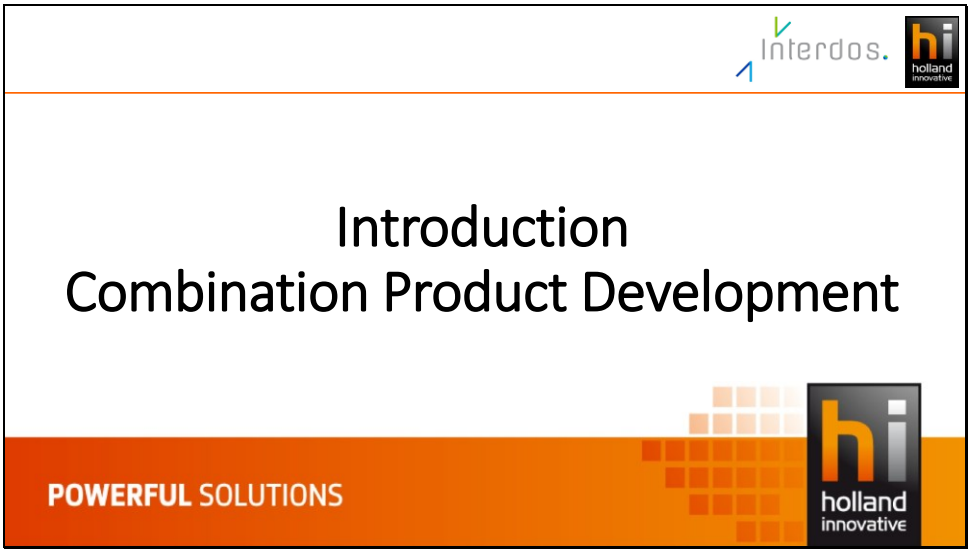
Slide 1



Welcome, introduction combination product development
Combination products are products which are a medical device and a pharmacological product combined. Rules and regulations for medical devices and pharma products, confusing and tangled.
Combined presentation by two expert companies in MD en MP.

Slide 2

Introduction speakers

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Slide 3

Introduction in legislation for combination products

Why do you need market approval?

How do you know which rules to follow?

What technical documentation do you need?

Slide 4

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Interdos.
holland innovative
CE-certification
Bringing a medical device on the European market
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Slide 6

CE stands for ‘’Conformité Européenne, which means: “This product is conform European Law”
The goal of the CE-mark is to have only safe and compliant products on the market, and to allow for free distribution of products within the European Economic Area

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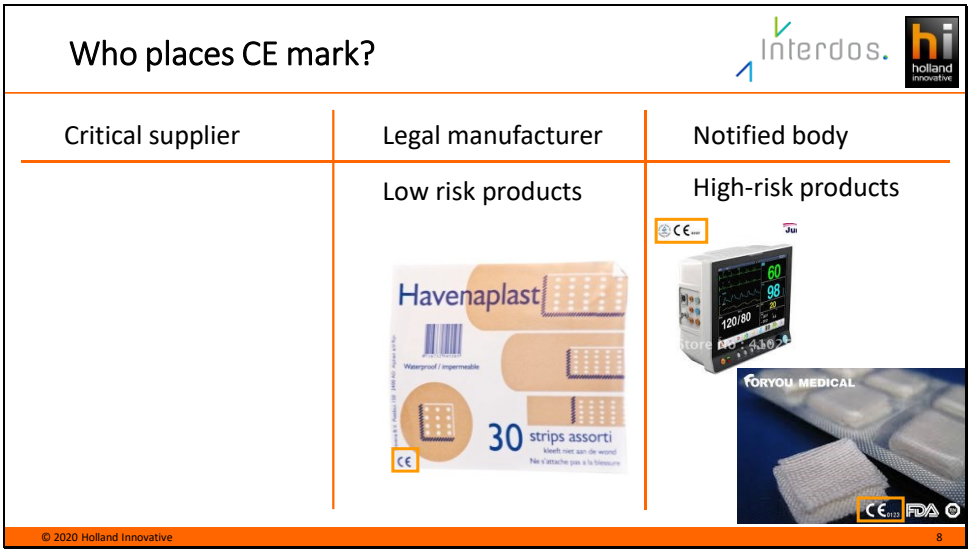
The major changes of the MDR compared to the MDD are:

- Life-cycle approach instead focus on pre-approval stage
- A strong empahsis on clinical data and evaluation
- The implementation of a unique device identifier (UDI) and a European database (EUDAMED) to allow for tracability of medical devices and prevent another PIP-scandal.

Slide 8



Determine which role you have in the supply chain:

- Legal manufacturer
- Critical supplier
- Distributor

The Legal Manufacturer = Responsible and accountable, the critical supplier delivers components to Legal manufacturer and a distributor distributes products from a legal manfufacturer and makes NO changes to these products.

Notified Body are also called ‘’NoBo’’, this is a commercial party, assigned & controlled by the IGJ **(in NL)** to examine if devices comply to the Medical Device Regulation

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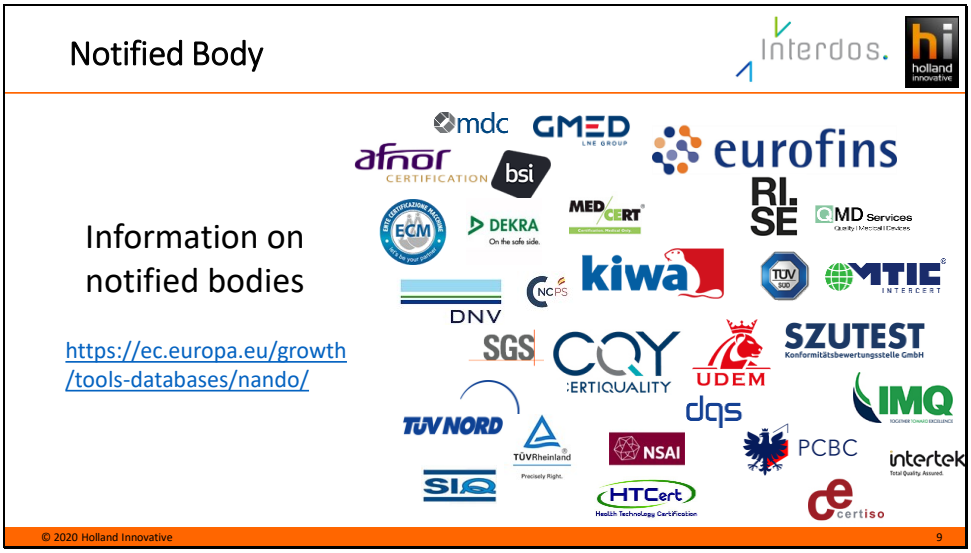

A notified body, in the European Union, is an entity that has been **accredited by a Member State** to **assess** whether a product to be placed on the market meets certain preordained standards. The Nando information system allow you to serach for notified bodies per legislation. Select the MDR: Regulation (EU) 2017/745 on medical devcies and you will see all accredited organizations for the MDR. If you select one, you see their scope. Always check if the notified body that you selected has your product in scope, and if they can do you conformity assessment procedure.
There are notified bodies which are specialized in certain types of combination products, ask if they have experience.

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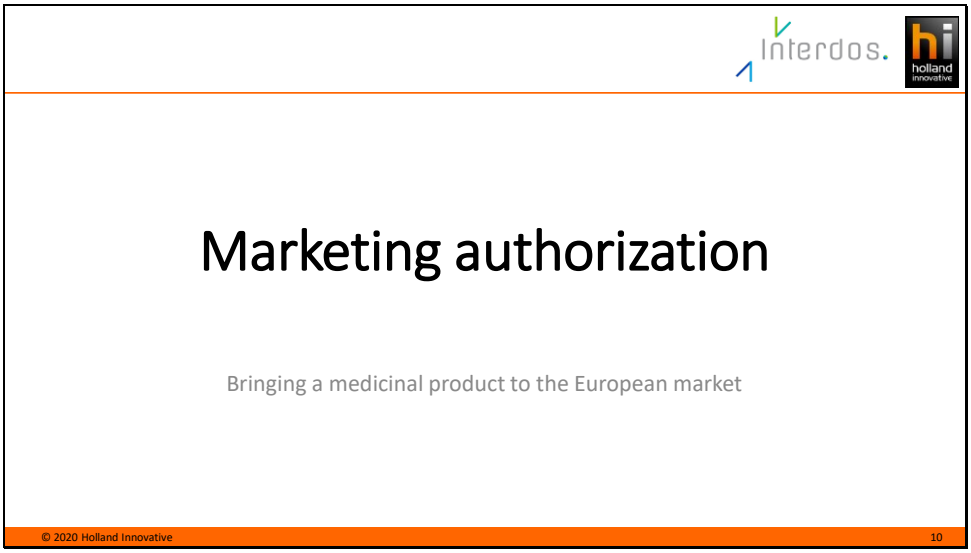

This part focuses on bringing a MP including DDC to the EU market.

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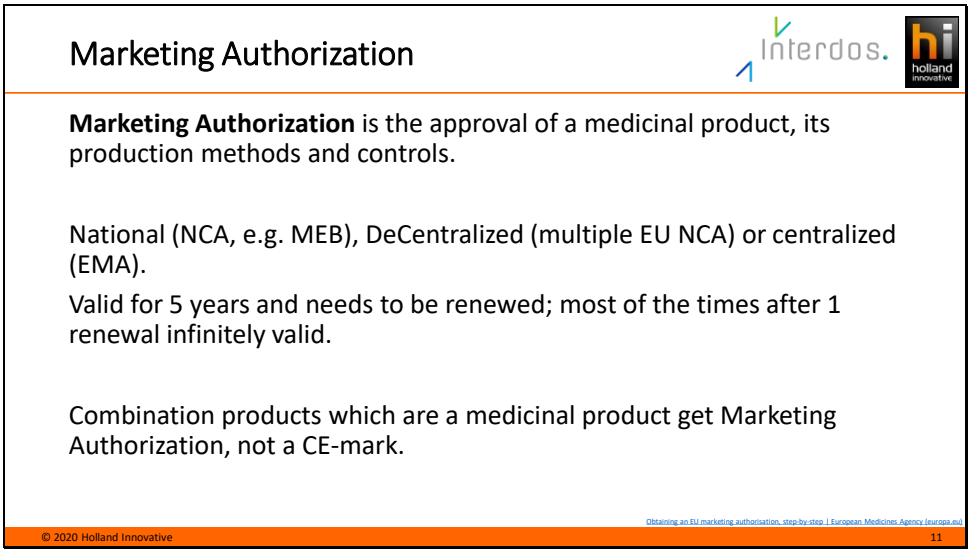

You can choose to go only national (1 NCA) or European (multiple NCA).

Only for innovators and specific product groups, you go via EMA. E.g. HIV, cancer, neurodegenerative, auto-immune, biotech, advanced-therapy medicines, medicines for rare diseases.
More information can be found here:
Authorisation of medicines | European Medicines Agency (europa.eu)

A marketing authorisation (MA) is valid for 5 years and may be renewed on the basis of a re-evaluation of the benefit/risk balance by the competent authority of the authorising Member State. Once renewed, the MA will become valid for an unlimited period unless the competent authority decides to proceed with one additional five-year renewal.

Important note: DDC need MA, not a CE mark.

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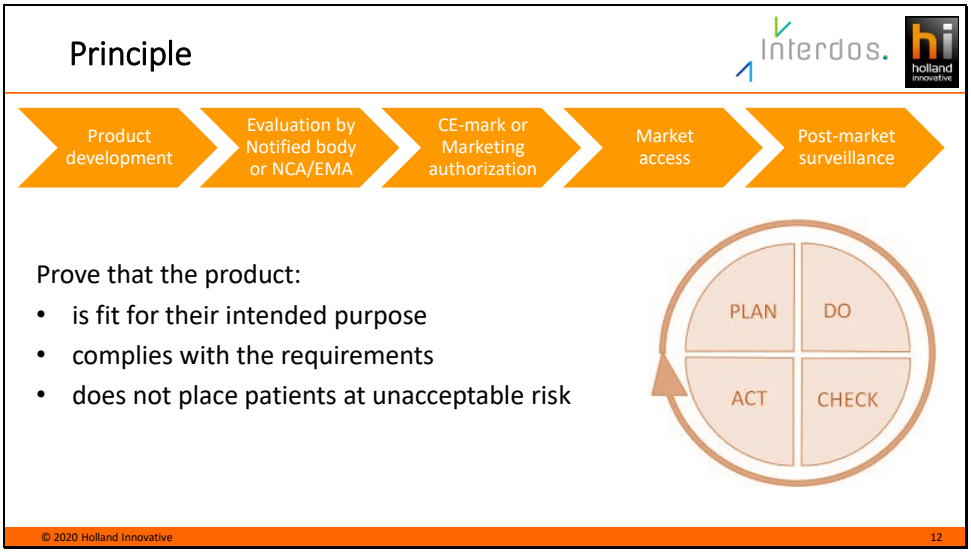

The life cycle of medical devices and medicinal product is similar. The product is developed and evaluated by the NB or the CA. After gaining market approval (CE-mark or MA) the product is allowed on the market, and the manufacturer is continuously responsible for the life cycle and post-market surveillance; following the safety and performance of the product in use.

The principle for both marketing authorization and CE-certification is the same. You must prove that your product is fit for its intended purpose, in other words it does what you claim it does. The product must comply with the applicable requirements, and the product must not place patients at an unacceptable risk.

Logically, both legislations also require the plan-do-check-act cycle.

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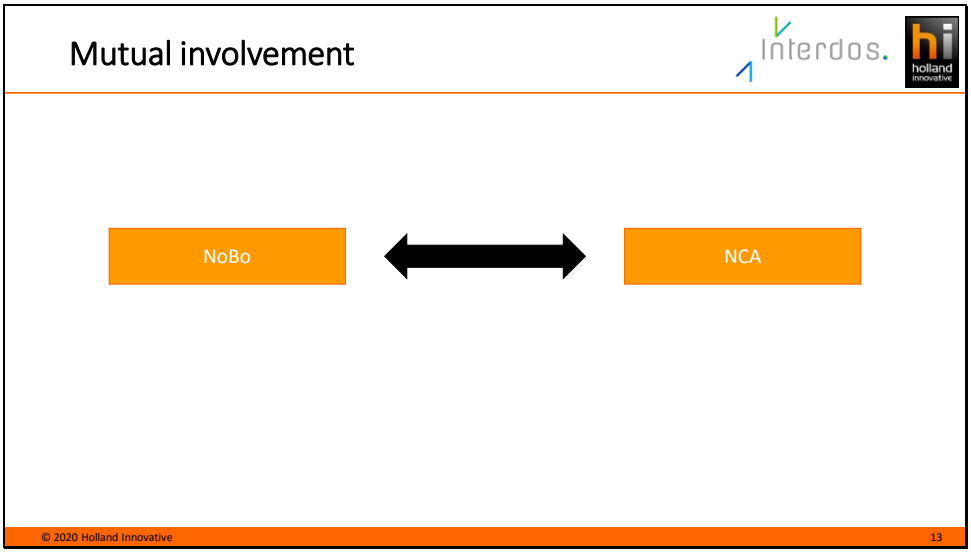

When you develop a drug device combination, you need to add the DoC of the class 1 medical device, or the NBOp for higher class devices. Vice versa, when you develop a medical device, your notified body needs to get a scientific opinion of the NCA or EMA concerning the dossier parts that cover the medicinal product. Notice the difference!

In any way, there is mutual involvement

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Introduction in legislation for combination products

Why do you need market approval?

Without market approval (CE-mark or marketing authorization), you are not allowed to sell in the European Economic Area.

How do you know which rules to follow?

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Qualification

Determining which rules apply, is my device a medical device or a medicinal product?

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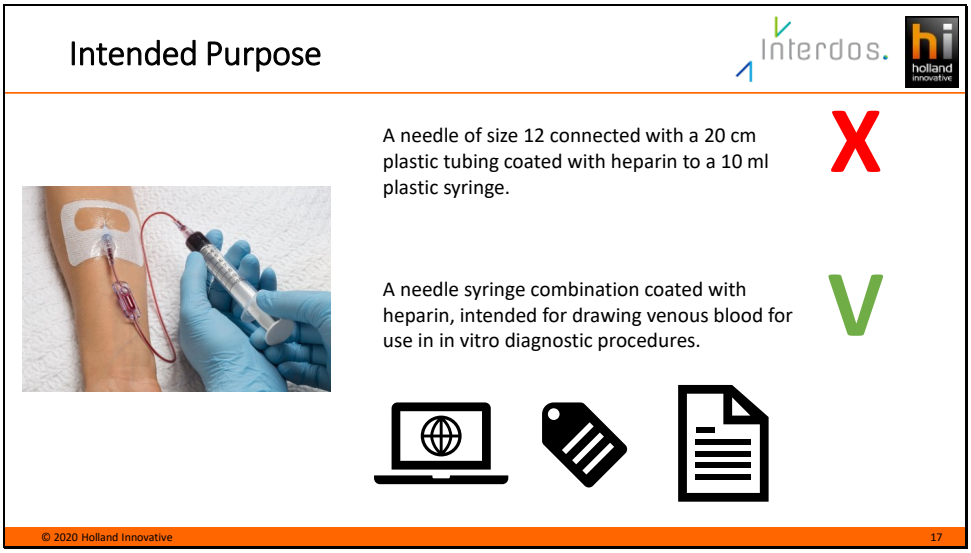

The definition of the intended purpose is stated in Article 2 of the MDR: ''use for which a device is intended according to the data supplied by the manufacturer on the **label**, in the **instructions for use** or in **promotional or sales materials** or statements and as specified by the manufacturer **in the clinical evaluation''**

The intended purpose is not a description of product features and specifications but a description of the intended medical use and should be written for the intended user group, medical professional or patient, using appropriate medical language. It is usually a short statement of two or three sentences that focuses on what the device is **intended to be used for**. In the product concept phase it is likely that the labels, instructions, promotional or sales materials don't yet exist. Nevertheless, one should start defining the intended purpose by considering how the product will be promoted, to who and with what messaging.

Also describe for your product the intended user(s) and use environment, the intended patient population, indications and

contra-indications. And the principles of operation and its mode of action.

The manufacturer must also describe the (expected) unintended use, which can already be foreseen. The manufacturer describes which use is safe and which is not safe with the product.

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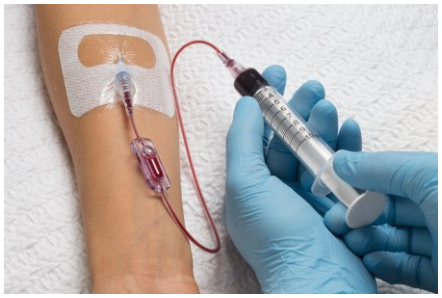
Medical device or medicinal product?



MDR art. 2 or medicinal product directive art. 1

any instrument, apparatus, appliance, software, implant, material or other article intended **to be used 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**

To determine if your device is a medical device or a medicinal product, you compare the intended purpose of your device to the definition of a medical device and that of a medicinal product. Determine which fits best.

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Whether a device is a medical device or a medicinal product depends on its intended purpose and the mode of action with which is achieves its intended purpose. Define the intended purpose and mode of action of your device, and compare these to the definition of a medical device and medicinal product, to determine which of the two it is. Note that a device can never be both. Either the MDR is applicable, or the pharmaceutical regulations are applicable. You have to decide as a manufacturer under which set of rules your product falls.

If the intended purpose of the device is supported by the drug which you apply to it, or if the mode of action of the device is physical rather than pharmacological (e.g. adsorption or lubrication), **the device is probably a medical device**. Examples of these devices are catheters coated with anticoagulants or active coal tablets that you can swallow to absorb toxins in your intestines.

On the other hand, **if the main function of the device is pharmacological and is supported in its function by a medical device, then it is a medicinal product.** Examples of these products are asthma inhalers, pre-filled syringes, and plasters that are intended to administer a drug. There are many products where the line between medical device and medicinal product is not clear. For the products where the European court has decided on which rules are applicable, there is the ‘’Borderline manual’’, see attachment. This document can help you decide which rules are applicable for you, by showing other example products. For more information see MDCG 2022-05: Guidance on borderline between medical devices and medicinal products under Regulation (EU) 2017/745 on medical devices mdcg_2022-5_en_0.pdf (europa.eu)

Slide 20

Are the following products medical devices or medicinal products?

Contact lens solution that is intended to disinfect, clean and hydrate contact lenses

Medical device

Syringe needle applicator and insulation that are an integral unit for the single-use administration of insulin

Medicinal product

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Introduction in legislation for combination products

Why do you need market approval?

Without market approval (CE-mark or marketing authorization), you are not allowed to sell in the European Economic Area.

How do you know which rules to follow?

Determine the intended purpose of your device and compare that to the definitions of medical device and medicinal product.

What technical documentation do you need?

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Introduction in legislation for combination products

Why do you need market approval?

Without market approval (CE-mark or marketing authorization), you are not allowed to sell in the European Economic Area.

How do you know which rules to follow?

Determine the intended purpose of your device and compare that to the definitions of medical device and medicinal product.

What technical documentation do you need?

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Technical documentation

Building up proof that your product is fit for its intended purpose, complies to the requirements and poses no unacceptable risk

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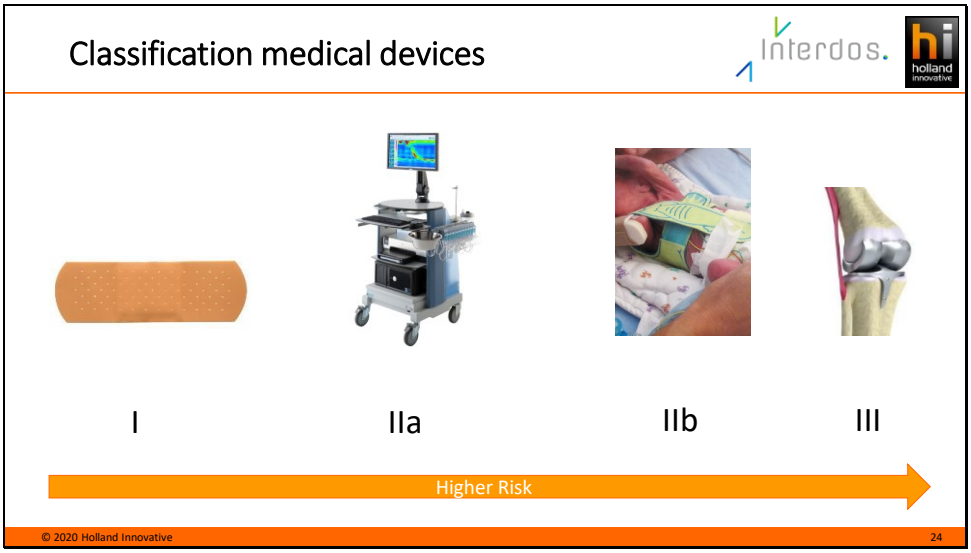
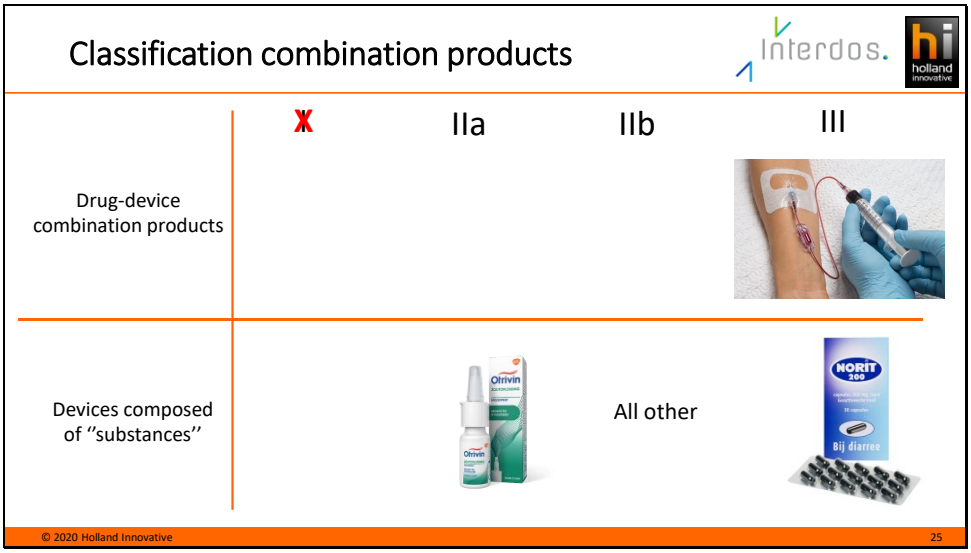


Medical Devices are split up in four classes, depending on the risk they bring during use. There are four risk classes: I, IIa, IIb and III.
Class I, wheelchair, plaster
Class IIa, diagnosis of non-vital functions e.g. gastroentrology device
Class IIb, diagnosis and monitoring of vital functions, e.g. respiratory monitoring systems, Ctscanners
Class III, implants e.g. pacemaker, stent.

Annex VIII of the MDR describes the risk classification rules of medical devices. You take your intended purpose and apply the classification rules in annex VIII. The rules which are applicable for your device determine the risk class.

Slide 25



Medical device with anciallary drug action fall under classification rule 14 of Annex VIII, these are for example e.g. bone cement with antibiotics, condoms with spermicide, cathethers coated with anticoagulants. All of these products are Class III.
There are also medical devices which are composed of substances (rule 21 of Annex VIII), this is e.g. active coal for oral administration. These fall in different classes depending on their intended use. Class IIa for products intended on the skin or nasal/oral cavity, class III for prodcuts which are systemically absorpted or function in stomach/gut, and Class IIb for all other.

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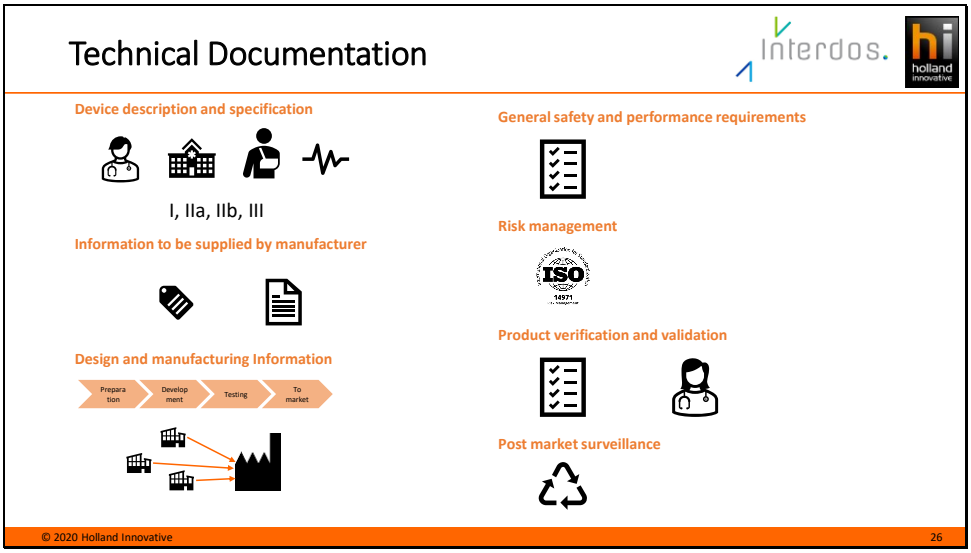

MDR annex II and III described which technical documentation is required for a medical device.

In the **device description and specification section** you describe the intended purpose, intended use, user, use environment, patient population and working principle. You write down what your product classification is, and which configurations there are, which features the device has, from which materials it is made and which accessories there are available. You also give an overview of any previous generations of the device. After this section, the auditor understands your device.
You are also asked to provide a copy of all **information that you provide with your product**, e.g. user manual, technical manual, instructions for use and the label.
The **design and manufacturing information** contains all information about the design and manufacuting of your device. You are expected to have a design and development process with a stage-gate model, where each phase is finished by a review. This process must be uploaded and explained. For each of the stages you have to have proof. In the preparation and planning phase you set up the specifications of your product. These have to be disclosed. Then you

are going to develop and make the product. The manufacturing specifications must be disclosed as well. Then you are going to test if the product that you have made performs according to the specifications that you have set-up in the first stage. How you do this, all the test plans and results are to be disclosed. If the product is good enough, you go to the notified body, and to the market. You must also identify any critical suppliers and manufacturing sites.

In the general safety and performance requirements, you identify which of the requirements from the MDR are applicable to your product. You have to prove that your product is safe and performs as it should. More on that later.

Risk management according to the ISO 14971 is obligatory, with a Risk Management Plan and Report. The **verification and validation section** contains the requirements for clinical evaluation. Here you are to show proof that your product fulfils the requirements you set for it by verification tests and proof that it complies with the appiclable standards that you use to show conformity of the GSPR. Part of the validation is clinical evaluation. This clinical evaluation contains a benefit risk analysis, where you compare the benefit of your device, as proven by clinical evaluation to the risks coming from risk management. As a manufacturer you are then to conduct a benefit-risk assessment. Only if this assessment is positive, meaning that the benefits outweigh the risks, it is allowed on the market.

The final section is about **post-market surveillance**, all activities that you as a manufacturer do after you product is put on the market to ensure that it stays state of the art and safe. You are required to write a Post-Market Surveillance Plan and if you are a higher risk class also a Periodic Safety Update Report.

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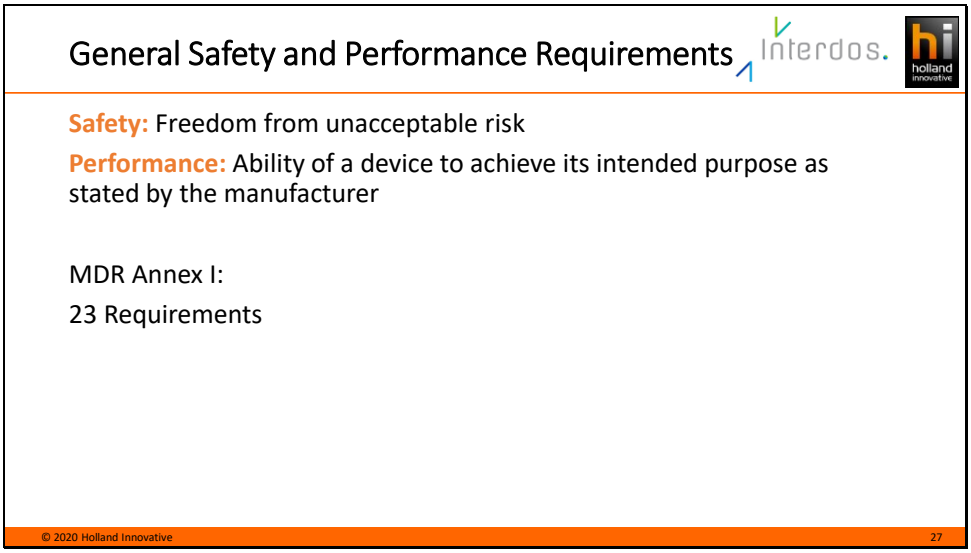

The GSPR are found in Annex I of the MDR. The GSPR cover a wide range of subjects. There are 23 requirements divided in 3 chapters:

I. General requirements

9 requirements about risks (e.g. risks related to use, packaging, transport, device lifetime, risk-benefit ratio)

II. Requirements regarding design and manufacture:

13 requirements about device and manufacturing process (e.g. materials, contamination, construction, software, active devices)

III. Requirements regarding, the information supplied with the device

1 extensive requirement about the label and the instruction for use

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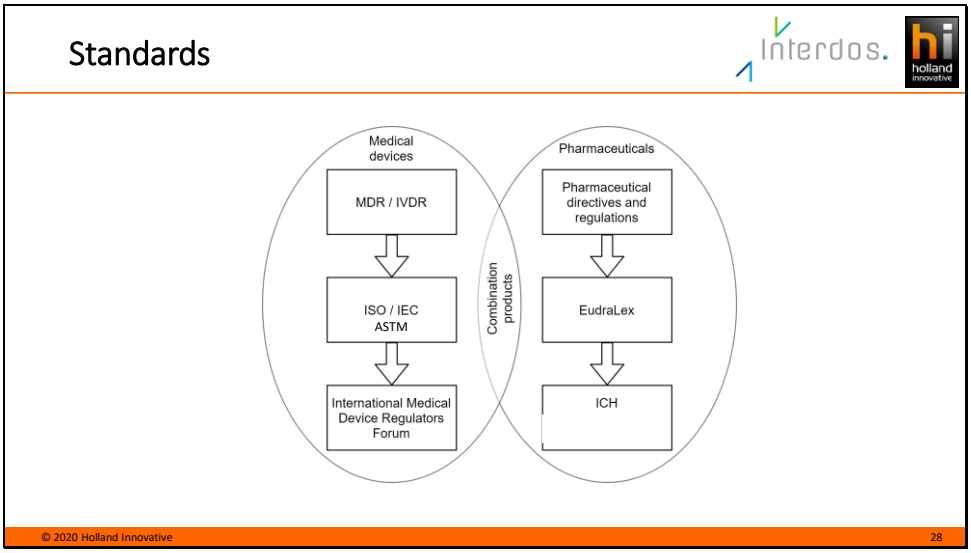

You fullfil a GSPR by complying to a standard. For the MDR there are the ISO, IEC and ASTM standards which can be used. Some of these standards are harmonized, which means that if you comply to the standard, you also automatically comply to the law. This is helpful, since often the law is quite vague and applicable ot a wide range of devices. The standards explain more clearly what you have to do, which documents you have to make, etc. There is an order in which you use the standards. On the top is the law, then you use the harmonized standards. If those are not available you use the non-harmonized standards. If there are no standards for your topic, there might be guidance from the IMDRF, which aims to align rules and regulations worldwide. Standards have to be bought from the webstores of e.g. the ISO and IEC.
For the pharmceuticals all the applicable guidance and standards can be found for free in EudraLex. On the same level as the IMDRF, the ICH standards exist for the pharmaeuticals.
When you make a medical device or a combination product, and there is no guidance for you subject, you can also check if the pharmaceutal standards have any available.

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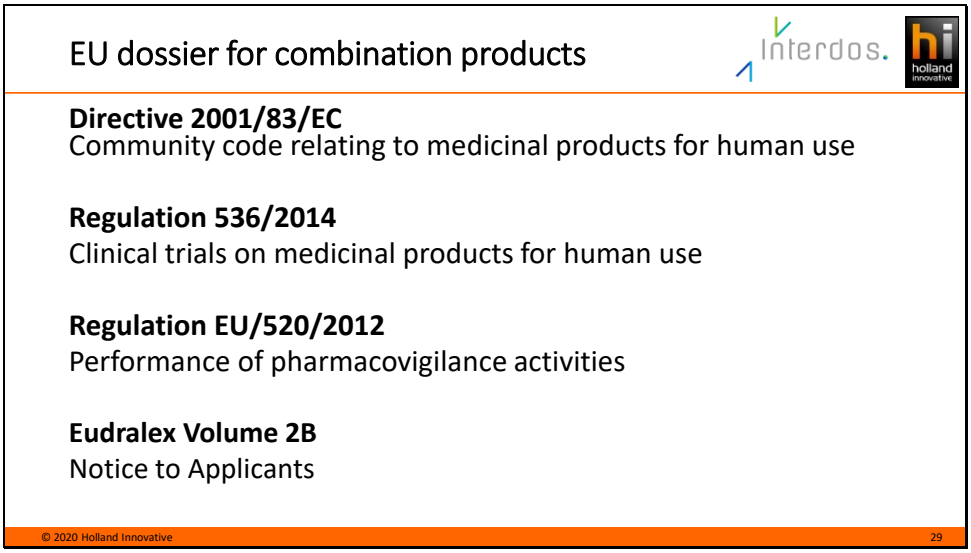

There are some important legislations and guidances you need to take into account. Here are some of them.

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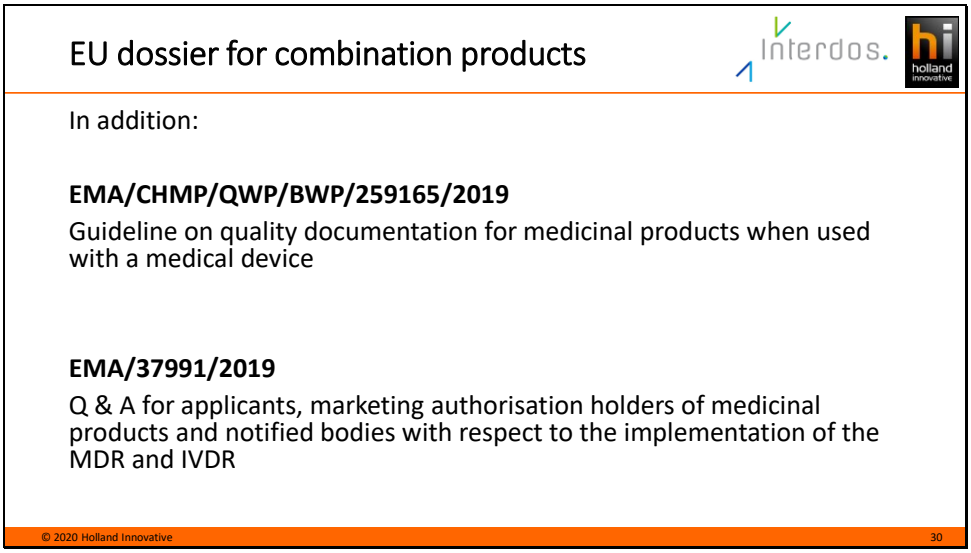

Additionally, there is some guidance specifically for combination products.

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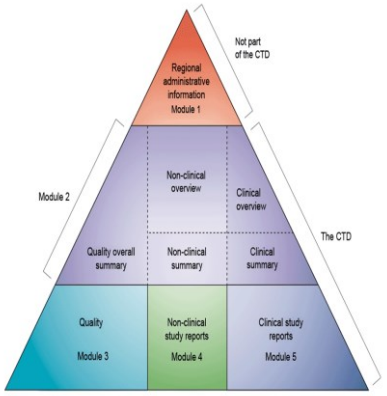
EU dossier for combination products

Same set of documents as for a dossier for medicinal products.

Well-organized folder structure; mandatory.



For a combination product (DDC) you need to generate the same set of documents as for a medicinal product.

This is the so-called CTD: Common Technical Document, also referred to as ‘dossier’.

It is represented by a pyramid, showing the different modules: 1-5

I will go into these modules in a bit more detail now.

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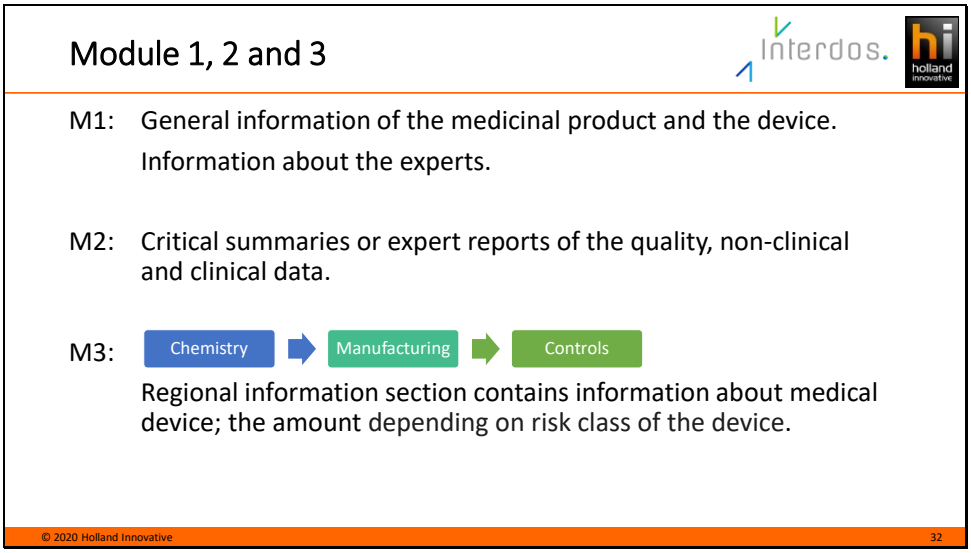

More details can be found in Notice to Applicants

For M3:
Class I devices: only DoC of device manufacturer
Class IIa/b, class III devices: NBOp

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Module 4 and 5

Non-clinical and clinical documentation according to ICH M4 guidelines and Eudralex Volume 2B

- Pharmacodynamics
- Pharmacokinetics
- Toxicity
- Local tolerance
- Studies on human subjects and related information

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What technical documentation do you need?

Same set of documents as for a medicinal product dossier, supplemented with information about the device, depending on risk class of the device.

Tips/tricks

- Take into account long timelines.
- Software needed to create and submit dossier to authorities.
- Do not underestimate the number of documents to be created.
- Use the CE tool to classify your device
  www.ce-tool.nl
- Do not try to re-invent the wheel. Knowledge is available, try to find it.

- **Try to make Quality and Regulatory live in your organization.**

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Questions?

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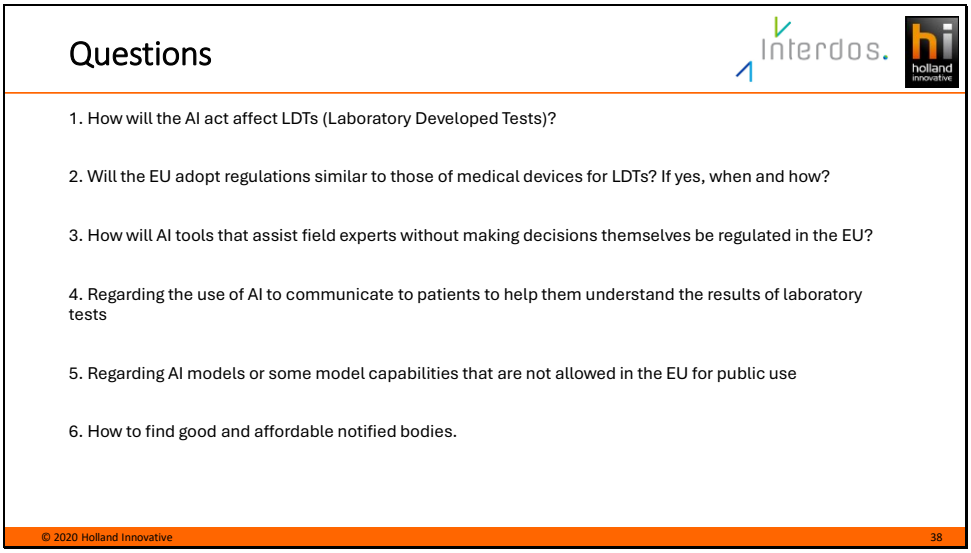

1. Recital 50 of the AI states that medical devices covered by a NoBo are high risk AI devices. However, in house developed tests are not covered by a NoBo (see article 5(5) of the IVDR). The spirit of the law here is that high risk medical devices using AI are also high risk AI devices. So if you are developing an in house class B, C or D IVD device, that contains AI, that would be a high risk device under the AI act. There is MDCG guidance planned for the interaction of the AI act and the IVDR/MDR in Q4 2024.
2. Yes, article 5(5) of the IVDR, this is already applicable.
3. Software tools can be a medical device, and if so they are most often class IIa, with therefore NoBo involvement and therefore they are also a high-risk AI product. If they are not a medical device the AI-act is still applicable.
4. Such a device becomes very quickly also a medical device. In that case the MDR and the AI act are applicable. If it is not a medical device, then Large Language models like ChatGPT are also covered by the AI-act.
5. AI not allowed in EU is also not allowed in Medical Devices.
6. There is MDCG guidance for notified bodies on how to disclose their prices. Classe B: 25k per jaar, 80k voor klasse D.