IVDR and FLOW CYTOMETRY

Impact on routine diagnostics and clinical trials

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European Society
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Conflict of Interest Declaration

The presenter has no commercial conflict of interest to disclose

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- ✓ **In-house tests: CE or not CE?**
- ✓ **The 5 key elements of Article 5.5**
- ✓ **IVDR and clinical trials**

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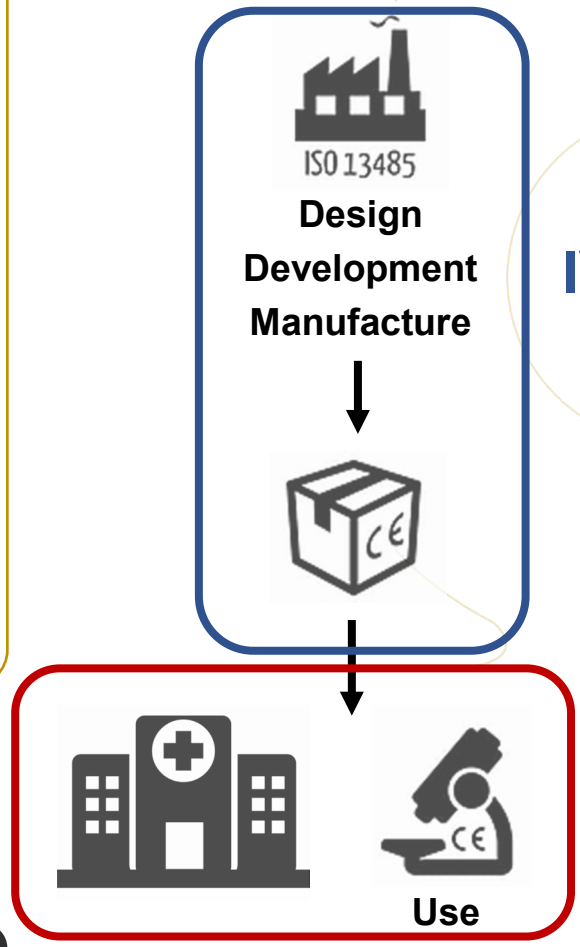
In-house developed tests: not CE-IVD's

- **Any product or a combination of products** (*whether commercially available or not*) that is used in the European Union and meets the definition of 'in vitro diagnostic medical device' **must comply with the IVDR**

- Laboratory-developed **'in-house test (IHT)'** (better not say 'LDT'):
  - IVD assay that is used by the laboratory while the test is **not CE-marked** or is used in a way that is **not compliant** with the conditions for which CE-marking was obtained. Typically, such assay is (partly) composed of:
    - RUO products
    - CE-marked IVD products that are used outside of their intended purpose
    - Laboratory-developed critical components

- IVDR (Recital 29) explicitly recognizes the – occasional – **need for** such IHT and recognizes that **certain rules** of the IVDR should **not** apply to such IHT
  - But the use of such assays is **restricted** and **regulated** by the IVDR through **Article 5.5**

- Implementation of a **CE-IVD test** in the lab is by default **not affected** by the IVDR



IVDR

FCM kits

Strictly defined intended purpose

All performance claims are verified/validated by manufacturer

and/or

Single mAb's

Less narrow intended purpose allowing user-defined assays

Manufacturer cannot verify/validate user-defined assay performance characteristics

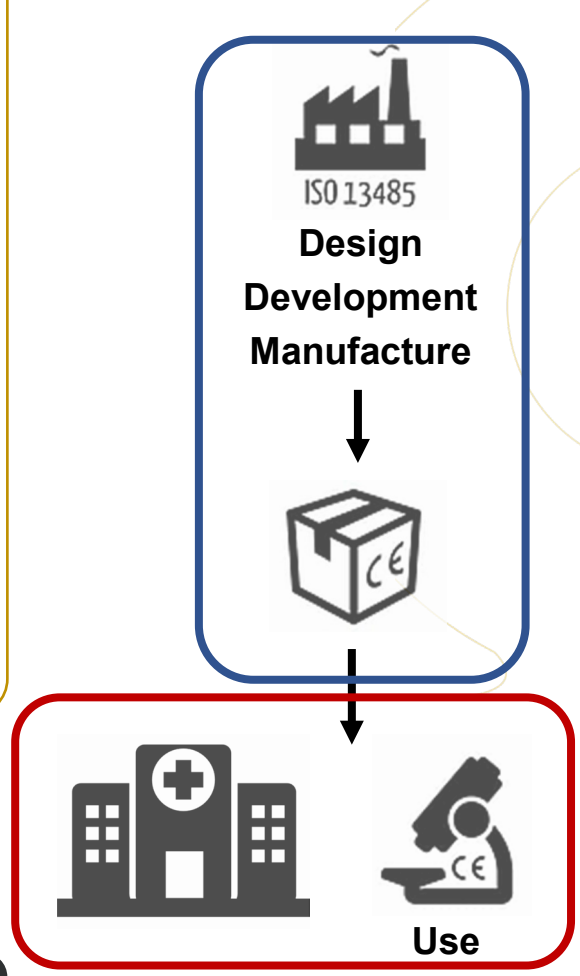
National accreditation requirements

Verification of manufacturer's performance claims

Validation of performance characteristics than cannot be established by manufacturer

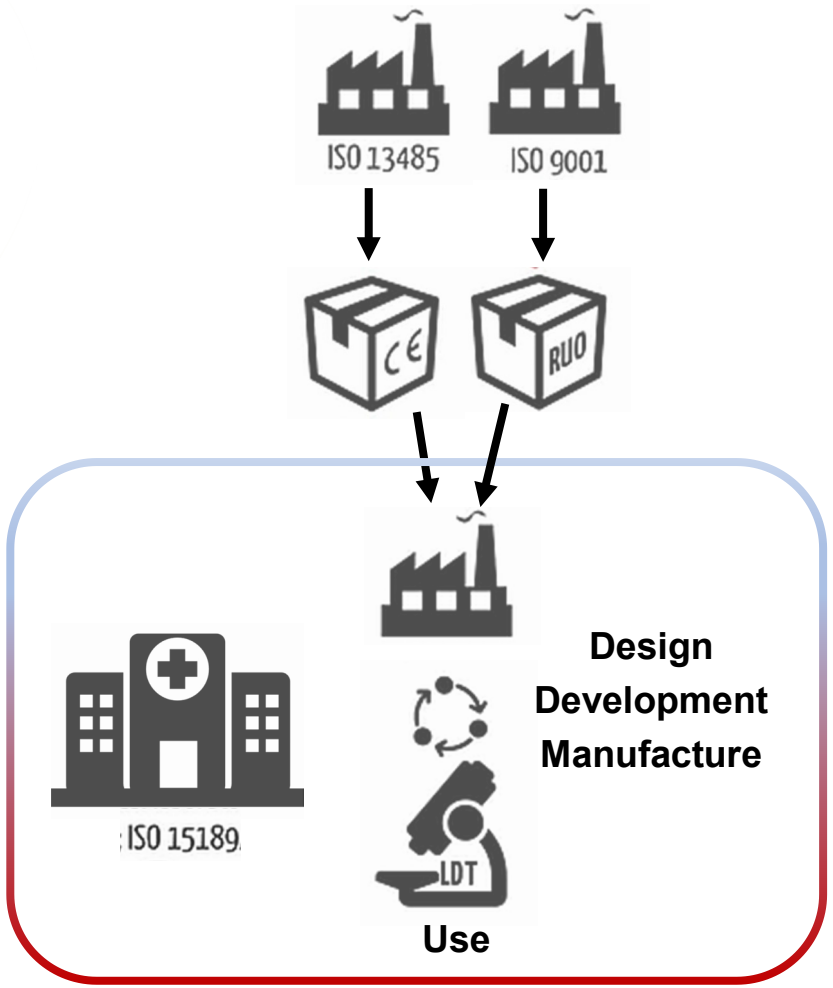
IVDR IMPACT ON LABS

- IVDR only impacts the **deliberate use** by the lab of **non-CE-IVD tests** and/or deviations from **intended purpose/IFU**



IVDR

National accreditation requirements



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The future of in-house developed FCM panels: CE-IVD

- It is arguable that the **combination of several mAb's** into a multicolor cocktail to serve in a specific user-defined panel **constitutes an IVD** in its own right
  - The **analytes** of the mAb's (e.g., CD3, CD4,…) are different from the panel analytes (multi-parameter immunophenotypes)
  - The **target condition** of the mAb's (e.g., hematological abnormality) is broader than the panel target condition (e.g., CLL)
- However, such mAb's have been **approved under the IVDR** already today
  - With the specific notion that they provide **little diagnostic information** on their own
  - With the recognition that they possess **no clinical performance** on their own
- Therefore, it remains our current opinion that **a cocktail of CE-marked mAb's, when used within their intended purpose, can be used within the lab as 'just another CE-IVD test'**.

The future of in-house developed FCM panels: IHT

- What if I currently run multi-color **flow cytometry panels**, consisting of self-defined **monoclonal antibody cocktails** that **cannot be regarded** as a CE-IVD test (**true IHT**)?

- **Option 1**: Switch to a **CE-IVD FCM kit**
  - For the laboratory: there will be **no change from today** to use CE-marked kits
  - As more and more ready-to-use FCM kits will become available, this will become more and more a viable option

- **Option 2**: Modify or switch to a **CE-IVD mAb cocktail**
  - For the laboratory: there will be **no change from today** to use a cocktail that is entirely composed of correctly chosen CE-marked components
  - This can be done by **carefully selecting** the mAb's of the cocktail
  - All mAb's have to be CE-marked with the **correct intended purpose**
  - Check with your manufacturer how the intended purpose will be under IVDR

The future of in-house developed FCM panels: IHT

- What if I currently run multi-color **flow cytometry panels**, consisting of self-defined **monoclonal antibody cocktails** that **cannot be regarded** as a CE-IVD test (**true IHT**)?

- **Option 3**: Keep running a **non-CE-IVD, true IHT**
  - by using
    - RUO mAb's,
    - CE-marked mAb's for a different clinical condition
    - Different specimen types than those mentioned in the IFU
    - …
  - Ensure compliance with **all requirements from Article 5.5**

- ✓ In-house tests: CE or not CE?
- ✓ **The 5 key elements of Article 5.5**
- ✓ IVDR and clinical trials

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ARTICLE 5.5

With the **exception of the relevant General Safety and Performance Requirements**, the requirements of the IVDR shall **not** apply to devices **manufactured and used only** within **EU-established health institutions** (HI), provided that **all of the following** conditions are met:

a) the devices are not transferred to another **legal entity**;

b) manufacture and use of the devices occur under appropriate **quality management systems**;

c) the HI's laboratory is compliant with **EN ISO 15189** or where applicable national provisions;

d) the HI justifies 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;

e) the HI 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;

f) the HI draws up a publicly available declaration, including [...] a declaration that the devices meet the General Safety and Performance Requirements and, where applicable, information on which requirements are not fully met with a reasoned justification therefor;

g) For class D devices, the HI draws up **documentation** that makes it possible to have an understanding of the manufacturing process and facility, the device design and performance data, and that is sufficiently detailed to ascertain that the General Safety and Performance Requirements are met. Member States may apply this provision also to class A, B or C devices;

h) the HI takes all necessary measures to ensure that all devices are manufactured in accordance with the documentation referred to in point (g); and

i) the HI reviews **experience gained from clinical use** of the devices and takes all necessary corrective actions.

Member States shall retain the right to restrict the manufacture and use of any specific type of such devices and shall be permitted access to inspect the activities of the health institutions.

This paragraph shall not apply to devices that are manufactured on an **industrial scale**.

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Timelines

NON-COMMERCIAL under ARTICLE 5.5 EXEMPTION

- GSPR conformity
- One legal entity
- No industrial scale

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5 key elements of Article 5.5 – GSPR

- **General Safety and Performance Requirements (GSPR) = IVDR Annex I**
  - Lists all the mandatory **regulatory requirements**, except those related to the implementation and use of the assay
    - **General Requirements** (§1 - §8): describes the establishment of a **risk management system** and the regular update of the **benefit-risk ratio assessment**. (Risks = not only patient risks but also to risks to the users, as well as to risks related to use error)
    - **Requirements regarding performance, design and manufacture** (§9 - §19): in the context of in-house IVD's, these requirements are also crucial to justify performance versus commercial products
    - **Requirements regarding Information Supplied with the Device** (§20): in the context of in-house IVD's, particularly operating instructions/protocols, information on substances or mixtures which may be considered as being dangerous, expiry or production dates of the manufactured devices or batches, storage and handling conditions, the lot/serial number or an equivalent means of identification for traceability purposes

5 key elements of Article 5.5 – EU health insitutions

- **Devices manufactured and used only within EU health institutions**:
  - **Manufactured**:
    - produce an IVD test from raw materials, from parts or components of an IVD test
    - combine an IVD test with another test or another product to produce a new IVD test
    - modify an existing IVD test in order to create a new IVD test
  - **EU Health institution**: an EU-based organisation with as primary purpose the care or treatment of patients or the promotion of public health
    - This includes **hospitals** as well as **(private) laboratories** and public health institutes that support the health care system and/or address patient needs, but which do not treat or care for patients directly
    - This does not include e.g., **CRO conducting laboratory component of clinical trials**
    - HI established outside the EU cannot seek exemption under Art. 5.5

ARTICLE 5.5

With the **exception of the relevant General Safety and Performance Requirements**, the requirements of the IVDR shall **not** apply to devices **manufactured and used only** within EU-established **health institutions** (HI), provided that **all of the following** conditions are met:

a) the devices are not transferred to another **legal entity**;

b) manufacture and use of the devices occur under appropriate **quality management systems**;

c) the HI's laboratory is compliant with **EN ISO 15189** or where applicable national provisions;

d) the HI justifies 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;

e) the HI 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;

f) the HI draws up a publicly available declaration, including [...] a declaration that the devices meet the General Safety and Performance Requirements and, where applicable, information on which requirements are not fully met with a reasoned justification therefor;

g) For class D devices, the HI draws up **documentation** that makes it possible to have an understanding of the manufacturing process and facility, the device design and performance data, and that is sufficiently detailed to ascertain that the General Safety and Performance Requirements are met. Member States may apply this provision also to class A, B or C devices;

h) the HI takes all necessary measures to ensure that all devices are manufactured in accordance with the documentation referred to in point (g); and

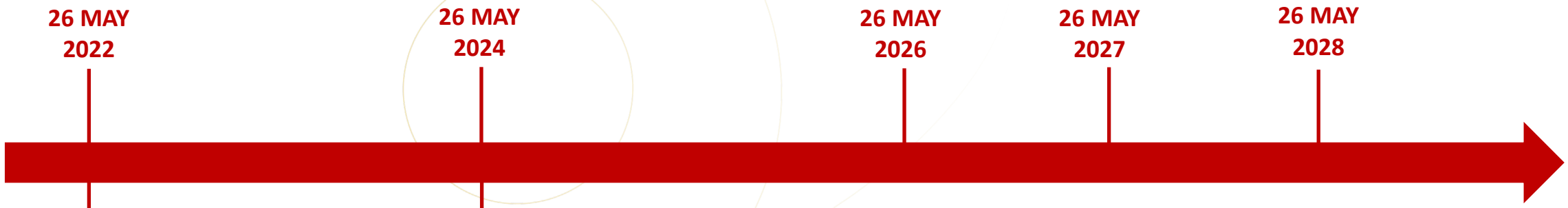
i) the HI reviews **experience gained from clinical use** of the devices and takes all necessary corrective actions.

Member States shall retain the right to restrict the manufacture and use of any specific type of such devices and shall be permitted access to inspect the activities of the health institutions.

This paragraph shall not apply to devices that are manufactured on an **industrial scale**.

Timelines

NON-COMMERCIAL under ARTICLE 5.5 EXEMPTION



- GSPR conformity
- One legal entity
- No industrial scale

- EN ISO 15189 compliance
- Manufacture under appropriate QMS
- Declaration of GSPR conformity
- Technical documentation
- Information to Competent Authority
- Review clinical experience

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5 key elements of Article 5.5 – Quality management systems

- **Manufactured and used** under appropriate **quality management systems**

5 key elements of Article 5.5 – Quality management systems

- **Manufactured and used** under appropriate **quality management systems**
  - Compliance with **EN ISO 15189:2013** (or **EN ISO 15189:2022**) is understood as having an appropriate QMS for the use of in-house IVD tests
  - But compliance with **EN ISO 15189 alone does not constitute an appropriate QMS** for the manufacture of in-house IVDs. Not in scope of EN ISO 15189 is:
    - IVD assay design & manufacturing, compliance with GSPR, assay-specific risk management
  - An appropriate QMS could mean **EN ISO 15189**, **supplemented** with the relevant sections from industry standards
    - The **extent to which** EN ISO 15189 should be supplemented depends on the **degree of manufacturing involved**
    - E.g., use of an **RUO kit** (no real manufacturing) versus **development of a novel FCM panel** consisting of RUO and/or in-house produced antibodies, and in-house buffers (true manufacturing)
    - But GSPR and assay-specific risk management must always be included
    - EN ISO 14971 is the international standard for medical device risk management
    - IVDR Article 10.8 describes the minimal aspects for a manufacturing QMS

5 key elements of Article 5.5 – Technical documentation

- **Technical Documentation** requirements
  - **Class D only??** → *Member States may apply this provision also to class A, B or C devices*
  - **But:**
    - HI must be prepared to provide detailed information to the CA at all times
    - Manufacturing QMS requires a documented approach for GSPR compliance, design and manufacturing process, risk management, performance evaluation, justification for Article 5.5 exemption, traceability and review of experience gained from clinical use
  - In practice, the HI is forced to build – at least to some extent – a **Technical Documentation for each IHT**, as part of the strategy for regulatory compliance

ARTICLE 5.5

With the **exception of the relevant General Safety and Performance Requirements**, the requirements of the IVDR shall **not** apply to devices **manufactured and used only** within EU-established **health institutions** (HI), provided that **all of the following** conditions are met:

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b) manufacture and use of the devices occur under appropriate **quality management systems**;

c) the HI's laboratory is compliant with **EN ISO 15189** or where applicable national provisions;

d) the HI justifies 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;

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Member States shall retain the right to restrict the manufacture and use of any specific type of such devices and shall be permitted access to inspect the activities of the health institutions.

This paragraph shall not apply to devices that are manufactured on an **industrial scale**.

Timelines

NON-COMMERCIAL under ARTICLE 5.5 EXEMPTION

26 MAY 2022

- GSPR conformity
- One legal entity
- No industrial scale

26 MAY 2024

- EN ISO 15189 compliance
- Manufacture under appropriate QMS
- Declaration of GSPR conformity
- Technical documentation
- Information to Competent Authority
- Review clinical experience

26 MAY 2026

26 MAY 2027

26 MAY 2028

Justification:
No commercial alternative

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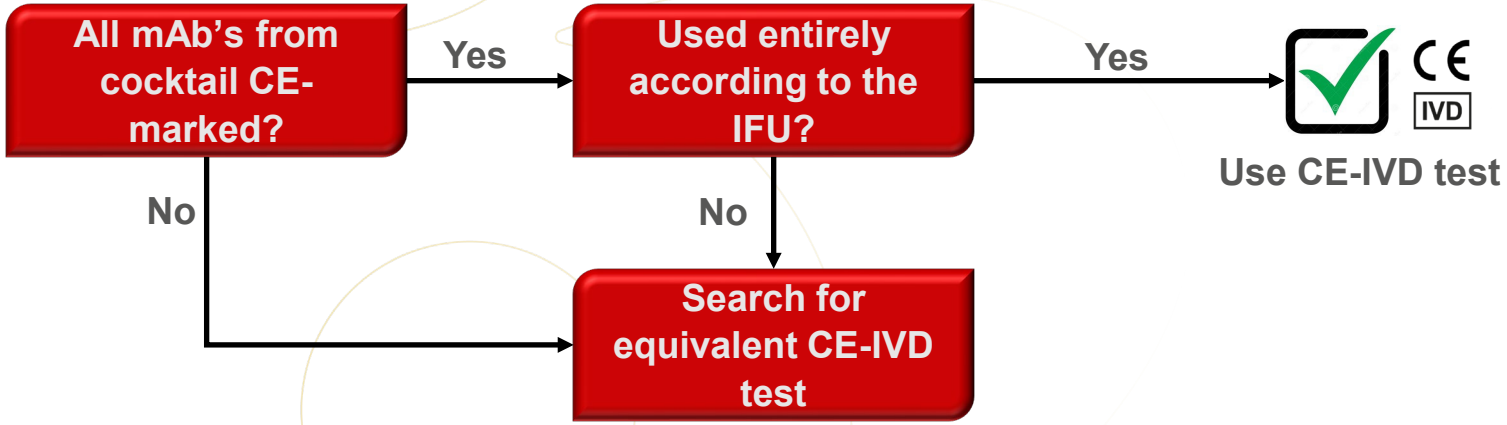
5 key elements of Article 5.5 – Equivalent device performance



- **Equivalence** should be understood as sharing the same technology (FCM) and the same main elements of their intended purpose
  - It is not necessarily the same combination of **antigen markers** or the **instrument** with which it is intended to run
  - Rather, equivalence will be determined primarily by the **medical purpose** and the **target patient** group
  - Therefore, an **FCM kit** used for the same medical purpose within the same target patient groups will be considered as an equivalent device for the lab-developed FCM panel

5 key elements of Article 5.5 – Equivalent device performance

- Information on **equivalent** **devices** and their **performance** can be found in the **Instructions for Use** **(IFU)** of **similar** **antibodies** and of **kits**, **similar** **to your FCM assay**

  - **Intended Purpose**
  - **Performance Data**

5 key elements of Article 5.5 – Equivalent device performance

- Information on **equivalent devices** and their **performance** can be found in the **Instructions for Use (IFU)** of **similar antibodies** and of **kits**, **similar to your FCM assay**
  - **Intended Purpose**: provides the laboratory the **specific context** in which to use the product
    - For in vitro diagnostic purpose (as opposed to research use only)
    - For **what diagnostic purpose**: (aid in) diagnosis, prognosis, prediction,…
    - In **which clinical or physiological condition**: target patient groups
    - With **which specimen**: blood, bone marrow, tissue,…
    - On **which instrument**: strictly defined or open platform
    - By **which user**: laboratory professional, training level

5 key elements of Article 5.5 – Equivalent device performance

- Information on **equivalent devices** and their **performance** can be found in the **Instructions for Use (IFU)** of **similar antibodies** and of **kits**, **similar to your FCM assay**

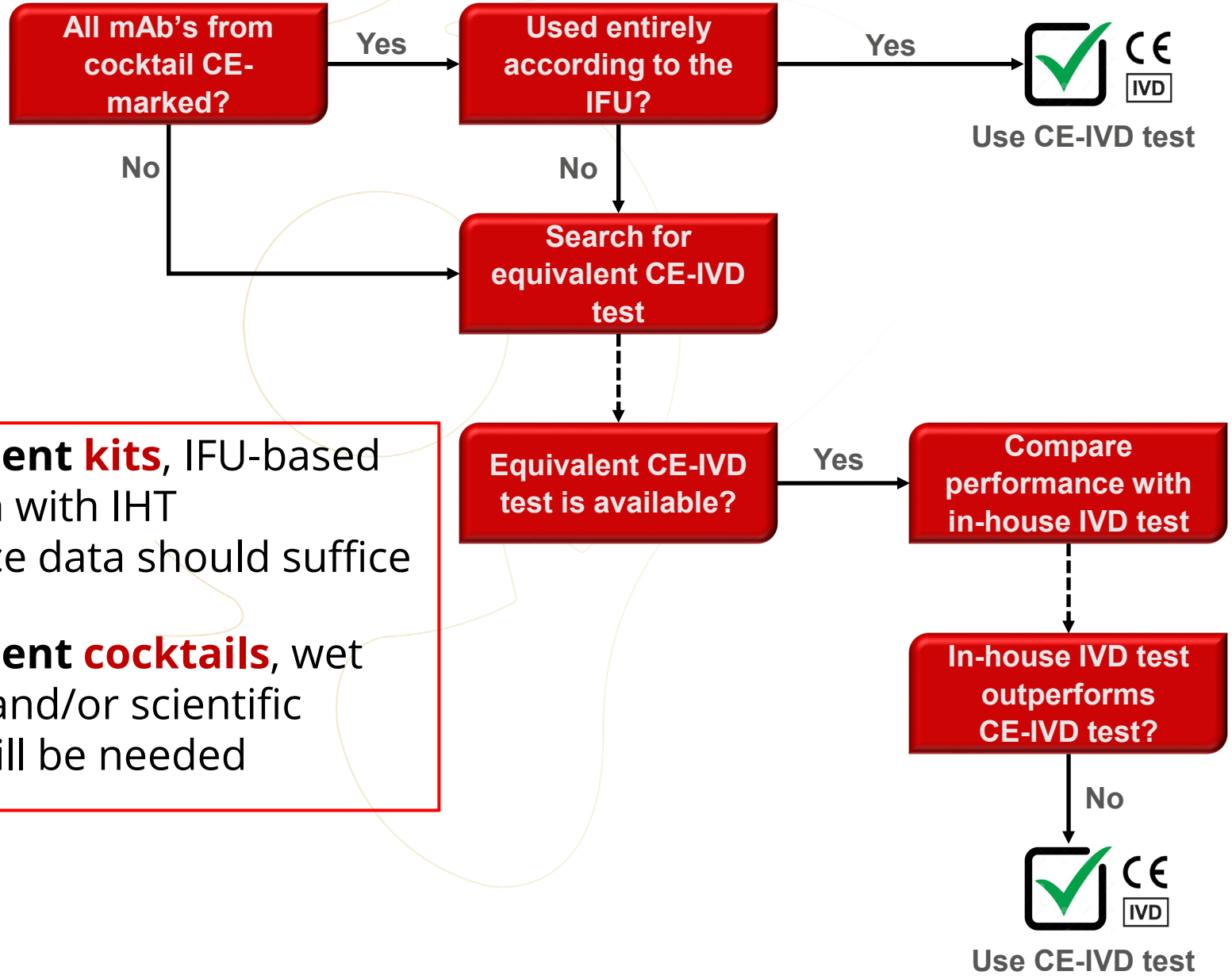
  - **Performance Data**: provides the laboratory the **expected performance** of the product

    - All applicable performance characteristics should be addressed by the manufacturer

    - **Analytical Performance**: precision, detection capability, analytical specificity, interference, measuring range, specimen stability,…

    - **Clinical Performance**: diagnostic sensitivity and specificity, positive and negative predictive value, expected values,…

5 key elements of Article 5.5 – Equivalent device performance



- For **equivalent kits**, IFU-based comparison with IHT performance data should suffice
- For **equivalent cocktails**, wet lab testing and/or scientific literature will be needed

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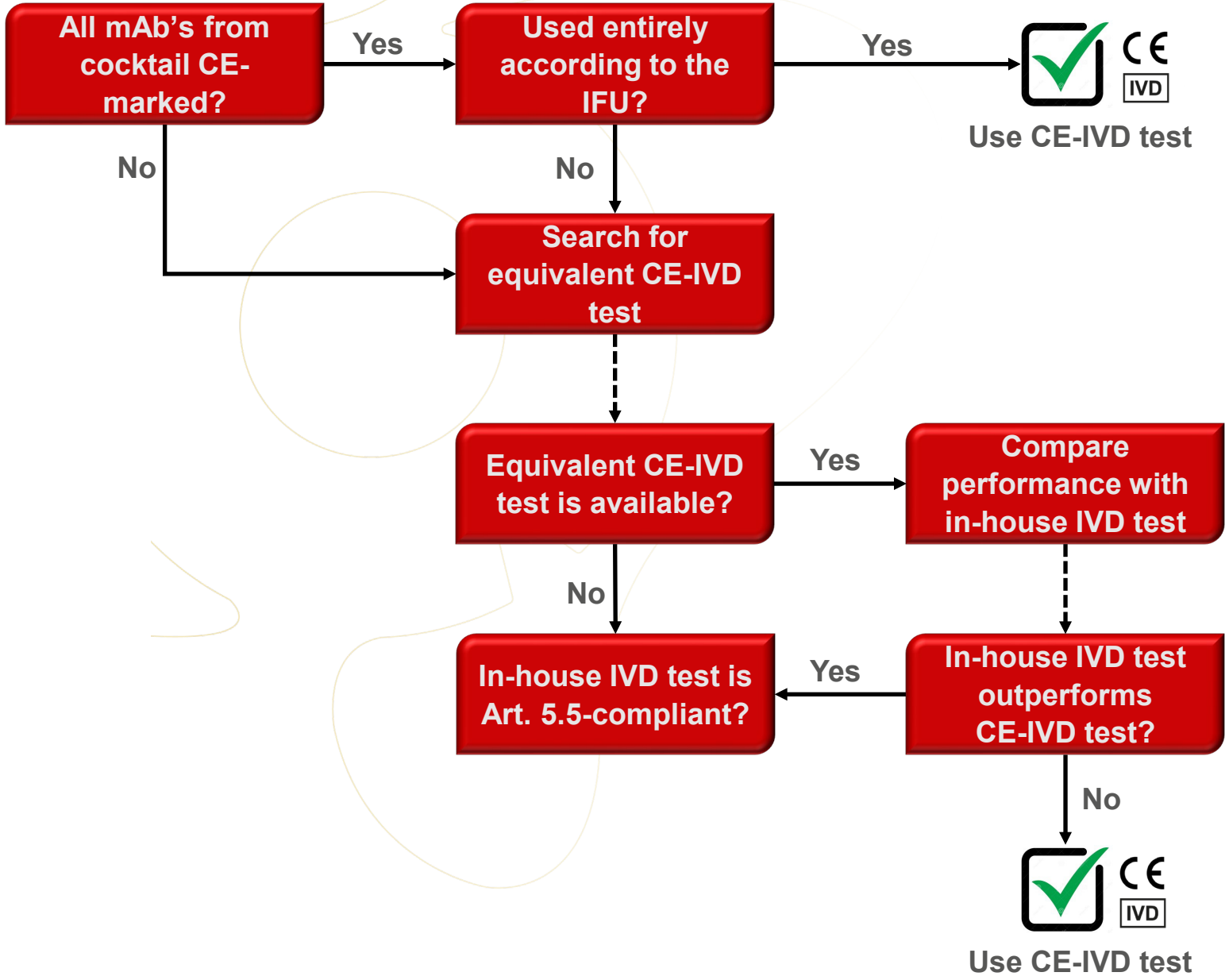
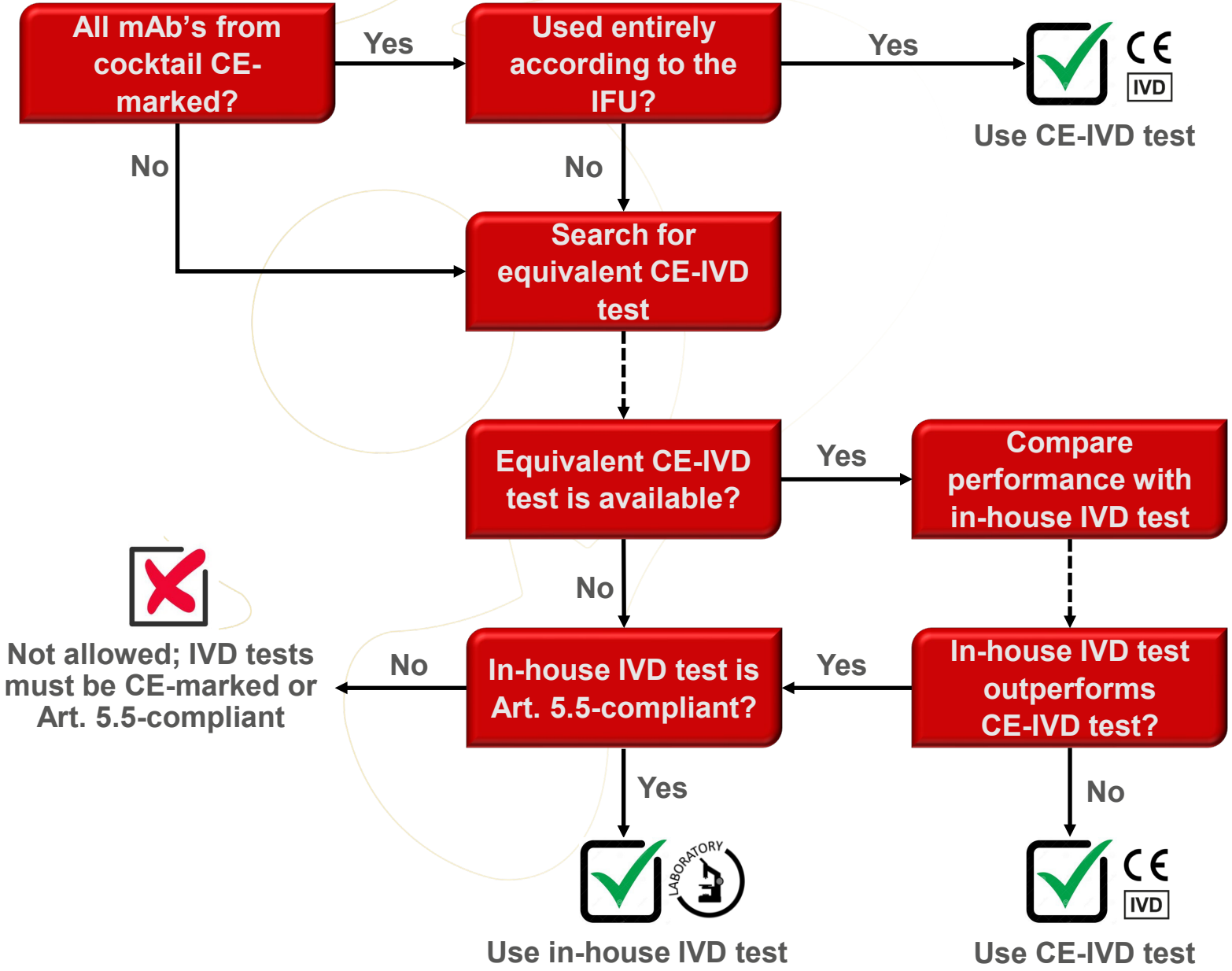
5 key elements of Article 5.5 – Equivalent device performance



5 key elements of Article 5.5 – Equivalent device performance



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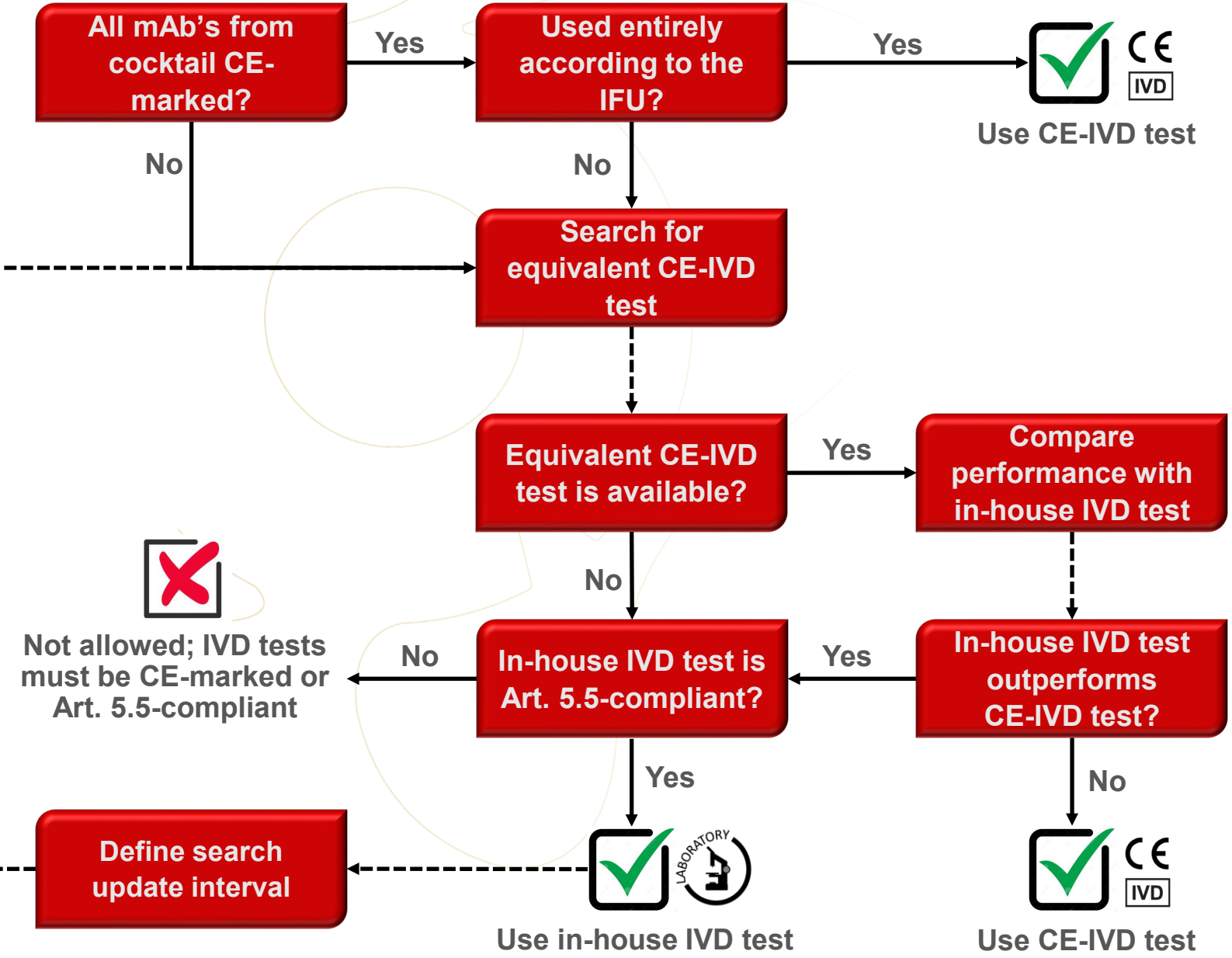

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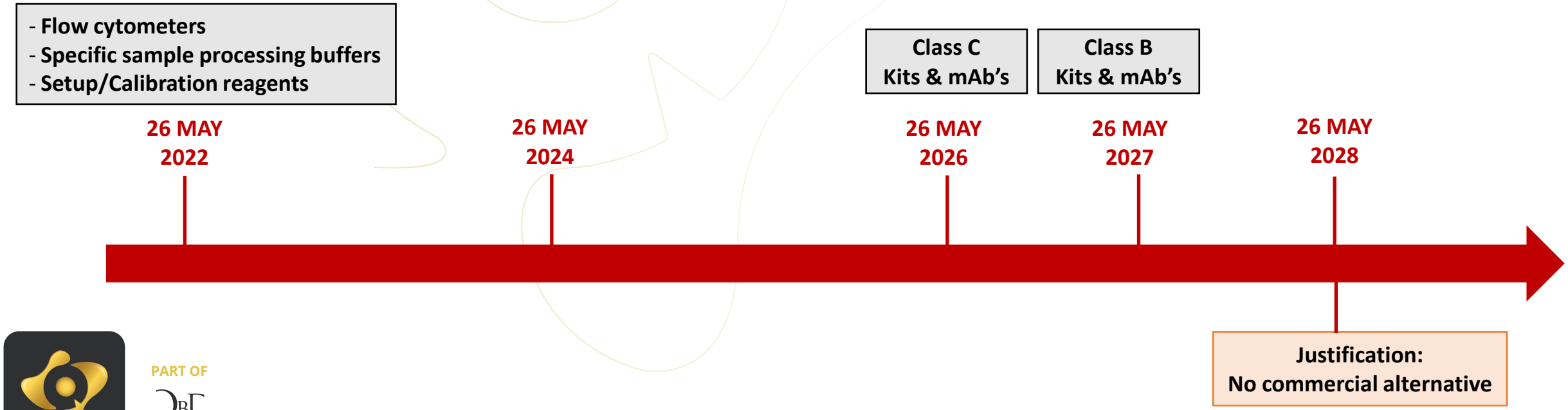
5 key elements of Article 5.5 – Equivalent device performance

- Information on **equivalent devices** and their **performance** can be found in the **Instructions for Use (IFU)** of **similar antibodies** and of **kits**, **similar to your FCM assay**

  - But **not all manufacturers** have certified their products already under the IVDR
    - Intended purpose may still change/be fine-tuned
    - Not always all performance data available in pre-IVDR IFU
    - IVDR-approved kits & mAb's: look for 4-digit number next to CE-mark e.g., CE 2797



Article 5.5 is not a revolution…

- **IVDR Article 5.5** is certainly **not a free pass** for laboratory developed IHT
  - For **any** laboratory, continuing the use of IHT's with a clear diagnostic intended purpose will require a **significant effort** with additional SOPs and resulting documentation
  - Moreover, Art. 5.5 is already **partly into force**
- National **Competent Authorities** are currently organizing to **enforce** Article 5.5 compliance
- However, profound **acquaintance with EN ISO 15189** already provides a solid basis
  - The effort to comply with design and manufacturing requirements is scalable with the amount of manufacturing that is involved
- Article 5.5 does not alter the main mission of a medical laboratory, which is to focus on
  - Day-to-day **consistent performance** of assays with a **favorable benefit-risk ratio** (i.e. ensuring the **patient is not exposed to any unacceptable risk**)

- ✓ In-house tests: CE or not CE?
- ✓ The 5 key elements of Article 5.5
- ✓ **IVDR and clinical trials**

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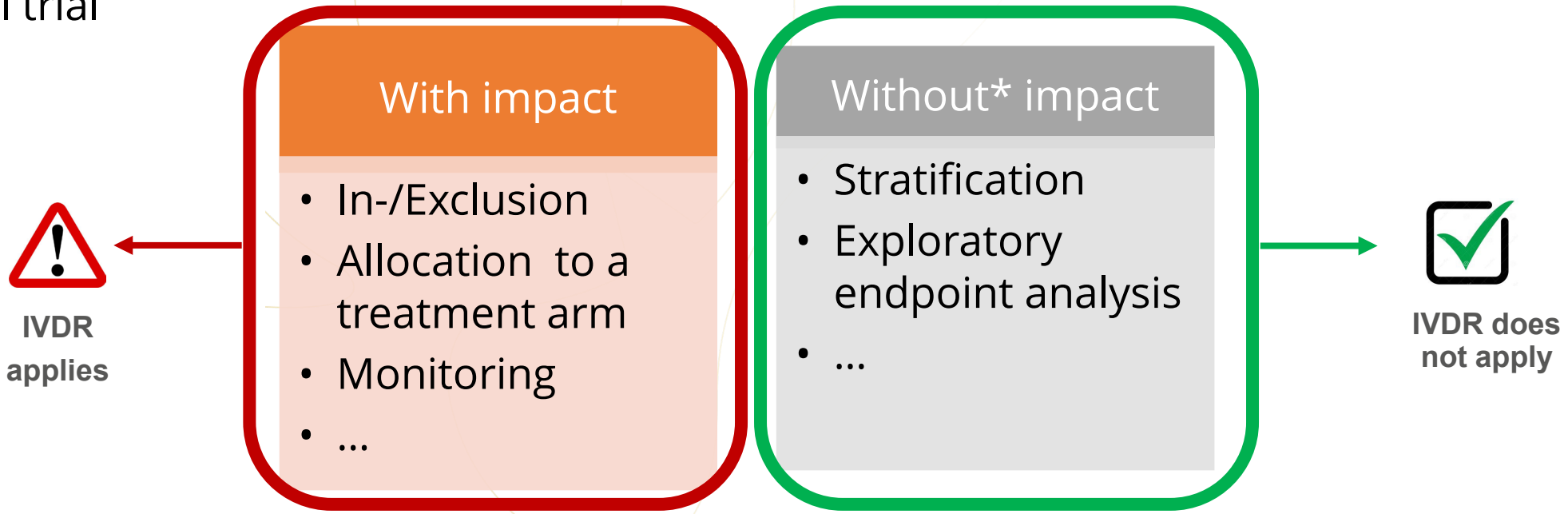
Lab tests in clinical trials

- IVDR applies to **all IVD's**, whether they are used for routine diagnostic purposes or in the context of clinical trials
  - But *not all lab tests are considered IVD's* in the context of clinical trials
- Typically, lab tests in clinical trials serve **different purposes**
  - Inclusion/exclusion
  - Safety monitoring
  - Primary/secondary endpoint
  - Exploratory endpoint
  - Development of a companion diagnostic (CDx)
- They typically have also **different regulatory characteristics**
  - Commercially available, **CE-marked tests** (**routine**, high throughput)
  - Not commercially available, **non-CE marked tests** (**in-house developed tests**, esoteric tests)
  - Tests under for **performance evaluation** (**biomarker** exploration, **CDx** development)

IVDR and clinical trials

- Is the lab test an **IVD in the context of a clinical trial**?
  - If the test has a **medical purpose**, **and** the result of the assay has an **impact on the medical management of the patient** which specimen has been analyzed, **then** the test is considered an *IVD in the context of the clinical trial*

- IVDR applies **only** to **lab tests that fulfill the definition** of an IVD in the context of the clinical trial



*When all trial participants are tested irrespective of treatment arm or medical management and the analysis of impact is conducted retrospectively and where medical management is not impacted by assay results

Article 5.5 and clinical trials

- **Typically, Article 5.5 will apply to assays used in clinical trials when**
  - The assay is **made and used by an EU Health Institution**
    - If not, Article 5.5 cannot be used
  - **AND**
  - The assay is **developed specifically** for the trial, OR
    - Specific novel biomarker of interest
    - Potential CDx
  - The assay is **available only as RUO**, OR
  - The assay is **not intended for the specimen** type analyzed in the clinical trial
  - **AND** the assay **results are used for medical decision** taking on subjects enrolled in the trial
  - These **in-house tests** can either be:
    - Fully pre-validated by the laboratory ('on-the-shelf' specialty assay), OR
    - Partly validated (analytical performance) by the laboratory at the start of the trial

Regulatory aspects of IHT used for trial subject management

- If the IHT is **available** **'on the shelf' before the start** of the clinical trial i.e., the lab has fully **validated the performance** of the assay
  - **Analytical performance**
    - Evidence that the assay correctly detects the analyte(s) of interest
      - Analytical specificity, trueness (bias), precision (repeatability and reproducibility), limits of detection and quantitation, measuring range, linearity, interference, …
  - **Clinical performance**
    - Evidence that the assay establishes correct results with regards to the clinical condition of the patient
      - Diagnostic sensitivity & specificity, positive predictive value, negative predictive value, likelihood ratio, expected values,…
- Then the IHT is subject **only** to **IVDR Article 5.5** during the clinical trial
  - Requirements to be met by laboratories in order to use non-CE marked assays for medical decision taking

Regulatory aspects of IHT used for trial subject management

- **Analytical performance** must **always** be established **before** using an assay for medical decision taking

- If the lab did **not** validate the **clinical performance** of the IHT **before the start** of the clinical trial
  - **Clinical performance** validation may not have been possible prior to analyzing trial subjects samples

- Then the IHT is a '**device for interventional performance study**' during the clinical trial
  - Subject to **IVDR Article 5.5**: requirements to be met by laboratories in order to use non-CE marked assays for medical decision taking
  - Subject to **IVDR Articles 57 & 58**: requirements to be met in order to conduct interventional performance studies)

Device for performance study in clinical trials

- **Clinical performance studies in clinical trials**
  - Lab test is an IVD in the context of clinical trials when used for **patient management decisions**
    - This is **interventional use**, with a risk of indirect harm for the subject
    - Clinical performance not yet established: required to do a **performance study**
    - → **Interventional performance studies**
      - These **require application for authorization** by **Competent Authorities**
      - The study (and the clinical trial) can only start after study authorization
    - **Specific case:** clinical performance study during development of **companion diagnostic**
      - If study is performed **retrospectively** (e.g., to confirm stratification) using **only left-over** samples
        - CDx assay is still **device for performance evaluation → CA notification**
      - If study results are used for **patient management** e.g. allocation to study treatment arm
        - **Application for authorization by CA**

Device for performance study in clinical trials

- **What about non-CE marked assays run outside of the EU?**
  - E.g., specialty tests performed by CLIA labs
  - IVDR applies when used on European clinical trial subjects
  - But Article 5.5 exemption is not possible
  - **‘Device for performance study’ is the only option left**
  - A clinical performance evaluation study must be designed
  - The clinical performance study must be authorized prior to start

Thank You!

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