Regulatory & Clinical Affairs
Quality Management

Monthey – October 13, 2016

The New IVDR and the Future Regulatory Framework in Europe

- Introduction -

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The evolution of the EU regulatory framework for MD

- Reasons for evolution in the regulatory approach
  - Inconsistencies between national transposition of the directives
  - Free trade not any more guaranteed within EU due to national «extras»
  - Political correctness between member states prevailed on patient safety…
    - NBs everywhere
    - NBs have scopes where there is no manufacturer 1000 km around
    - NBs did not do their job / are not capable to do their job because either incompetent or too academic
    - DA and national accreditation bodies incompetent
    - CA did not do their job, no communication…
  - Public awareness and pressure triggered by the PIP scandal
- A recast of directives would not have addressed the root cause : too much national “cuisine” in legislation, monitoring and enforcement
  - Correction: DALLI plan (check designations of NB, force NB to use powers, joint assessment by DA/ CA)
  - Corrective Action: REGULATION

Directive vs Regulation in EU

EU - Directive

- A "directive" is a legislative act that sets out a **goal** that all EU countries must achieve. However, it is up to the individual member state **to decide how** by transposition in **national law**.

EU - Regulation

- A "regulation" is a **binding** legislative act. It must be applied in its **entirety** across the EU.
- A regulation **replaces national law**.
- Regulations are passed either jointly by the EU Council and European Parliament, or by the Commission alone.

Regulations' objectives

- One single text applicable over all member states – no national interpretations or "Sonderfälle"
- Catch up with technological innovation
- Enhance control over NBs
- Ensure competence of stakeholders (MAID)
- Eliminate grey zones in current regulation
- Leverage available competences within DA and CA by "joint" activities
- Improve transparency and information exchange between stakeholders
- Technical improvements in the texts to clarify requirements

⇨ All for promoting the objective of safety

Key players and roles under IVDR

- Economic Operators (MAID)
  - Manufacturers
    - Manufacture and market medical devices
  - Authorized Representative
    - Substitute manufacturers with no place of business in a member state with regard to legal obligations related to medical devices
  - Importer
    - Natural or legal person established within the Union placing a device from a third country on the EU market
  - Distributor
    - Natural or legal person in the supply chain, other than the manufacturer or the importer, who makes a device available on the market

Expectations on economic operators

Manufacturer, authorized representative, importer, distributor are economic operators.

Each of them must guarantee:

- Compliance with relevant requirements
- Conformity assessment complete
- Product marking and technical file available

-> longer distribution channel setup time

Structure overview summary of regulation (IVDR)

10 Chapters

1 – Scope & definitions

2 – Making available of medical devices, MAID, reprocessing, CE marking

3 – Identification & traceability, registration of operators, EU database

4 – Notified Bodies

5 – Classification, conformity assessment

6 – Clinical evidence, performance evaluation and performance studies

7 – Post Market Surveillance, Vigilance and market surveillance

8 – Cooperation between Member States, Medical Device Coordination Group, EU reference laboratories, device registers

9 – Confidentiality, data protection, funding, penalties,

10 – Final Provisions

Structure overview summary of regulation (IVDR)

14 Annexes

I General safety and performance requirements
II Technical documentation
IIa Technical documentation on post-market surveillance
III EU Declaration of conformity
IV CE marking of conformity
V Information to be submitted with the registration of devices and economic operators / UDI
VI Requirements to be met by Notified Bodies
VII Classification criteria
VIII Conformity assessment Full QA + technical documentation
IX Conformity assessment based on type examination
X Conformity assessment based on production quality assurance
XI Certificates issued by a notified body
XII Performance evaluation and post-market follow-up
XIII Interventional clinical performance studies and other performance studies involving risks for the subjects of the studies
XIV Correlation table

Some Key Changes with IVDR

Subject	Change impacting Mfg
Technical documentation	Annex II, aligned to ToC
Classification	More rules, precisions. Change from a positive list to a risk based system: - IVDR: 4 classes of risk A-D (individual / public health risk)
Conformity assessment	- Special procedure: Class D IVD - scrutiny - NB to notify CA along with safety & performance summary, IFU, assessment report and if applicable designated reference lab's scientific opinion
Competence	Article 13: Person responsible for regulatory compliance

Some Key Changes with IVDR

Subject	Change impacting Mfg
IVDR Performance evaluation	**- Performance evaluation report (C+D) to be regularly updated logically interlinked with RM and PMS / Vigilance.**
IVDR Interventional clinical performance studies / other performance studies	**- Always required unless duly justifiable** **- Performance evaluation subject of any NB review**

Some Key Changes with IVDR

Subject	Change impacting Mfg
Standards	**CS (common specifications) may be adopted by the commission in areas where standardization is lacking in addition to standards**
Transparency	**Making results of Performance evaluation (D) publicly available (certain devices)**
PMS	**PMS system, PMS plan**

Key changes - classification

GHTF based classification (A, B, C, D) – Annex VII

- previously : positive list A, list B, self test, other

A : no NOtified BOdy, except sterile and near-patient

B : NOBO to assess the QMS

C : NOBO to assess the QMS and Technical File

D : NOBO to assess the QMS, the TF and the Design

Key changes - classification

Near patient testing: devices used by healthcare professionals, but not laboratory professional considered as self test -> class B or C

Classes A, B, C used in a single healthcare site will be exempt if the lab is ISO 17025 accredited

Companion diagnostic: IVD targeted at predicting treatment response, like for oncology will be class C – with consultation procedure (MRB / EMA).

Conformity assessment pre-market control enhanced

Class A: No NB (unless sterile or having a measuring function)

Class B, C and D : proportionate with risk, involvement of a Notified Body

In addition for class D:

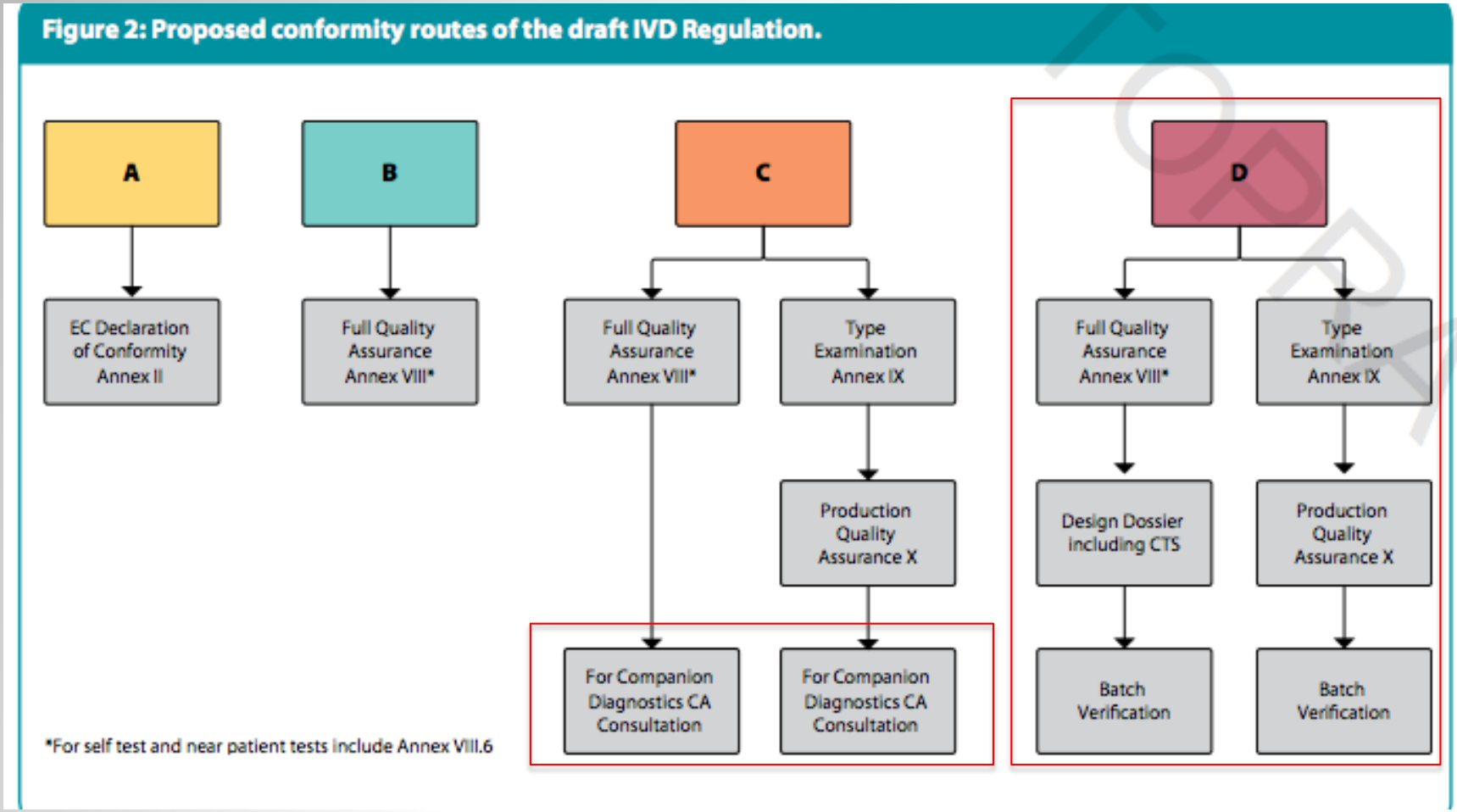
Involvement of a Reference Laboratory to verify compliance with applicable CS + Batch Verification

OR

Involvement of a Reference Laboratory to verify compliance with applicable CS + Scrutiny (by expert panels) if no CS and if initial certification

Companion diagnostics: consultation procedure with a MRB / EMA

Conformity assessment routes



Source Topra

Key changes – Person responsible for regulatory compliance

1) A diploma, certificate or other evidence of formal qualification awarded on completion of a university degree or equivalent course of study, in a relevant discipline, and at least one year of professional experience in regulatory affairs or in quality management systems relating to IVD medical devices;

2) Four years of professional experience in regulatory affairs or in quality management systems relating to IVD medical devices.

Key changes – Person responsible for regulatory compliance

Micro and small enterprises are not required to have the person responsible for regulatory compliance within their organisation but shall have such person permanently and continuously at their disposal.

Company category	Staff headcount	Turnover	or	Balance sheet total
Medium-sized	< 250	≤ € 50 m		≤ € 43 m
Small	< 50	≤ € 10 m		≤ € 10 m
Micro	< 10	≤ € 2 m		≤ € 2 m

http://ec.europa.eu/growth/smes/business-friendly-environment/sme-definition_en

Person responsible for regulatory compliance - mission

Formal functions of the Person responsible for regulatory compliance:

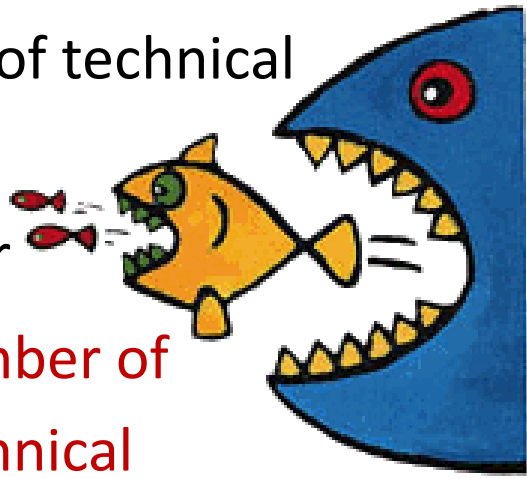
- Batch release
- Technical documentation / DoC release
- PMS & Vigilance executed in conformity
- Compliance in the framework of (interventional) clinical performance studies

Presumed functions:

- Regulatory watch
- QMS maintenance
- Risk management

Technical Documentation: Notified Body Review under **IVDR**

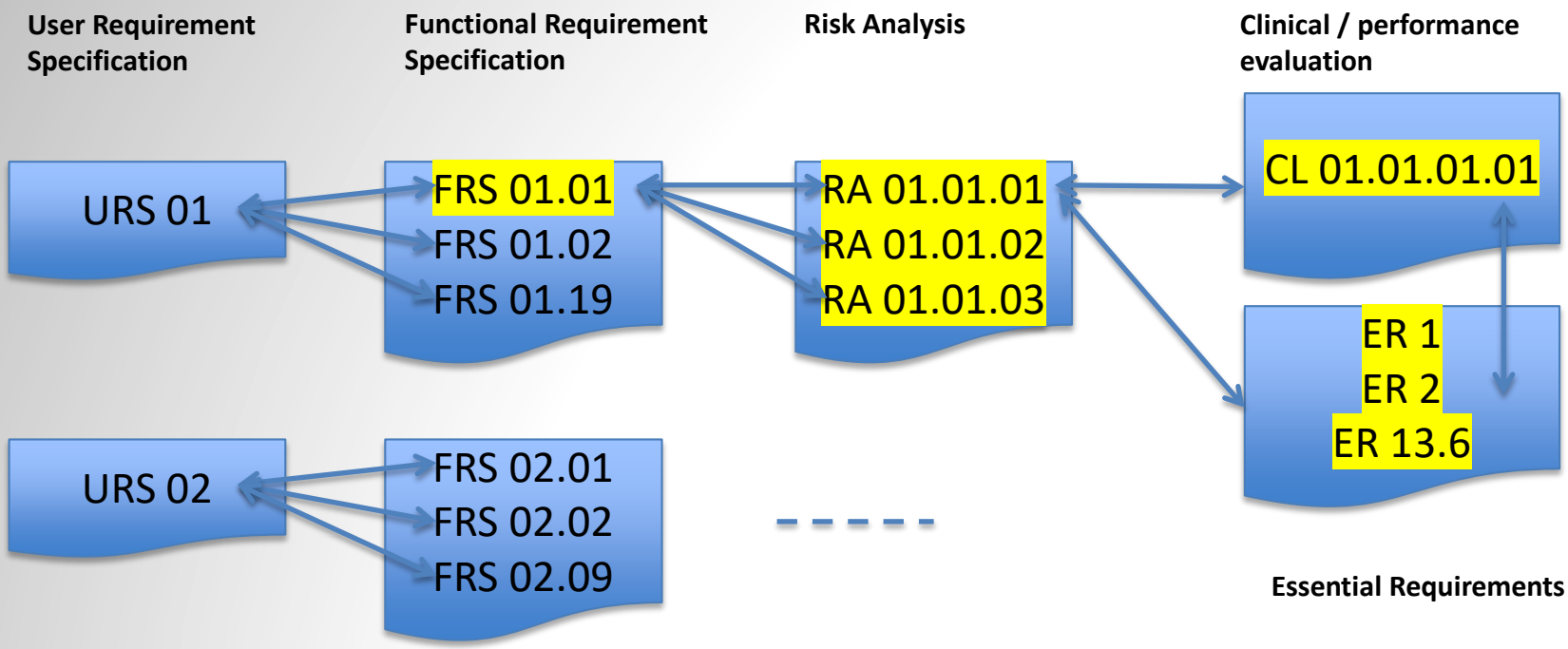
Article 33a - Review of notified body assessment of technical documentation and performance evaluation



Summary: "The national authority responsible for notified bodies … shall assess an appropriate number of notified body assessments of manufacturers' technical documentation and performance evaluations to verify the conclusions drawn by the notified body based on the information presented by the manufacturer… . This shall include the manufacturer's technical and performance evaluation documentation upon which the notified body has based its assessment."

Information related to IVDR – version 10618/16 as of 27.06.2016 – M.Maier / medidee services – 19.08.2016

Process & logical links - CE technical documentation



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Key change UDI – Unique Device Identification

UDI made of:

- a device identifier specific to a manufacturer and a device model
- a production identifier that identifies data related to the unit of device production = batch number

UDI will be recorded by the economic operators and the health institutions = traceability system

Agencies approved by EC will supply identifiers: GS1 / HIBC

Electronic system on registration

Art 23.

- Before placing on the market: registration in database by manufacturer or ER.
- Every two years: economic operators must confirm the accuracy of the data.

This means that CA will know which products are on which market.

Electronic system on vigilance (chap VII)

Art. 60.

Database will allow entering and record:

- Serious Incidents
- Periodic summaries
- Trending records (C & D)
- Field Safety Corrective Actions
- Field Safety Notices

Eudamed database summary

Public access will gradually extend to:

- the electronic system on UDI referred to in Article 22
- the electronic system on registration of devices and economic operators referred to in Article 23
- the electronic system on information on certificates referred to in Article 43(4);
- the electronic system on interventional clinical performance studies and clinical performance studies involving risks for the subjects set up in Article 51
- the electronic system on vigilance referred to in Article 60 / 61
- the electronic system on market surveillance referred to in Article 66

Clinical performance (chap VI)

Changes:

- Stronger requirement for interventional studies
- Balance between studies and literature still possible
- Need for a performance study report in technical file
- For devices classified as class B the clinical performance study report may be limited to a summary of the study protocol, results and conclusion
- Continuous update by PMS required

Performance evaluation

Reinforcement of performance evaluation requirements for approval and throughout the lifetime

- Scientific validity
- Analytical performance
- Clinical performance

- Specific requirements for certain types of performance studies (e.g. approval & registration procedure)

Source: Erik Hansson, Deputy Head of Unit, European Commission, DG Internal Market, Industry, Entrepreneurship and SMEs

PMS requirements

Requirements to have a PMS plan per product:

- What information do we want to gather
- How will we collect it
- What will we do with this information

Deliverables:

- Post Market (Clinical) Performance Follow-up plan
- PMPF yearly report

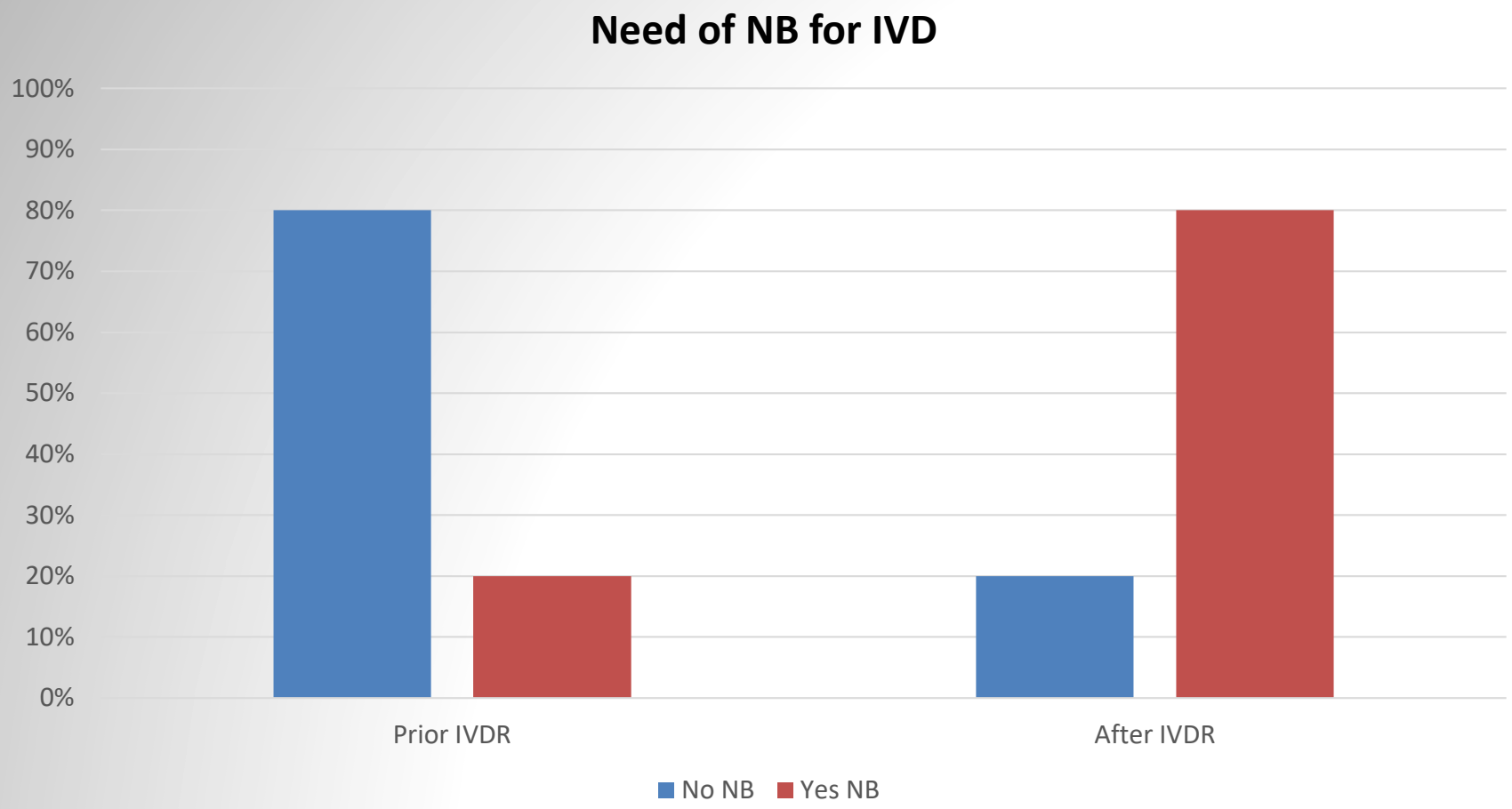
IVDR: impact on manufacturers

- Check capability of your NB timely (will your NB likely keep the NBOG scopes it has today)
- Consultation / scrutiny for high risk & innovative IVD may be much longer (today typically 4 to 8 months with leading NBs – you may add 6 months at least if no questions)
- Manufacturers must take possibility of consultation / scrutiny procedure into account for:
  - Time to market
  - Financing & resource management

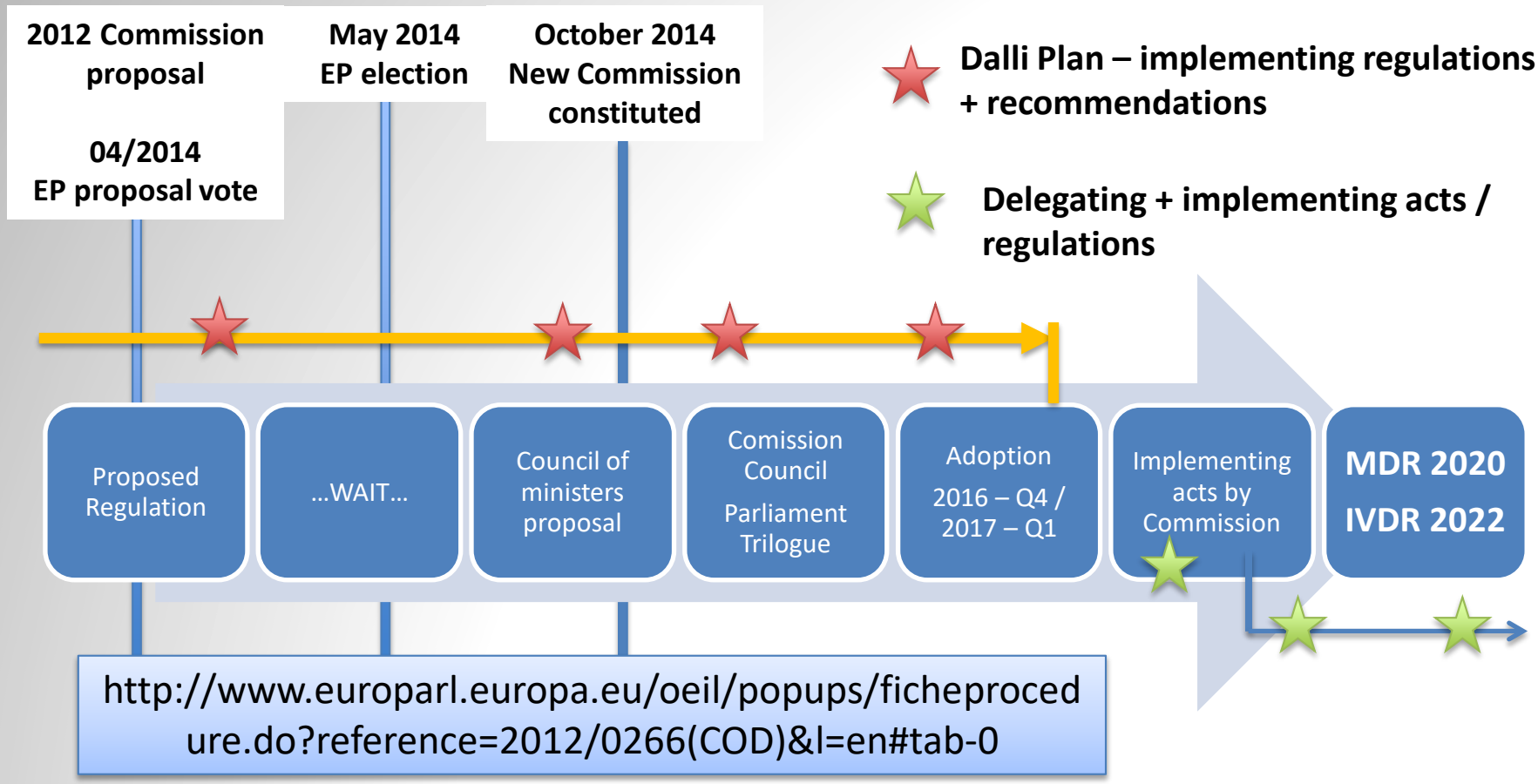
Impacts of Regs on manufacturers
(strategic questions for 2017/2018)

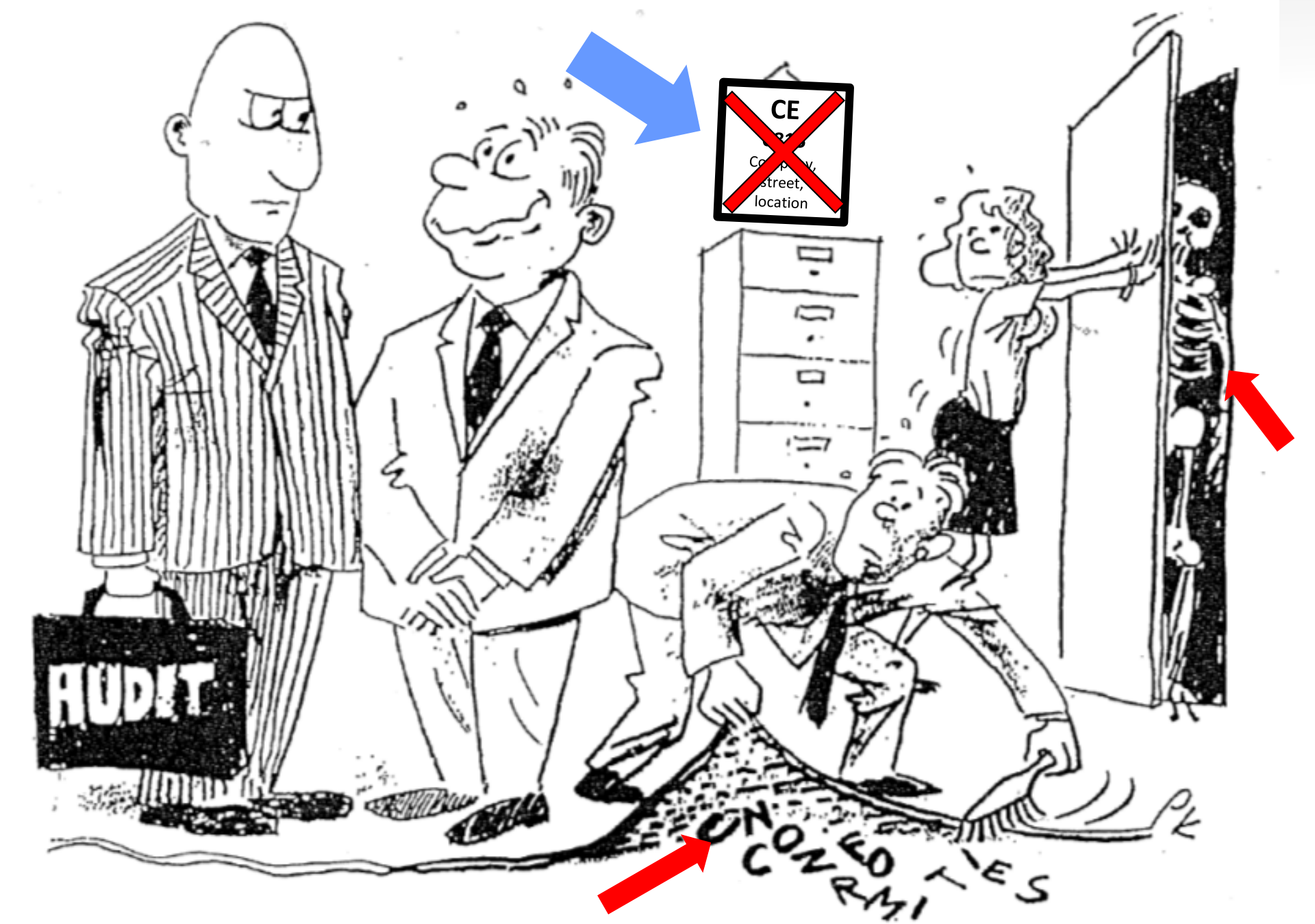
- Will your NB drop the IVD business ?
- Resources of remaining NBs ?
- Innovation: development projects / start-ups requiring funding ?
- HR ?

Impacts of IVDR on manufacturers
(Is there anybody out there?)



Implementation scenario





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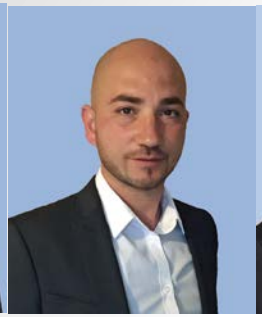

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