STATE OF THE ART
Dispositifs médicaux de diagnostic *in vitro* (IVDR)

Elisabeth Dequeker, Louvain, Belgique & Antoinette Lemoine, Villejuif

LINKS OF INTEREST (A. Lemoine)

- **Astra Zeneca, BMS, Amgen**
- **Membre de la commission EXPAMED pour l'évaluation des DM-DIV**
- **Membre du jury de sélection des LBMR et présidente de la commission « génétique et cancer » au Ministère**

Le règlement IVDR *(EU 746/2017)*

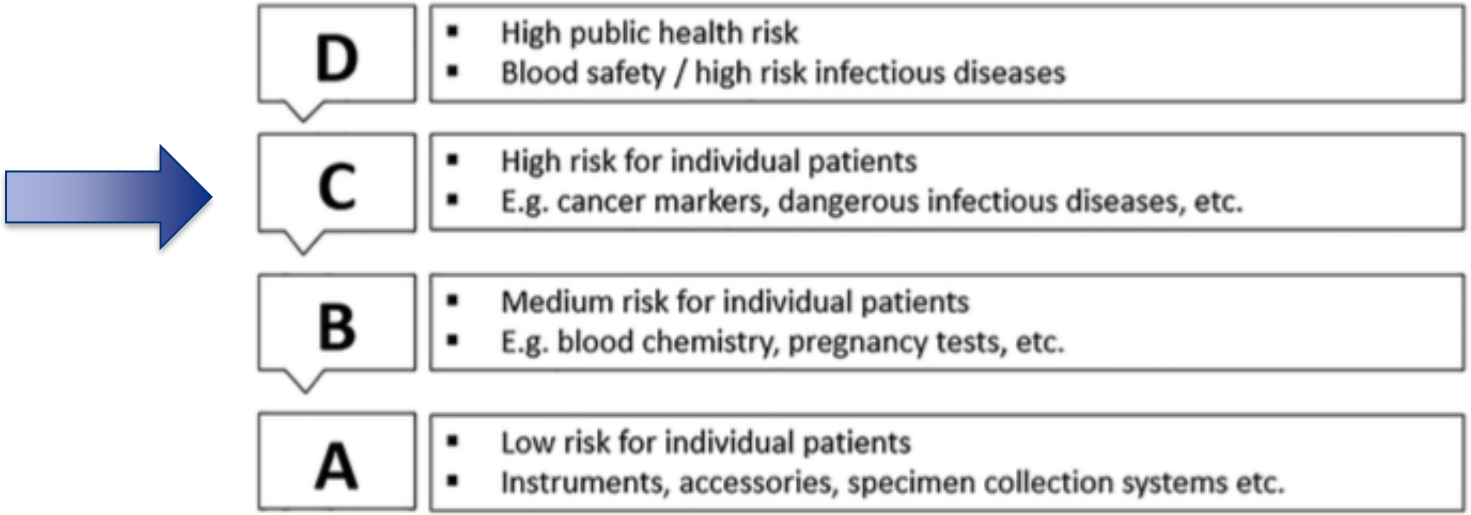
- **Le 26 Mai 2022**, entrée en vigueur du nouveau règlement européen IVDR,
  - Garantie des exigences élevées de **qualité**, **sécurité** et de **performances** des DMDIV, apportant un niveau élevé de protection de la santé
  - Cadre réglementaire rigoureux, transparent, durable, et harmonisé du marquage CE de DMDIV – marché unique en Europe

- **En juillet 2022 / Ordonnance droit français** (Texte de Loi et Annexes de 157 pages), des documents d'interprétation (Medical Device Coordination Group Document, MDCG), **d'autres documents à venir, des groupes de travail**
  -> **complexité des interprétations et mise en application**

***->. Application dans nos laboratoires* de biologie et de pathologie**
-> Impacts majeurs sur nos fonctionnements quotidiens,
-> Risques et enjeux pour l'avenir du diagnostic oncogénétique

Nouvelle classification en fonction des risques

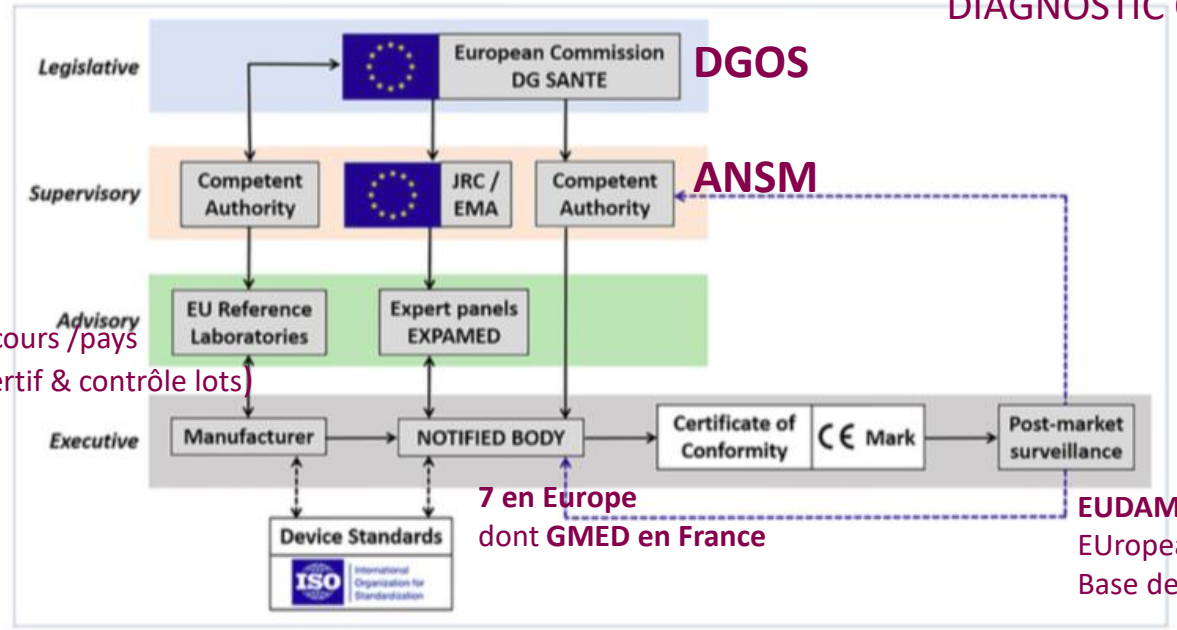
- **<u>Risque pour le patient /</u> Pas de classification par technologie :**
- **7 règles de classement**



Diagnostic oncogénétique à visée thérapeutique : **diagnostic compagnon = classe C**
(Risque vital si résultat faux)
Dans la classe C, les textes décrivent : dépistage , diagnostic, suivi des cancers, Génétique,…;

Encadrement européen des performances des DM

Place et délai
DIAGNOSTIC COMPAGNON



Appel offre en cours /pays
Classe D (1ère certif & contrôle lots)

7 en Europe
dont **GMED en France**

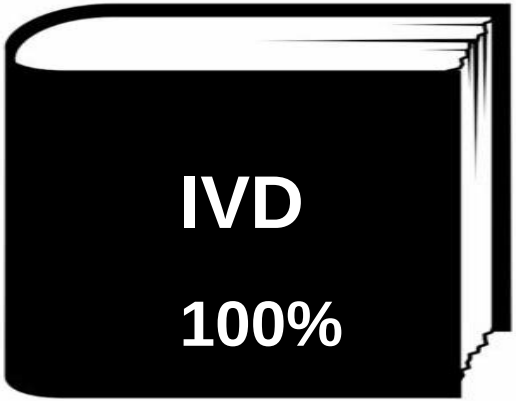
EUDAMED
EUropean DAtabase on MEdical Devices
Base de données, Q2, 2024

Nouvelles obligations pour les opérateurs économiques
(distributeurs, importateurs, mandataires, fabricants)

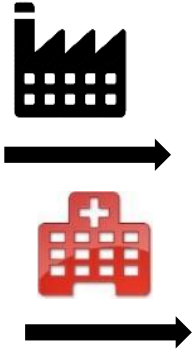
Quels impacts pour les professionnels & laboratoires ?

- **IVDD régulait les DIV commerciaux (CE-IVDs)**
- **IVDR régule CE-IVDs & LDTs/IH**

1998 – 2022
(CE-IVD
10%)



Date d'application: May 26th, 2022
Période de transition (2026-2029)

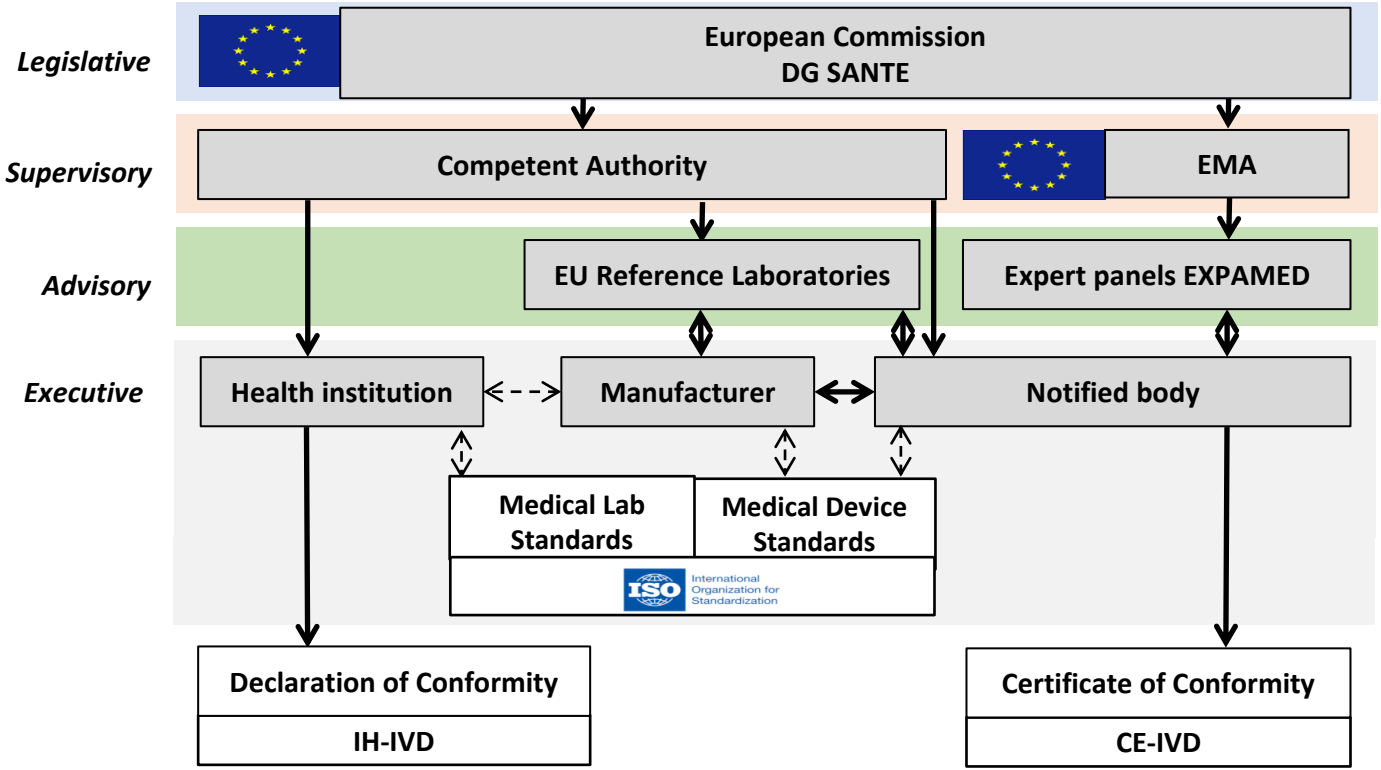


CE-IVDs

In House tests (ou LDT)
(établissements de santé)

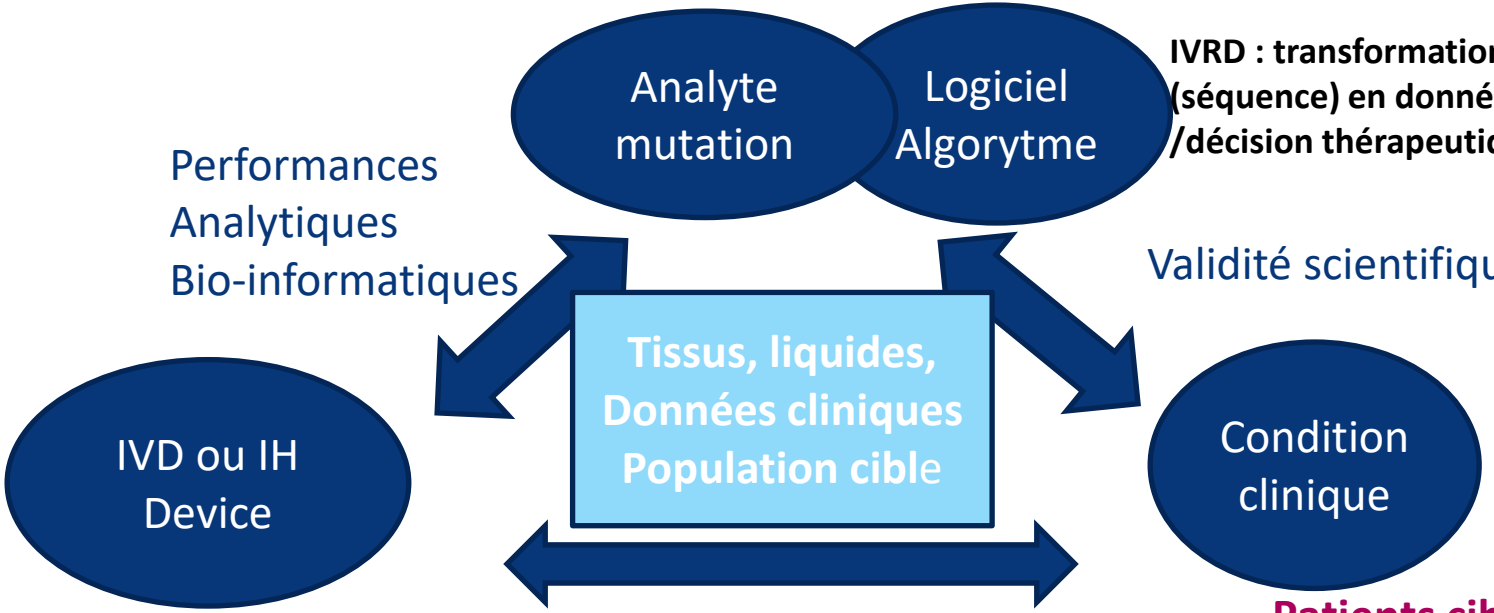
Article 5.5 du Réglement

Un circuit différent pour les IH-IVDs (article 5.5) des Etablissements de Santé (ES)



Un guide européen actuellement en cours de finalisation pour expliciter le champ et les exigences liées aux DMDIV In House (beaucoup d'inconnues)

DM-IVDR ou DM-IH, les sous-processus à respecter par un fournisseur ou **un ES**



Question posée : recours aux tissus, liquides et données cliniques : Par qui et quelles réglementations ?

Exigences générales en matière de sécurité et de performances des CE IVD et IH IVD (**Annexe 1)**

- **Exigences générales**
  - Sécurité et efficacité / risques acceptables / bénéfices / compte tenu de l'état de l'art
  - Performances (analytiques, cliniques)
- **Exigences relatives à la fabrication**
- **Exigences relatives aux informations fournies avec le dispositif**
  - Notice d'utilisation du fabricant (contenu important – à discuter)
  - Dossier à remonter par ES

Exigences spécifiques de l'article 5.5 -> DM IH IVD pourrait être exceptionnel !

- **Un ES (entité juridique / soin) peut fabriquer, transformer, utiliser un DM IH dans le cadre du respect de la réglementation décrite dans l'Annexe I et l'article 5.5. = des contraintes importantes**
  - a) ne transfère pas vers une autre entité juridique;
  - b) effectue la fabrication et l'utilisation des dispositifs dans le cadre de systèmes de gestion de la qualité appropriés (décrits) ;
  - c) respecte la norme EN ISO 15189
  - **d) fournit une documentation justifiant que les besoins spécifiques du groupe cible de patients ne peuvent pas être satisfaits, y compris par un dispositif équivalent disponible sur le marché;**
  - e) fournit, sur demande, **à son autorité compétente des informations** concernant l'utilisation de ces dispositifs, qui comportent une justification de leur fabrication, de leur modification et de leur utilisation;
  - f) établit une déclaration, qu'il rend publique garantissant l'activité et la sécurité

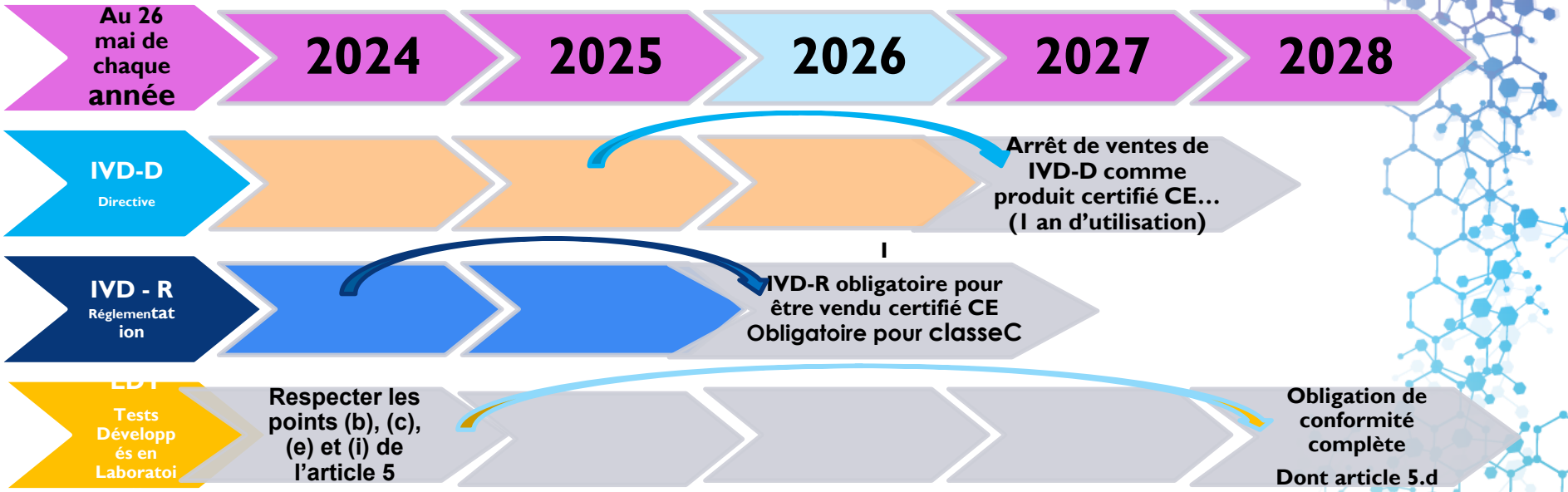
Mais aussi,

- **Surveillance post fabrication du DM / ES inspecté**
- **Et surtout, l'ES endosse la responsabilité pleine et entière du risque**

Périodes transitoires d'application : report de certaines obligations

Pour les produits marqués CE avant le 26 mai 2022,

à condition que ceux-ci ne fassent pas l'objet de changements significatifs pendant la période de transition (NOTICE d'utilisation)



En pratique

Utilisation de tests RUO, CE-IVD-D ou IVD-R selon le respect des IFU (instructions for use)
Selon leur disponibilité (seront-ils disponibles dans les temps ?) / coût acceptable

L' évolution de nos panels de gènes NGS, devenus IVDR, devrait rester possible
Travailler avec les fournisseurs sur la Notice d'Utilisation pour qu'elles soient larges (testées let déclarées, ex Exome, tissus, liquides..)

En mai 2028,
on utilisera (tous) des DM-CE IVDR en accord avec la notice d'utilisation du fabricant

En cas de modification majeure de la notice d'utilisation -> usage non réglementaire

-> possibilité de fabriquer, transformer et utiliser pour un ES un DM In House, déclaré et autorisé selon l'article 5.5 du règlement (lourd)
Nécessité et difficulté de justifier les besoins spécifiques du groupe cible de patients non couvert par un DMDIV **équivalent** disponible (ou **imminent**) sur le **marché européen**

Risques & Enjeux

- **Risques**

- Contraintes, Coût, temps RH

- Dépendance de nos ES aux fabricants/fournisseurs du commerce

- Délais longs de certification, en particulier pour les tests compagnons/calendrier des AMM/ accès précoces

- Approvisionnement : rupture de tests IVDR (embouteillage par les ON ; produits existants avec changement significatif ; arrêt de commercialisation

- Contraintes des études cliniques (pour les industriels, PME, ES) -> délais

- Risque de perte d'attractivité de la France et perte de chance des citoyens

- **Enjeux**

- Ressources biologiques avec données cliniques (groupe cible de patients dans les ES) : & leurs recours par les fabricants non ES/labo pharma

- Innovation & Indépendance

Suggestions

- **Le règlement doit s'accompagner de mesures permettant une transition harmonieuse et la sécurisation des DM-IVDR pour répondre aux besoins de diagnostics de la population cible**
  - **Groupes de travail d'experts, européens** :
    biologistes & pathologistes (GFCO?)
    fournisseurs (SIDIV ?)
    Pharma (LEEM ?)
    > Délais, Essais cliniques, CRB, Recommandations, notices d'utilisation, innovation
  - Proposer **un panel d'experts européens nommé pour les DIV compagnons en oncogénétique** de classe C (prévu pour les dispositifs de classe D)
  - Proposer **un EURL / pays pour valider les tests IH compagnon** proposés par un ou des ES (pour la première certification – et contrôle, comme pour classe D)

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LINKS OF INTEREST (E. DEQUEKER)

- **EUR-Lex access to European Union law – IVDR 2017/746**

https://eur-lex.europa.eu/eli/reg/2017/746/oj

- **Guidance - MDCG endorsed documents and other guidance**

https://health.ec.europa.eu/medical-devices-sector/new-regulations/guidance-mdcg-endorsed-documents-and-other-guidance_enxxxxx

Understanding key points of IVDR
Find answers to questions

1. When is an IVD an IH-IVD? Guidelines available?
2. Which IVD test can and may be used under IVDR?
3. Health institutes also become manufacturer under IVDR
4. Can laboratories still collaborate with other laboratories?

   And if yes, where can collaboration take place and where not according to IVDR?
5. Is participation to EQA important ? Is an ISO 15189 accreditation an added value?
6. Is innovation still going to be possible?

Conclusion

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When is an IVD an in-house IVD?
Do we have guidance documents for IH-IVD?

Significant deviation from IFU

Addition of medical purpose to RUO

In-house IVD (IH-IVD)

Laboratories developed their own tests in-house by:

- Putting together raw materials and components (RUO & CE)
- Device software development

- **"Put into service"** device manufactured and used **within health institution**
- Device developed by labs to diagnose very **specific patient conditions** for which there is **no commercial test available**
- **Subject to EU regulations** (IVDR 2017/746)

Article 5.5 of the IVDR (2017/746)

"Health Institution Exemption"

EU guidance draft MDCG

IVDR 2017/746

- **European regulation**
  - CE-IVD & In-house (IH)-IVD
  - Industry & Health Institution

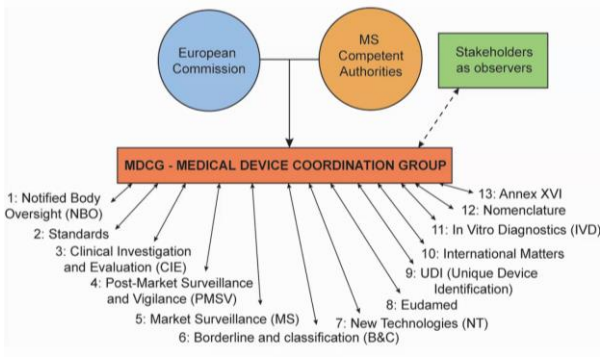
CE - IVDs

IH - IVDs

175 pages
- *10 chapters, 123 articles*
- *XVII Annexes*

Date of application May 26th 2022

- **EU guidelines / interpretation documents**



...

MDCG 2022-15,
MDCG 2022-22 rev1,
MDCG 2022-9, …

MDCG Guidelines

Draft EU MDCG Guidance for IH-IVD

- **First draft Oktober 2021**
- **Second draft May 2022** - > 400 comments from stakeholders
  - *What devices are referred to in Article 5.5*
  - *How to understand the terms 'manufactured and used'?*
  - *Legal entity*
  - *What is an appropriate quality management system?*
  - *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.*
  - *What kind of information can be requested from health institutions by competent authorities?*
  - *Public declaration*
  - *Documentation requirements*
  - *Vigilance, incidents and corrective actions*
  - *Industrial scale*

BioMed Alliance (EFLM, ESP, ESHG, ESCMID, …), …

MDCG work in progress

Ongoing guidance documents EN

https://health.ec.europa.eu/system/files/2022-06/mdcg_ongoing_guidancedocs_en.pdf

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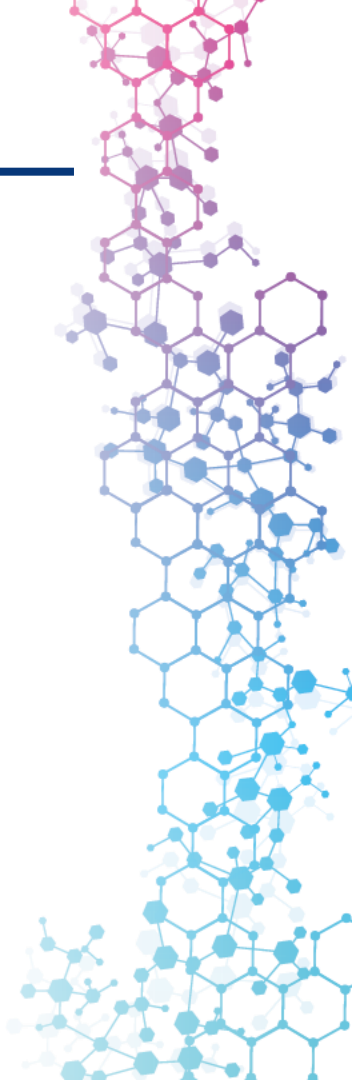

Which IVD test can and may be used under IVDR?

IH-IVD

=

CE-IVD

- **Yes, but …** ?

Which IVD test can and may be used under IVDR?

IH-IVD

- Equivalent CE-IVD available → **Swith to CE-IVD** → **CE-IVD**
- CE-IVD available; not equivalant? → **Carefully justify use of IH-IVD**
- CE-IVD not available → **Justify use of IH-IVD**

Obligation to document all IVDR requirements for in house IVD (article 5.5 + annex I)
competent authority can ask this data

Waiting for guidance document MDCG In-house devices - due Q3 –Q4 2022?

CE-IVD → adjustments compared to IFU required

MDCG 2022-6
Guidance on significant changes regarding the transitional provision under Article 110(3) of the IVDR

- **IH-IVD**
- **CE-IVD**

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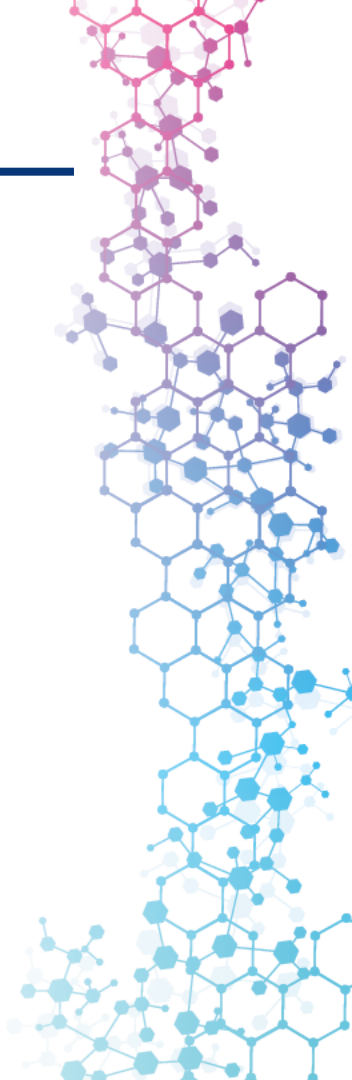
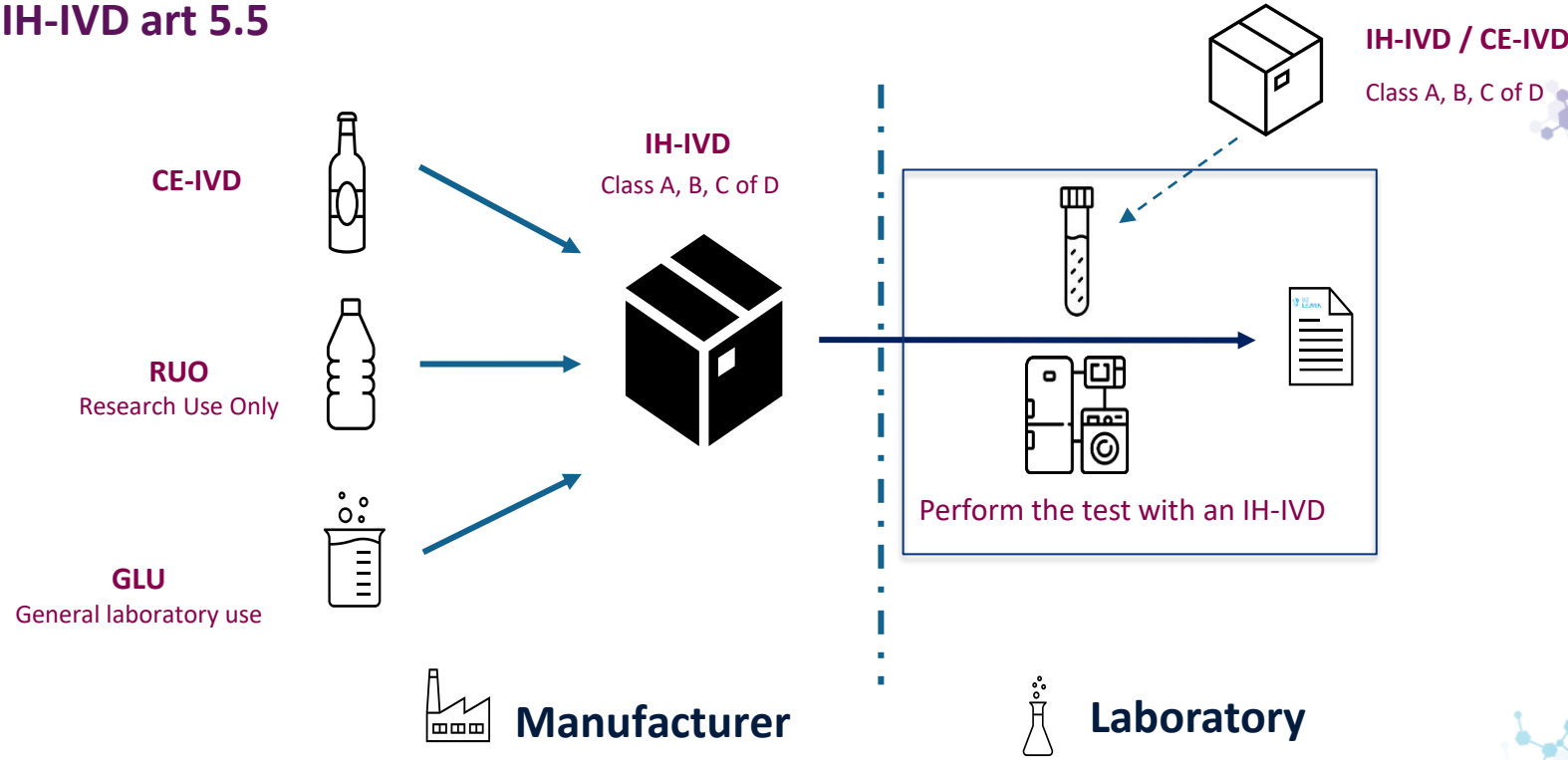


Health institutes also become manufacturer under IVDR

IH-IVD art 5.5



Health institutes also become manufacturer under IVDR

- **adapting the quality system to the manufacturer's requirements**

  - > used standard ISO 13485, not necessary to be certified

  (Art 5.5 b - DoA May 2024)

  - other accents then ISO 15189
  - design of device (inclusive software)
  - purchase and approval of 'raw materials' (CE-IVD, RUO, GLU, GLE, in house reagents, COTS software ..)
  - labelling
  - …

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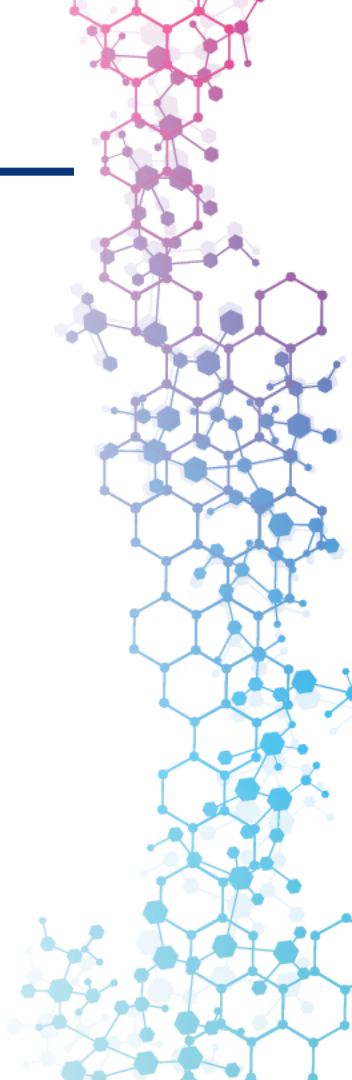


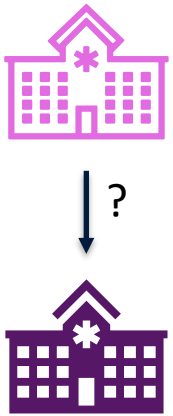
Can laboratories still collaborate with other laboratories? And if yes, where can collaboration take place and where not according to IVDR?

- **No transfer of device to other legal entities** (DoA May 2022)

  Transfer which is allowed:

  - sharing laboratory protocols,
  - information about technologies, tools and reagents is possible
  - Patient samples (not considered as being a device)

  (2nd draft IH-IVD MDCG guideline)



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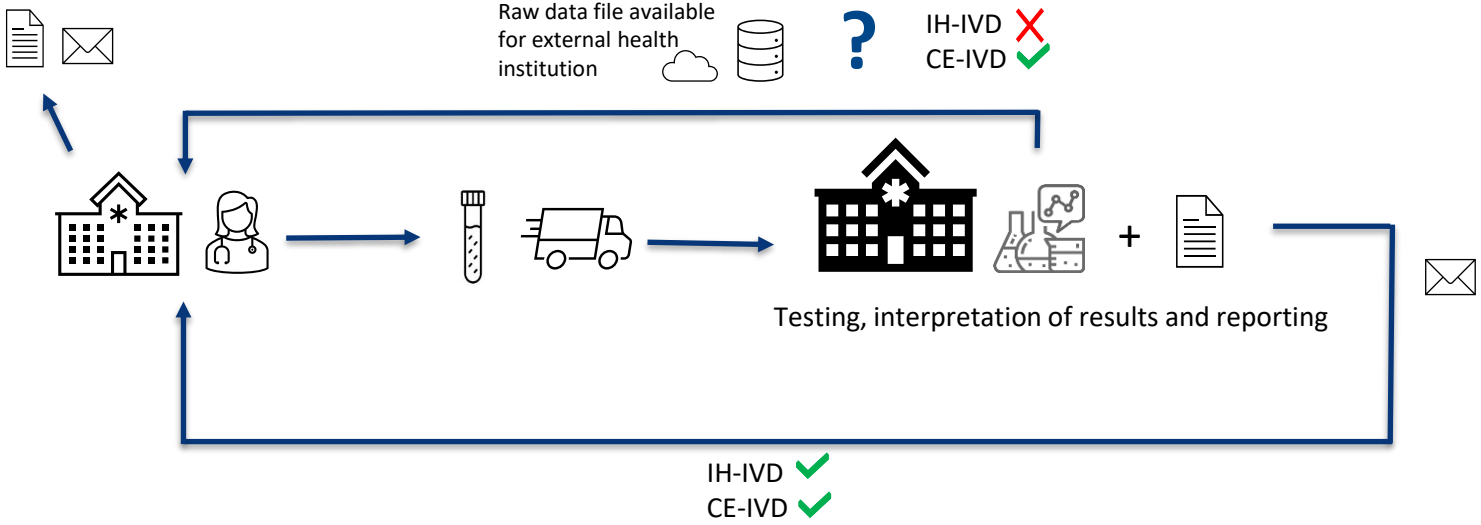
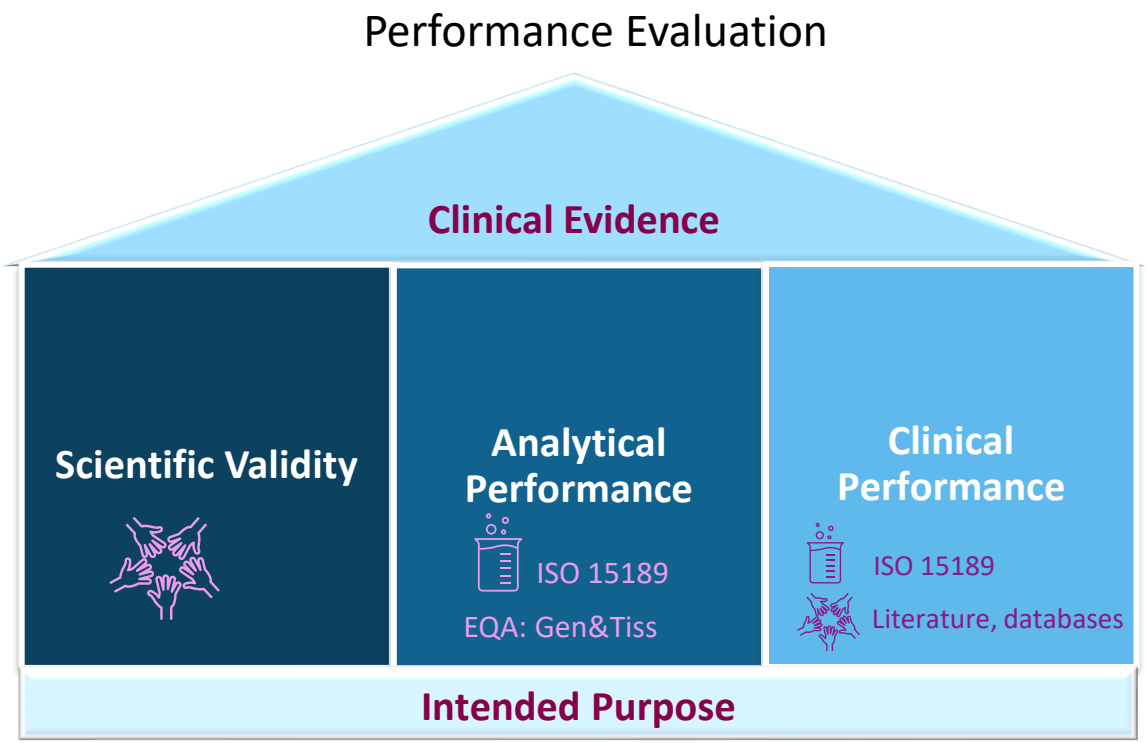


- A patient sample is not an IVD – external patients will be seen as own patients (in Belgium)
- In case of IH-IVD reporting should be included
  - ✓ If reporting <u>isn't included</u> -> is seen as a commercial activity ->

Can laboratories still collaborate with other laboratories? And if yes, where can collaboration take place and where not according to IVDR?



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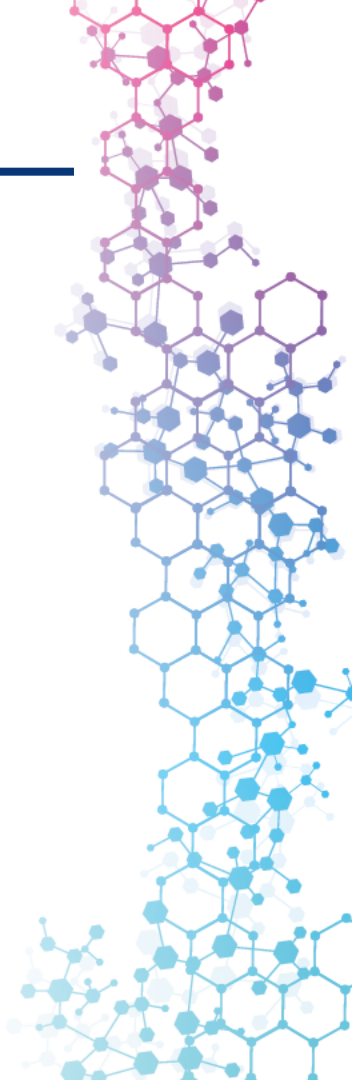

Is participation to EQA important ?

- **Recommended for ISO 15189** (article 5.5 c)
- **Useful for IVDR**
  - Analytical performance
  - Post Market Surveillance Performance Follow-up (PMSF)
  - Market study

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Is an ISO 15189 accreditation an added value?

- **GAP analysis article 5.5 & ANNEX I and accredited ISO 15189 QMS**
  - Documents available in QMS for a test which is accreditated according ISO 15189
  - Dutch document drafted by the Task Force IVDR NL

Lab-Developed Tests
Handvat gebruik Lab-Developed Tests zoals beschreven in
VERORDENING (EU) 2017/746 VAN HET EUROPEES PARLEMENT EN DE
RAAD van 5 april 2017 betreffende medische hulpmiddelen voor invitrodiagnostiek
L Jacobs, *et al* versie 2.0 December 2020

- **Results of GAP analysis**
- **Dutch document:**
  - ~70% of the requirements in Annex I are (nearly) covered by requirements in ISO 15189

- **Case study in UZ Leuven**
  - ~60% of the requirements in Annex I are (nearly) covered by requirements in ISO 15189
  - For the remaining 40%, additional documentation, studies or evidence will be needed

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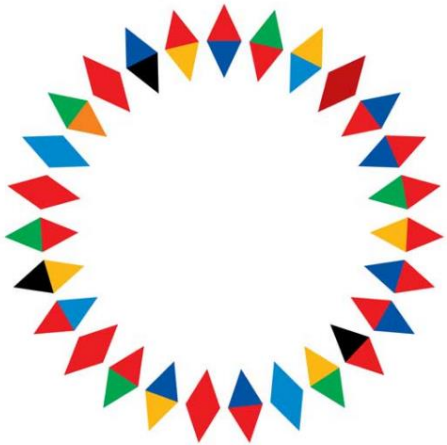
Is innovation still going to be possible?

- **Czech Presidency of the European Council**



EU2022.CZ

Czech Presidency of the Council
of the European Union

Conformity assessment is needed before use of the device

IH-IVD article 5.5

Competent authority

Justification of use of IH-IVD

Quality Management System

General Safety Performance Requirements

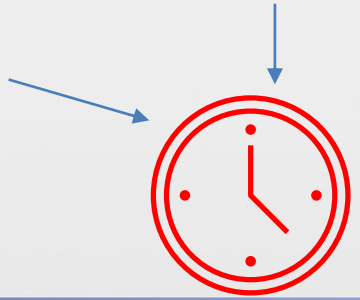
- Risk management
- Performance evaluation studies
  - Scientific validity
  - Analytical validity
  - Clinical validity
- Post market surveillance studies

CE-IVD

Notified Body

175 pages

- *10 chapters, 123 articles*
- *XVII Annexes*



Orphan diagnostics

Flexibility will be the key

Request for an incubation period for new technologies in rare diseases

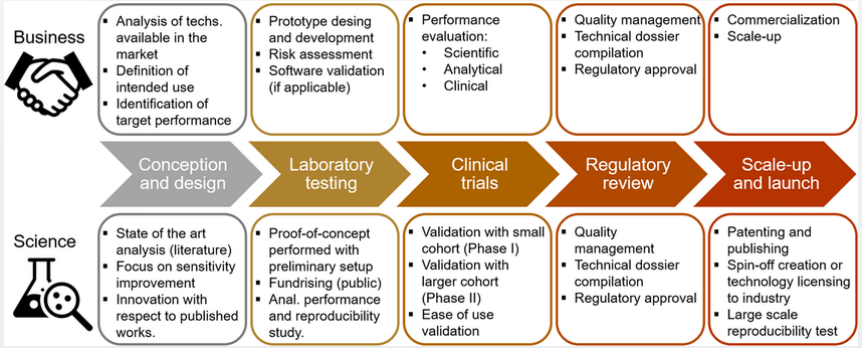
ESHG
EUROPEAN SOCIETY OF HUMAN GENETICS

if no incubation time

discourage investment in technological and medical innovations

- jeopardize patient health
- reverse all the initiatives of Europe to reduce the diagnosis time

European Commission



Development process of a diagnostic device

G Rosati et al, ACS Nano 2021, 15, 11, 17137–17149

Proposal "*NEW*" MDCG guideline / paragraph

ESHG
EUROPEAN SOCIETY OF HUMAN GENETICS

Importance: Keep harmonization in EU and protecting the aim of the IVDR

Article 54: Derogation from the conformity assessment procedures possible

54.1: …level of member state to bring a product on the market (limited time period)

54.2-4: … possibility to made derogation European wide for the device

Article 54 of the IVDR provides that the national authorities may authorise the use of a specific device even though the conformity assessment procedures have not been carried out if the use of the device in question is in the interest of public health or patient safety or health. The European Commission has the possibility of extending national derogations to the entire territory of the Union.

Proposal *"NEW"* MDCG guideline / paragraph

ESHG
EUROPEAN SOCIETY OF HUMAN GENETICS

Importance: Keep harmonization in EU and protecting the aim of the IVDR

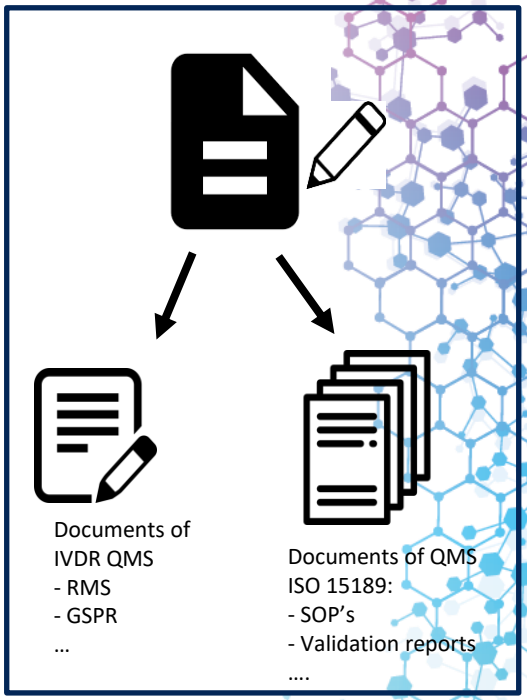
***"NEW "* MDCG guideline/ paragraph for orphan diagnostics**

- the **minimum level of IVDR conformity** required in relation to the nature of the orphan diagnostic
- the organization has a **minimum level of a quality management system**
- a **minimum level of performance** of the device to ensure patient safety
- **a realistic incubation period** (several years) **for orphan diagnostics** to encourage continued to innovate and truly help families and patients with rare disease

These conditions explained in the MDCG document shall guide the organization and the member states and keep harmonization in EU

Conclusion

- **Implementation of IVDR is a challenge**
- **Where to start hospital exemption (article 5.5)?**
  - Make an inventory of the tests in orde to get a better picture of which devices are IH-IVD?
  - Which information is available in the QMS for annex I and article 5.5?
  - Start developing templates for your QMS to collect the information required for IH-IVD's



Important: the regulation is a law and its contents will not change !

More clarification will come in the next weeks /months !

THANK YOU FOR YOUR ATTENTION