain arm is capped at a certain number or percentage of subjects (eg, 30% with Biomarker X). Treatment groups are balanced with respect to biomarker

In this case after the targeted cap is achieved, the results become a de-facto inclusion/exclusion criteria

Case Study-2 – Secondary endpoint (biomarker) used for patient monitoring

Situation:

- Drug is a large molecule depletor of an immune cell fraction
- Single Ascending Dose in clinical trial
- Monitor the depletion of immune cell fraction in blood by Flow cytometry
- Data shared back with the sites/HCPs just for informational purpose

Requirement from FDA – Patient needs to be followed up in the clinics until the cells have returned back to baseline

EU-IVDR

- **CoU of data** - Patient monitoring – decide on follow-up visit of individual patient after single dose but no treatment implication
- **Assay status** - LDT at a CRO was standardly run for immune cell profiling in blood – stability to measure the sample within 14 days of collection
- Required a switch to a CE marked Flow cytometry assay but limited sample stability – 2 days

Potential approaches:

- Extend stability testing of CE marked assay at CRO – but would be outside of intended use (CE mark) and hence require a submission
- IFU was updated by manufacturer – “should” to “recommended” to be tested within 48h of collection

Clinical Solution implemented:

- Study started before May 2022 – continue using the LDT. Can open new sites in existing EU countries, but not onboarding new countries
- Use LDT for routine monitoring and run additional CE marked assay at the FU visit. Risk of missing stability window for testing – organize an additional unscheduled visit if that happens

Case Study-3 – Target biomarker expression by IHC used as inclusion criteria

Situation:

- Large molecule program in Oncology
- Biopsies used to measure target expression prior to enrollment

EU-IVDR

- The assay used was a LDT – got the status of “Investigational IVD” in the clinical program
- Clinical Performance Study Protocol (CPSP) and Diagnostic Investigator’s Brochure (IB) had to be developed for the IHC assay and supplementary to the Drug Trial Protocol

Case Study-4 – RUO genetic testing

Situation:

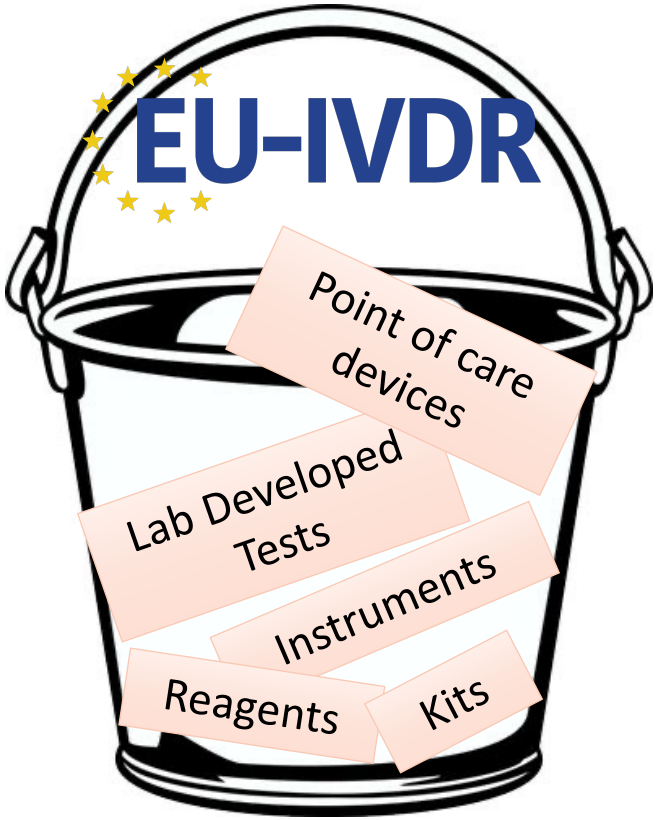
- Patient inclusion based on a certain genotype
- Research use only method based on Long Read sequencing
- Dx reagents and instrument not available

EU-IVDR

- Start with an epidemiological study → no drug intervention, patients can be recontacted if needed for later clinical trials
  - Collect data on the patient genotype using the LDT assay
- Phase-1 (non-EU) – Use pre identified patients (enriched based on genotyping)
- Based on the study risk determination from HA:
  - Non-significant risk - Use the existing LDT results or rerun the LDT in phase-1 at CRO
  - Significant risk - Run IDE assay (Investigational Device Exempt) at a CRO CDx Lab
  - Use the data for CPSP application in Phase-2 study in EU

Reflections

- Is IVDR a blockbuster or a showstopper?
- Interpretation of scope
- Start as early as possible
- Involve health authorities
- Infrastructure setup – internal and external



Keep Calm but don’t just ´´Carry On´´

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Doing now what patients need next