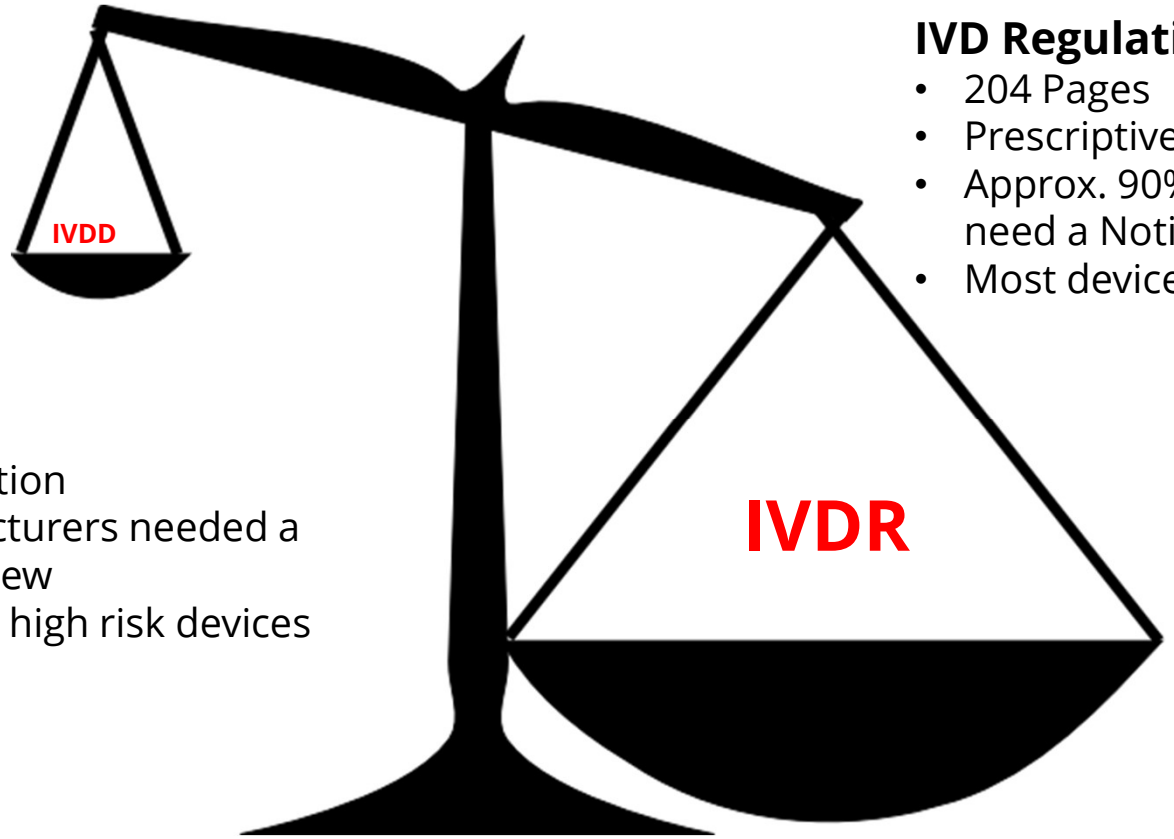
.....the practical approach

Select Science/ LGC
Changes to the IVDR Transitional Arrangements

Sue Spencer

IVD Directive (IVDD) v IVD Regulation (IVDR)



IVD Regulation

- 204 Pages
- Prescriptive regulation
- Approx. 90% manufacturers need a Notified Body Review
- Most devices impacted

IVD Directive

- 37 Pages
- Light touch regulation
- Only 20% manufacturers needed a Notified Body Review
- Mainly focused on high risk devices

What does this mean in practice?

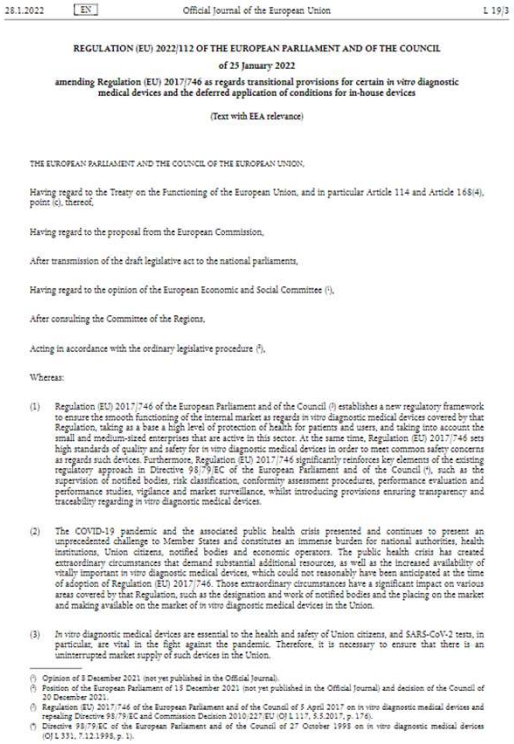
- **More precise**
- **More detail**
- **More evidence especially clinical needed**
- **More Notified Body oversight**
- **More post market activities**
- **More responsibilities for Economic operators**
  - Manufacturer
  - Authorised Representative
  - Importer
  - Distributor

=

- **More time to prepare**
- **Current data can be repurposed but is it enough?**
- **Longer time to prepare documents**
- **Longer approval process**
- **Change to relationships with Economic Operators**
- **Greater cost associated with all these activities**

Extension to transitional arrangements

- The extension aims to give more time for the conformity assessment work and implementation of infrastructure without delaying the date of application
- This is not a unilateral delay to the regulations and needs to be studied carefully



28.1.2022 EN Official Journal of the European Union L 19/3

REGULATION (EU) 2022/112 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 25 January 2022

amending Regulation (EU) 2017/746 as regards transitional provisions for certain *in vitro* diagnostic medical devices and the deferred application of conditions for in-house devices

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Article 114 and Article 168(4), point (c), thereof,

Having regard to the proposal from the European Commission,

After transmission of the draft legislative act to the national parliaments,

Having regard to the opinion of the European Economic and Social Committee (1),

After consulting the Committee of the Regions,

Acting in accordance with the ordinary legislative procedure (2),

Whereas:

(1) Regulation (EU) 2017/746 of the European Parliament and of the Council (3) establishes a new regulatory framework to ensure the smooth functioning of the internal market as regards *in vitro* diagnostic medical devices covered by that Regulation, taking as a base a high level of protection of health for patients and users, and taking into account the small and medium-sized enterprises that are active in this sector. At the same time, Regulation (EU) 2017/746 sets high standards of quality and safety for *in vitro* diagnostic medical devices in order to meet common safety concerns as regards such devices. Furthermore, Regulation (EU) 2017/746 significantly reinforces key elements of the existing regulatory approach in Directive 98/79/EC of the European Parliament and of the Council (4), such as the supervision of notified bodies, risk classification, conformity assessment procedures, performance evaluation and performance studies, vigilance and market surveillance, whilst introducing provisions ensuring transparency and traceability regarding *in vitro* diagnostic medical devices.

(2) The COVID-19 pandemic and the associated public health crisis presented and continues to present an unprecedented challenge to Member States and constitutes an immense burden for national authorities, health institutions, Union citizens, notified bodies and economic operators. The public health crisis has created extraordinary circumstances that demand substantial additional resources, as well as the increased availability of vitally important *in vitro* diagnostic medical devices, which could not reasonably have been anticipated at the time of adoption of Regulation (EU) 2017/746. Those extraordinary circumstances have a significant impact on various areas covered by that Regulation, such as the designation and work of notified bodies and the placing on the market and making available on the market of *in vitro* diagnostic medical devices in the Union.

(3) *In vitro* diagnostic medical devices are essential to the health and safety of Union citizens, and SARS-CoV-2 tests, in particular, are vital in the fight against the pandemic. Therefore, it is necessary to ensure that there is an uninterrupted market supply of such devices in the Union.

(1) Opinion of 8 December 2021 (not yet published in the Official Journal).
(2) Position of the European Parliament of 15 December 2021 (not yet published in the Official Journal) and decision of the Council of 20 December 2021.
(3) 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 (OJ L 117, 5.5.2017, p. 176).
(4) Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices (OJ L 331, 7.12.1998, p. 1).

Key Points

- This does not delay the date of application and as a result vigilance, PMS and registration of economic operators apply from 26 May 2022
- Manufacturers should be upgrading their QMS to IVDR before 26 May 2022
- The transition does not apply to new devices
  (Devices where the DoC is signed after DoA)
- It extends the transitional period for certain devices balancing risk classification verses NB capacity
- Devices that undergo a significant change after DoA will have to meet the full IVDR including any NB review necessary (More from Julien)
- There is no extension for non sterile class A devices
  This is because there is no third party required in conformity assessment so NB capacity should not be an issue

New transitional arrangements

- The Sell-off period
  More from Erik
- There are additional extensions for elements of the in-house exemption
- Important to understand the difference between in-house exemption and distance sales

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Mechanisms to provide IVDs in the IVDR

In-house exemption

Distance Sales

IVD
Reagent, calibrator, control, instrument, kit

No direct comparison with an Lab Developed Test (LDT) in the US

In-house Exception	Distance Sales	IVD
• Only applies to labs in the EU which are healthcare institutions (not gyms etc) • Devices for unmet need, there should be no equivalent CE marked test • Not used in the context of a commercial activity • Must be made at lab and cannot be transferred to another lab	• Tests offered over the internet to a doctor or patient in EU for testing EU citizens • Tests not provided as a kit but part of a commercial activity provides a diagnostic or therapeutic service to a doctor or patient in EU (direct to patient are self tests) • Used in the context of a commercial activity	• Kit, reagents, calibrators, controls or instruments physically supplied to a customer/ lab • Provided as a commercial product or free of charge
• Need to justify why no equivalent/ appropriate CE marked test and make this public • Must have QMS equivalent to ISO 15189	• Must meet IVDR in full including Technical File, clinical data, QMS, Post Market requirements Notified Body audit • Some NBs expect ISO 15189 for lab	• Must meet the IVDR in full including Technical File, clinical data, quality management system, Post Market requirements Notified Body audit
• Must make a declaration that the device meets the IVDR GSPRs*	• Must make a declaration of conformity	• Must make a declaration of conformity
• Must make declaration available	• Must register in EUDAMED	• Must register in EUDAMED

*GSPR – General Safety and Performance Requirements (Annex I)

In-house exemption transitional arrangements

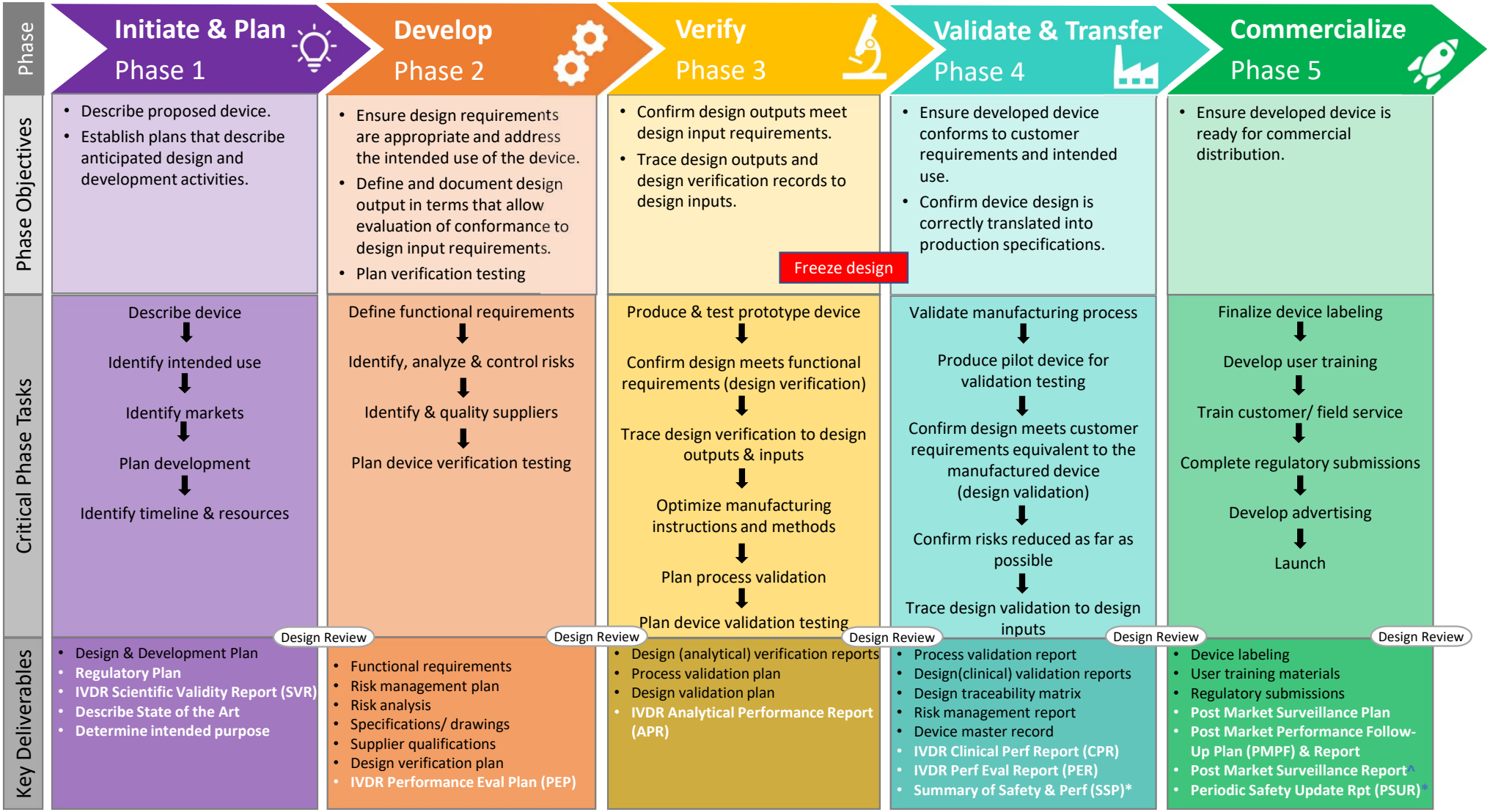
Devices put into service under the in-house exemption must meet the IVDR GSPRs from DoA 26 May 2022 but there are some extensions to the transition

IVDR Requirement under Article 5	Transition
manufacture and use of the devices occur under appropriate QMS	shall apply from 26 May 2024
laboratory of the health institution is compliant with standard EN ISO 15189 or where applicable national provisions, including national provisions regarding accreditation	shall apply from 26 May 2024
the health institution justifies in its documentation 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	shall apply from 26 May 2028
the health institution 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	shall apply from 26 May 2024
the health institution reviews experience gained from clinical use of the devices and takes all necessary corrective actions	shall apply from 26 May 2024

What applies from 26th May 2022?

- **QMS should be IVDR ready**
  New devices should be designed under the IVDR and design changes should consider whether changes are significant and either trigger an IVDR approval or notification to the Notified Body.
- Performance evaluation should be conducted according to Annex XIII and XIV according to ISO 20916
  In vitro diagnostic medical devices — Clinical performance studies using specimens from human subjects — Good study practice
- Post market activities including PMS/ PSUR/ SSP/ PMPF/ vigilance should be conducted to the IVDR

In Vitro Diagnostic Device Design & Development Process



*IVDR Class C and D devices

^IVDR Class A and B devices

In conclusion

- The extension to the transitional arrangements has brought huge relief but at the same time introduced new complications
- Remember NB approvals are already taking 9-11 months and could be 18 months for CDx so beware delaying implementation this time will be needed just to get through the NB process
- The NB queue is not getting shorter and they will soon have maintenance of certificates including sampling on top of new reviews!
- Make sure you understand the expectations for Clinical Performance Studies and determine where data collected prior to or outside the EU can be used as part of a submission.

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Thank you for your attention

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How to handle changes during the transition period

Julien Senac, Ph.D.

How to deal with changes after May 26, 2022?

Based on MDCG 2020-3

Pre-Conditions	▪ Valid IVDD certificate or ▪ DoC issued **before** IVDR DoA
Changes	▪ No significant changes (design, intended purpose) permitted ▪ New devices need certification under IVDR
Manufacturer responsibility	▪ Must have process to evaluate changes ▪ Must report to NB for evaluation
Notified Bodies	▪ Verification of changes ▪ May confirm changes in writing for correction or complementation of certificate information

Changes not concerning the design and intended purpose

Manufacturer organization

- Changes on manufacturer name, address or legal form
- Merger and acquisition
- Change of authorized representative
- Relocation or addition of new manufacturing sites
- Change of subcontractors

Manufacturing processes

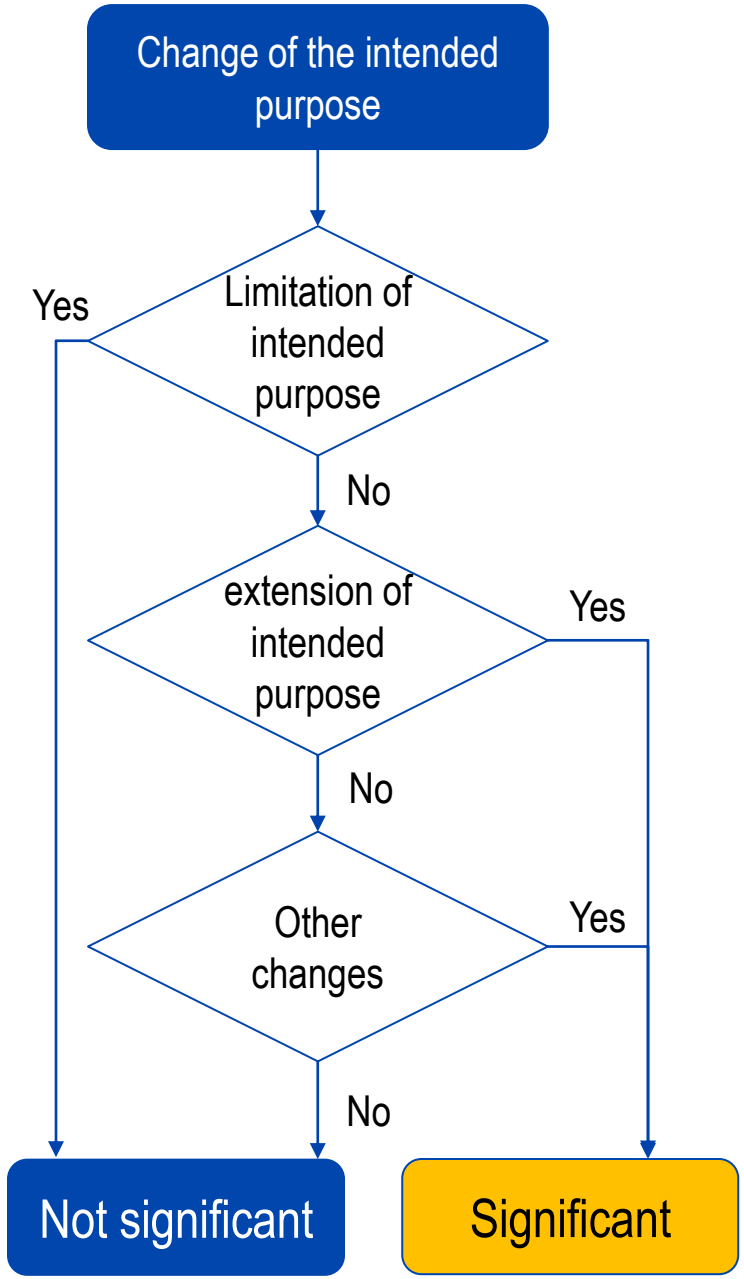
- Change the supplier of material, ingredient, or component (**provided NO change of specifications**)
- Adding or replacing a new material number for logistic reasons (**NO change to the material**)
- Changes to external packaging (size, layout, material) (**NO impact on the sterility or microbiological state of the device**)

Changes in the intended purpose

- Limitation of intended purpose, such as restricting the target population, specimen type, specimen location → **Not significant**

- Extension of intended purpose → **Significant**
  - *Addition regarding what is detected or measured*
  - *Additional functions of the device (screening, monitoring, diagnosis)*
  - *Addition of specimen type(s)*
  - *For CDx: extension of associated medicinal product, of target population or of the tissue type*

- Other major changes of the intended purpose → **Significant**
  - *Change in assay type (e.g. qualitative to quantitative assay)*
  - *Change of the intended user (e.g. professional to lay user)*
  - *Change of operation (e.g. automatic to manual)*
  - *Change of specimen type(s)*

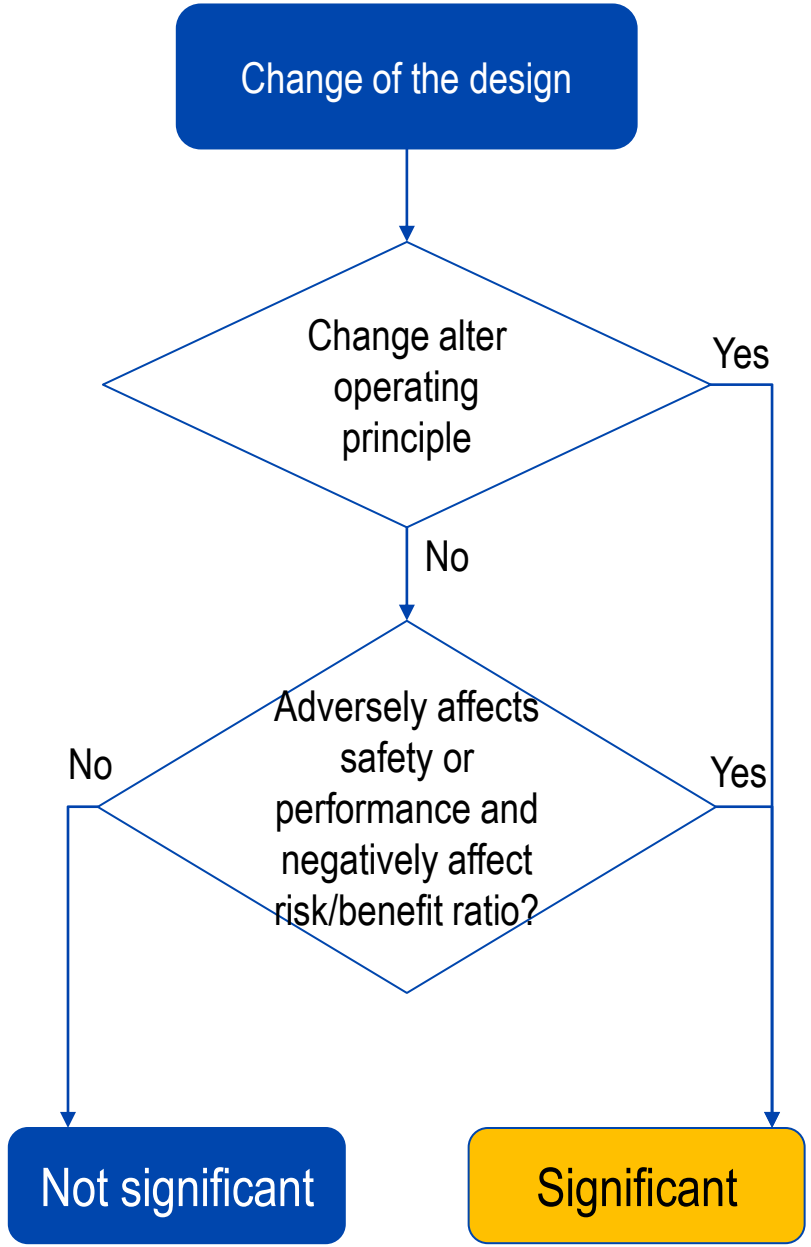


Changes in the design

- Changes of the design that **DO NOT** alter the device operating principle, that **DO NOT** adversely affect the safety or performance and that **DO NOT** negatively affect the risk/benefit ratio of the device: → **Not Significant**
  - *Use of a new PCR cycler*
  - *Change of IFU to refer to better precision or addition of a new interfering substances (based on post-market surveillance)*

- Changes that alter the device's operating principle: → **Significant**
  - *Change from immunofluorescence to enzyme-linked immunoasorbent assay*

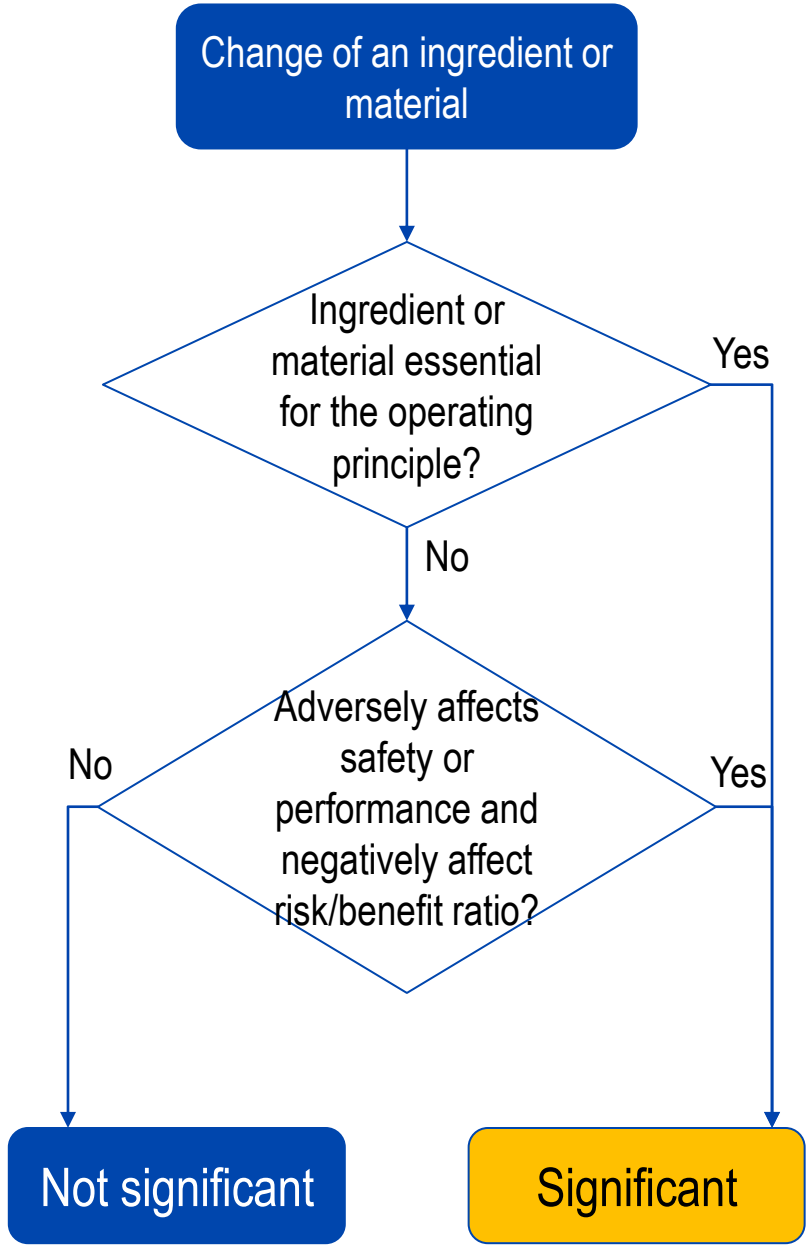
- Changes that adversely affect the safety or performance and negatively affect the risk/benefit ratio of the device → **Significant**
  - *Change of IFU to refer to reduced sensitivity of the device (based on PMS)*



Changes of an ingredient or material

- Changes that is **NOT** essential for the device's operating principle, that **DO NOT** adversely affect the safety or performance and that **DO NOT** negatively affect the risk/benefit ratio of the device: → Not Significant
  - *Replacing a preservative*
  - *Use of a new buffer whose pH is slightly different and more adapted to the assay.*
  - *Substitution of a chemical substance in order to comply with the REACH regulation. (Significant if: an adverse impact on performance of the device)*

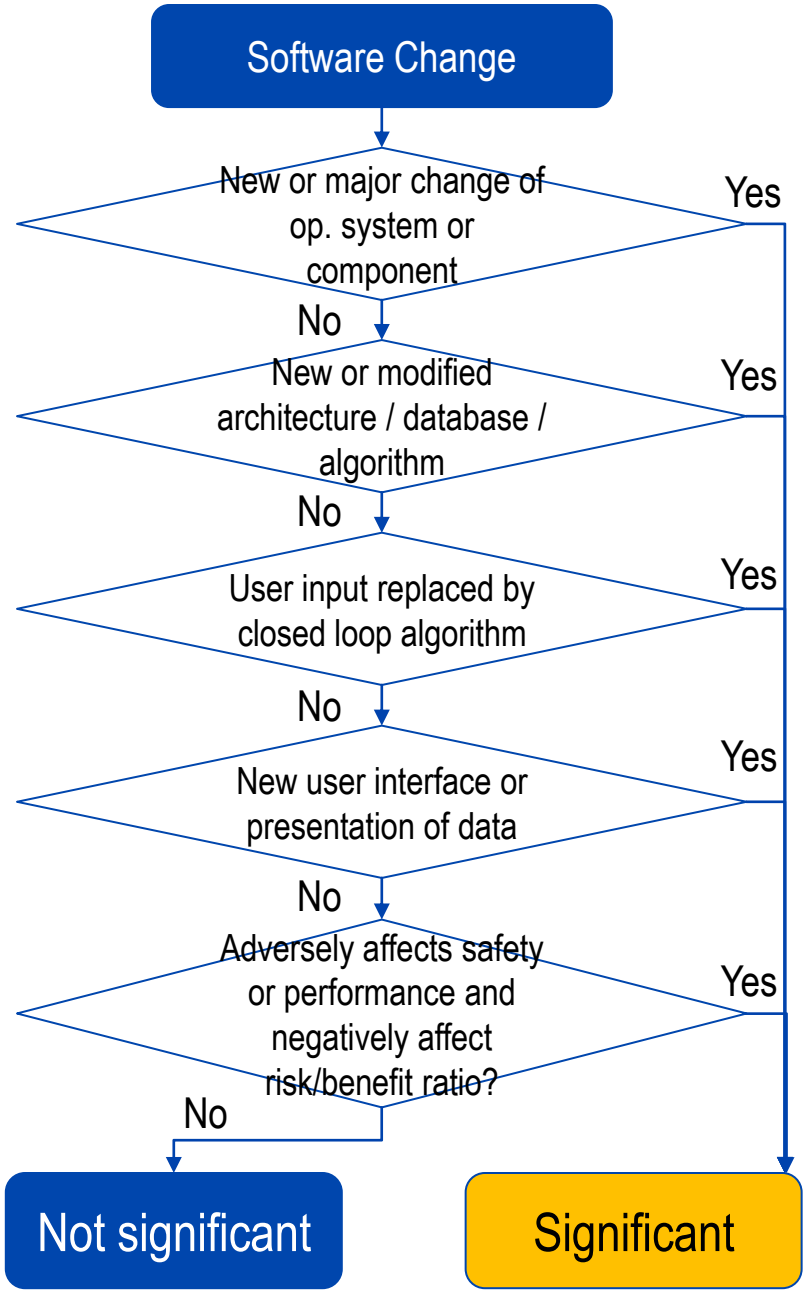
- Changes that is essential for the operating principle of the device:
  - *Primers for PCR*
  - *Capture antibodies for ELISA*
  - *Detection market for chromatography*



Software change

- Non-significant changes:
  - Correction of an error which does not pose a safety or performance risk
  - Security updates. (e.g.: cyber-security enhancements)
  - Appearance of the user interface (e.g.: new languages, layouts or graphics)
  - Operating efficiencies
  - Changes to enhance the user interface without changes in performance

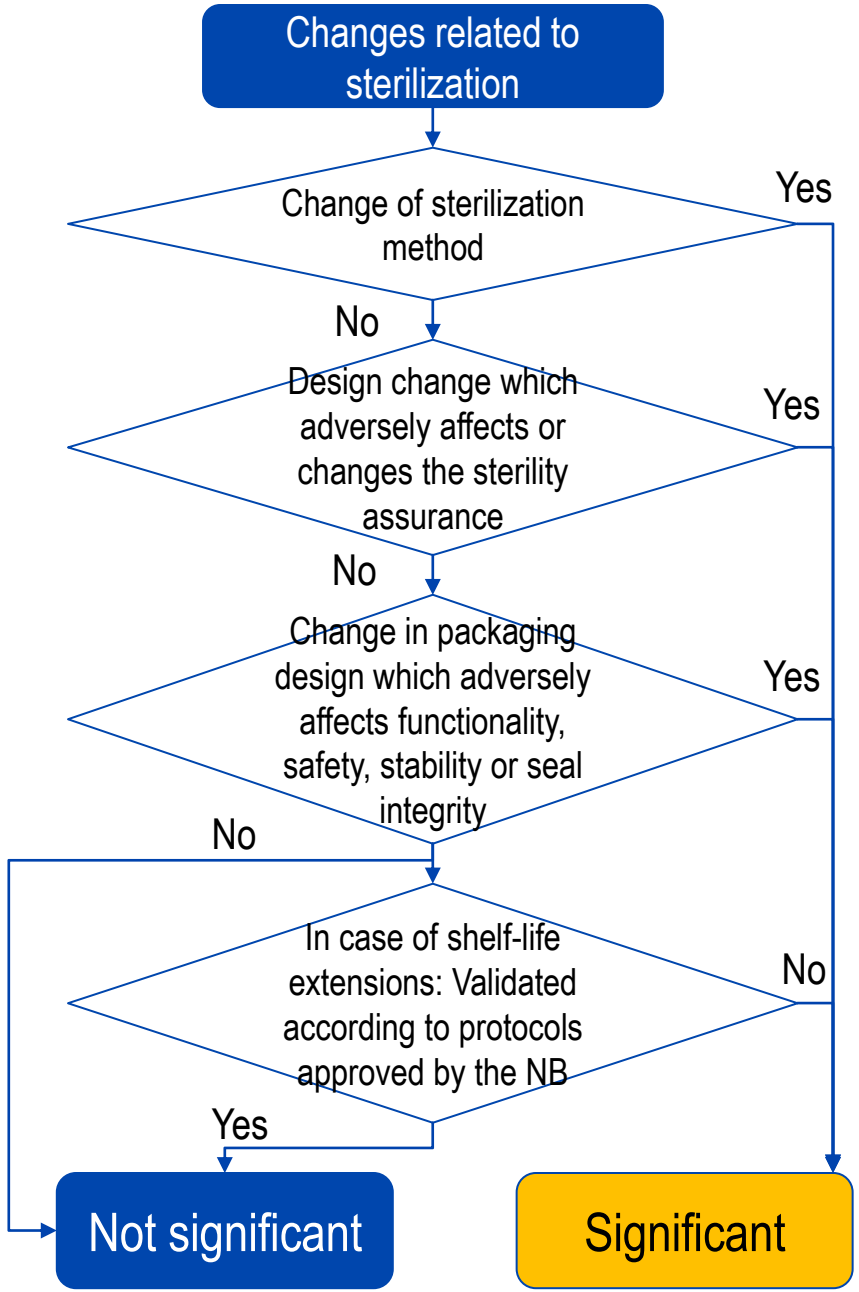
- Significant changes:
  - New or major changes of operating system or any component
  - New or modified architecture or database structure, change of algorithm
  - Addition of a new database with new content that is used to compare genetic assay results with
  - Required user input replaced by closed loop algorithm
  - New user interface or presentation of medical data in a new format or by a new dimension or measuring unit



Changes related to sterilization

- Significant changes:
  - Change of sterilization method, including changing a device from ‘non-sterile’ to ‘sterile’
  - Changes in the design or packaging that adversely affect the sterility assurance or the effectiveness of the sterilization (e.g. integrity of a seal)
  - Extension of shelf life with modification of protocols approved by the Notified body

- Non-Significant changes:
  - Change of the shelf life validated by protocols approved by the Notified Body



Conclusions

- Plan and evaluate all changes upcoming for the manufacturer portfolio
- Contact Notified Body for all significant changes and to prepare the transition to IVDR
- Collect and analyze all data
- Conduct all necessary studies
- Get in touch with a Notified Body with your transition plan as soon as possible

? QUESTIONS ?

спасибо
GRACIAS 谢谢
THANK YOU
ありがとうございました MERCI
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감사합니다

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LEGAL ISSUES ARISING FROM THE IVDR COMING APPLICABLE

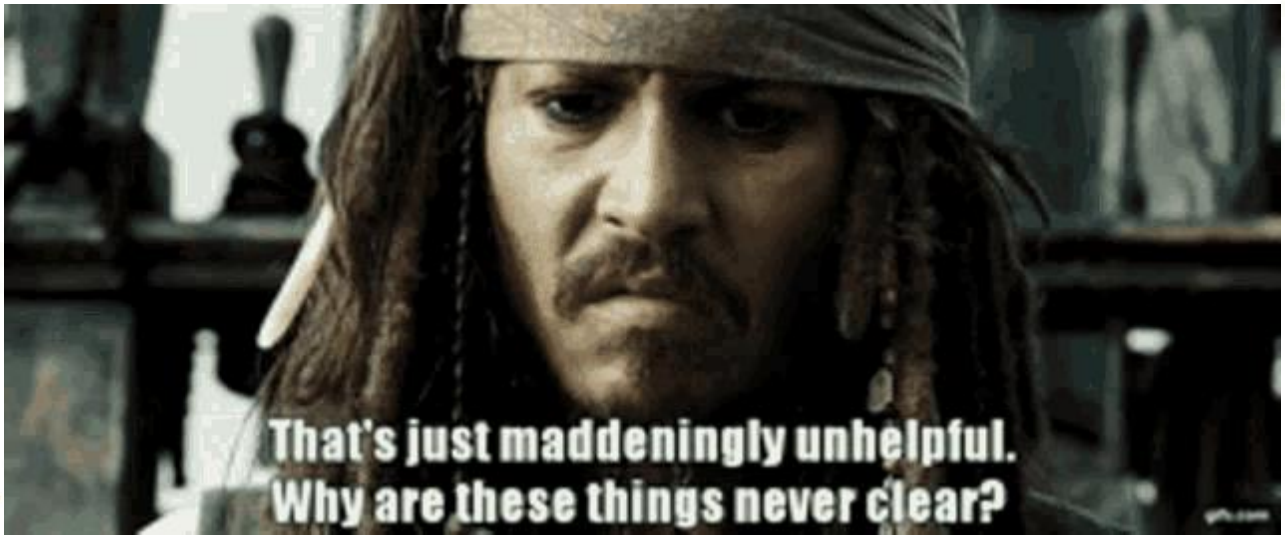
SelectScience Webinar
28 March 2022

health
food
technology

Erik Vollebregt
www.axonadvocaten.nl

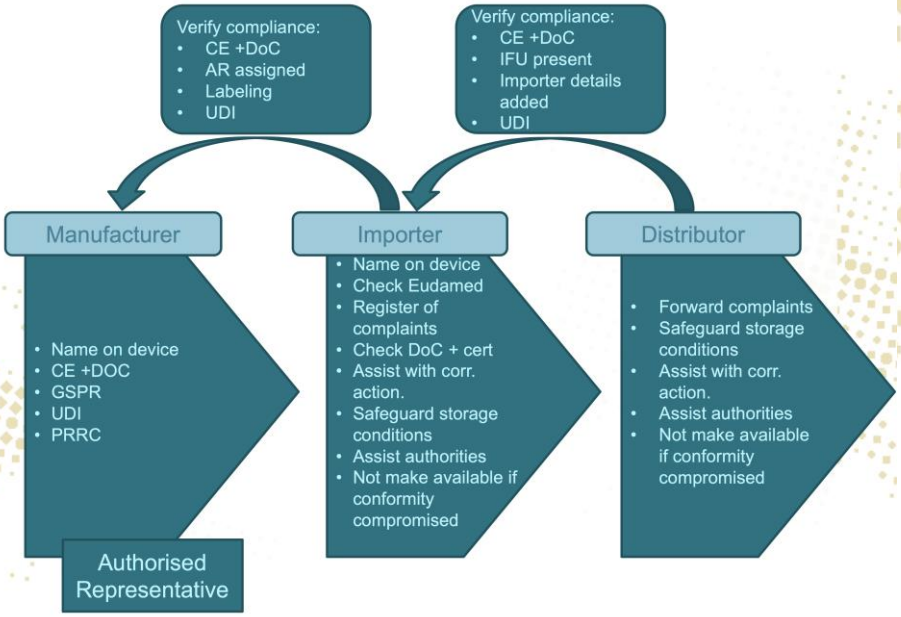
Agenda

- Economic operators, placing on the market and legacy IVDs
- What are the criteria for the use up period?
- Does the Clinical Trial Regulation apply to IVDs or IVDs used in Clinical Trials?
- Consequences for agreements and M&A



Economic operators

- Understand new supply chain rules and what they mean for
    - contracts with third parties in the supply chain
    - the company's own supply chain
- Update / renegotiate agreements where necessary or opportune
- Use IVDR as opportunity for more cooperative supply chain model to achieve your PMPF data goals
    - Or be prepared for questions and NCs during NB audits



Economic operators and legacy devices

- Legacy devices?
    - Devices in scope of article 110 (3): all IVDR covered devices with valid IVDD DoC or EC certificate at IVDR DoA
- Legacy devices economic operator obligations?
    - MDCG 2021-25 on economic operators and legacy devices under MDR
    - Scope of article 110 (3) IVDR – certain IVDR vigilance, PMS and economic operator obligations
- Who is importer or distributor?
    - Making available and placing on the market as core concepts still poorly understood
    - Lots of colloquial use of term distributor to refer to an importer
    - MDCG 2021-27 on Q&A on importers and distributors

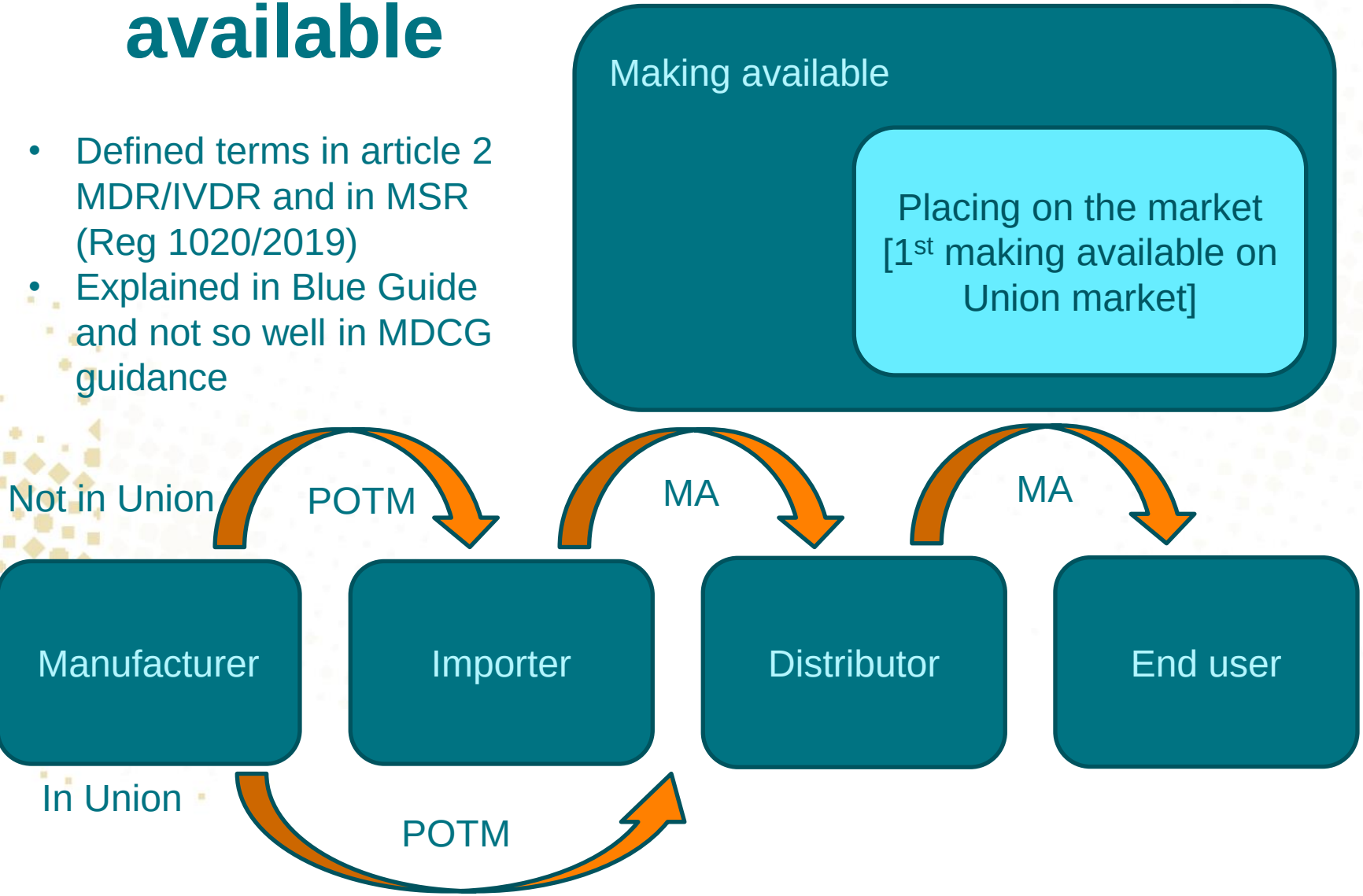
Legacy devices after IVDR amendment

Placing on the market and making available

- Core concepts for economic operator regime
  - Relevant for qualification as economic operator
    - And for difference between importer and distributor
  - Relevant for knowing what products are covered by what rules
    - IVDR date of application
    - staggered grace periods introduced with IVDR amendment

Placing on the market and making available

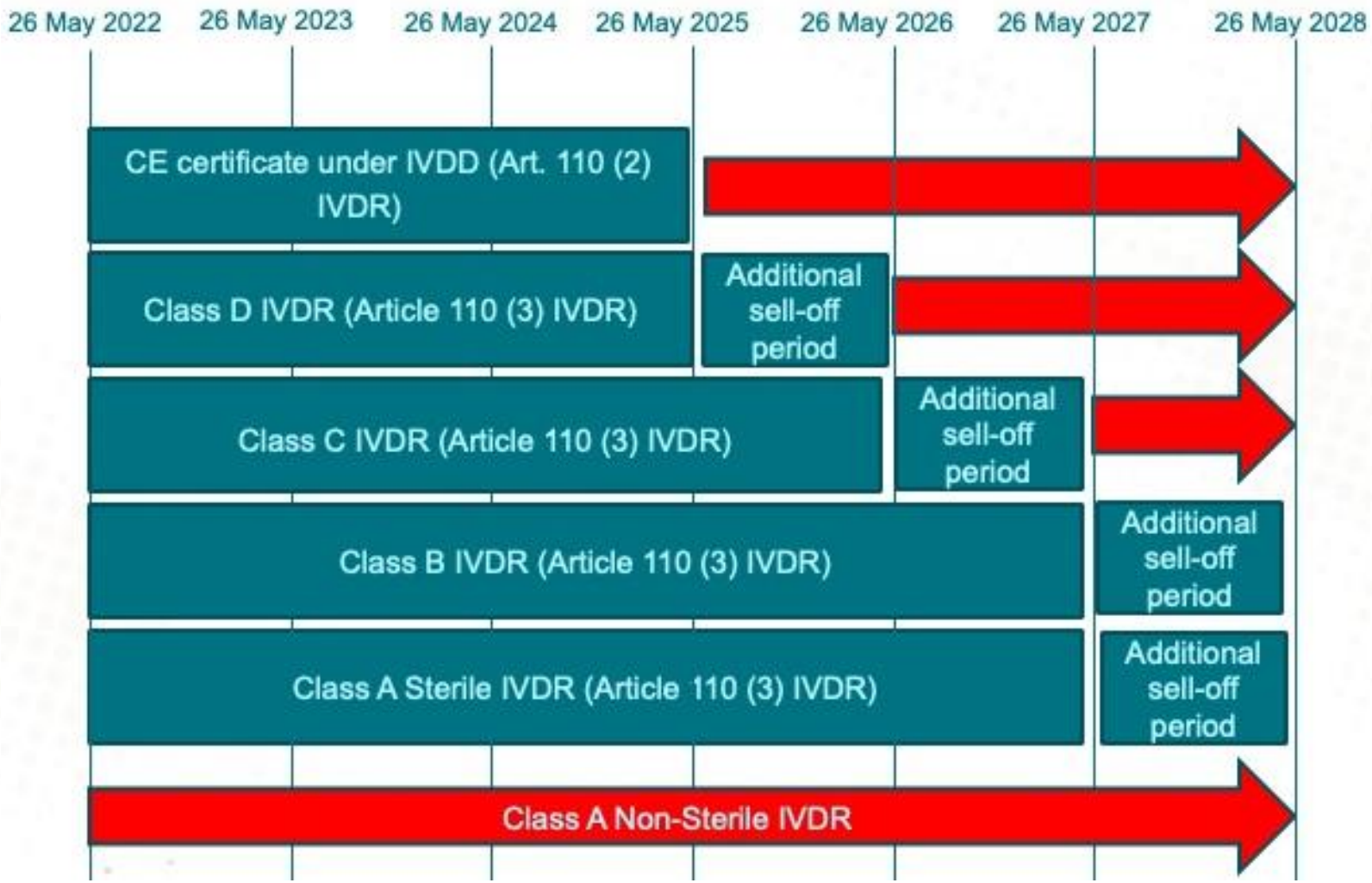
- Defined terms in article 2 MDR/IVDR and in MSR (Reg 1020/2019)
- Explained in Blue Guide and not so well in MDCG guidance



Use up period / sell-off period

- Article 110 (4) IVDR applies to:
  - Devices
  - Lawfully placed on the market
    - Before DoA under the IVDD
    - After DoA before end of the grace period
  - May continue to be made available or put into service
  - Until 1 year after end of grace period
  - In other words: devices have to reach the end user before end of grace period + 1 years
    - If not, cannot be made available or put into service anymore in the Union after that date

Use up period



IVDs and CTR

- Does the CTR apply to IVDs?
    - CTR is framework to regulate studies with medicinal products (not studies with IVDs)
    - IVDR has a CTR-like regime for performance studies with IVDs (i.e. testing of an IVD for market access)
    - IVD may be relevant in clinical trials for diagnostic procedures in addition to normal clinical practice (article 2 (2) (2) CTR)

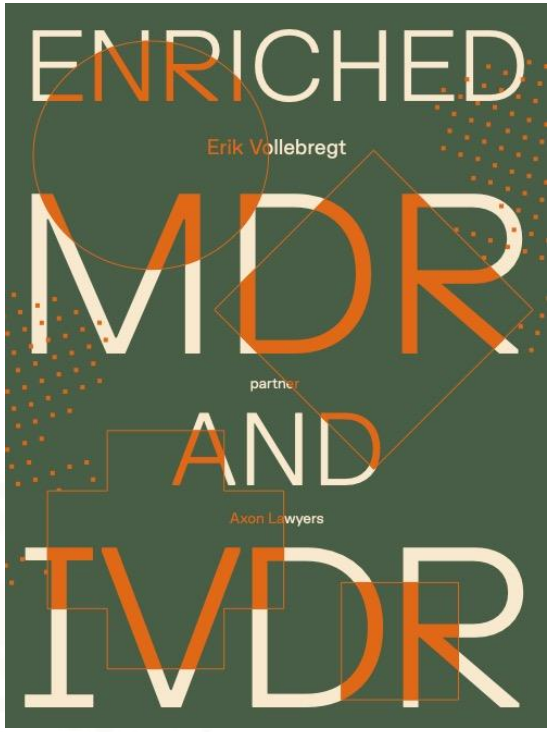
IVDs and CTR

- Does the CTR apply to IVDs in clinical trials?
    - CTR does refer to devices that can be investigated in addition to the IMP (Annex I B (7) (i) CTR) but a clinical trial under CTR is not a performance study for IVDR purposes
    - However, using an IVD that does not comply with the IVDR in a clinical trial does have consequences under the CTR
        - Clinical data obtained will be invalid, unless this accounted for in the protocol of the clinical trial

IVDR and M&A

- Article 110 (3) IVDR makes significant changes to the IVD during the grace period impossible
    - Significant change is for example a change to the identity of the manufacturer (e.g. in asset purchase)
    - Manufacturers with IVDs in grace period will not be able to make significant changes to devices until the device is IVDR CE marked, so be careful with M&A targets that claim changes to functionality, intended purpose, design, etc.
    - See MDCG 2020-3 for MDR medical devices for inspiration on what can be a significant change (e.g. most software changes, material changes, sterilization changes, extension of patient groups, test indications)
        - No IVDR specific significant changes guidance available yet but underway

Thanks for your attention!



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