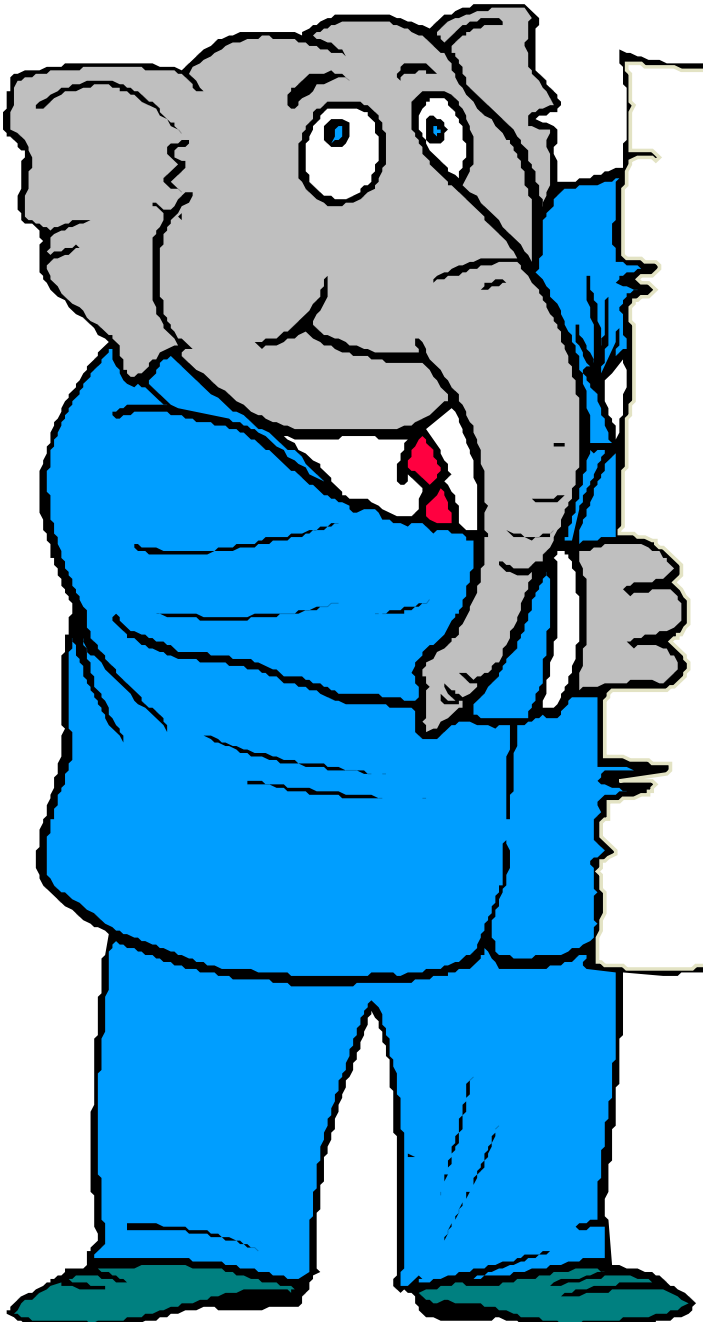
From a barrier to competitive edge

BUSINESS FINLAND



9.30-11.30 Setting the scheme

Post-market phase:

- MD on the market?
- Distributors? AR?
- CE: dealing with authorities?
- Rest of the world?
- Production and …?

12.30-14.30 **Pre-market phase:**

- Intended Use, risk classification
- Laws and standards
- GSPR and conformity
- Registration, Eudamed, UDI
- QMS: developing, obstacles

14.30-16.20 The Real Stuff

16.20-16.30 Q&A, conclusions

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Regulatory strategy

Usually neglected or done too late

Some questions to be asked:

How large or narrow Intended Use?

Which risk class?

Which countries – which regulatory demands?

How to: usability, risk management, Clinical/Performance Evaluation and, if needed, also Clinical investigation/Performance study (interventional or not?)

Design Reviews 1-5 or only 2?

(USR, Specs, verifications, validations, launch)

EU: Notified Body or not?

Submission: USA 510(k), PMA or other (De Novo)

Registration of the manufacturer?

Authorised representative, UKRP, US Agent, Russian Agent…

My point is: Develop a strategy early enough!!

Placing on the market

Placing on the market: for sales or free of charge – it does not matter!

An IVD/MD cannot be placed on the market before it is CE marked, which denotes that the product confirms with all requirements of all applicable regulations

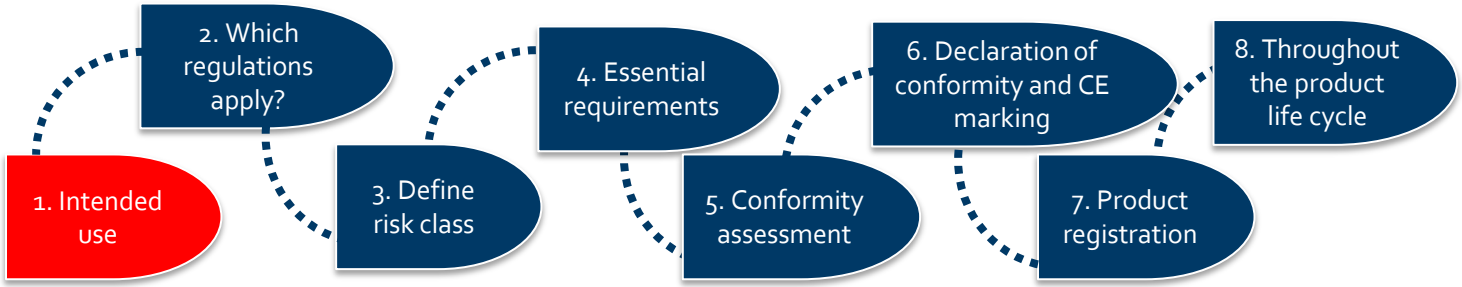
If not IVD/MD – not allowed to CE mark!

Special situations when CE-marking is not needed:

- **Clinical investigations and performance studies**
- **Custom-made products**
- **Humanitarian use (emergency medical situations)**

  Covid-19: masks, diagnostic tests, ventilators

Intended Use is compared with the IVD/MD Definition



Intended Use

Requires a thorough understanding of the clinical need and how your solution fits in

The larger intended use, the more you have to prove, but, the narrower your intended use is, the smaller market size

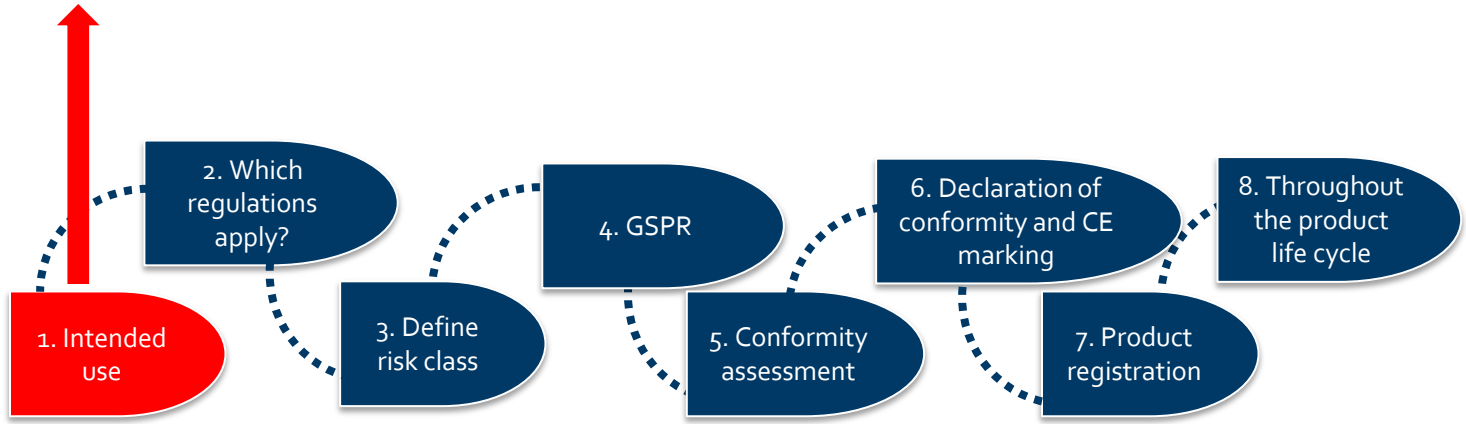
The intended use is decisive for the risk classification

Because it is the most critical part for a medical device it deserves and requires a lot of work!

Make sure that the company has made this crisp and clear!

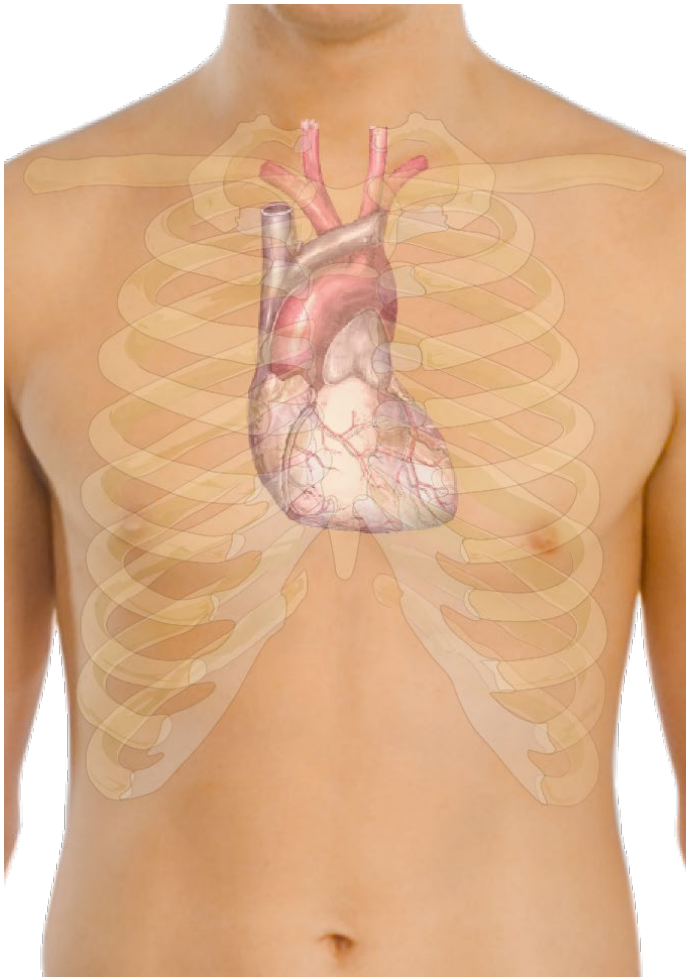
Intended Use is compared with the IVD/MD definition

Who is the patient?
What clinical need is fulfilled?
Who is the user?
Professional use or layman?
How does our product fit in?



The patients and their needs are truly different!

MDR def (37)
'user' means any healthcare professional or lay person who uses a device
MDR def (38)
'lay person' means an individual who does not have formal education in a relevant field of healthcare or medical discipline



Intended Use is compared with the MD definition

‘medical device’ means **any** instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for **human beings** for one or more of the following **specific medical purposes**:

— diagnosis, prevention, monitoring, **prediction**, **prognosis**, treatment or alleviation of disease,
— diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,
— investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,
— providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations,

and which **does not achieve its principal intended action** by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

The following products shall also be deemed to be medical devices:

- **devices for the control or support of conception;**
- **products specifically intended for the cleaning, disinfection or sterilisation of devices as referred to in Article 1(4) and of those referred to in the first paragraph of this point.**

Accessories to MDs?

Intended Use is compared with the IVD definition

(2) '*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:

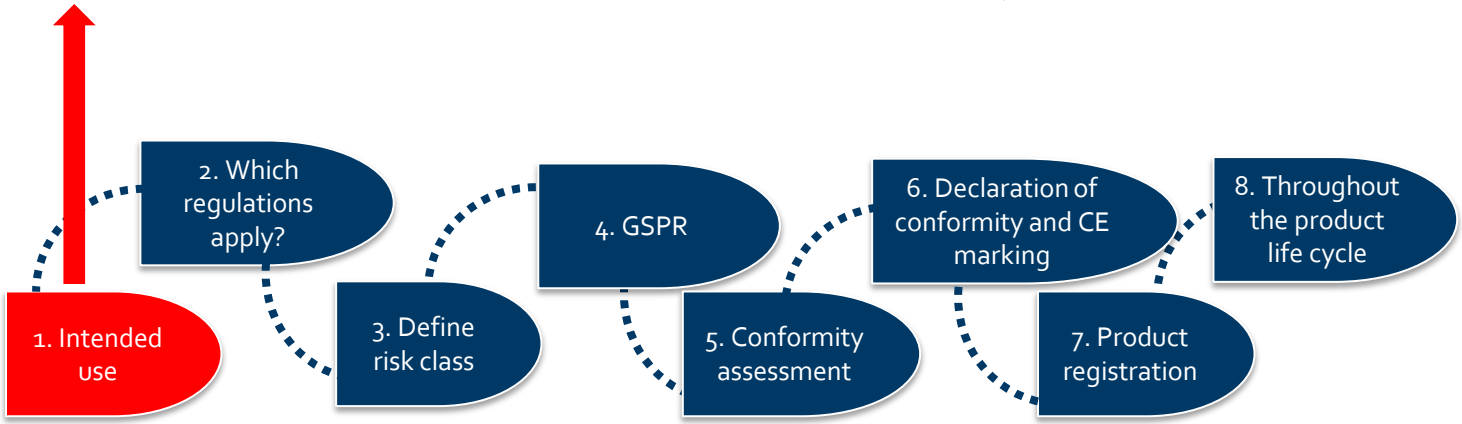
(a) concerning a physiological or pathological process or state;
(b) concerning congenital physical or mental impairments;
(c) concerning the predisposition to a medical condition or a disease;
(d) to determine the safety and compatibility with potential recipients;
(e) to predict treatment response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

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

Intended Use is compared with the IVD/MD definition

Not too big changes in the MDR/IVDR
Usually not too difficult

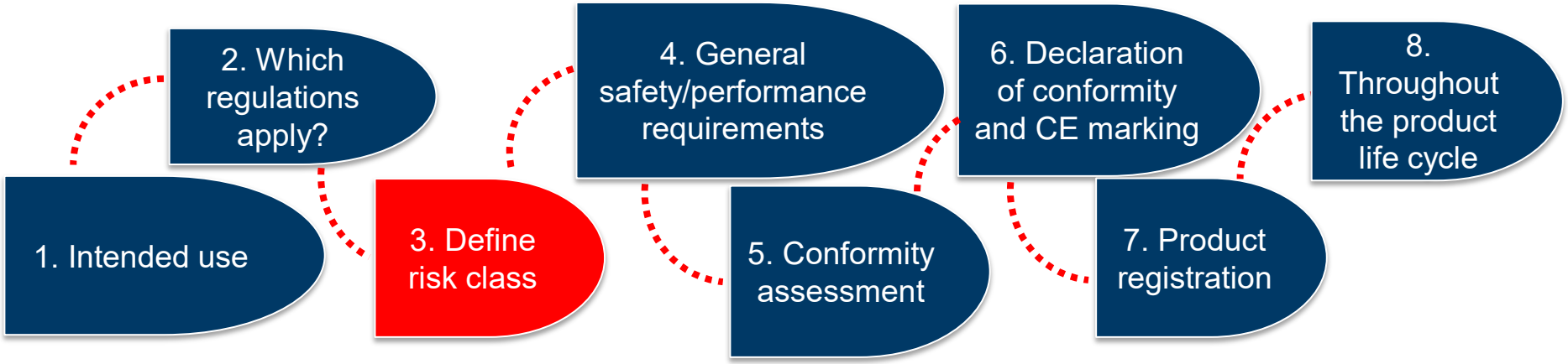
Done too late
Too vague
Too broad
Borderline issues



Are these companies aware of this change?

ANNEX XVI
LIST OF GROUPS OF PRODUCTS WITHOUT AN INTENDED MEDICAL PURPOSE REFERRED TO IN ARTICLE 1(2)

1. Contact lenses or other items intended to be introduced into or onto the eye.
2. Products intended to be totally or partially introduced into the human body through surgically invasive means for the purpose of modifying the anatomy or fixation of body parts with the exception of tattooing products and piercings.
3. Substances, combinations of substances, or items intended to be used for facial or other dermal or mucous membrane filling by subcutaneous, submucous or intradermal injection or other introduction, excluding those for tattooing.
4. Equipment intended to be used to reduce, remove or destroy adipose tissue, such as equipment for liposuction, lipolysis or lipoplasty.
5. High intensity electromagnetic radiation (e.g. infra-red, visible light and ultra-violet) emitting equipment intended for use on the human body, including coherent and non-coherent sources, monochromatic and broad spectrum, such as lasers and intense pulsed light equipment, for skin resurfacing, tattoo or hair removal or other skin treatment.
6. Equipment intended for brain stimulation that apply electrical currents or magnetic or electromagnetic fields that penetrate the cranium to modify neuronal activity in the brain.



Risk class critical!

The higher risk class:

The more you have to prove – longer development time

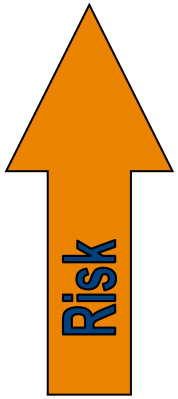
Notified body will be involved

The more likely that you must do clinical investigations (MD) or performance studies (IVD)

Lower threshold to do vigilance actions

Higher demands on post-market surveillance and post-market clinical/performance follow-up

IVD Directive (IVDD): Risk classes



Annex II list A	e.g. HIV, HTLV, hepatitis, blood grouping
Annex II list B	e.g. PSA, trisomy 21 risk, PKU, toxoplasmosis, Chlamydia
Self-testing	
General	

Except Annex II List A very artificial
Not in line with international classifications

IVDR Risk classification

IVDD 10-15 % higher risk class
IVDR 80 %

A-D, Annex VIII

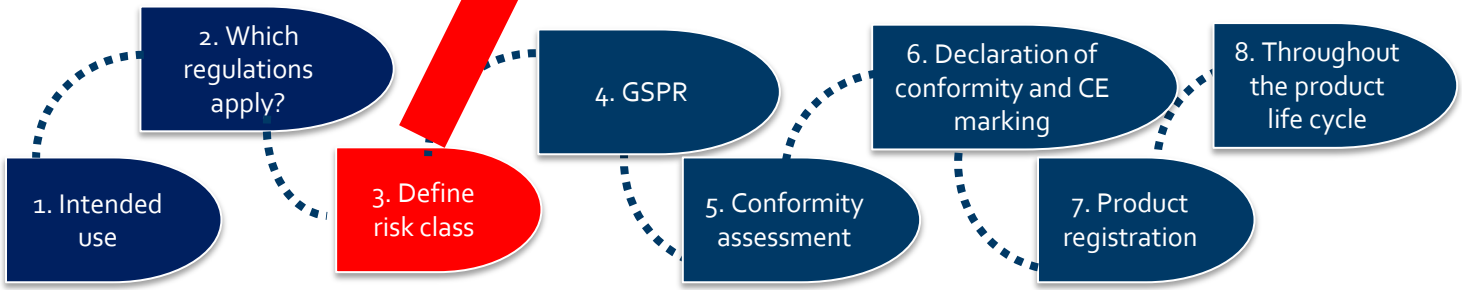
D Highest risk

D = Rule 1

C = Rules 2-4

A = Rule 5

B = The rest (Rules 6-7)



Extremely useful tools

MDCG 2020-16

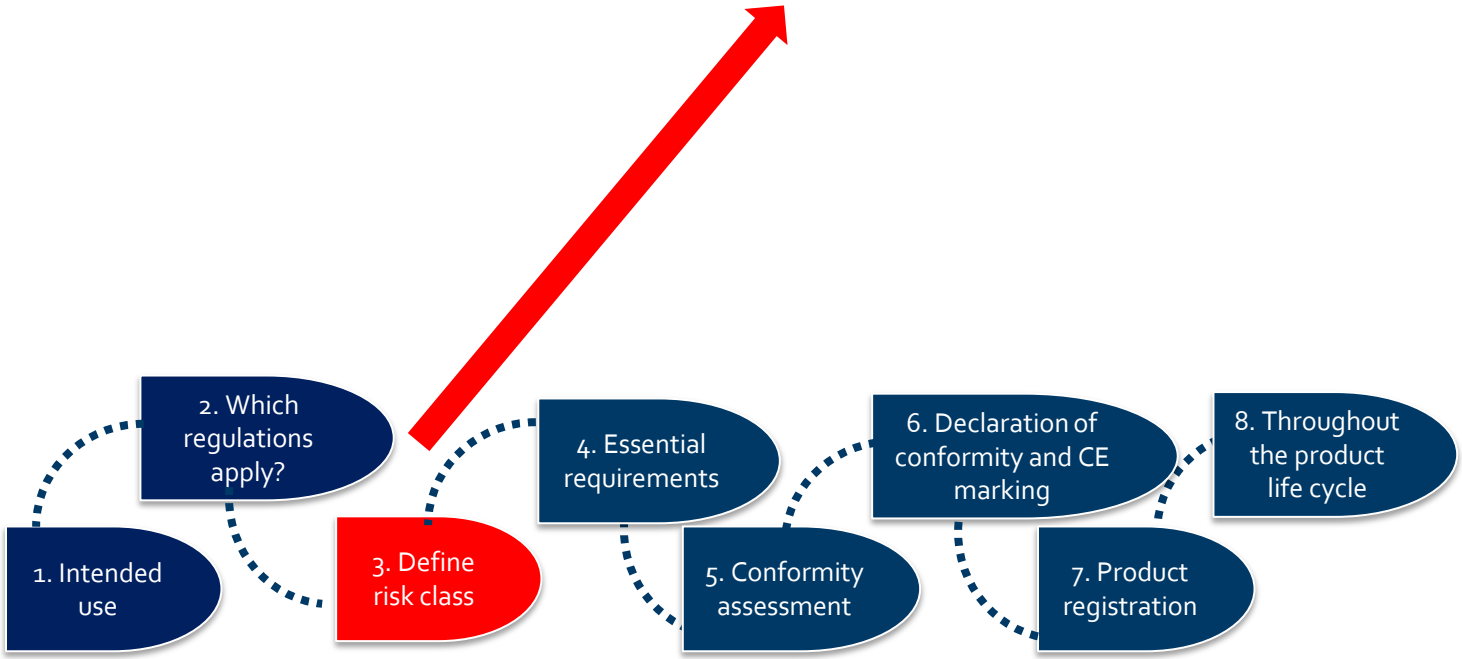
Guidance on Classification Rules for *in vitro* Diagnostic Medical Devices under Regulation (EU) 2017/746

November 2020

Risk classification

MDR

Except for software, no significant changes



Classification of devices

1. Devices shall be divided into classes I, IIa, IIb and III, taking into account the intended purpose of the devices and their inherent risks. Classification shall be carried out in accordance with Annex VIII.

MD Risk category

Class III
Class IIb
Class IIa
Class I

Define immediately!
Decisive for GSPR
Decisive if NB

I:	self declared
Is (sterile):	Notified Body
Im (measuring function):	Notified Body
Ir (reusable surgical instrumets)	Notified Body
IIa:	Notified Body
IIb:	Notified Body
III:	Notified Body

SW Risk classification: Class I gone in practice!

SW are all in demanding risk classes!

State of Healthcare situation or patient condition		Significance of Information provided by the SW to a healthcare situation related to diagnosis/therapy		
		High Treat or diagnose ~ *IMDRF 5.1.1*	**Medium** Drives clinical management ~ *IMDRF 5.1.2*	**Low** Informs clinical management *(everything else)*
	Critical situation or patient condition ~ *IMDRF 5.2.1*	**Class III** *Category IV.i*	**Class IIb** *Category III.i*	**Class IIa** *Category II.i*
	Serious situation or patient condition ~ *IMDRF 5.2.2*	**Class IIb** *Category III.ii*	**Class IIa** *Category II.ii*	**Class IIa** *Category I.ii*
	Non-serious situation or patient condition *(everything else)*	**Class IIa** *Category II.iii*	**Class IIa** *Category I.iii*	**Class IIa** *Category I.i*

Table 1: Classification Guidance on Rule 11

Medical device classification, MDR Annex VIII

The application of the classification rules will be governed by the

- intended purpose of the device and
- their inherent risks linked to the duration of use, part of the body, whether it is active or not, whether it is invasive or non-invasive

If more than one rule according to Annex VIII applies to the intended purposes of the device, the highest classification applies to the device, i.e. it must be classified on the basis of the most critical specified use

Check ALL rules that apply!!!!!
Justify your decision!!!!

For those investing in a company

If the company you support does not know the risk classification, they have no idea about the requirements

thus,

no realistic estimation of a valid time schedule nor resource needs can be available!

Why should you risk your money on such amateurs!

I hope this audience forgives me that I took this slide from my training given to business angels!

From a barrier to competitive edge

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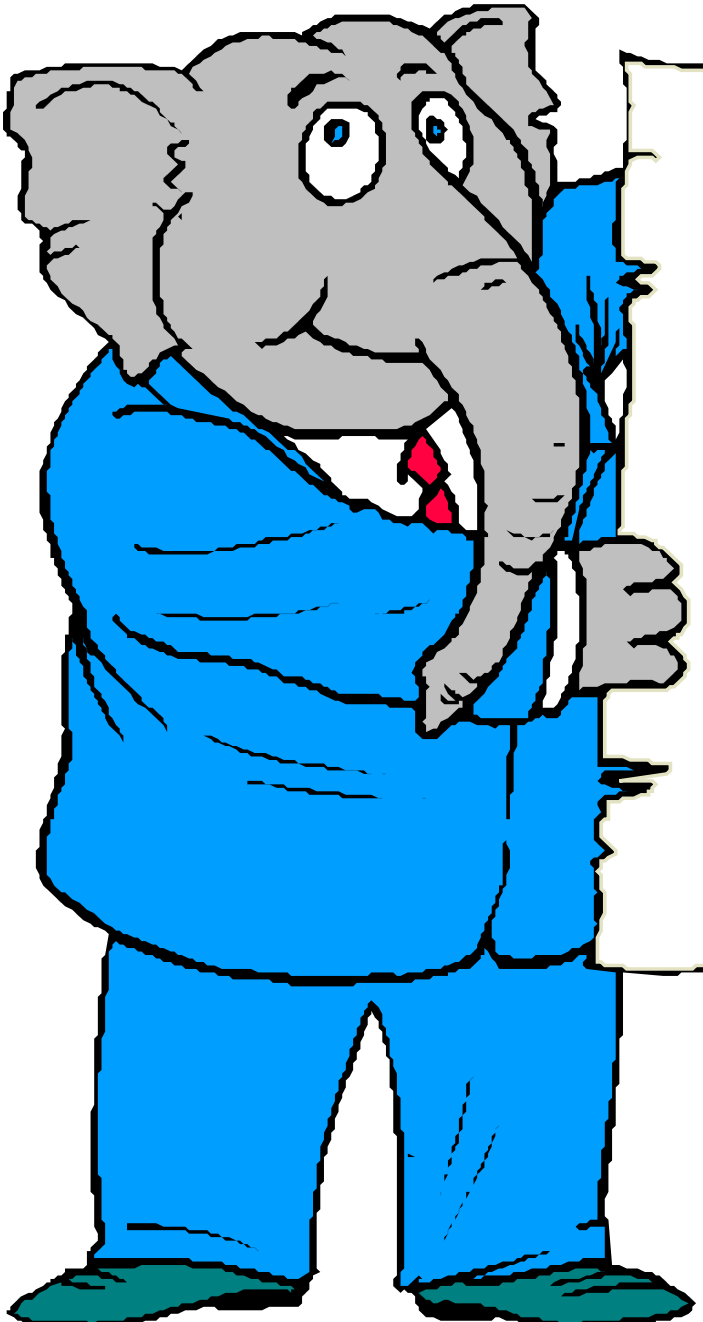

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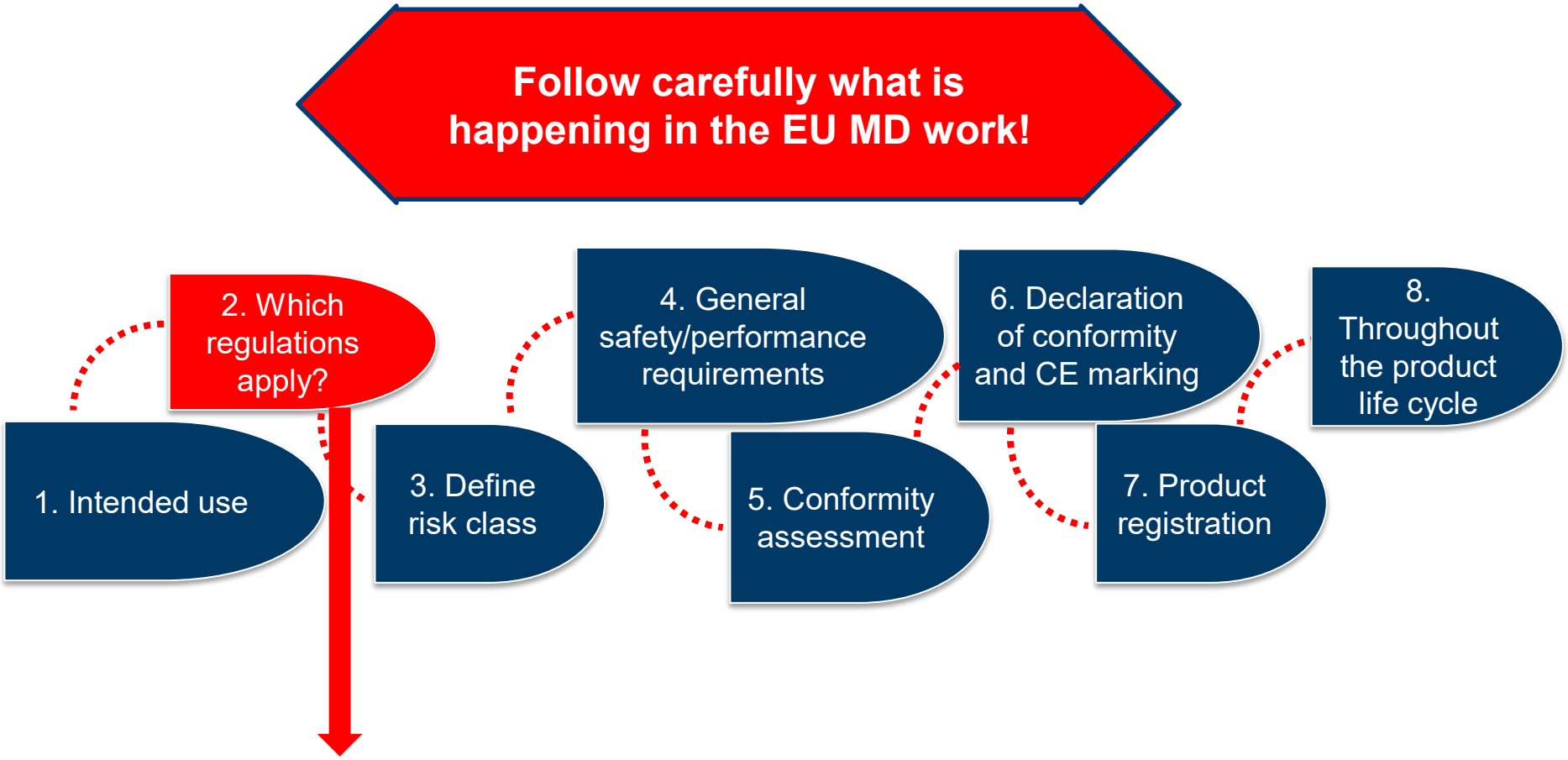
Regulations? EU still a lot of work in progress!



IVDR/MDR
Delegated and implementing acts
(to some extent: national legislation)
Guidance documents (MDCG), CTS
Harmonized standards

Some major changes in the MDR and IVDR?

Intended use

- in general no changes, but clarifications
- new group of products without medical purpose included

Classification

- MD: almost all software products are moving to a higher risk class
- IVD: directives 85 % lowest risk class, IVDR 85 % higher risk class

Some major changes in the MDR and IVDR?

Clear responsibilities for manfacturers, importers, distributors and authorised representatives

Strong emphasis on benefit-risk ratio, also benefits must be exploited

Risk management throughout product life cycle – stronger emphasis

More demanding General safety and performance requirements

Clinical and performance evaluation – several changes

Strong demands on post-market surveillance activities

Shorter deadlines for reporting incidences

Eudamed, UDI, Person responsible for regulatory compliance (PRRC)

Quality management system obligatory

EU MDR/IVDR: Content

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

REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

101 General principles and definitions

Neglected! Although providing understanding

Definitions (also from applicable standards)
= correct terminology to be used! Common language!!
Create your own terminology bank!

10 Chapters, 123 articles

15 Annexes (MDR one more annex)

Neglected! Still, meat on the bones

Similar structure as for MDR, neither have a list of content!

EU MDR/IVDR: Content

In red: most relevant for product development phase

General safety and performance requirements	Annex I
Technical documentation	Annex II
Technical documentation on post-market surveillance	Annex III
EU declaration of conformity	Annex IV
CE marking of conformity	Annex V
Registration of devices and economic operators; UDI	Annex VI
Requirements to be met by notified bodies	Annex VII
Classification rules	Annex VIII

EU IVDR: Content/Annexes

Conformity assessment based on a quality management system and on assessment of technical documentation	Annex IX
Conformity assessment based on type-examination	Annex X
Conformity assessment based on product conformity verification	Annex XI
Certificates issued by a notified body	Annex XII
Performance evaluation, performance studies and post-market performance follow-up	Annex XIII
Interventional clinical performance studies and certain other performance studies	Annex XIV
Correlation table	Annex XVII

EU MDR: Content/Annexes

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Certificates issued by a notified body	Annex XII
Procedure for custom-made devices	Annex XIII
Clinical evaluation and post-market clinical follow-up	Annex XIV
Clinical investigations	Annex XV
List of groups of products without an intended medical purpose	Annex XVI
Correlation table showing: Council Directive 90/385/EEC/Council Directive 93/42/EEC vs. the MDR	Annex XVII

From a barrier to competitive edge

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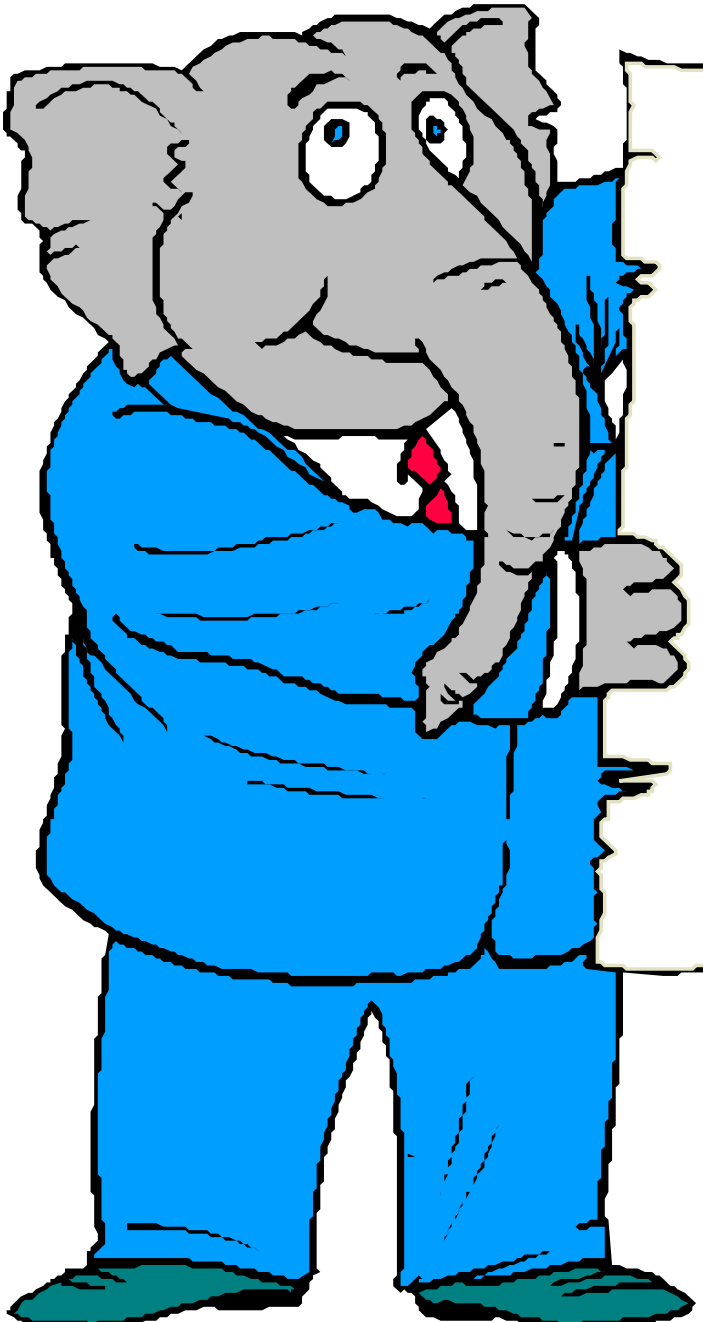

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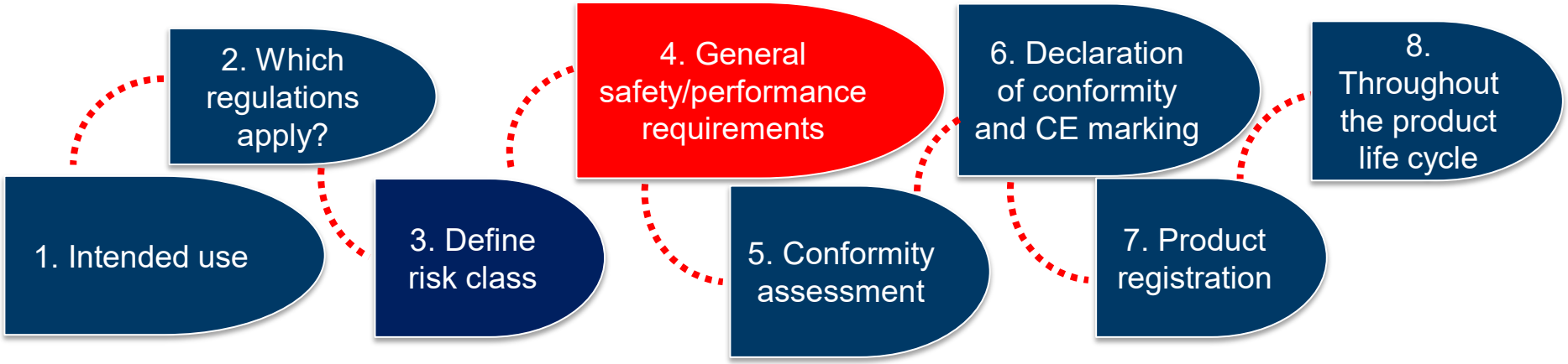


General safety and performance requirements

Annex I

In the Directives = Essential requirements

Very general, 14 pages

Needs to be interpreted line by line by the manufacturer and changed into practical demands

You have to make it specific

To be supported by leaning on the harmonized standards

EU has mocked this up!
Use what is available!
Justification: State of the Art

General safety and performance requirements

Risk management	Chapter I
Performance, design manufacture	Chapter II
Information supplied with the device	Chapter III

Benefit > risks!
State of art?

Risk management: all company
Emphasize also the benefit

Throughout the MD life cycle!

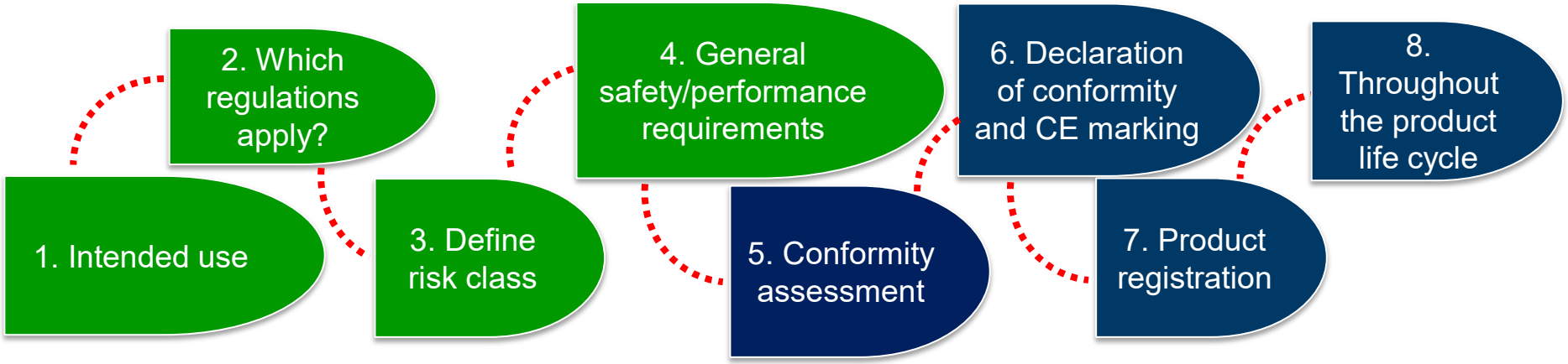
General safety and performance requirements

Risk management	Chapter I
Performance, design manufacture	Chapter II
Information supplied with the device	Chapter III

Truthful labelling
Misbranded
Benefit/Risks
Accepted symbols
And promotional material may put all at risk!

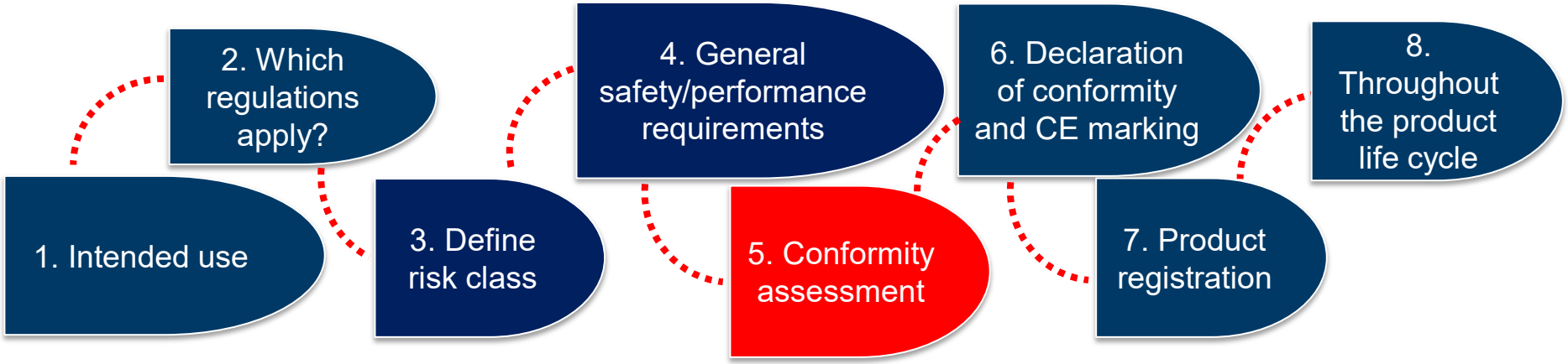
Design input, Lähtötiedot

Use enough time and effort!
Clarify all open questions, use external help
Remember: design output must meet design input



Red Line:
From Patient/User/other stakeholder demands to product specifications to final MD

(40) 'conformity assessment' means the process demonstrating whether the requirements of this Regulation relating to a device have been fulfilled;



Prerequisite: you have to know the requirements vs. your particular product(s)

You have to provide written evidence: Technical documentation files

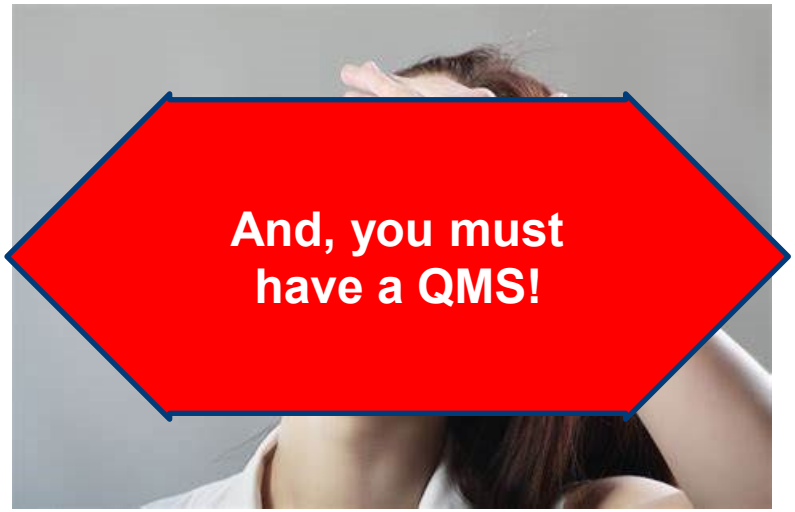
Conformity assessment: Responsibility

The responsibility remains with the manufacturer, despite the possible assessment done by the NB or registration by the CA

“Myyntilupa” “Permission to sell” – this concept not valid for MDs!

Conformity assessment: Responsibility (Class I)

(60) The conformity assessment procedure for class I devices should be carried out, as a general rule, under the sole responsibility of manufacturers in view of the low level of vulnerability associated with such devices.



Still, everything must be in place and may be asked for

NB if measuring function, sterility or reusable surgical instrument

Conformity assessment: if NB involved

ANNEX II

TECHNICAL DOCUMENTATION

1. DEVICE DESCRIPTION AND SPECIFICATION, INCLUDING VARIANTS AND ACCESSORIES

Typical pitfalls

Intended purpose, users and patient populations: vague and ambiguous

No rationale for: being MD, risk classification

Accessories not included

Technical descriptions: scientific and statistical rationales weak

ANNEX II

TECHNICAL DOCUMENTATION

2. INFORMATION TO BE SUPPLIED BY THE MANUFACTURER

Typical pitfalls

Usability check of provided information forgotten

Using symbols not officially accepted

Language versions may be a real barrier

I recently saw a complete ”fake” instructions for use (e.g. referring to non-existing NBs)…

ANNEX II

TECHNICAL DOCUMENTATION

3. DESIGN AND MANUFACTURING INFORMATION

Typical pitfalls

No design reviews (especially huge problem in the eyes of US FDA

Patient/user/other stakeholder requirements not done early enough

No link: Stakeholder requirements – specifications – final product

Validation (of manufacturing) processes:

- **Not done for final product, scope superficial**
- **Acceptance criteria approved after starting implementation or included not until the validation report**
- **No criteria for revalidations**

ANNEX II

TECHNICAL DOCUMENTATION

4. GENERAL SAFETY AND PERFORMANCE REQUIREMENTS

Typical pitfalls

- Exclusions not listed or not justified
- GSPR not translated to your particular MD
- Test methods not validated
- Not sufficient use of (harmonized) standards
- Risk management:
  - Not started early enough
  - Jump directly to risks without
    - Top management defined criteria
    - Identifying hazards, hazardous situations
  - No strict order: eliminate-reduce-control-inform
  - No conclusions on residual risk levels
  - Only restricted to the device (need: overall)
  - No link to and from the post-market phase

ANNEX II

TECHNICAL DOCUMENTATION

4. GENERAL SAFETY AND PERFORMANCE REQUIREMENTS

Typical pitfalls

Benefit-ratio unclear: especially the benefit part and comparisons to competitors or alternative approaches

Verification and validation mixed-up

Usability not in focus

Data provided but no conclusions drawn

Some specific areas may be excluded, but no conclusions/justifications

No plan for post-market surveillance

…

MDR: Clinical evaluation

The overall and highest level, whereas clinical investigations are a possible subpart of the evaluation

Always obligatory, even for Class I medical devices 

Final assessment to make sure that the MD is safe and fit for its purpose

Is the medical benefit > risks, are the risks and the ratio acceptable in comparison to the state of art?

Can be based on: history of own or similar products, clinical/scientific literature, clinical investigations

Clinical investigations

Always obligatory for Class III and implanted medical devices

For other classes obligatory if there is not otherwise enough evidence/information to cover the clinical evaluation

Usually needed for Class IIb and Class IIa

More rarely needed for Class I

Not allowed to be done if not needed 

Strict rules! 

IVDR: Performance evaluation and study

Clinical evidence, performance evaluation and performance studies

Chapter VI, Articles 56-77

Performance evaluation, performance studies and post-market performance follow-up

Annex XIII

Interventional clinical performance studies and certain other performance studies

Annex XIV

ANNEX II

TECHNICAL DOCUMENTATION

4. GENERAL SAFETY AND PERFORMANCE REQUIREMENTS

Typical pitfalls

Clinical evaluations/Performance evaluations:

- **”substantial equivalent” not justifiable**
- **poor description on how information has been collected**
- **Unfavourable data not appreciated**
- **No post-market clinical/performance follow-up plan**

Clinical investigations/Performance evaluations

- **If no experience, ”impossible to know ”n”**
- **Underestimating the time needed**
- **Ethical committees not always used to MDs**
- **Sponsors too amateurish**
- **Incident handling during the study lacking**
- **Informed consent poorly handled**
- **…**
- **Ask somebody to help you out!**

EU Notified Bodies Part II

Check your product(s) vs. the NB competencies!

Are not allowed to consult you!
Do not waste their time – be ready!

Choose carefully!

Competence: MDD/IVDD or MDR/IVD, risk class, Product family, horizontal technical competence

Make sure that you can justify the matching: your MD(s) and their codes

Be careful when filing an application: provide enough information/justifications

Assessment: documentation. Provide what is needed!
Assessment: audit. Make their life easy!
Assessment: ISO 13485 certificate separately in advance will speed up the process. Accept that they still need to check ”the regulatory” compliance.

No shame to get deviations. Correct them appropriately and timely. Especially US FDA: cure the disease and not only the symptom!

MDD/IVDD products: they will now be scrutinized from scratch from the MDR/IVDR point of view (not only based on your gap analysis)

From a barrier to competitive edge

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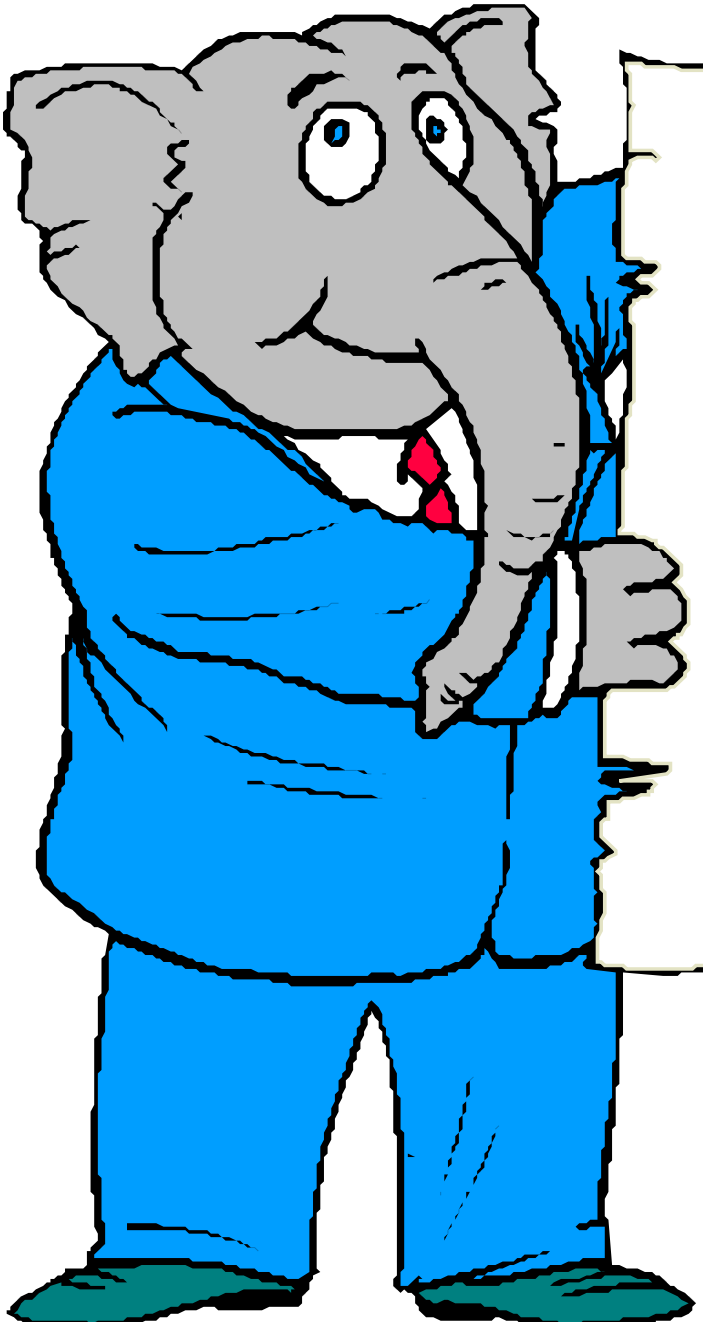

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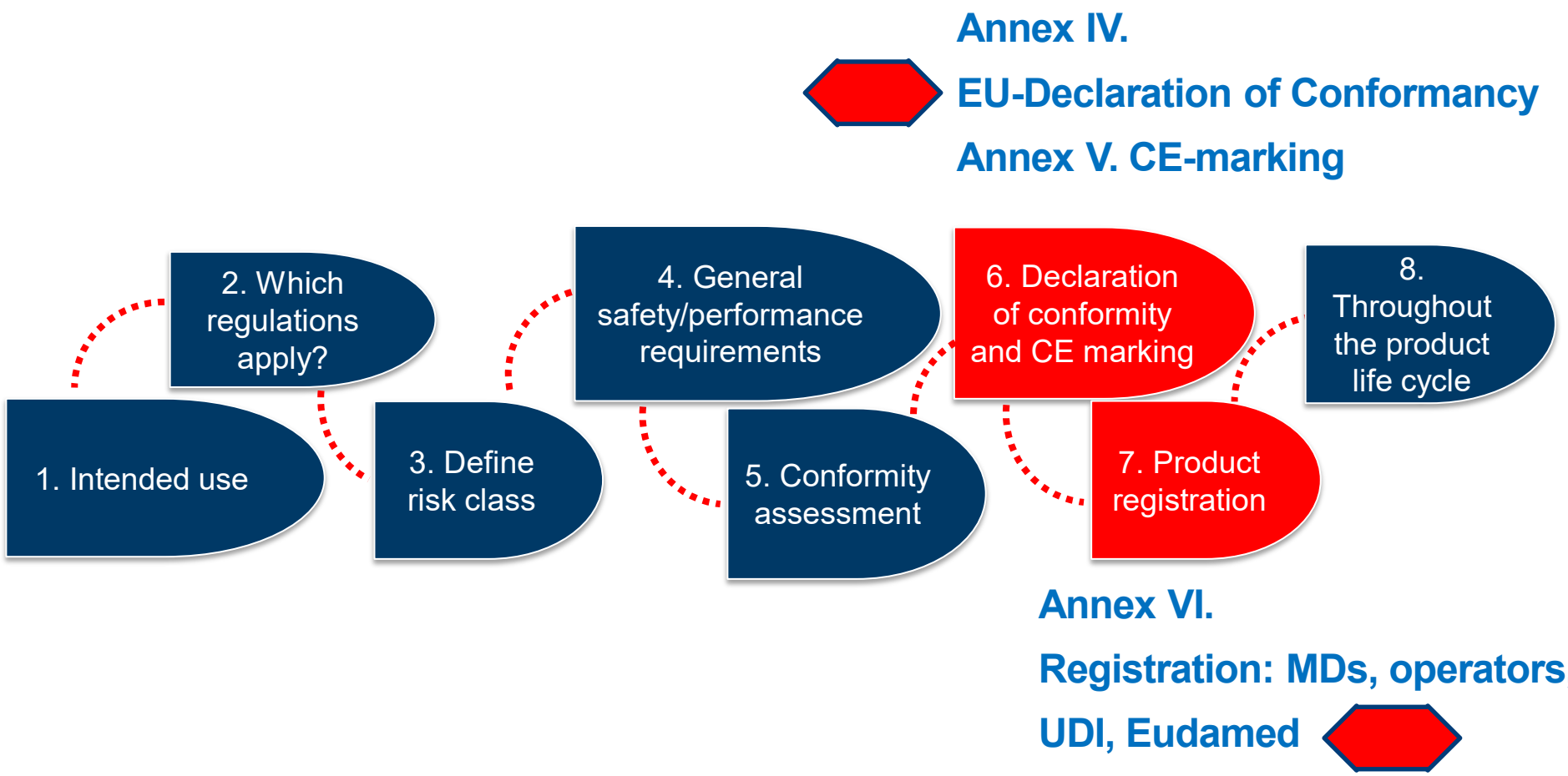
CE-Marking and Registration

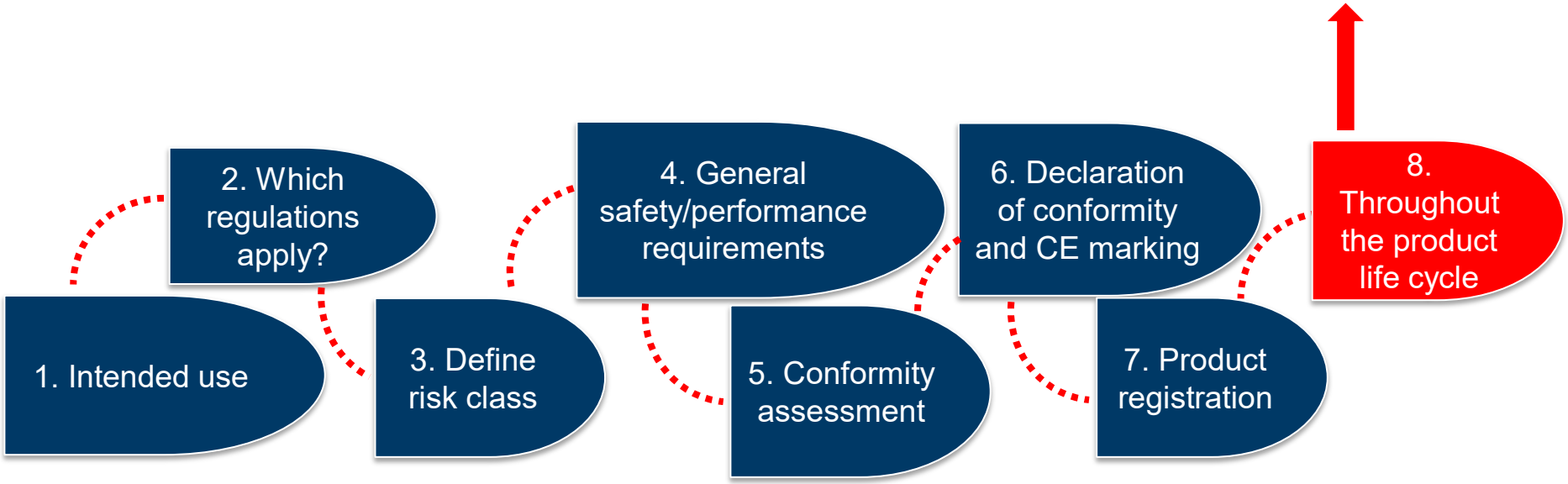


Starting already in the premarket phase!

Post-market phase:

reactive = vigilance, field safety corrective actions

proactive = post-market surveillance, continuous, active monitoring



From a barrier to competitive edge

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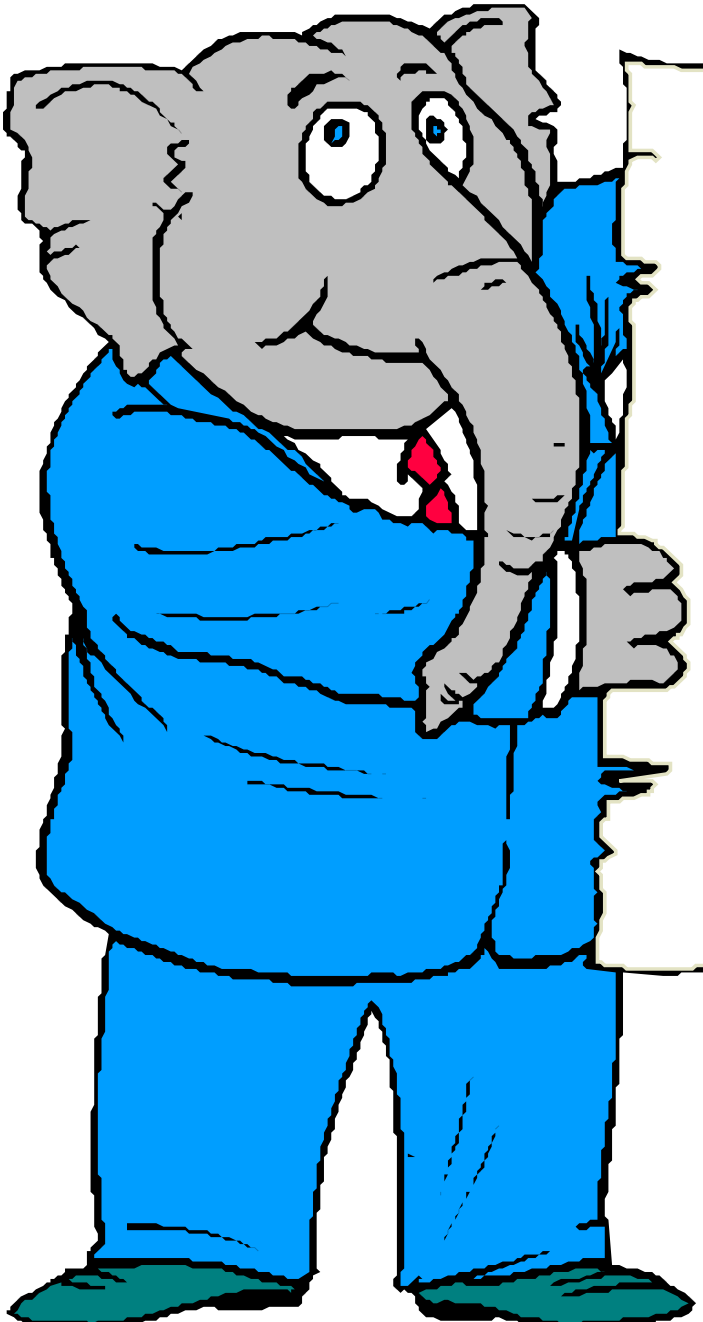

9.30-11.30 Setting the scheme

Post-market phase:

- MD on the market?
- Distributors? AR?
- CE: dealing with authorities?
- Rest of the world?
- Production and …?

12.30-14.30 **Pre-market phase:**

- Intended Use, risk classification
- Laws and standards
- GSPR and conformity
- Registration, Eudamed, UDI
- QMS: developing, obstacles

14.30-16.20 The Real Stuff

16.20-16.30 Q&A, conclusions

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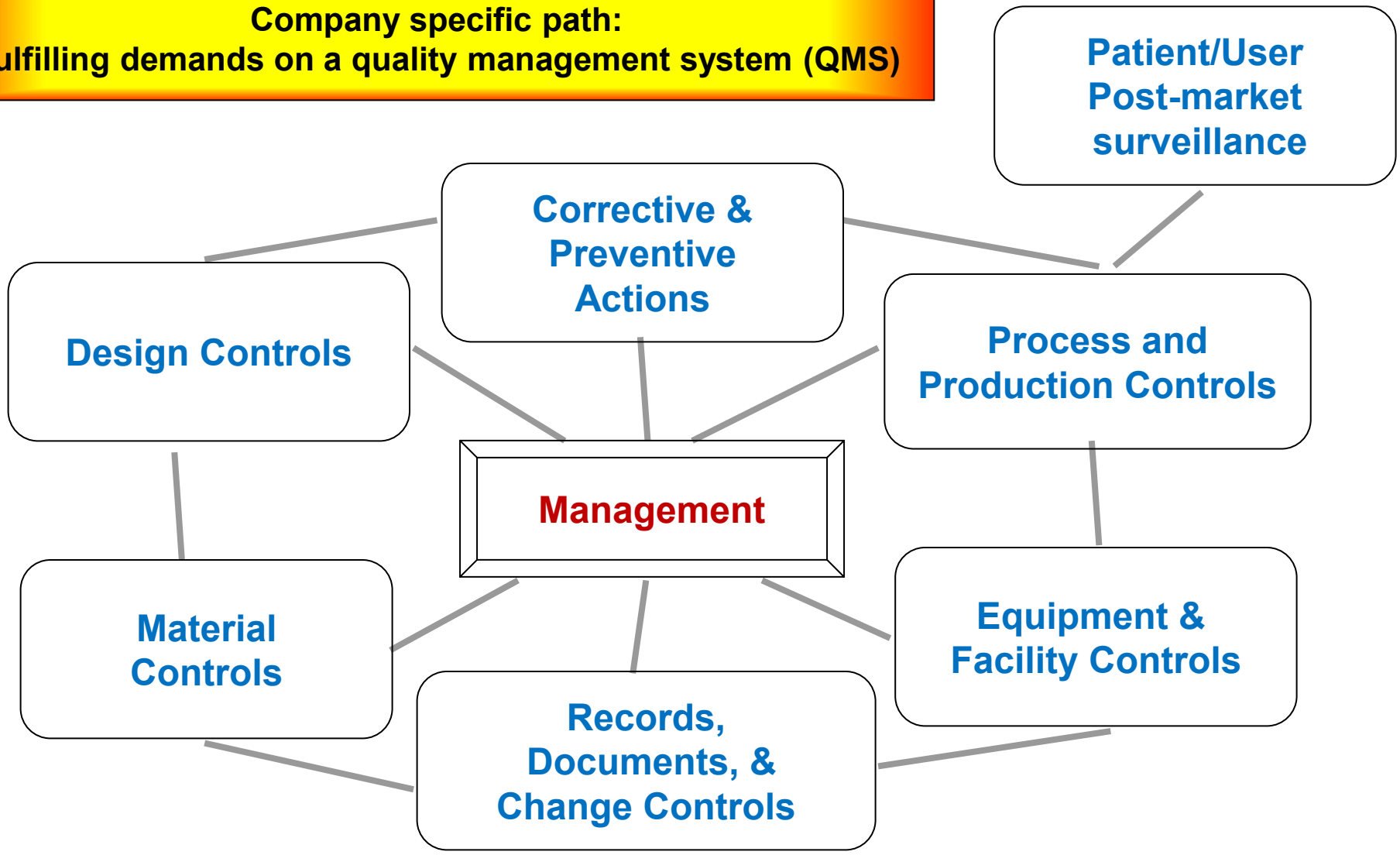
What about the other map: QMS?

Product specific path:
Fulfilling regulatory affairs demands (RA)

Company specific path:
Fulfilling demands on a quality management system (QMS)

Our compass:
Patient safety and MDs fit for their intended use

Company specific path:
Fulfilling demands on a quality management system (QMS)



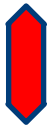
ISO 13485:2016 …for regulatory purposes

+ ISO 14971 Risk management

ISO 13485:2016

Medical devices – Quality management systems – Requirements for regulatory purposes

Regulations including standards



Quality management system

Activities performed

QMS strategy

May be first a simple QMS based on ISO 9001:2015
e.g. if first only non-MD products, if strong cultural/change resistance
and, thereafter, expansion to ISO 13485:2016

Directly building an ISO 13485:2016 compliant QMS including MDR or IVDR requirements

- First certification based on complete process descriptions
- For processes which are possible: give evidence that applied
- Later on also proofs needed that all is implemented

When first product under development: improve the regulatory parts and recertification and possible Notified Body

When non-EU market goal: incorporate the market country's regulations

Regulatory part neglected

Risk management not ”everywhere”

Not started from Day 1!

Oldfashioned quality-focused and not a modern management system

Not expanded to the beginning (suppliers) and not to the end (customers)

Not implemented

Not used during crisis

Specific pitfalls in each part: we need another day!

From a barrier to competitive edge

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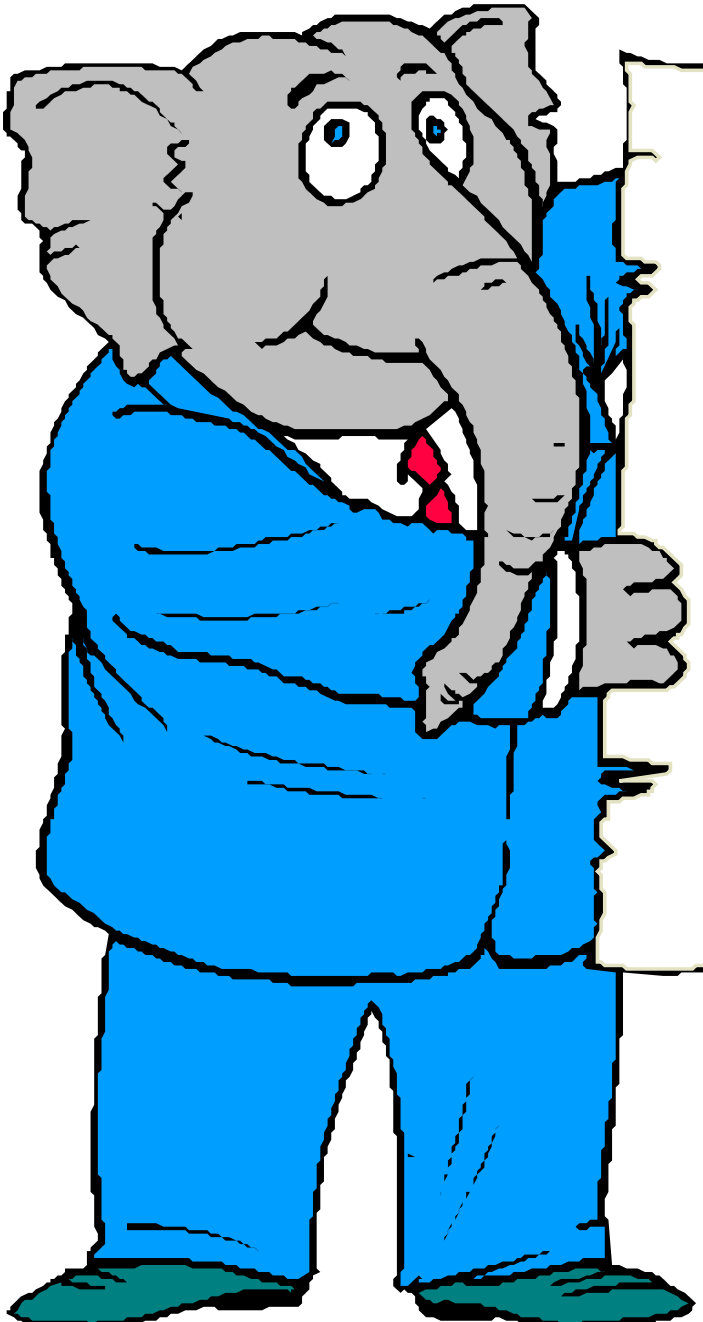

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