The European Society
of Human Genetics

"IVDR - Beneficial or just an expensive straitjacket?"

General Information

Date:	**Wednesday, June 22, 2022**
Time:	**10:00 - 16:30 hrs**
Format:	**Online Webinar**
Programme Outline:	The new IVD EU regulation (IDVR 2017/746) has major implications on the use, availability and associated costs of in vitro diagnostic tests. But on the other hand, it also builds in many ways new assurance points to improve and monitor the quality of our diagnostic services. The previous directive (IVDD 198/79/EC) exempted laboratory developed tests (LDTs / in-house IVD) from all requirements of an IVD. Under the IVDR, LDTs are subject to additional requirements and may only be used if no alternative CE IVD kit is available on the market. A justification for hospital exemption of the use of an IH-IVD has to be given. A European study shows that genetic diagnostics is largely based on tests developed in-house. All players in the field of medical genetics will have to comply with the new European Regulation on in vitro diagnostic medical devices (IVDR) by May 2022 (and for some parts May 2024 and May

Section 1 - Introduction to IVDR

Section 2 - IVDR – Impact on a diagnostic laboratory

https://www.eshg.org/index.php?id=ivdrday

The European Society of Human Genetics

ESHG Policy Statements

Regulation EU 2017/746 (the IVD Regulation) is a threat to both precision medicine and crisis management if the Article 5-§5 conditions (d)-(i) are not removed

September 21, 2020

Conclusion

ESHG strongly recommends that Article 5-§5 conditions (d) to (i) for in-house exemptions are removed from the IVD Regulation, while conditions (a) to (c) are kept. Failure to do so will increase health care costs and jeopardize our ability to design precise "personalized" laboratory tests (necessary for precision medicine) and to adapt to shifting test needs (like repurposing instruments for covid-19 testing).

Background

Regulation EU 2017/746 on *in vitro* diagnostic medical devices (the IVD Regulation) will be European law from May 26th, 2022. The intentions of the legislators have been appropriate: to secure quality of all kinds of medical diagnostic tests, and to make sure such tests are performed within the frame of the health care system. An apparently convenient means to obtain this is to demand industry standard CE marking of tests and instruments.

https://www.eshg.org/index.php?id=477#c5607

In-house exemption to CE marking

Since CE marking is too cumbersome and expensive for the low-volume specialized tests designed in many diagnostic laboratories, also as part of precision medicine, an in-house exemption to the requirement for CE marking has been made (article 5-§5). Such in-house tests are very common in medical genetics. However, this in-house exemption can only be invoked if several conditions are fulfilled (numbered a-i). One condition is that the laboratory must be accredited according to EN ISO 15189 or a similar nationally approved system. This condition makes much sense since such accreditation automatically implies quality management and risk evaluation (other requirements). More problematic, however, is condition (d): "*the health institution justifies in its documentation that the target patient group's specific needs cannot be met […] by an equivalent device available on the market*". In other words: If a CE marked commercial test exists that gives similar test results, that test must be used – and cost is not an issue.

Precision medicine out of control

So far commercial CE marked tests for rare conditions are exceptional, likely because the "market" is too small, i.e. not worth the investment. This may change when next generation (whole-exome or whole-genome) sequencing (NGS) is established as the basis for all kind of rare disease diagnostics; companies that now label their sequencing instruments "*for research use only*" may suddenly introduce a CE marked diagnostic "NGS-package" using the same instruments that will return a standardized set of sequencing data for local interpretation, like they have done for NIPT (non-invasive prenatal testing). This will turn in-house laboratory skills into an unaffordable luxury.

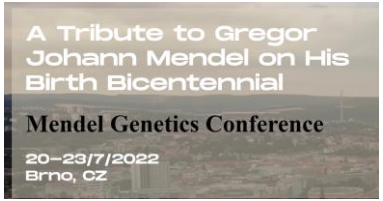
Furthermore, it will be too expensive to develop test reagents (like unique FISH probes) since the documentation requirements for non-commercial reagents in the IVD-Regulation goes beyond ISO 15189. The need for control measures that goes beyond EN ISO 15189 has not been documented as necessary for securing good laboratory quality. Practice in line with the well-established ISO-standard is in our view a sufficient quality control. We are, however, unsure if it is wise to allow national exemptions to this standard, like Article 5-§5 now allows. If Article 5-§5 stays as it is, commercial interests will govern precision medicine, and patient interests will suffer because in-house personalized testing will not be possible.

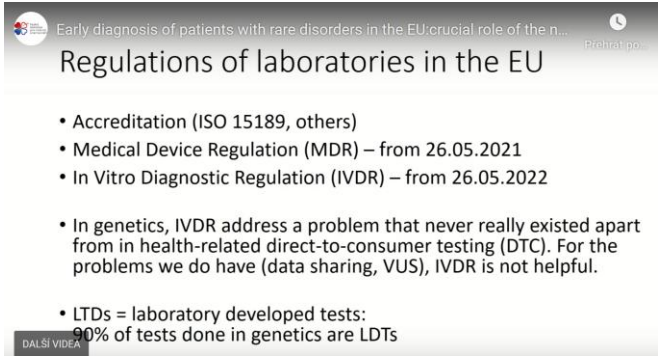
Let us keep the flexibility and creativity alive

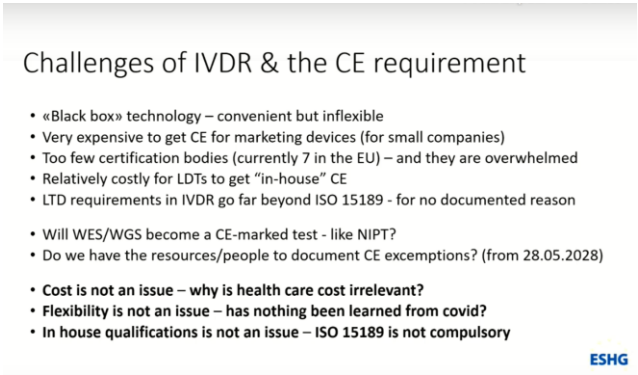
Standardization is fine if you want to mass produce a car, but not if you suddenly need to find a creative solution to novel problems in patient diagnostics (as part of precision medicine) or pandemic control (to enhance covid-19 test capacity). The ability to rapidly repurpose testing was crucial to obtain pandemic control in Europe, and here Europe had an advantage over the more rigorous US system. Let us not lose this capacity because a too rigorous IVD Regulation becomes EU law. That would really be a threat to public health.

On behalf of the Executive Board of the European Society of Human Genetics

EARLY DIAGNOSIS OF PATIENTS WITH RARE DISORDERS IN THE EU: CRUCIAL ROLE OF THE NEWBORN SCREENING







IVD-R: BENEFICIAL OR JUST AN EXPENSIVE STRAIT JACKET? NORWAY

Prof. Gunnar Douzgos Houge

In-vitro diagnostic regulation
IVDR

Gunnar D Houge MD PhD
ESHG treasurer

http://novorozeneckyscreening.vzacna-onemocneni.cz/

Was there ever a big problem that the IVDR needed to be solve?

Cost ↑

Bureaucracy ↑

Competence ↓

«Nobody» wants it...

Will health care be improved - or can we just do less?

The European Society of Human Genetics

ESHG has published a declaration on IVDR and the LDT problem:

https://www.eshg.org/index.php?id=477#c5607

adopted by other societies (e.g. the European Society of Microbiology),
and link to a recent webinar on this subject can also be found on our website.

Towards a New European Policy Framework: Building the future together for rare diseases

Vytvořeno: 14. 6. 2022 Poslední aktualizace: 16. 11. 2022

Expert Conference on Rare Diseases

25 – 26 October 2022, Prague, Czech Republic

- Photo Gallery
- Presentations

https://www.mzcr.cz/towards-a-new-european-policy-framework-building-the-future-together-for-rare-diseases/

EU2022.CZ

Call to Action

from the Expert Conference on Rare Diseases

Towards a new European policy framework on rare diseases:

"Building the future together for rare diseases"

On 25 and 26 October 2022, in Prague

The Czech Presidency of the EU Council organised the Expert Conference on Rare Diseases in Prague on 25-26 October 2022 to explore how the European Union can take continued steps towards a coordinated strategy for rare diseases to better addresses current unmet needs by setting meaningful goals for patients, families and for society at large, integrated at the national and regional levels.

Rare diseases, including rare cancers, are a heterogeneous group of largely incurable, complex conditions. There are over 6000 rare diseases, and more than 70% have a genetic origin. Although individually characterised by low prevalence, the sheer number of rare diseases results in a directly affected community of 20 million people across the EU. Rare diseases are chronic, progressive, degenerative, disabling and frequently life threatening.

The CZ PRES calls on the EU and its Member States

B. to support such an approach to an expanded number of disease areas and countries across Europe to better diagnose currently "unsolvable" cases.

Accessibility of medical devices necessary for diagnostics of rare diseases is of crucial importance. Regulation (EU) 2017/746 on in vitro diagnostic medical devices sets several ways for derogation from the generally applicable rules for safety and performance requirements when placing the medical devices on the market. Nevertheless, further specification that would ensure that in vitro medical devices necessary for proper diagnostics of rare diseases remain available on the market is needed. The CZ PRES:

A. Appreciates the ongoing work of the Medical Device Coordination Group MDCG guidance document concerning the art. 54 of the Regulation that will include clear statement when it comes to possible derogation from the Regulation for medical devices necessary for rare diseases diagnostics.
B. Calls upon the MDCG and the European Commission to prepare without any further delay guidance document on art. 5.5 of the Regulation that would in detail define based on practical experience and including practical ways for their implementation.

https://www.mzcr.cz/wp-content/uploads/2022/10/CZPRES_Expert_Conference_on_Rare_Diseases_brochure.pdf

IVDR 2017/746

Quite a **challenge** for **new tests for "rare diseases"** to preserve the final purpose of the regulation

►B REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 5 April 2017

on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

(Text with EEA relevance)

(OJ L 117, 5.5.2017, p. 176)

Call for **embedding an incubation period**

for accessibility to **Orphan Diagnostics/ Devices**

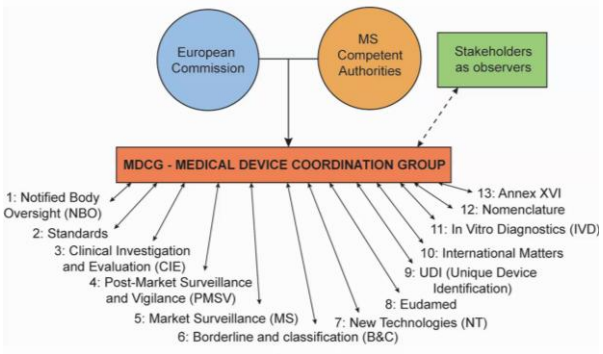
Prof dr E Dequeker, Belgium

Representative for the ESHG

IVDR 2017/746 (May, 26th 2022) – *Harmonization*

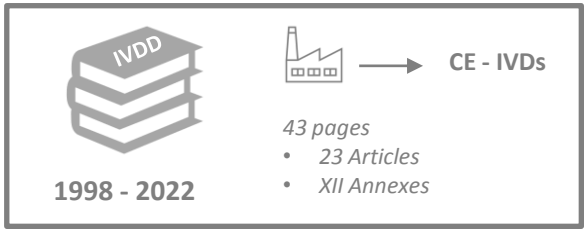
- **European regulation**
  - CE-IVD & In-house (IH)-IVD
  - Industry & Health Institution

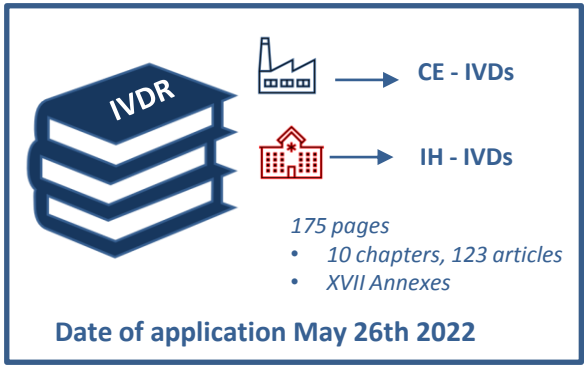
- **EU guidelines / interpretation documents – MDCG**



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

MDCG Guidelines



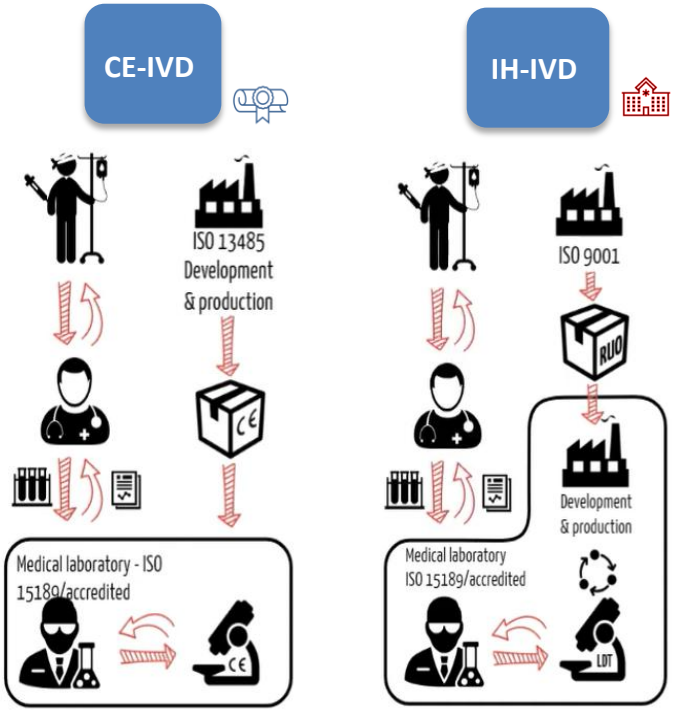


IVD's under the IVDR

Main goal:
Regulating medical devices' quality, safety and reliability

Impact:

- More demanding requirements for manufacturers and health institutions
- Use of IH-IVDs will be restricted
- Discouraging innovation for diagnostics



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

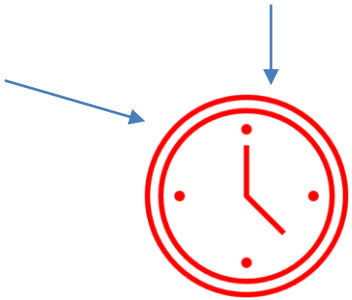
- Risk management
- Performance evaluation studies
  - Scientific validity
  - Analytical validity
  - Clinical validity
- Post market surveillance studies

CE-IVD

Notified Body

175 pages

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



Orphan diagnostics

Flexibility will be the key

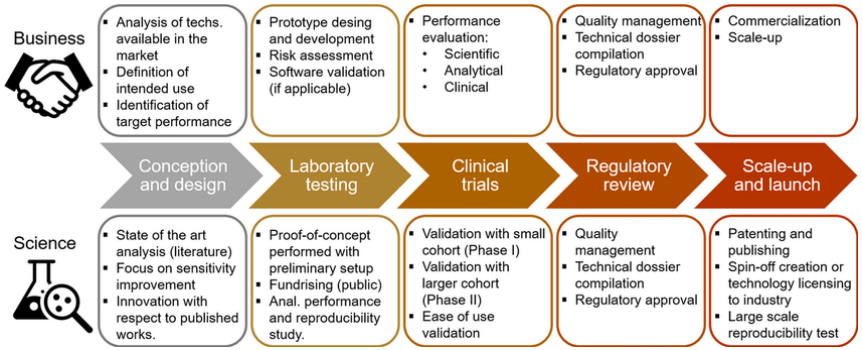
Request for an incubation period for new technologies in rare diseases

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

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

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

MDCG 2022-14

MDCG Position Paper **Transition to the MDR and IVDR** Notified body capacity and **availability of medical devices and IVDs**

August 2022

…

18. The MDCG acknowledges the specific situation of **‘orphan devices’** and will pursue work with a view to providing a definition for ‘orphan devices’ and ***suggesting specific guidance or other means of assistance for those products*** to be able to meet the legal requirements. Sustainable solutions are also needed in the mid- and long-term for orphan devices. [actors: MDCG TF on orphan devices]

…

Task Force of IVDR of ESHG is willing to support