.....the practical approach

Industry Perspective IVDR

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Your MedTech Partner for **Regulatory, Quality Affairs & Clinical Trials**

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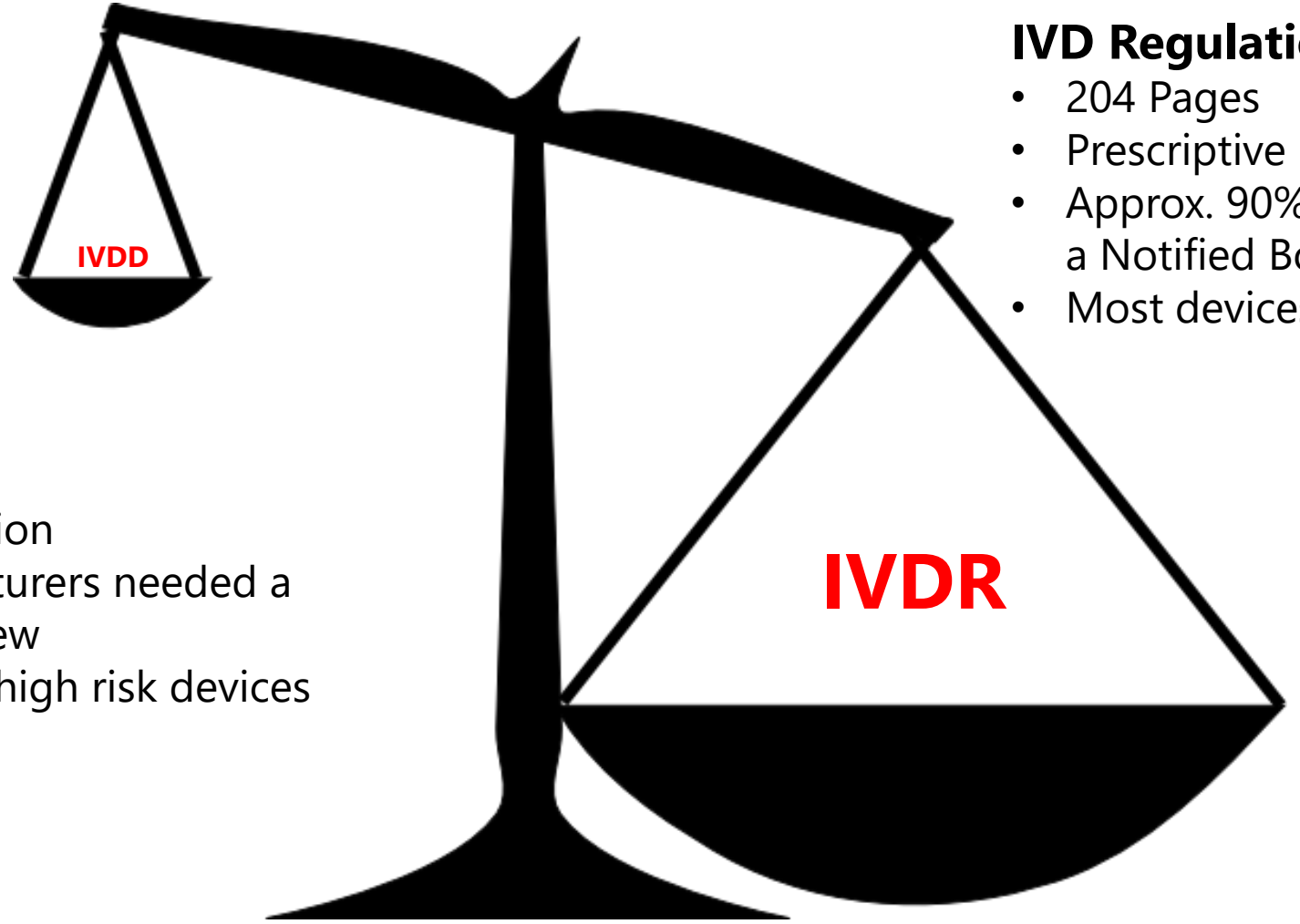
Todays Presenter

Sue Spencer - IVD Lead and Principal Consultant

- Sue leads Qserve's IVD service, she has over 30 years' experience in the Medical Device and IVD industries including extensive notified body experience.
- Sue has worked for several IVD companies ranging from start up to large multinationals, where she has held positions in R&D, manufacturing and quality assurance.
- Sue worked for 3 notified bodies establishing two from scratch.
- Sue chaired the European IVD Notified Body Working Group coordinating the notified body responses to the regulations. Sue also participated in the Commission IVD Technical Work Group for many years.

IVD Directive (IVDD) v IVD Regulation (IVDR)



IVD Directive

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

IVD Regulation

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

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

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- **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**

How prepared is industry?

Data from RAPS Workshop Feb 2021

How ready are you for the IVDR?	%
Not started	0
Planning	32
Completed gap analysis	21
Prepare initial Technical File	26
Submitted to the Notified Body	11
CE marking under the IVDR	5
Other	5

- Manufacturers have a long way to go

What is the greatest barrier to IVDR implementation?	%
The availability of qualified resources	11
Notified Body capacity	42
Cost remediation	0
Time remaining until the date of application	47
Other	0

- Currently only 4 IVD Notified Bodies
  BSI, TUV-Sud, TUV Rhineland, DEKRA Germany
- Already capacity issues at Notified Bodies
- They estimate the peak in Jun-Jul 2021

What are the key pitfalls?

Is it an IVD?

Definition IVD

- *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.

Specimen receptacles shall also be deemed to be *in vitro* diagnostic medical devices;

- **You have to justify why your product is an IVD in your Technical File.**
- **This has to be consistent with your broader claims**

Claims

Article 7 Claims
In the labelling, instructions for use, making available, putting into service and advertising of devices, it is prohibited to use text, names, trademarks, pictures and figurative or other signs that may mislead the user or the patient with regard to the device's intended purpose, safety and performance by:

(a) ascribing functions and properties to the product which the product does not have;

(b) creating a false impression regarding treatment or diagnosis, functions or properties which the product does not have;

(c) failing to inform of a likely risk associated with the use of the product in line with its intended purpose;

(d) suggesting uses of the product other than those declared in the intended purpose when the conformity assessment was carried out.

New requirement must have data to support each claim

Do I have an IVD?

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!

Swabs and lancets even supplied inside kits are medical devices and will need to meet IVDR from May 2021

Can I still Own Brand or Private Label?

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 this would have stopped 8 years ago but not enforced as most IVDs did not have NB oversight

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 who make the entire device are likely to be audited by the manufacturers Notified Body and are eligible for unannounced audits, on behalf of the legal manufacturer
- Access by the NB should be described in the contract

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Intended Purpose?

Key pitfall!

Intended purpose

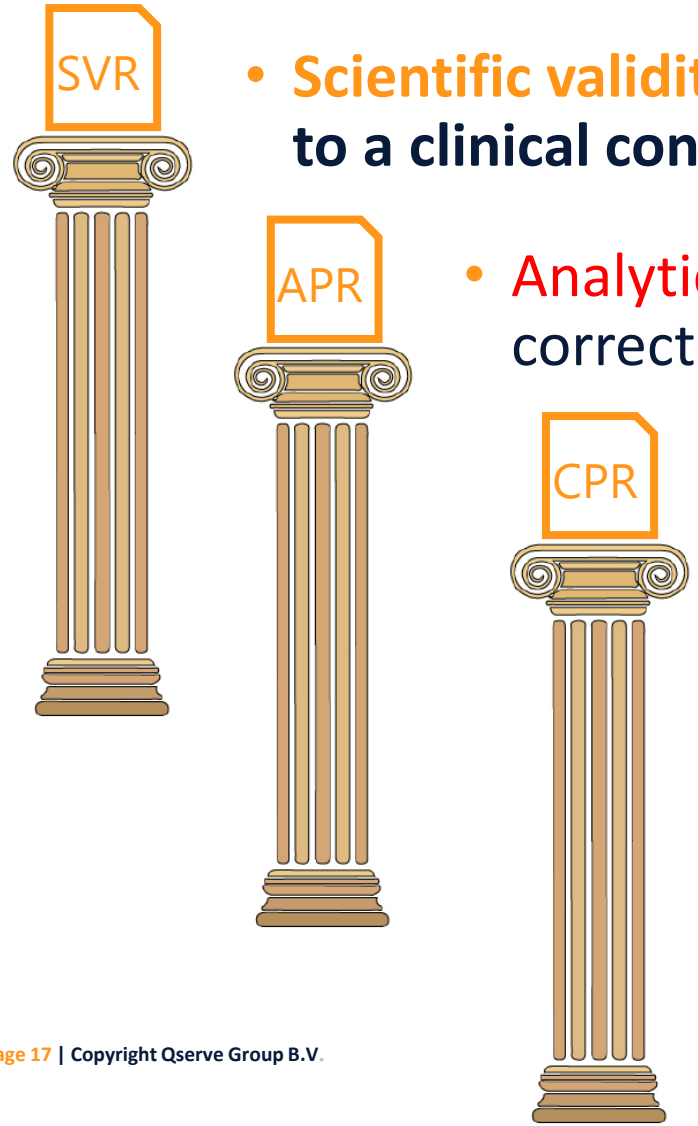
'Intended purpose' means the use for which the device is intended according to the data supplied by the manufacturer on the label, in the instructions for use or in promotional or sales materials or statements and as specified by the manufacturer in the performance evaluation.

- The requirement is now much more prescriptive and may drive the need to update the intended purpose stated in the IFU.
- Annex II, 1.1c the intended purpose should detail:
  - What is being detected/measured
  - Intended function (e.g., screening, monitoring, diagnosis or aid to diagnosis, prognosis, prediction, or companion diagnostic)
  - Specific disorder, condition, or risk factor the test is intended to detect, define, or differentiate
  - Whether or not the test is automated
  - Whether test is qualitative, semi-quantitative, or quantitative
  - Who is the intended user?
  - Intended population if applicable
  - Specimen type
- **Data is needed to support each intended use**

Impact

- The definition is prescriptive and precise
- Notified Bodies expect all elements to be covered
- If a change to claims is required it makes it difficult to continue to use current IFU and their can be ROW registration impact
- During the Notified Body review they will cross reference the intended purpose to the elements of performance evaluation

Clinical Evidence



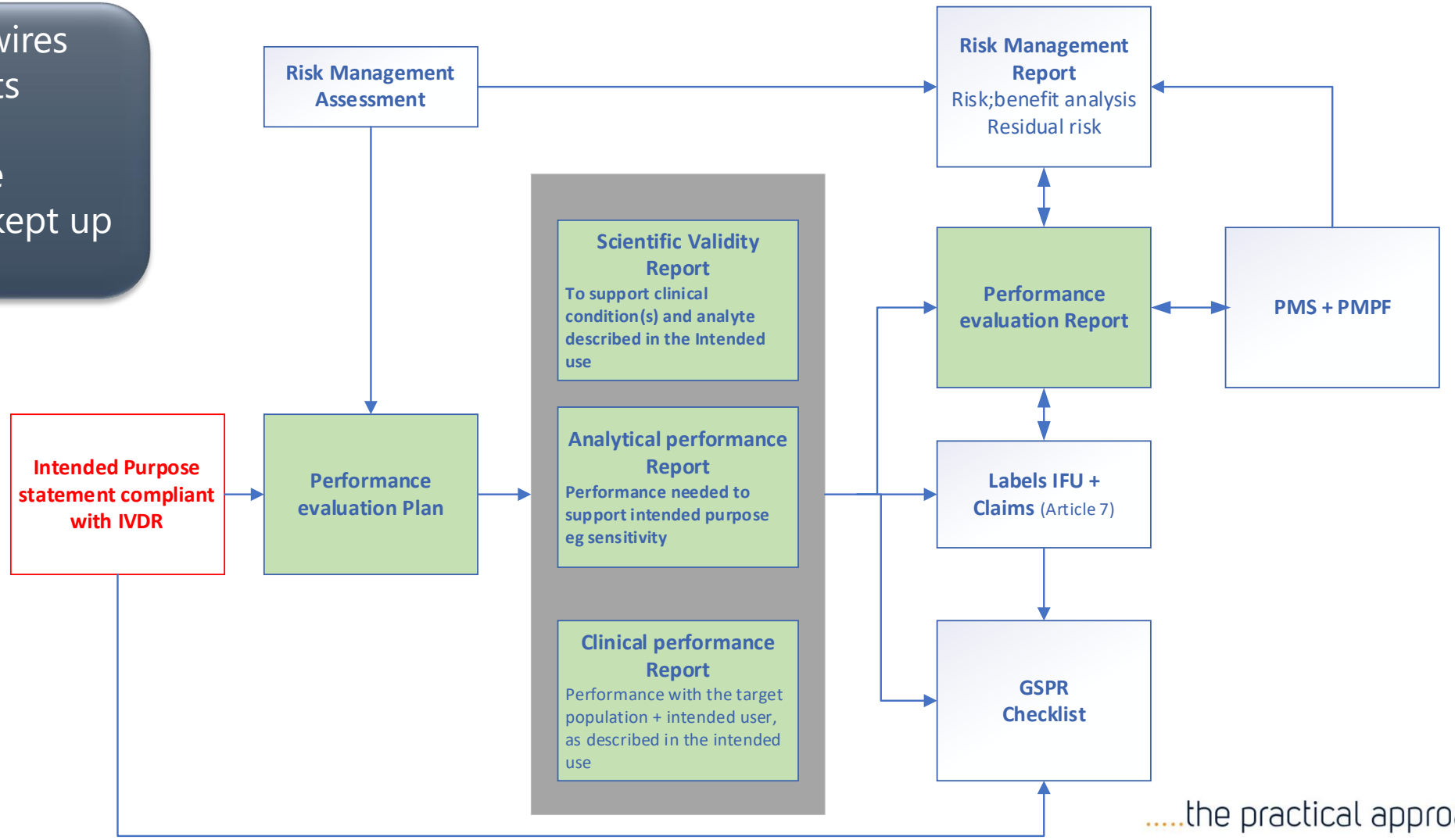
- **Scientific validity of an analyte means the association of an analyte to a clinical condition or a physiological state;**
- Analytical performance means the ability of a device to correctly detect or measure a particular analyte
- Clinical performance means the ability of a device to yield results 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

Map to the Intended Purpose

i. what is to be detected and/or measured;
ii. its function such as screening, monitoring, diagnosis or aid to diagnosis, prognosis, prediction, companion diagnostic;
iii. the specific disorder, condition or risk factor of interest that it is intended to detect, define or differentiate;
iv. whether it is automated or not;
v. whether it is qualitative, semi-quantitative or quantitative;
vi. the type of specimen(s) required;
vii. where applicable, the testing population;
viii. the intended user;
ix. in addition, for companion diagnostics, the relevant target population and the associated medicinal product(s).

More prescriptive requirements

- The IVDR hard wires these documents together
- They need to be consistent and kept up to date



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The Notified Body review

The Devil is in the detail

The IVDR is more prescriptive and much more precise

Annex II states:

The technical documentation and, if applicable, the summary thereof to be drawn up by the manufacturer shall be presented in a clear, organised, readily searchable and unambiguous manner and shall include in particular the elements listed in this Annex.

Annex II 4.d

the precise identity of the controlled documents offering evidence of conformity with each harmonised standard, CS or other method applied to demonstrate conformity with the general safety and performance requirements.

The information referred to under this point shall incorporate a cross-reference to the location of such evidence within the technical file.

No Grandfathering

- You will often hear that there is no grandfathering between the IVDD and IVDR
- Even if you have an existing (legacy) device you still need a PEP, an SVR, APR, CPR and PER
- The PEP is similar to a V+V plan but you can’t just supply this, but you can repurpose the content
- You need to make clear conclusions and summarize the data
- There needs to be enough evidence and supporting data to prove your point.
- If you provide existing study reports conclusions about compliance to the IVDR are still required and the files has to be easy to navigate

Notified Body review

- NB's have to prove to Competent Authorities they checked all the requirements
- If the IVDR says you "shall" they expect to see something or an explanation why it is not applicable
- They will use checklists and record where in your documentation they saw the proof and they only review what you provide in the TF so you can't reference other documents you have to attach them
- If you do not state a clear conclusion, the NB can't make a conclusion for you, regardless of how good the data is!
- NB's start with your conclusion; if there is no conclusion it will lead to a question or non-conformity

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Is there an LDT equivalent in Europe under IVDR?

Centralised labs under the IVDR ?

- In 1998 the IVDD did not anticipate testing services or personalised medicine
- The IVDD does require reagent and reagent products to be CE marked and should be CE marked but many are sold as Research Use Only and used by labs using an in-house exemption
- The IVD Regulation tightens up on testing services under the distance sales requirements and also tightens up on the in-house exemption
- Competent Authorities are much more aware of how personalised medicine is delivered

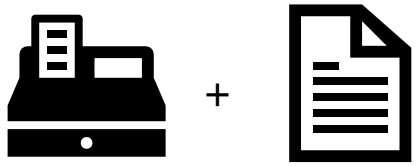
Placing on the marking and putting into service

‘making available on the market’ means any supply of a device, other than a device for performance study, for distribution, consumption or use on the Union market in the course of a commercial activity, whether in return for payment or free of charge;

‘placing on the market’ means the first making available of a device, other than a device for performance study, on the Union market;

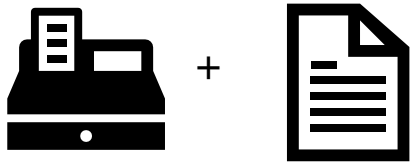
‘putting into service’ means the stage at which a device, other than a device for performance study, has been made available to the final user as being ready for use on the Union market for the first time for its intended purpose;

Placing on the market and putting into service



- A kit or analyser is placed on the market and then put into service and becomes available to users

- If a testing service is provided, nothing is placed on the market there is no kit but it is put into service as a result is provided to the doctor or patient



- If the testing service provides a sample collection kit to the patient or doctor then the sample collection kit is placed on the market and put into service. However, since there is patient contact it is a medical device not an IVD

Distance sales (Article 6)

1.A device offered by means of information society services, as defined in point (b) of Article 1(1) of Directive (EU) 2015/1535, to a natural or legal person established in the Union shall comply with this Regulation.

2.Without prejudice to national law regarding the exercise of the medical profession, a device that is not placed on the market but used in the context of a commercial activity, whether in return for payment or free of charge, for the provision of a diagnostic or therapeutic service offered by means of information society services, as defined in point (b) of Article 1(1) of Directive (EU) 2015/1535, or by other means of communication, directly or through intermediaries, to a natural or legal person established in the Union shall comply with this Regulation.

3.Upon request by a competent authority, any natural or legal person offering a device in accordance with paragraph 1 or providing a service in accordance with paragraph 2 shall make available a copy of the EU declaration of conformity of the device concerned.

4.A Member State may, on grounds of protection of public health, require a provider of information society services, as defined in point (b) of Article 1(1) of Directive (EU) 2015/1535, to cease its activity.

"information society services" = internet sales

Distance sales (Article 6) simplified

In summary this says

1. Devices provided over the internet to a doctor or patient in Europe shall comply with the Regulation.
2. IVDs that are not placed on the market but used in the context of a commercial activity, to provide a diagnostic or therapeutic service offered using the internet or by other means of communication, directly or through intermediaries, to a doctor or patient in Europe shall comply with the Regulation whether this is free of charge or for payment
3. In both cases the person taking legal responsibility shall make available a copy of the EU declaration of conformity of the device concerned.
4. A Member State may, on grounds of protection of public health, require an internet provider to cease its activity.

This means that if you sell a product over the web or provide a testing service you need to meet all the requirements this includes the appropriate NB conformity assessment

Testing Services

- Testing services that do not use CE marked devices have to meet the requirements of the IVDR including the conformity assessment requirements and will require a Notified Body approval
- Labs that use CE tests are just users because the kit has already been approved so there are no additional requirements unless the lab changes the intended purpose or method then they become the manufacturer
- This applies to labs anywhere in the world testing EU samples
- If the testing lab provides swabs or specimen receptacles to patients, these would also need to be CE marked as medical devices or IVDs respectively
- There is no US style LDT but there is an in-house exemption

Health institution exemption

‘health institution’ means an organisation the primary purpose of which is the care or treatment of patients or the promotion of public health;

Health institutions should have the possibility of manufacturing, modifying and using devices in-house and thereby addressing, on a non-industrial scale, the specific needs of target patient groups which cannot be met at the appropriate level of performance by an equivalent device available on the market.

In that context, it is appropriate to provide that certain rules of this Regulation, as regards devices manufactured and used only within health institutions, including hospitals as well as institutions, such as laboratories and public health institutes that support the health care system and/or address patient needs, but which do not treat or care for patients directly, should not apply, since the aims of this Regulation would still be met in a proportionate manner.

It should be noted that the concept of ‘health institution’ does not cover establishments primarily claiming to pursue health interests or healthy lifestyles, such as gyms, spas, wellness and fitness centres. As a result, the exemption applicable to health institutions does not apply to such establishments.

Exception Conditions

5. With the exception of the relevant general safety and performance requirements set out in Annex I, the requirements of this Regulation shall not apply to devices manufactured and used only within health institutions established in the Union, provided that all of the following conditions are met:

(a) the devices are not transferred to another legal entity;

(b) manufacture and use of the devices occur under appropriate quality management systems;

(c)the laboratory of the health institution is compliant with standard EN ISO 15189 or where applicable national provisions, including national provisions regarding accreditation;

(d)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;

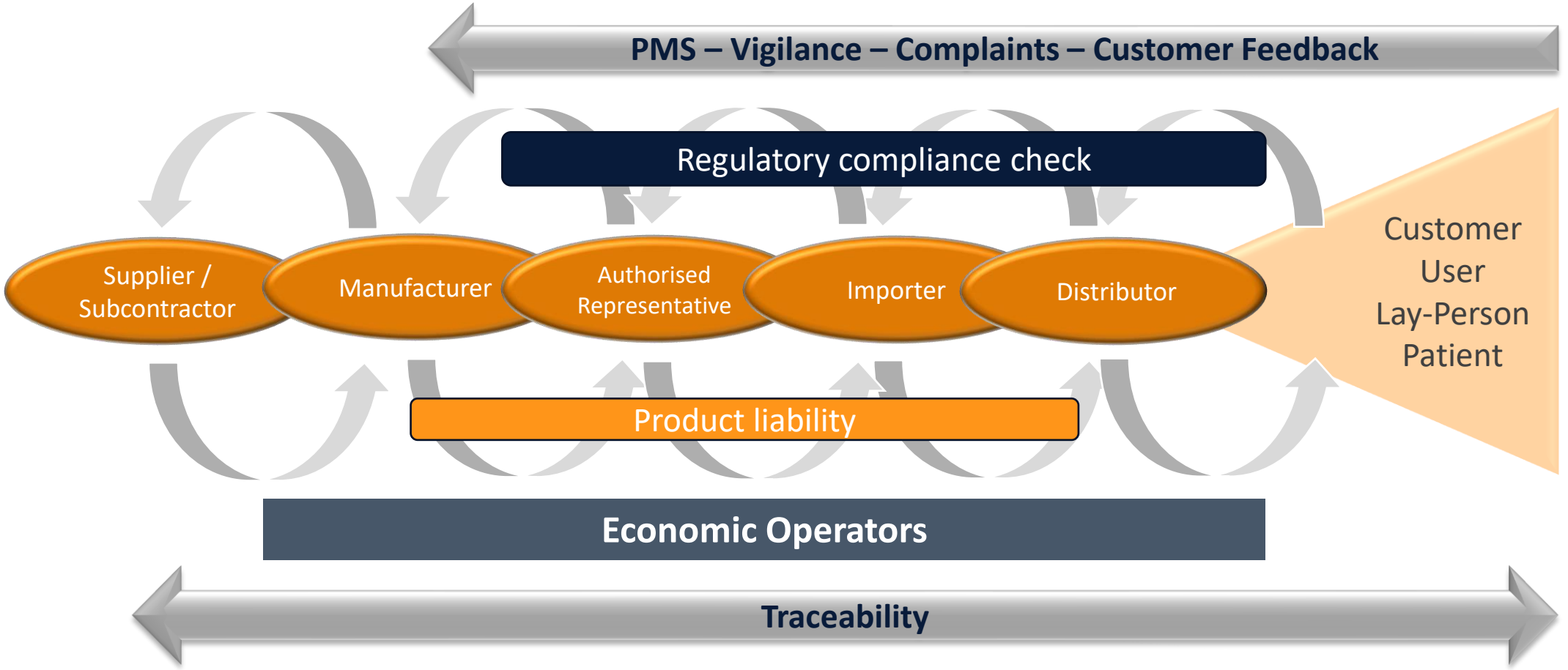
(e)the health institution provides information upon request on the use of such devices to its competent authority, which shall include a justification of their manufacturing, modification and use;

(f) the health institution draws up a declaration which it shall make publicly available, including:

(i) the name and address of the manufacturing health institution,
(ii) the details necessary to identify the devices,
(iii)a declaration that the devices meet the general safety and performance requirements set out in Annex I to this Regulation and, where applicable, information on which requirements are not fully met with a reasoned justification therefor;

What are the key Post Market changes under the IVDR

Economic Operators



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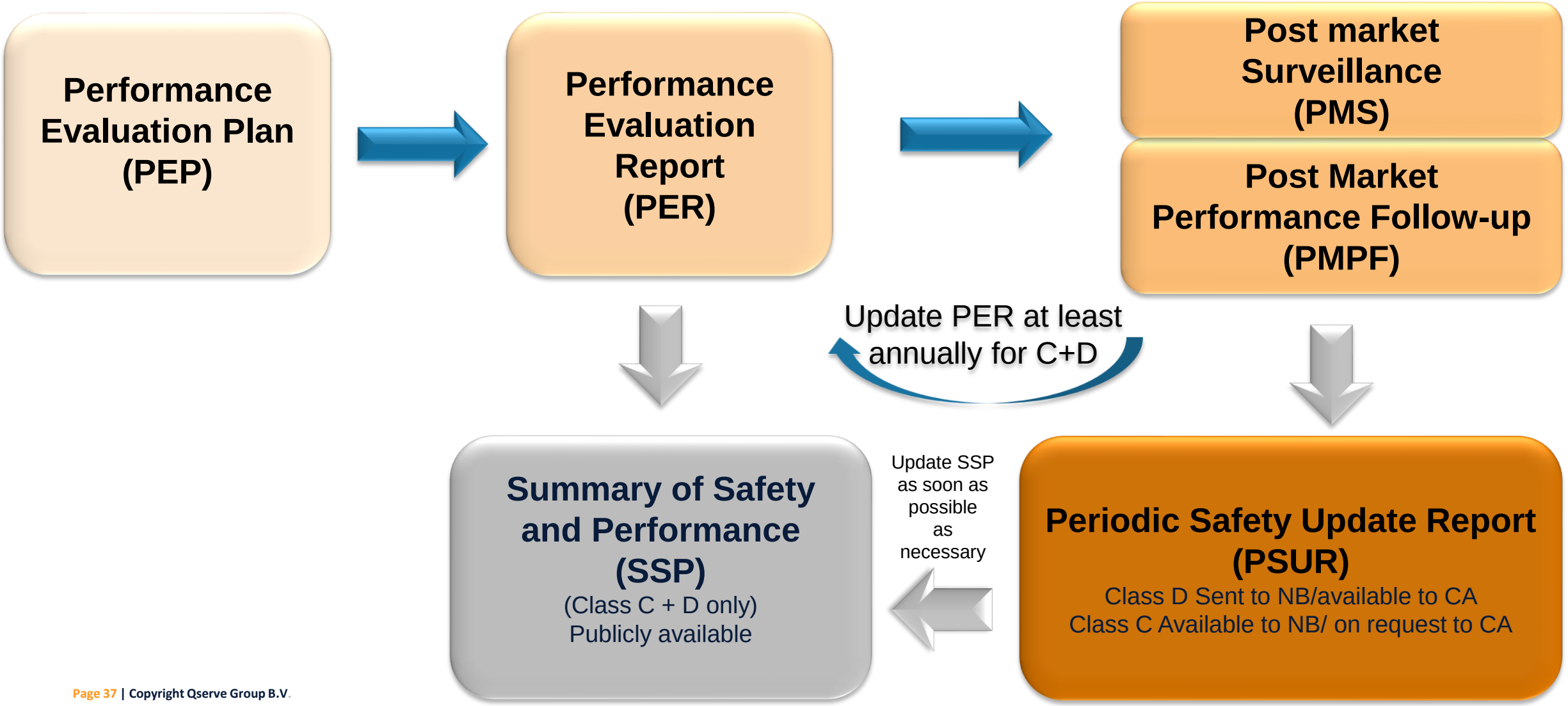
Post Market

- There are changes to post market responsibilities which will impact contracts
- There is an expectation that there will be an additive check for compliance down the supply chain
- Authorised representatives and manufacturers require a Person Responsible for Regulatory Compliance (PRRC)
- US manufacturers PRRC must be in the US and the Authorised Reps must be in Europe and not UK (there is MDCG Guidance)
- Be careful of using Switzerland as there is no MRA in place yet

Post Market Performance Follow Up (PMPF)

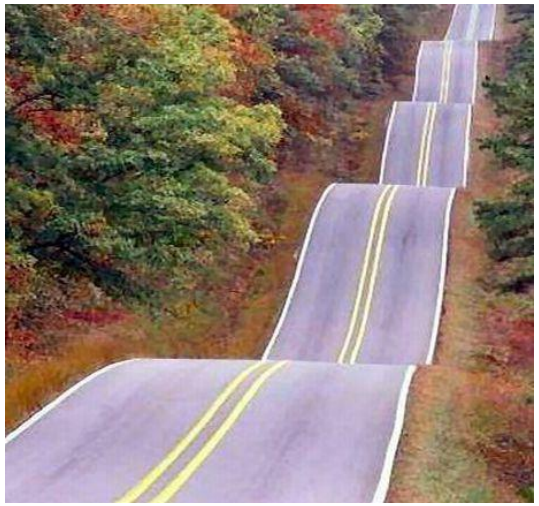
- Many manufacturers are surprised that they have to supply their PMPF plan when they apply to the NB
- PMPF plan keeps the Performance Evaluation data up to date
- PMPF is a subset of PMS
- Is you think a PMPF plan is not required you need to explain why
- PMPF does not always require studies
- There are more post market oversight activities that take time and resource
  - Sampling of class B+C technical file
  - Creation of Periodic Safety Report (Class C+D)
  - Summary of Safety and Performance (Class C+D)

Post market requirements



Finally

- It is going to be a bumpy road for the IVD industry
- The hard truth is if you have a class B or C device and you have not yet started you are unlikely to be able to CE mark by 22 May 2022
- NBs estimate you need to start the conformity process by June or July 2021 at the latest.
- We expect that products will be discontinued
- Any extension to the IVDR is far from clear and likely to be for a limited range of devices if it happens at all
- If you are in this unfortunate position you need to think about building stock
- If you use the CE mark for ROW market access, are there alternative routes to keep you on market in these countries in the interim?
- Network events like this are essential, as getting it right first time will be a key to success



Thank you for your attention

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