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GENOMIC ANALYSIS BY LGC

Commercial readiness in light of IVDR

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Meet our speakers

BIOSEARCH™ TECHNOLOGIES
GENOMIC ANALYSIS BY LGC

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LGC

Mehr Sicherheit.
Mehr Wert.

Choose certainty.
Add value.

Impact of the new device classification under IVDR

Julien Senac, Ph.D.

In Vitro Diagnostic Device - Definition

'in vitro diagnostic medical device' means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:

a. concerning a physiological or pathological process or state;
b. concerning congenital physical or mental impairments;
c. concerning the predisposition to a medical condition or a disease;
d. to determine the safety and compatibility with potential recipients;
e. to predict treatment response or reactions;
f. to define or monitoring therapeutic measures.

IVD classification

Directive 98/79/EC (IVDD)

Article 9: Conformity assessment

Products

Annex II List A

Annex II List B

Self-Testing devices

Other products

Regulation EU 2017/746 (IVDR)

Chapter V: Classification and conformity assessment

Article 47: Classification of products

Annex VIII – Classification rules

- Implementing rules
- Classification rules (Rules 1 – Rules 7)

Products – Risk-class

Class D

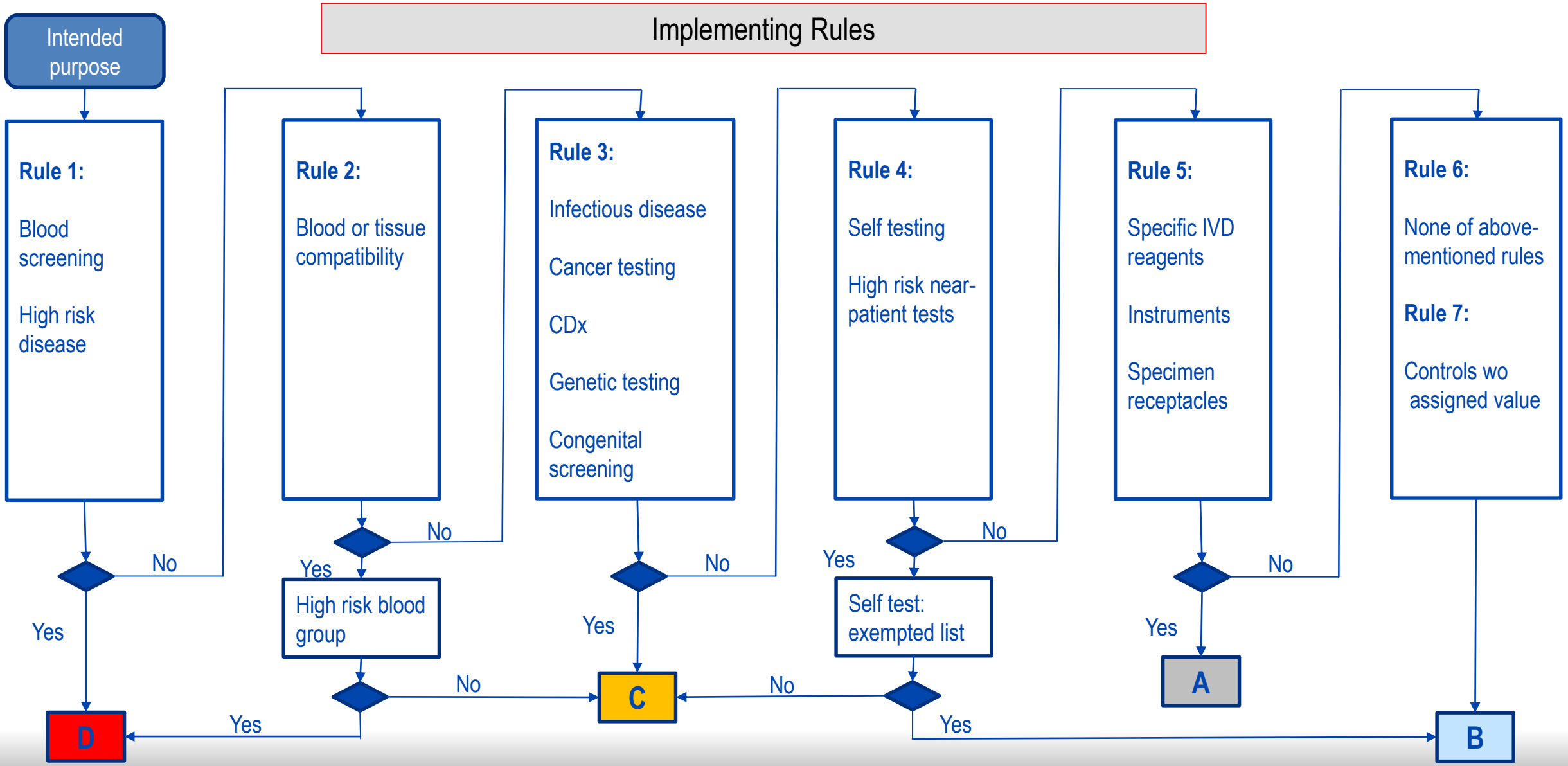
Class C

Class B

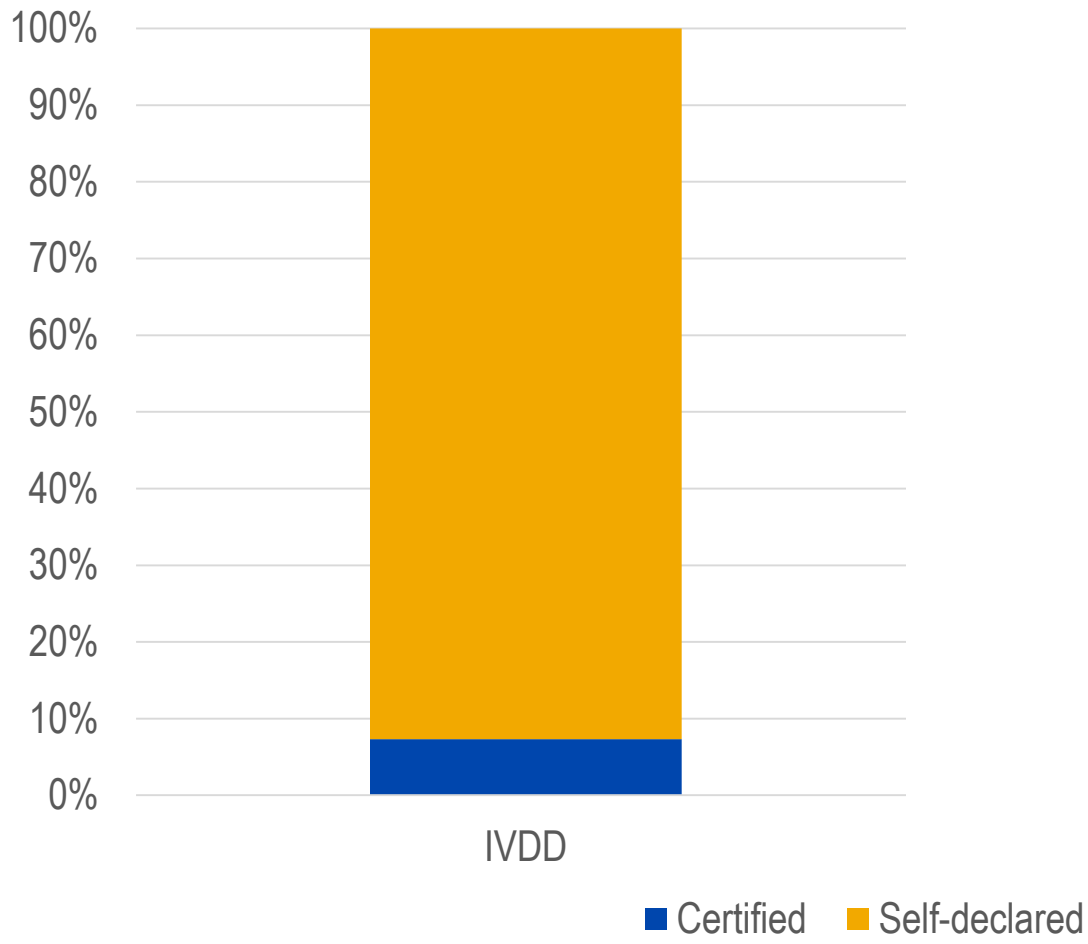
Class A

(Self-testing or near-patient devices, companion diagnostics)

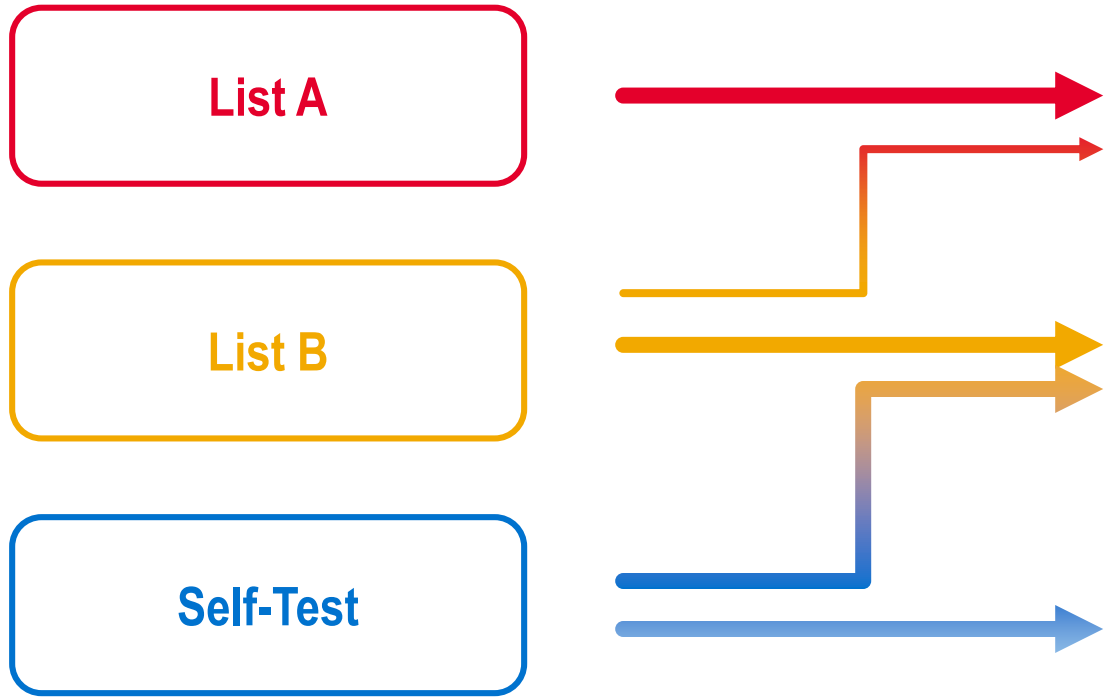
IVD classification



New classification impact



New classification impact



Class D

Class C

Class B

Class A

Up-classified

anti-duffy, anti-kidd
syphilis, chagas

Cancer biomarkers
CDx, genetic tests

Other self-declared
devices

New classification impact – Interpretation

New classification impact – Don’t forget software

New classification (non) impact

Plans for all devices

- Strategy for Regulatory Compliance (Article 10 & Annex IX)
- Risk Management Plan (Annex I)
- Performance Evaluation Plan (Article 56 & Annex XIII)
- Performance Study Plan (Annex XIII)
- Post-Market Surveillance Plan (article 79 & Annex III)
- Post-Market Performance Follow-up Plan (Annex XIII)

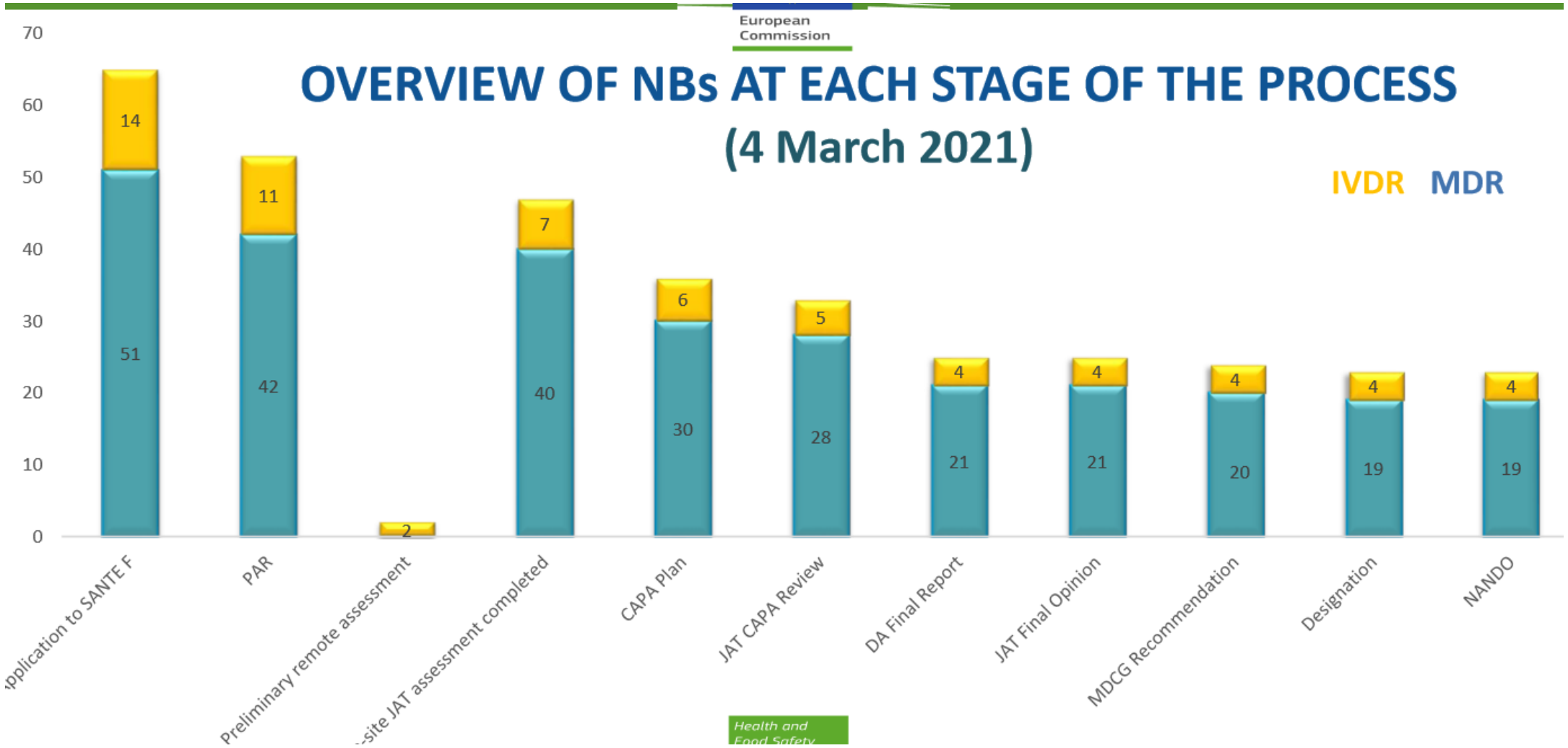
Reports for all devices

- Risk Management Report (Article 10 & Annex I)
- Scientific Validity Report (Annex XIII)
- Analytical Performance Report (Annex XIII)
- Clinical Performance Report (Annex XIII)
- Performance Evidence Report (Annex XIII)
- Clinical Performance Study report (Annex XIII)
- Post-Market Surveillance Report (Article 80)
- Periodic Safety Update Report or PSUR (Article 81) (C and D)
- Periodic Summary report (Article 82) (A and B)
- Trending report (Article 83)
- Post-Market Performance Follow-up Report (Annex XIII)
- Summary of Safety and Performance or SSP (Article 29)
- IFU/Labeling (Document) (Chapter III, Annex I)
- Claims (Document) (Article 7)
- Declaration of Conformity (Annex IV)

What should I do with my portfolio?

- Determine which products will be maintain on the market
- Clearly define the intended purpose according to Annex II, exclude claims to avoid ambiguity
- Determine the class of the product and discuss it with NB
- Renew certificates for List A, List B, and self-tests
- Prioritize my entire portfolio
- Anticipate the bottleneck

New classification impact



? QUESTIONS ?

спасибо
GRACIAS 谢谢
THANK YOU
ありがとうございました MERCI
DANKE धन्यवाद
شُكراً OBRIGADO
Gracie
감사합니다

Dr. Julien Senac
Director – IVD Global Focus team

Julien.senac@tuvsud.com

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LGC webinar

health
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Erik Vollebregt
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MedTech Europe
from diagnosis to cure

Overview of requirements under the IVD Regulation

Regulation 2017/746/EU on *In Vitro* Diagnostic Medical Devices

December 2017

This flowchart has been prepared by MedTech Europe as a 'high-level overview' of the requirements of the IVD Regulation. While MedTech Europe considers the information herein to be reliable it makes no warranty or representation as to its accuracy, completeness or correctness. This flowchart is intended for informational purpose only and should not be construed as legal advice for any particular facts or circumstances.

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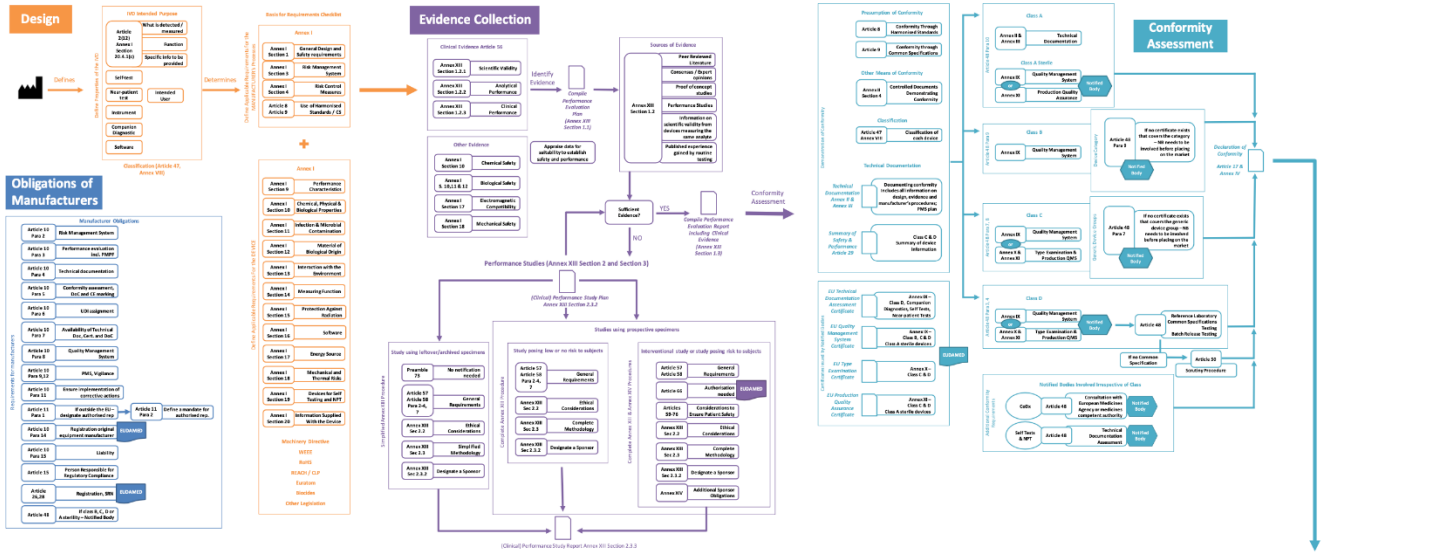
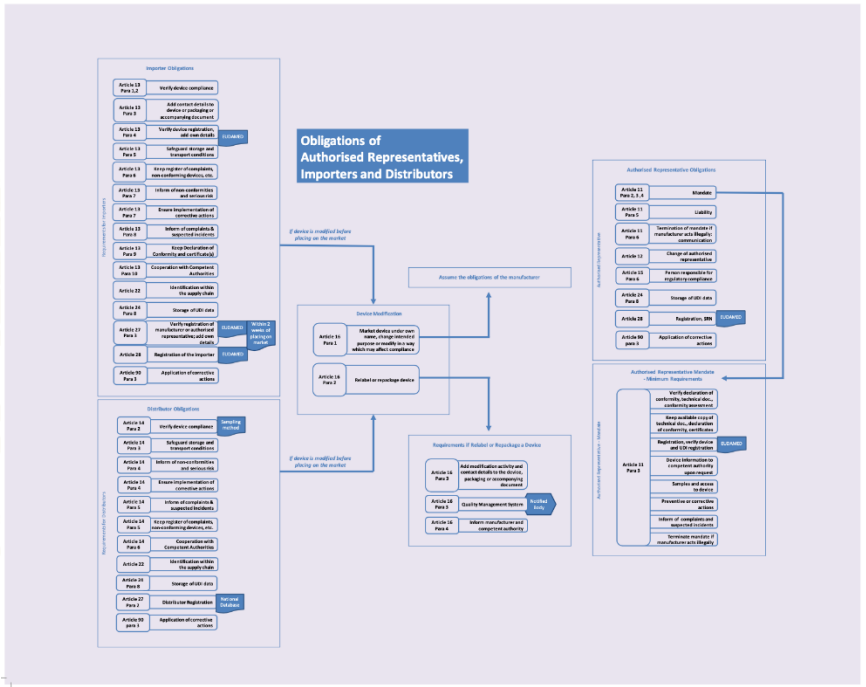
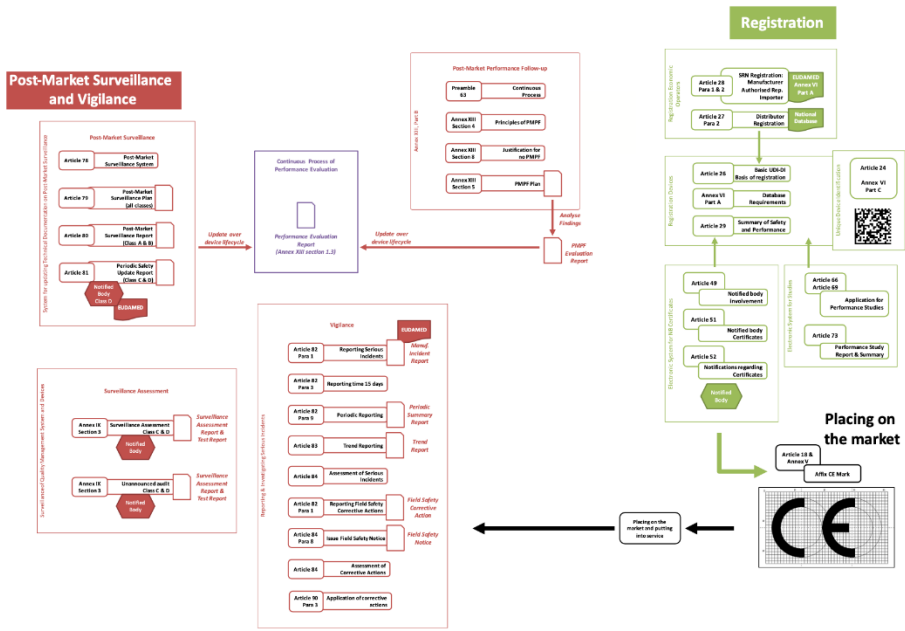
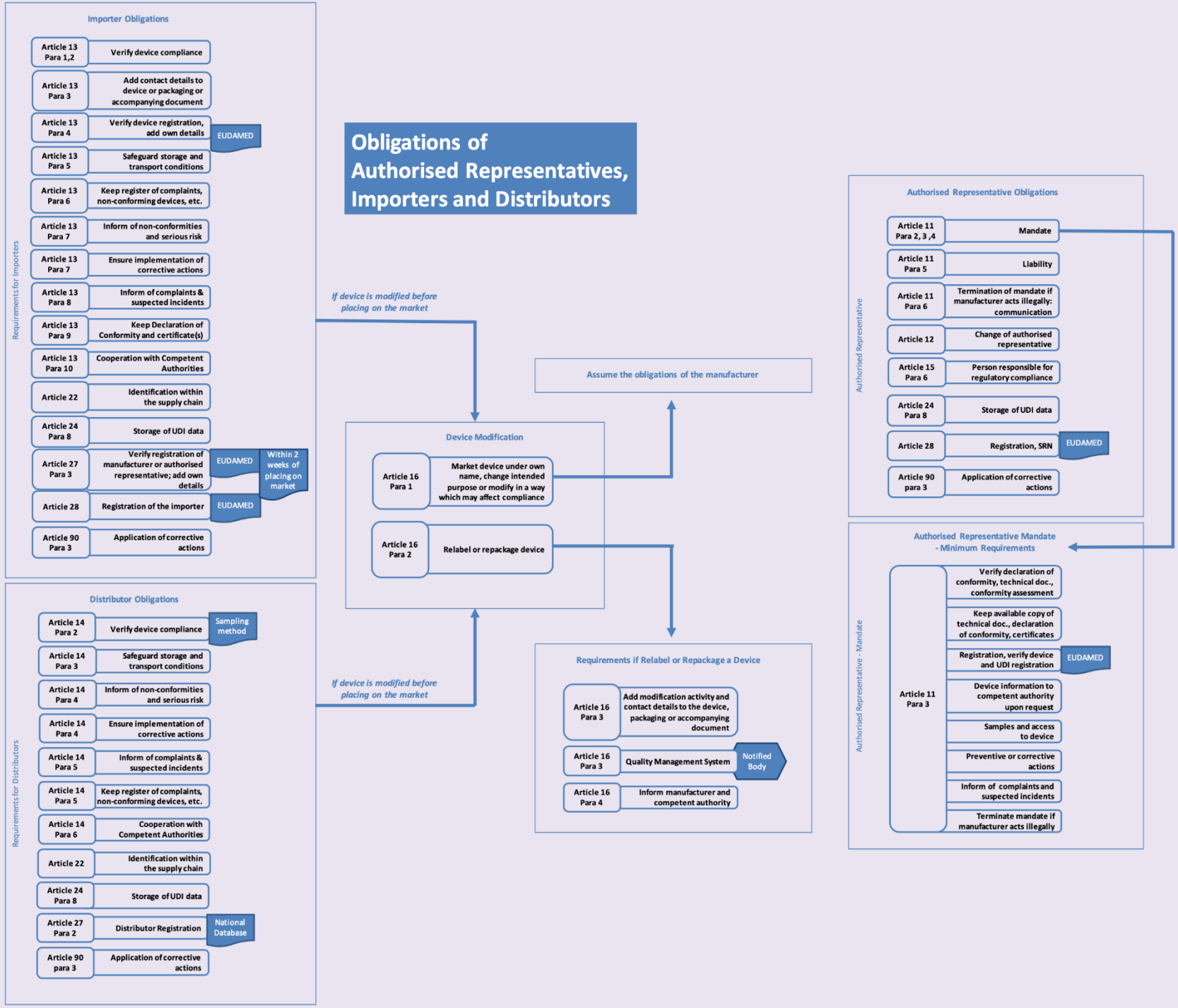




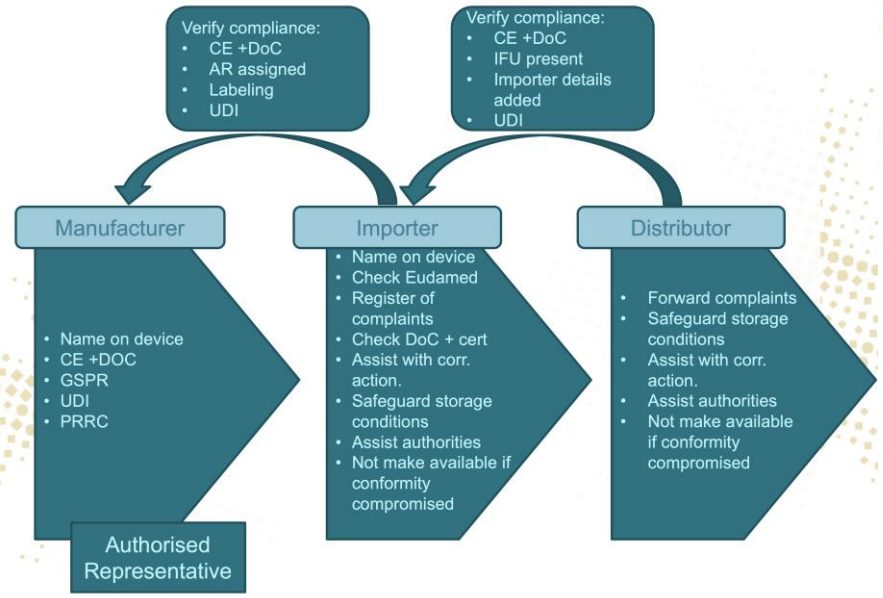


Obligations of Authorised Representatives, Importers and Distributors



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 MDR as opportunity for more cooperative supply chain model to achieve your PMCF data goals
    - Or be prepared for questions and NCs during NB audits



How to qualify economic operator?

Manufacturer

- Places non-imported devices on the market

Importer

- Places imported devices on the market
- Established in the Union

Distributor

- Makes devices available
- Can be manufacturer (or not) under art. 16 conditions (branded distribution
- May put devices into service

Authorised Representative

Clearance, logistics and storage providers

- Does not make devices available on own behalf

System integrator / procedure pack steriliser

- Has general EO obligations (e.g. UDI)

How to qualify economic operator?

Understanding of concepts of “placing on the market” and “making available” crucial for EO characterisation

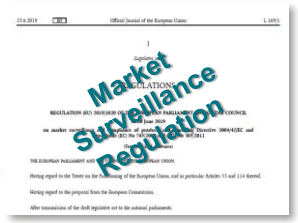
Placing on the market

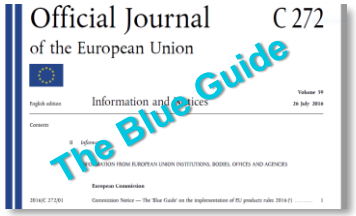
- first transfer of a device from the manufacturing stage into the Union distribution chain after final quality control release as finished goods (includes packaging or labelling); and
- the device must be freely available for supply or final use within the Union supply chain (customs cleared and intent to distribute in Union)

Making available

- device must be supplied for distribution, consumption or use in the Union in the course of a commercial activity, either for payment or free of charge
- Implies offer or agreement, physical handover not required

Toolbox EOs: understand these to understand EO





Be prepared to educate your company's legal department to avoid costly mistakes

Supply and distribution agreements

- Wholesalers – also qualify as importers or distributors even if they don’t want to

- How to work together for

  - autonomous obligations of importers and distributors
  - overlapping responsibilities in supply chain
  - Article 25 MDR obligation of traceability

- Manufacturer must be able to demonstrate for PMS plan purposes that he leverages PMS information in supply chain (Annex III, 1.1 and 1.2)

  - Goes beyond mere complaints logging and vigilance
  - E.g. ensure access to article 13 (5) MDR/IVDR distributor registers of user/patient complaints, non-conforming devices, recalls and withdrawals

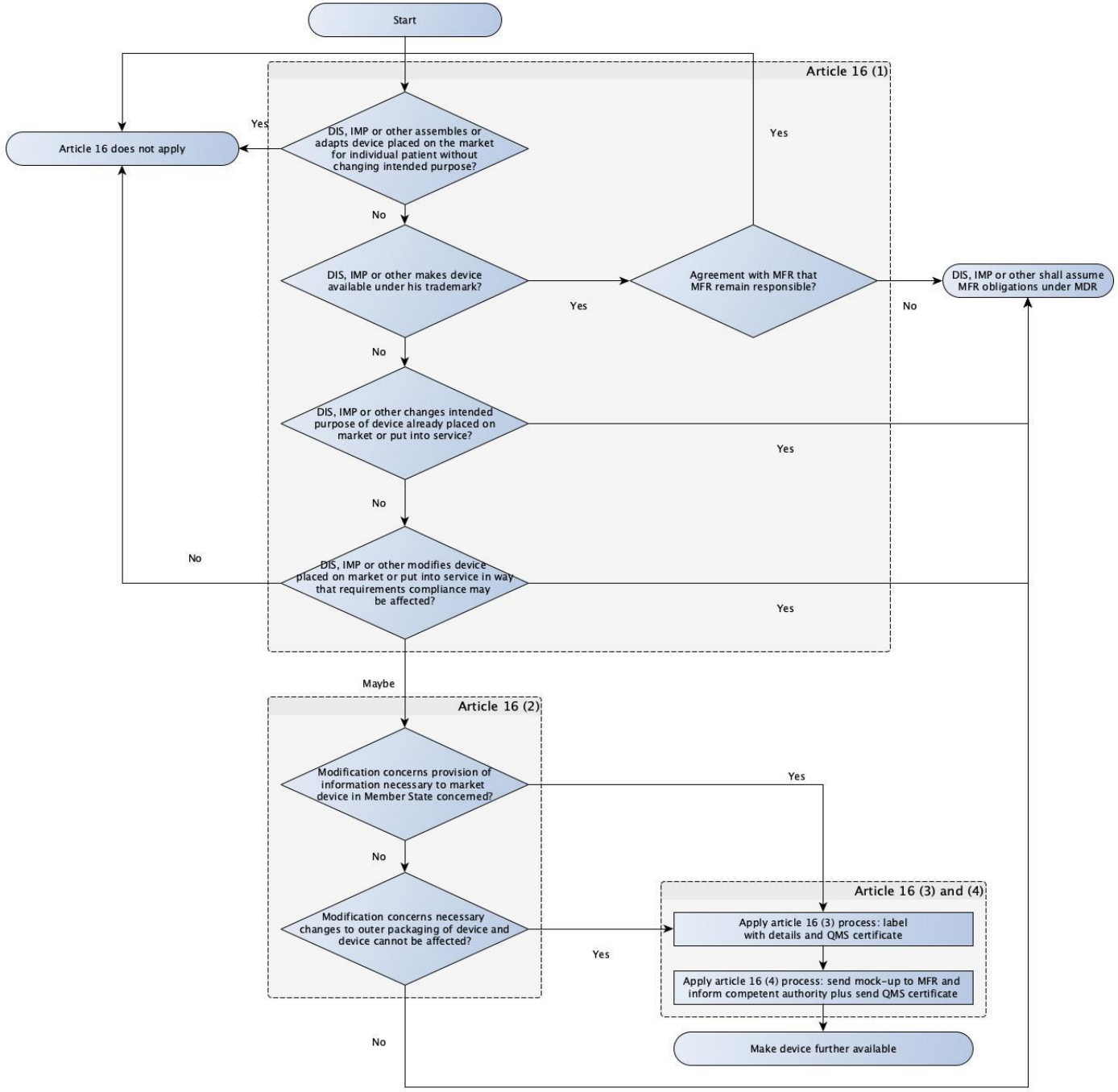
- Requires careful and precise revisions of agreements

Third parties: repacking & relabelling

- Basically pharma repacking case law written down for devices
- Strangely enough stricter regime than outcome of the EU Court Servoprax case (C-277/15) and Lohman & Rauscher Case (C-662/15)

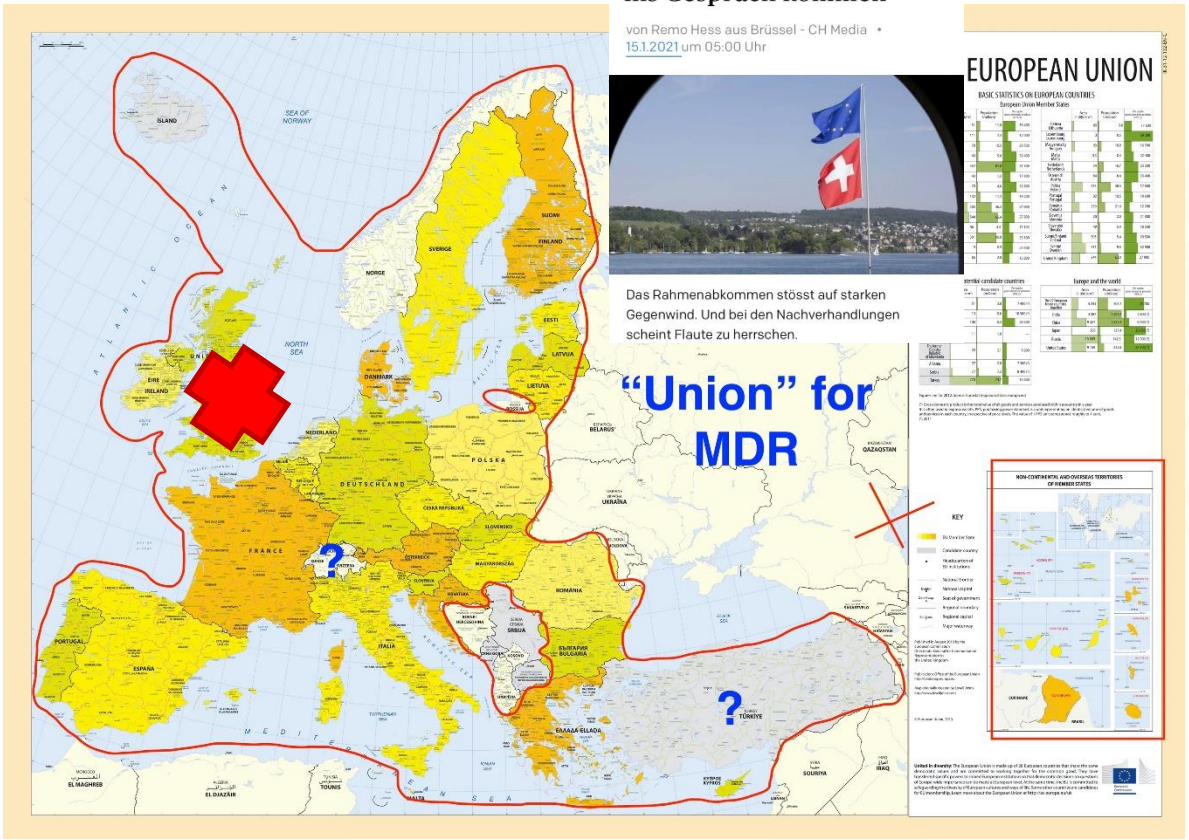
- Article 16 (2) – (4) MDR/IVDR:

    - Translation of IFU and other information and repacking do not make someone a manufacturer
    - “necessary”
    - Indicated person responsible for activity on the pack or accompanying document
    - Have notified body blessed QMS for activity and have access to manufacturer vigilance action
    - Reporting and mock-up to manufacturer and NCA for each time repacked / relabelled device is made available

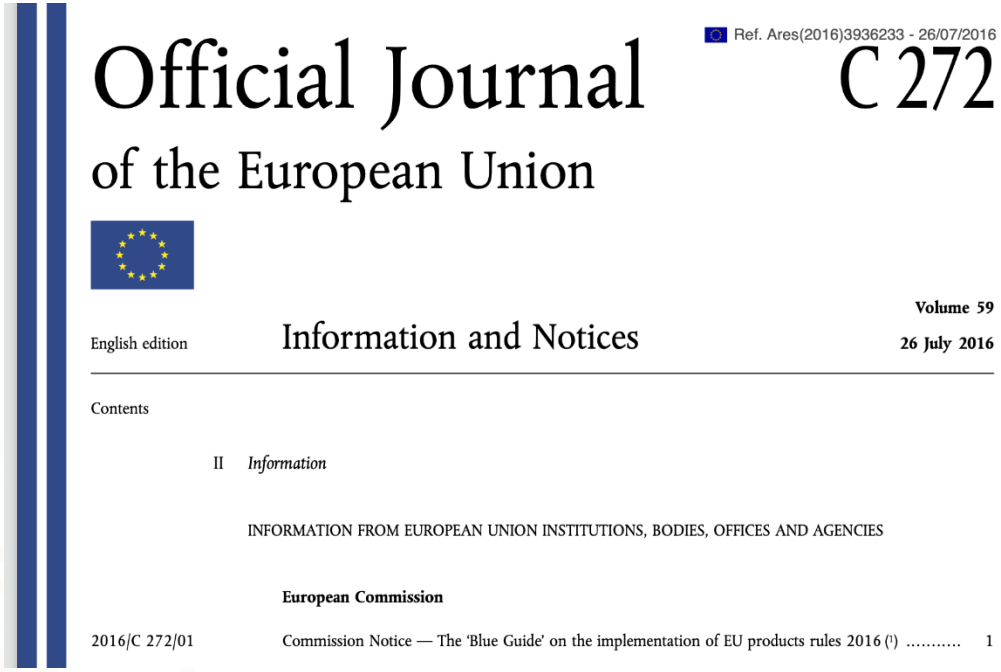

Start
Article 16 (1)
DIS, IMP or other assembles or adapts device placed on the market for individual patient without changing intended purpose?
Yes
Article 16 does not apply
No
DIS, IMP or other makes device available under his trademark?
Yes
Agreement with MFR that MFR remain responsible?
Yes
DIS, IMP or other shall assume MFR obligations under MDR
No
No
DIS, IMP or other changes intended purpose of device already placed on market or put into service?
Yes
No
DIS, IMP or other modifies device placed on market or put into service in way that requirements compliance may be affected?
Yes
No
Maybe
Article 16 (2)
Modification concerns provision of information necessary to market device in Member State concerned?
Yes
No
Modification concerns necessary changes to outer packaging of device and device cannot be affected?
Yes
Article 16 (3) and (4)
Apply article 16 (3) process: label with details and QMS certificate
Apply article 16 (4) process: send mock-up to MFR and inform competent authority plus send QMS certificate
Make device further available
No

Exits

- Brexit – happened 31/12/20
- Swixit – likely 26/05/21
- Turkxit – maybe 26/05/21



MDR, IVDR and the Union



Ref. Ares(2016)3936233 - 26/07/2016

Official Journal of the European Union

C 272

English edition

Information and Notices

Volume 59

26 July 2016

Contents

II *Information*

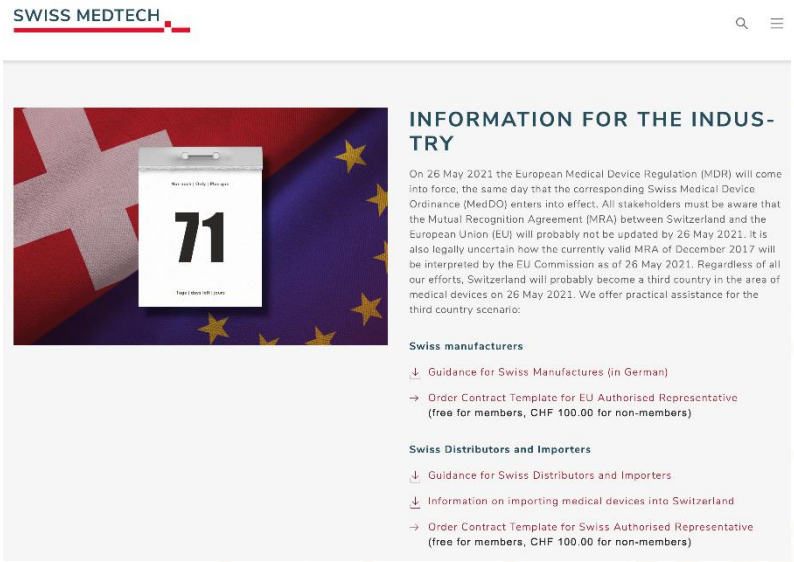
INFORMATION FROM EUROPEAN UNION INSTITUTIONS, BODIES, OFFICES AND AGENCIES

European Commission

Brexit

- Brexit agreement of Christmas 2020
  - Still not ratified by European Parliament
  - UK is now ‘third’ country for Union
  - No special rules for medical devices
    - UK notified bodies no longer Union NBs
    - UK allows CE marked devices on its market for fixed period; EU does not allow UK approved devices on EU market
    - UK starts with roll-out of UKCA system
    - UKCA devices
- ‘Breaking Europe up from the inside didn’t work, now back to breaking it up from the outside - it’s called diplomacy’

Swixit



- MRA with Switserland only covers medical devices and IVD directives and the transitional regime
- There is a negotiated Institutional Framework Agreement with the EU but this has not yet been approved at political level
    - So the EU pushes Switserland out of the Union, one MRA at a time – end of May 2021 medical devices, end of May 2022 IVDs
    - Switserland has synched its own Medizinprodukteverordnung (MepV) with the MDR and IVDR but misses mutual recognition without the IFA

Turkxit

- Turkey is linked to EU by Association Agreement that contains a customs union based on Decision 1/95, removal of technical barriers (Decision 1/97) and notification of Turkish notified bodies plus equivalence of CE and Turkish legislation for a number of EU directives, including those for medical devices and IVDs (Decision 1/2006)
  - Same situation as Switzerland: legislation is aligned but are the MDR and IVDR on the list in time?
  - Complex political situation between EU and Turkey
  - European Commission: ‘all will be well, just one small personal data thing to take care of’
    - Yet: no Turkish MDR / IVDR NB so far, no EUDAMED for Turkey

NB 1783	TURKISH STANDARDS INSTITUTION (TSE)	Turkey
NB 1984	Kiwa Belgelendirme Hizmetleri A.Ş.	Turkey
NB 2195	Szutest Uygunluk Değerlendirme A.Ş.	Turkey
NB 2292	UDEM Uluslararasi Belgelendirme Denetim Egitim Merkezi San. ve Tic. A.Ş.	Turkey
NB 2764	Notice Belgelendirme, Muayene ve Denetim Hizmetleri Anonim Şirketi	Turkey

How to work with the exits?

- Blue Guide (new version underway)
  - Economic operators regime
    - Placing on the market
    - Importer
    - Authorised representative

EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR INTERNAL MARKET, INDUSTRY, ENTREPRENEURSHIP AND SMEs
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY
DIRECTORATE-GENERAL FOR MOBILITY AND TRANSPORT
DIRECTORATE-GENERAL FOR JUSTICE AND CONSUMERS
DIRECTORATE-GENERAL FOR ENVIRONMENT
DIRECTORATE-GENERAL FOR ENERGY

Brussels, 13 March 2020
REV2 – replaces the notice (REV1) dated 22 January 2018 and the Q&A document dated 1 February 2019

NOTICE TO STAKEHOLDERS

WITHDRAWAL OF THE UNITED KINGDOM AND EU RULES IN THE FIELD OF INDUSTRIAL PRODUCTS[1]

- Brexit guidance industrial products version 13 March 2020
  - Economic operators
  - Notified bodies and certificates
  - Transitional regime and placing on the market around the transitional regime
  - Explain the complex NI situation (including UK(NI) marking by Irish notified bodies – which have their own NANDO page now: https://ec.europa.eu/growth/tools-databases/nando/index.cfm?fuseaction=ireland.main)

Scenario anyone?

- Does your company have the possible scenarios managed?
  - I have an MDD certificate of a Turkish notified body for a device in a kit – they say it will all be fine after 26 May.
  - I’m a US multinational and my European supply chain runs via my importer in Switserland for tax reasons, with the stock in a 3PL in the Netherlands.
  - I’m a manufacturer that sells a lot of IVDs into the UK. When do I need a UKCA mark for the devices?

Finally: the MSR, MDR and IVDR

- The Union becomes stronger and more tightly knit in terms of market surveillance
    - MDR market surveillance regime enters into force on 26 May 2021 (Chapter VII, section 3 MDR)
    - Market Surveillance Regulation (Regulation (EU) 1020/2019) by 16 July 2021 – applies to MDR en IVDD/IVDR and insofar as things are not regulated in MDR/IVDR
        - Especially relevant for devices in the fields of
            - Online sales (FSP responsibilities if you dropship via FSP)
            - Following first enforcement action by other competent authorities
            - Costs of enforcement may be charged to infringer

Thanks for your attention!

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.....the practical approach

The IVD, RUO or General Lab use?

Sue Spencer

IVD Lead Principal Consultant

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Scope of the IVDR

- Do I have an IVD, medical devices, general laboratory or research use only product?

- The IVDR does not apply to:

  (a) products for general laboratory use or research-use only products, unless such products, in view of their characteristics, are specifically intended by their manufacturer to be used for *in vitro* diagnostic examination;

  (b) invasive sampling products or products which are directly applied to the human body for the purpose of obtaining a specimen;

  (c) internationally certified reference materials;

  (d) materials used for external quality assessment schemes.

IVDR does not apply to medical devices, general lab or RUO!

General Laboratory Use

- No IVDR guidance
- IVDD Guidance MEDDEV 2.14/1 Contains examples of product of general laboratory use and IVD
- However

	Laboratory use product	Covered by IVD Directive
Centrifuges	General centrifuges, cytospin	Hematocrite centrifuge
Pipettes	General purpose pipettes (e.g. single or multiple pipettes, plastic pipettes, Pasteur pipettes)	Blood coagulation pipettes with automatic timing (Accessory of coagulometer)
Tubes and flasks	Erlenmeyers, plastic tubes	Blood collection tubes, urine sample containers
Plates	Empty ELISA plates, empty Petri dishes,	Coated microtiter plates for the diagnosis of Lyme's disease
Nucleic Acid extraction products	DNA and RNA extraction kits that only provide a specimen without an intended IVD detection combination	DNA and RNA extraction kits intended to provide a specimen to be used with an IVD device (validation for at least one combination is to be provided)
General equipment	Scales, balances, microtomes, incubators, sterilizers for laboratory equipment, paraffin embedding machine,	
HPLC products	size-exclusion HPLC columns	HPLC columns for IVD purposes: e.g. HbA1c
Detection equipment	Mass spectrometer, spectrophotometers, ELISA readers providing raw data which is not readily readable and understandable by the user (e.g. peaks, OD).	McFarland bacteria density testing
Others	Foetal calf serum, cell culture media, fixation solution, mounting media, buffers (e.g. PBS), chemicals (e.g. sulphuric acid, formol, water)	

RULE 5

The following devices are classified as class A:

(a) Products for general laboratory use, accessories which possess no critical characteristics, buffer solutions, washing solutions, and general culture media and histological stains, intended by the manufacturer to make them suitable for *in vitro* diagnostic procedures relating to a specific examination

RATIONALE

Rule 5a applies to general laboratory products like pipettes, stain powders, glass microscope slides, centrifuges, pipette tips or instrument liquid collection containers, buffers which usually do not fall under the definition of an IVD medical device. However, as specified in Regulation (EU) 2017/746 Article 1 (3a) *'This regulation does not apply to (a) products for general laboratory use (...), unless such products, in view (...) are specifically intended by their manufacturer to be used for in vitro diagnostic examinations.'*

As a consequence, if such products are specifically intended by the manufacturer to be used for *in vitro* diagnostic examinations, then they are considered as IVDs and are captured by rule 5.

'Accessory for an *in vitro* diagnostic medical device' as defined under Regulation (EU) 2017/746 article 2 (4), *'means an article which, whilst not being itself an in vitro diagnostic medical device, is intended by its manufacturer to be used together with one or several particular in vitro diagnostic medical device(s) to specifically enable the in vitro diagnostic medical device(s) to be used in accordance with its/their intended purpose(s) or to specifically and directly assist the medical functionality of the in vitro diagnostic medical device(s) in terms of its/their intended purpose(s)'*.

Whilst not being an IVD in themselves, accessories are to be used in conjunction with a specific IVD. They possess *one or more specific characteristics* to specifically enable an IVD to be used in accordance with its intended purpose or to assist the medical functionality of the IVD. Accessories are mentioned in rule 5 (a) in combination with the attribute *'accessories which possess no critical characteristics'*. This emphasizes that such products can negatively influence the benefit-risk ratio of the entire *in vitro* diagnostic medical device.

EXAMPLES (non-exhaustive)

- General microbiological culture media containing selecting agents, antimicrobial chromogenic agents, chemical indicators for colour differentiation.
- Solutions like cleaners, buffer solutions, lysing solutions, diluents specified for use with an IVD.
- Pipette with a specific fixed one volume specifically intended for a particular IVD test with specified human sample, e.g. blood coagulation pipettes with automatic timing (Accessory of coagulometer).
- General staining reagents like hematoxylin, eosin, pap and grams iodine.
- Kits for Isolation and purification of nucleic acids from human specimens.
- Library Prep reagents for preparation of DNA for downstream analysis by NGS sequencing.
- Nucleic acid quantitation kits.
- General reagents (not assay specific) used with a Class A instrument, e.g. general sequencing consumable reagents used with a sequencer.

If they are specifically intended for IVD use they are IVDs under rule 5 but class A

IVDD Guidance RUO MEDDEV. 2.14/2 rev.1

- Therefore once a medical device is intended by the manufacturer to be used for medical purposes it must either fall under the category of a product undergoing performance evaluation for the purpose of CE marking or be a product which is CE marked.
- 'For research use only' products do not have an intended medical purpose.
- When a medical purpose has been established based on sufficient and broadly agreed upon scientific, diagnostic and clinical evidence, then the product must comply with the requirements of the Directive before the manufacturer can place it on the market with an intended IVD use.

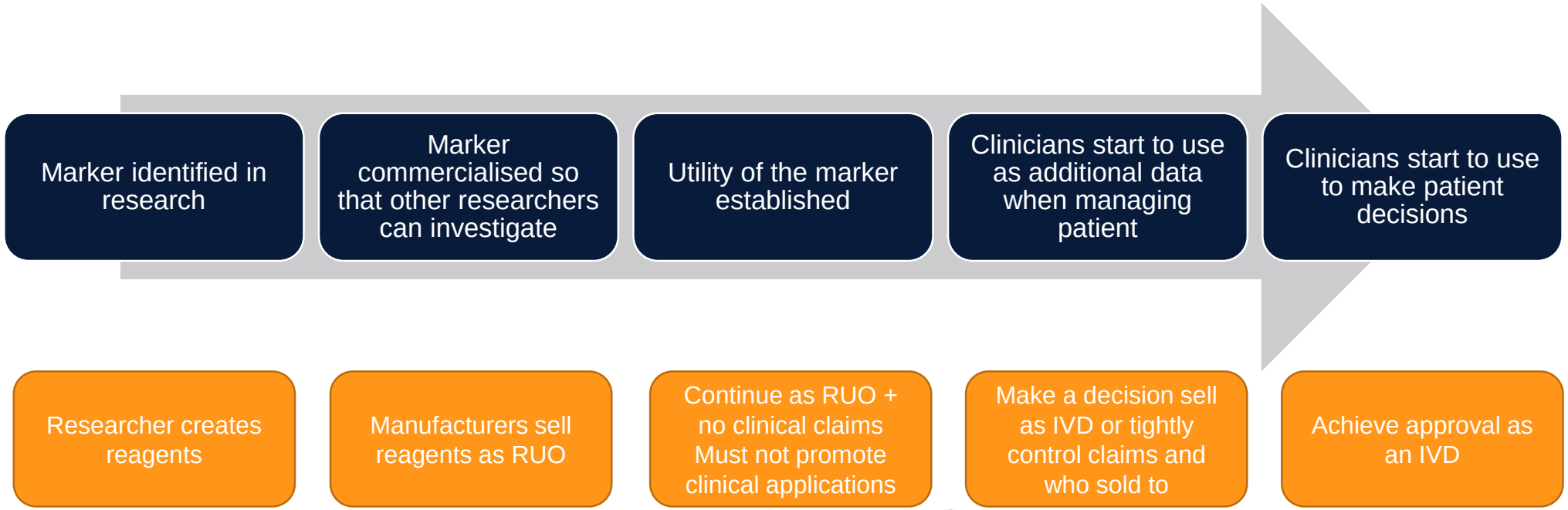
Examples

- **RUO products used for Basic Research:**
- **RUO products used in Pharmaceutical Research:**
- **RUO products used for a better identification and quantification of individual chemical substances or ligands in biological specimens:**
- **In house manufacturing of so called "home brew kits" by a legal entity for the purpose of research:**

Novel Devices

- **If you are developing a device the first thing you need to think,**
  - What is the intended purpose now
  - What are my aspirations for future intended purpose?
  - Do you intend it to become an IVD or just a research tool?

Novel Analyte – e.g. New biomarker for cancer



- What is your intended purpose and does it meet the IVDR definition?
- Who do you sell it to?
- What claims do you make when you sell it?

DANGER ZONE

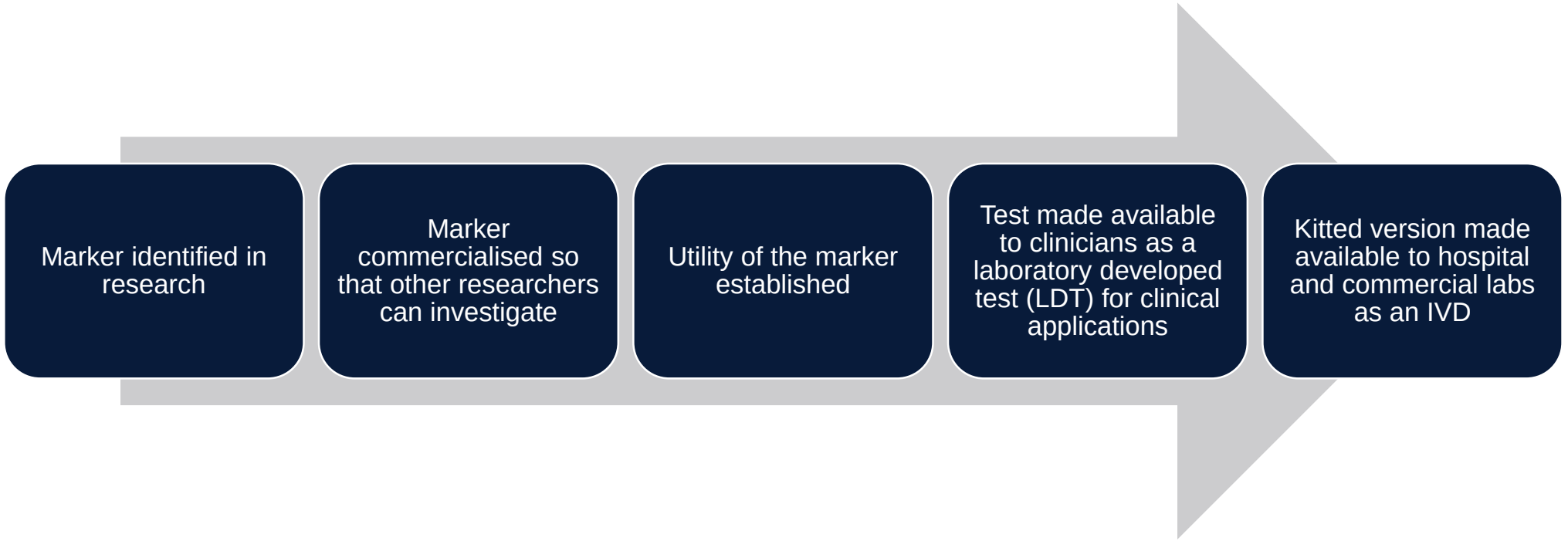
Manufacturers Responsibilities

Manufacturer

- Means a natural or legal person who manufactures or fully refurbishes a device or has a device designed, manufactured or fully refurbished, and markets that device under its name or trademark;

- Previously some countries allowed piggybacking off of OEM CE certificates where the manufacturer only held a Summary Technical Documentation (STED) these OBL/ private label arrangement are no longer accepted
- Manufacturers must:
  - Hold the full technical documentation under the manufacturers QMS
  - Responsible for design, design changes and manufacturing
  - Make arrangements for PMS/PMPF and vigilance activities with the OEM
  - Draw up a Declaration of Conformity
  - OEMs likely to be audited by the manufacturers Notified Body and are eligible for unannounced audits, on behalf of the legal manufacturer and access by the NB should be described in the contract

Alternative routes to market in the US What about EU?



More to follow in the next webinar!!!!

.....the practical approach

Thank you for your attention

Sue Spencer – IVD Lead /Principal consultant

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https://www.qservegroup.com/en/c67/sue--spencer

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