CDDF WORKSHOP

25 - 26 April 2022

HYBRID WORKSHOP

Measurable Residual Disease (MRD) and Circulating Tumour Nucleotides (ct DNA) in cancer drug development

IVDR –
Industry perspective

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Disclaimer

- Roche employee

Opinions expressed are solely my own and do not express the views or opinions of my employer

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Introduction- goal of today

- Bring awareness to academia, patients, caregivers, patient advocacy groups, industry and regulators of the need for guidance and clarification related to the **European In Vitro Diagnostic Regulations (applicable 26 May 2022**).

- Raise awareness of **new requirements for** In Vitro Diagnostics:
  - An increasing number of medicines authorised in Europe recommend or require biomarker-based patient selection.
  - For some the use of a **companion diagnostic (CDx),** a subset of in vitro diagnostics (IVDs), to identify patient populations eligible for a specific medicinal product is required.

Changes introduced with In Vitro Diagnostic Regulation 2017/746

- New risk-based classification system
- Definition of Companion Diagnostics introduced
- Performance Evaluation/ interventional clinical performance study introduced
- In house tests in scope
- Consultation procedure EMA-Notified bodies
- Transparency via EUDAMED for patients and caregivers

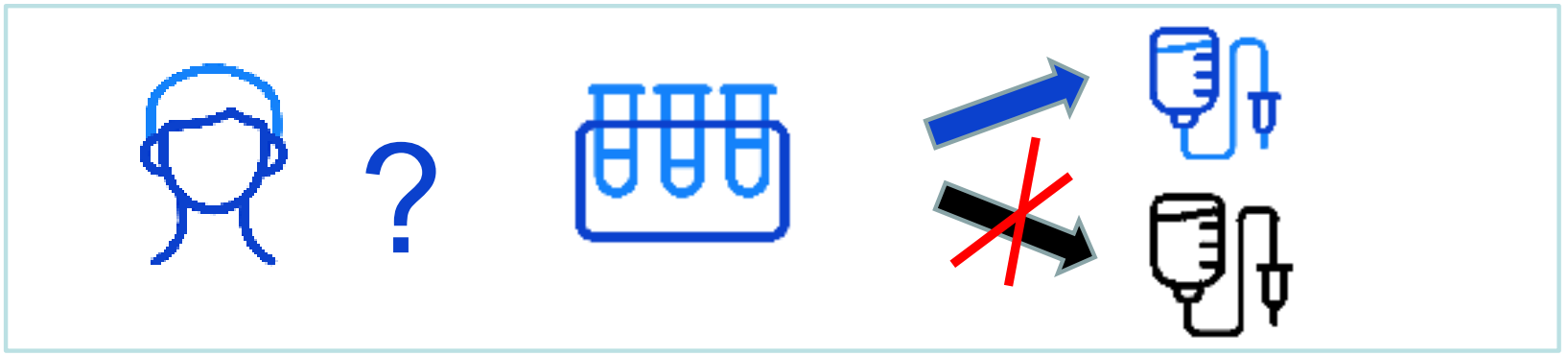
Right intent of the IVDR: To ensure patients are treated based on high quality IVDs!

New risk-based classification system introduced

Class*	Description	Examples	NB?
A	Low individual risk and low risk to public health	General lab supply, media, sample containers	No
B	Moderate individual risk and/or low risk to public health	Pregnancy self-tests, urine test strips, Vitamine B12	Yes
C	High individual risk and/or medium risk for public health	HLA typing, PSA, Rubella, Cancer diagnostics, -staging, **CDx**	Yes
D	High individual risk and high risk for public health	Blood donor screening (HIV/HCV), blood grouping (A,B,O)	Yes

*- Classification is done by the manufacturer based on rules set forth in IVDR Annex VIII
- The classification defines the applicable conformity assessment route (=what needs to done for CE-marking)
- A Notified Body must be involved, except for Class A IVDs for ALL existing and new IVDs
- CDx require additional review by EMA

New definition companion diagnostics introduced

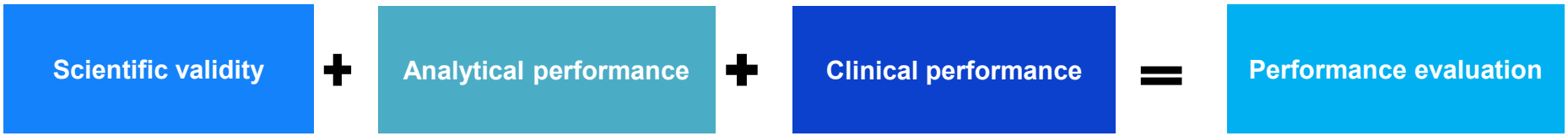


CDx: 'companion diagnostic' means a device which **is essential for the safe and effective use of a corresponding medicinal product** to:

- identify, before and/or during treatment, patients who are **most likely to benefit** from the corresponding medicinal product; or
- 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

Performance evaluation

IVDR Art. 2 (41)
“clinical performance” means the ability of a device to yield results that are **correlated** with a particular **clinical condition** or a physiological or **pathological process** or state in accordance with the target population and intended user



IVDR Art. 2 (46)
“**interventional** clinical performance study” means a clinical performance study **where the test results may influence patient management decisions and/or may be used to guide treatment**

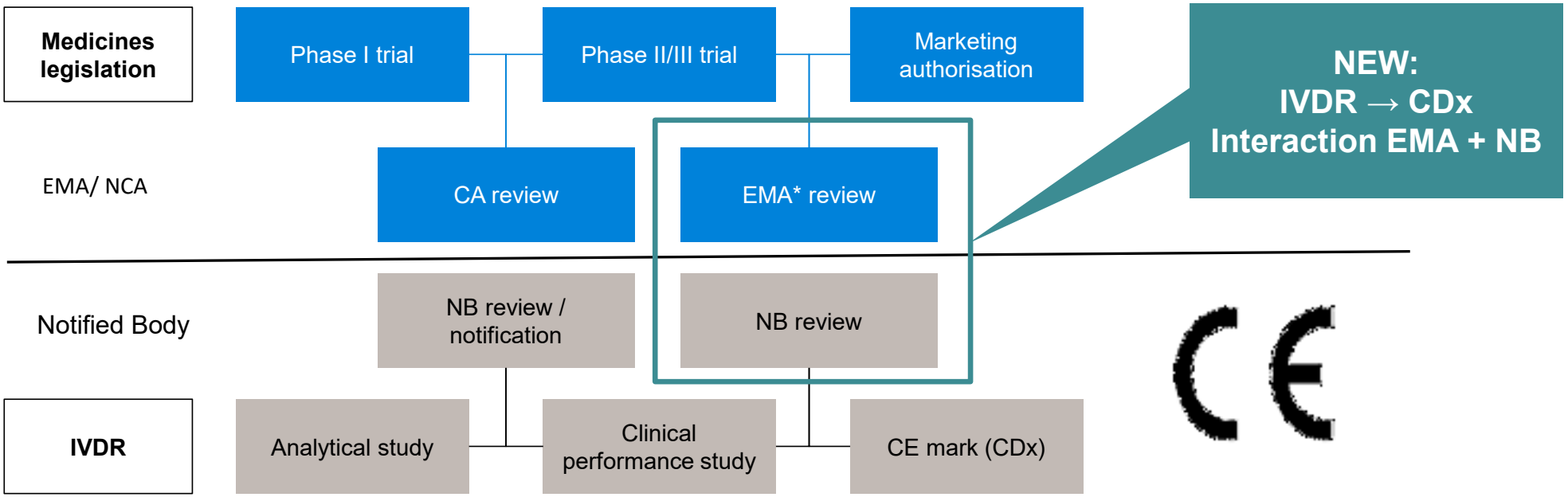
IVDR-consultation procedure

According to the IVDR (Annex IX, Section 5.2), the conformity assessment process for CDx foresees a **consultation procedure** between a **Notified Body and a Medicine Authority**. This consultation could take place between an EU National Competent Authority or the EMA.

The Competent Authority Involvement **is a significant departure from the current directives (IVDD)**; to date, the interaction between medicines authorities, EMA and notified bodies has been limited to consultation procedures of devices that incorporate a medicinal substance.

IVDR-consultation procedure

Dialogue to be established between medicine authorities, device authorities and Notified Bodies on establishing the details of the consultation procedure:



*Centralised Procedure

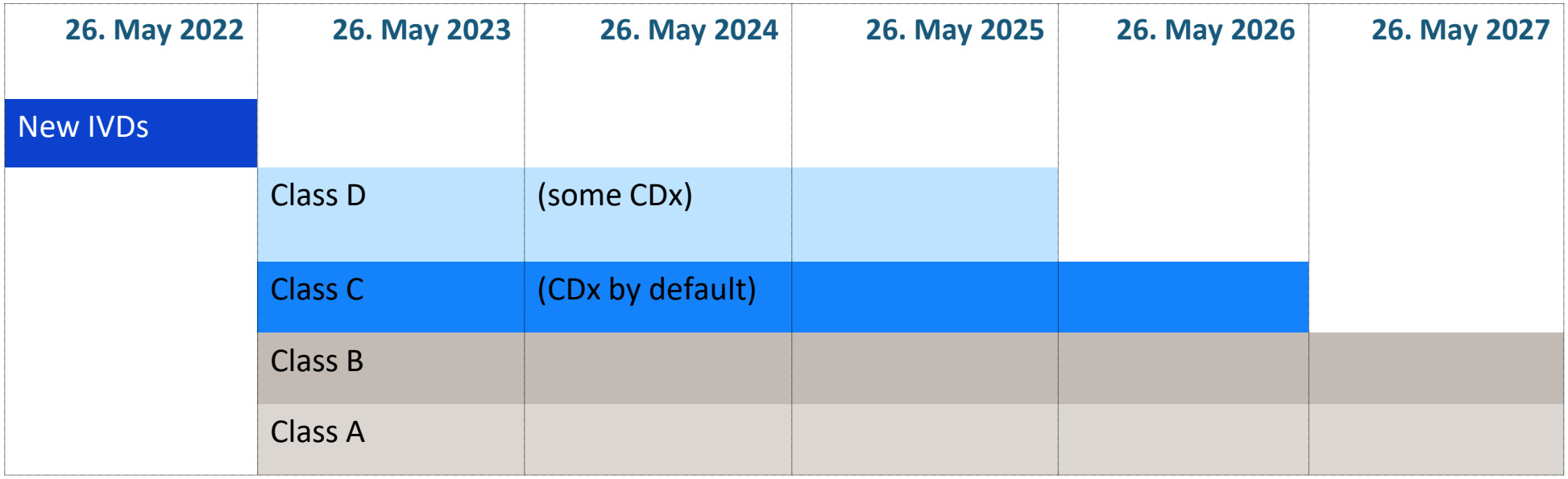
IVDR – Amendment: application timelines

- Date of Application: May 26th 2022 **but:**

- In October 2021, the European Commission **amended the IVDR** to allow for a progressive roll-out of the IVDR.

- The amending Regulation **does not change any requirements** of the original IVDR of 2017. It only changes the dates of application of some of these requirements for certain medical devices.

IVDR – Amendment: application timelines

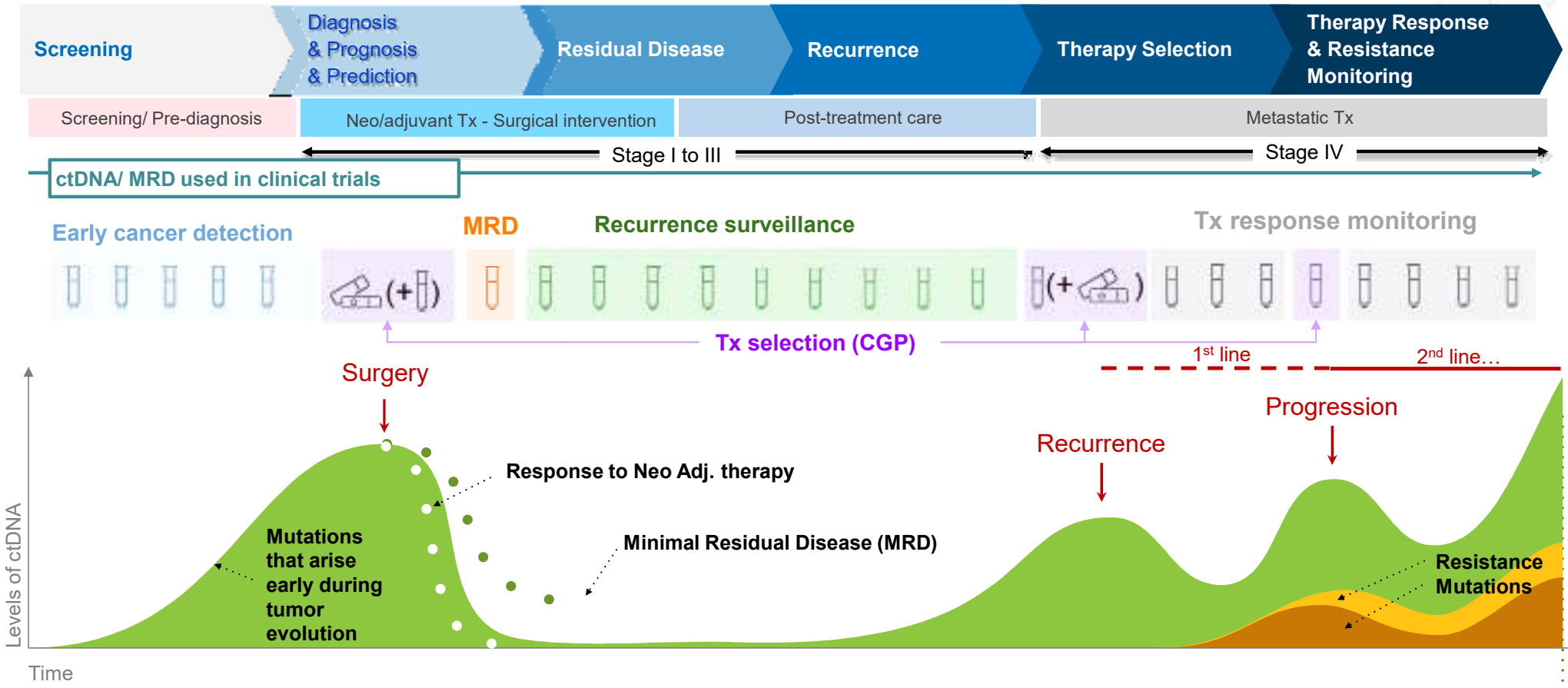


Prerequisites for extended timelines are that the manufacturer:

- A declaration of conformity according to IVDD is/ was issued before May 26, 2022
- Will not introduce any significant changes to the design, manufacture or intended purpose
- Established post-market surveillance (Articles 78-81, Annex III) and vigilance (Articles 82-87) according to the IVDR
- Registers in EUDAMED according to the IVDR

IVDR – link to ctDNA tests- MRD

Role of ctDNA tests during the patient journey



Adapted from Wan et al. Nature Reviews Cancer. Apr 2017
Theoretical concept. Requires clinical validation.

ctDNA test classification?

CDx vs. «other» IVD, depends if definition of CDx is fulfilled

EU - US

Definition Companion Diagnotsic	
Device which is essential for the safe and effective use of a corresponding medicinal product	Device which essential for the safe and effective use of a corresponding therapeutic product.
Identify patients who are most likely to benefit	Identify patients who are most likely to benefit from the therapeutic product
Identify patients likely to be at increased risk of serious adverse reactions	Identify patients likely to be at increased risk for serious adverse reactions
-	Monitor response to treatment with the therapeutic product for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness

Not all ctDNA (MRD) test will be classified as CDx

IVDR – summary impact

IVDR – Change of classification

EU IVDD	IVDR	Impact	Un-knowns
Self-certification	CDx Class C	Increased regulatory control	Pre-submission alignment manufacturer-NB-EMA?
Low risk	High Risk	NB review of technical dossier	Resolution of disagreement?
		CDx: EMA/ CA- NB involved: consultation procedure	EMA involvement performance evaluation plan?
			SmPC CDx wording?

IVDR – Clinical evidence & performance evaluation

EU IVDD	IVDR	Impact	Un-knowns
Annex VIII	Chapter IV significant & detailed requirements	Increased clinical evidence required for application (& review)	No alignment of "amount" of data clinical evidence is required?
Section 3	Carried out in compliance with Annex VIII	Detailed performance evaluation	Definition significant change ?
		General Safety and Performance Requirements needs to be met	CTA* CTR-IVDR-link?

*Clinical Trial Applications (CTAs):

- Complex approval process for CTAs using CDx (e.g. 2 submissions are required, one drug application, one IVD application).
- There is a high risk that CTAs will be delayed, and potentially may not be conducted in Europe (further challenges with the CTA process with relation to the rollout of the CTR and use of the CTIS portal)

IVDR – In-house tests- developed & used in hospital setting

EU IVDD

In house test completely exempt

IVDR

Exempt except….
Art 5 (5)

Impact

Annex I-GSPR* apply

Justification needed for pts needs

Member States may require tech dossiers for in house Class C (incl. CDx)

Impact on centralised model for personal therapies

Un-knowns

Which institutions will be able to meet the definitions?

Degree of justification pts needs?

Ability of labs to comply with the requirements?

*General Safety and Performance Requirement

IVDR – Requirements for Medicine Authority Review

EU IVDD	IVDR	Impact	Un-knowns
Self certification (no 3rd party review)	EMA/CA involved in conformity assessment	60-day for medicine authority to provide an opinion	Pre-alignment* procedure between stakeholders (manufacturers-NB- EMA)?
		+ additional 60 days with "justification"	Resources/* Expertise?
		Consultation needed in case of siginficant changes to the CDx	Consultation process*- NB-EMA (organizational steps)?

*There is a high risk of delay of Marketing Authorization Approvals for medicine using CDx due to consultation procedure and limited Notified Body/ EMA/NCA resources.

IVDR – expected challenges Notified Body ressources

- The implementation of IVDR, has created a situation where there is **a shift in the number of organizations requiring Notified Body (NB) review**.
- It has been assessed that where 20% of IVD manufacturers went through a NB review under the IVDD, **90% of IVD manufacturers will require NB** review under the IVDR.
- Adding to this complication, the number of NBs able to provide CE-marking for IVD product has been reduced due to the requirements for accreditation under the IVDR: There were approximately 30 NBs that would provide CE Mark from the IVDD; now, there **are only six NBs accredited under the IVDR.**

IVDR- Potential Impact on patients- on innovation

- The IVDR sets high standards of quality, safety and reliability to safeguard patients and enhance innovation. +

- Potential delay of initiation of clinical trials within the European Union for oncology products requiring a companion diagnostic due to uncertainties: -?
  - how will CTR embed the IVDR (IVDR date of application only 5 months after CTR!) -?
  - complex process performance evaluation submission
    (sponsors could start to look outside EU for clinical trial sites)
- Potential delays of patient treatments due to complex situation related to in-house tests -?
- Potential delays of registration of new medicines within the European Union which require a companion diagnostic (NB consultation?) -?

More guidance from EMA/ EC is needed for the use of biomarker especially during drug development (simplify processes).

Thank you very much for your attendance

Questions?

Acronyms

CA	Competent Authority
CDx	Companion Diagnostic
CTA	Clinical Trial Application
CTIS	Clinical Trials Information System
CTR	Clinical Trial Regulation
EMA	European Medicines Agency
EUDAMED	European Database on Medical Devices
IVDD	In Vitro Diagnostic Directive
IVDR	In Vitro Diagnostic Regulation
GSPR	General Safety and Performance Requirement
NB	Notifed Body
NCA	National Competent Authority
SmPC	Summary of Product Characteristics