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PROJECTS

INTERIM MANAGEMENT

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Drugs, devices and combination products

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Company



Leading consultancy and project management organisation in the fields of (bio)pharmaceutical products, medical devices and healthcare.

- Headquarters in Leiden
- Affiliates in Berlin, London, Stockholm, Tokyo



**REGULATORY
AFFAIRS**



**PRODUCT
DEVELOPMENT**



**QUALIFICATION
& VALIDATION**



**PHARMACO
VIGILANCE**



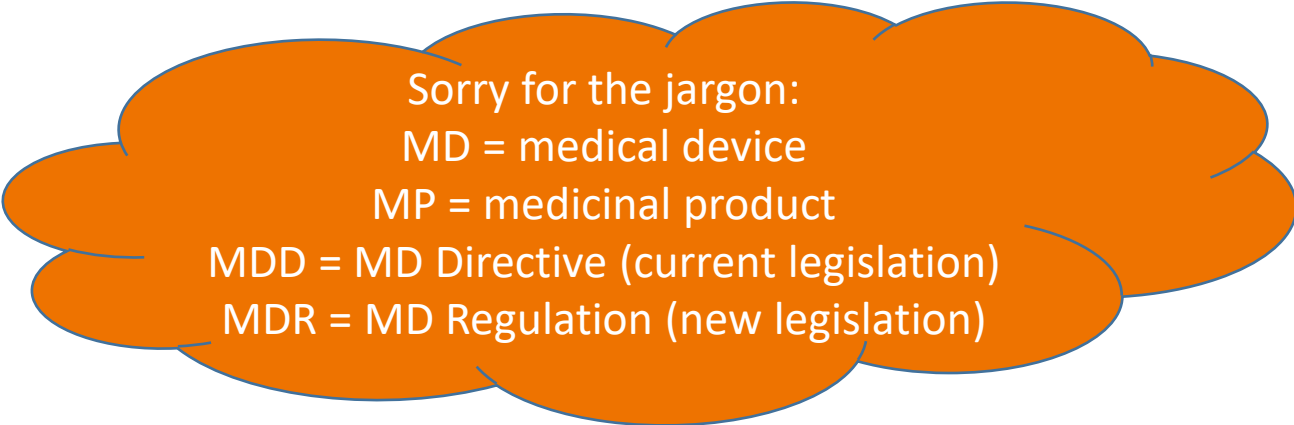
**QUALITY MANAGEMENT
& LEAN SIX SIGMA**



**ENGINEERING
& FACILITY SUPPORT**

AGENDA: Drugs, devices and combination products

- Definitions device, medicinal and combination product
 - MDD, MDR and MEDDEV 2.1/3
- Legislation
- Case
- From MDD to MDR
- Conclusion and messages



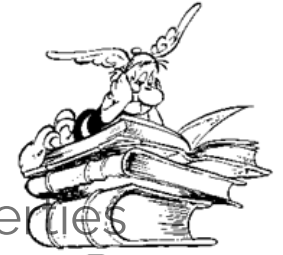
Sorry for the jargon:
MD = medical device
MP = medicinal product
MDD = MD Directive (current legislation)
MDR = MD Regulation (new legislation)

Medical Device



- '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 (IVDR),
- 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.

Medicinal product



- Medicinal product
 - Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or
 - Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a **pharmacological, immunological** or **metabolic** action, or to making a medical diagnosis."

Combination products



Definition:

- a device is placed on the market in such a way that the device and the medicinal product form a **single integral** unit which is intended **exclusively** for use in the given **combination** and which is **not reusable**, that single-unit product shall be governed by Directive 65/65/EEC;
- whereas a distinction must be drawn between the abovementioned devices and medical devices incorporating, inter alia, substances which, if used separately, may be considered to be a medicinal substance within the meaning of Directive 65/65/EEC;
- whereas in such cases, if the substances incorporated in the medical devices are liable to act upon the body with action **ancillary to that of the device**, the placing of the devices on the market is governed by the MDD

Combination and combined products

Examples:

- **Drug-delivery products regulated as medicinal products**

- Prefilled syringe
- **Nebulizer** pre-charged with a specific medicinal product



- **Drug-delivery products regulated as medical devices**

- Drug delivery pump
- **Nebulizer**, multiple use, not pre charged



- **Medical devices** incorporating, as an integral part, an ancillary medicinal substance

- Bone cements containing antibiotic
- Drug eluting coronary stent



Example of a powder inhaler

SPC:

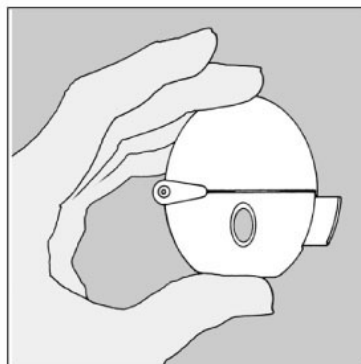
1. NAME OF THE MEDICINAL PRODUCT

Srivasso 18 microgram inhalation powder,
hard capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 22.5 microgram
tiotropium bromide monohydrate equivalent
to 18 microgram tiotropium.

The delivered dose (the dose that leaves the
mouthpiece of the HandiHaler device) is 1
microgram tiotropium.



!:

MP & MD in one registration

No CE mark for the Handihaler

?:

Correct?

How was the trial done?

During development

- Compatibility of medicinal compound and medical device (MD) should be verified
 - Based on pre-clinical testing
 - Clinical study might be necessary
- Review the need for a clinical study for both products
(in case of a MD, this is established in the Clinical Evaluation Report)
- In case a MD is not CE marked, it cannot be used in a medicinal product clinical trial as such: it should be treated as an **investigational medical device**
- In case a MD is CE marked for an intended use that differs from the intended use in the medicinal product clinical trial, it cannot be as such: it should be treated as an **investigational medical device**
- In case a MD is CE marked and the intended use in the medicinal product clinical trial = the intended use as defined in the instructions, it can be used as such



Clinical study guidelines and legislation

	Combination product	Stand alone
Investigational Medical Device (IMD)	<u>Either</u> ISO 14155 and MDD	ISO 14155 and MDD
Investigational Medicinal Product (IMP)	<u>Or</u> GCP (ICH E6) and MPD	GCP (ICH E6) and MPD
IMD and MP		ISO 14155 and MDD
MD and IMP		GCP (ICH E6) and MPD
Both MD and MP investigational		ISO 14155 and MDD GCP (ICH E6) and MPD

Investigational MD

The medical device is not CE marked **or**

The device is CE marked but not used according to intended use/instructions for use

- i.e. used outside registered domain

MDD-Annex X and ISO 14155 must be followed in addition to IMP requirements for clinical studies:

1. **Clinical Evaluation Report** must be generated before the submissions and is input to the study documentation
2. Prepare Investigational Medical Device Dossier (**IMDD**) (**local Dutch requirement**)
3. Generate the Annex X statement
4. Dual submission:
 - MEC

New legislation: the MD Regulation



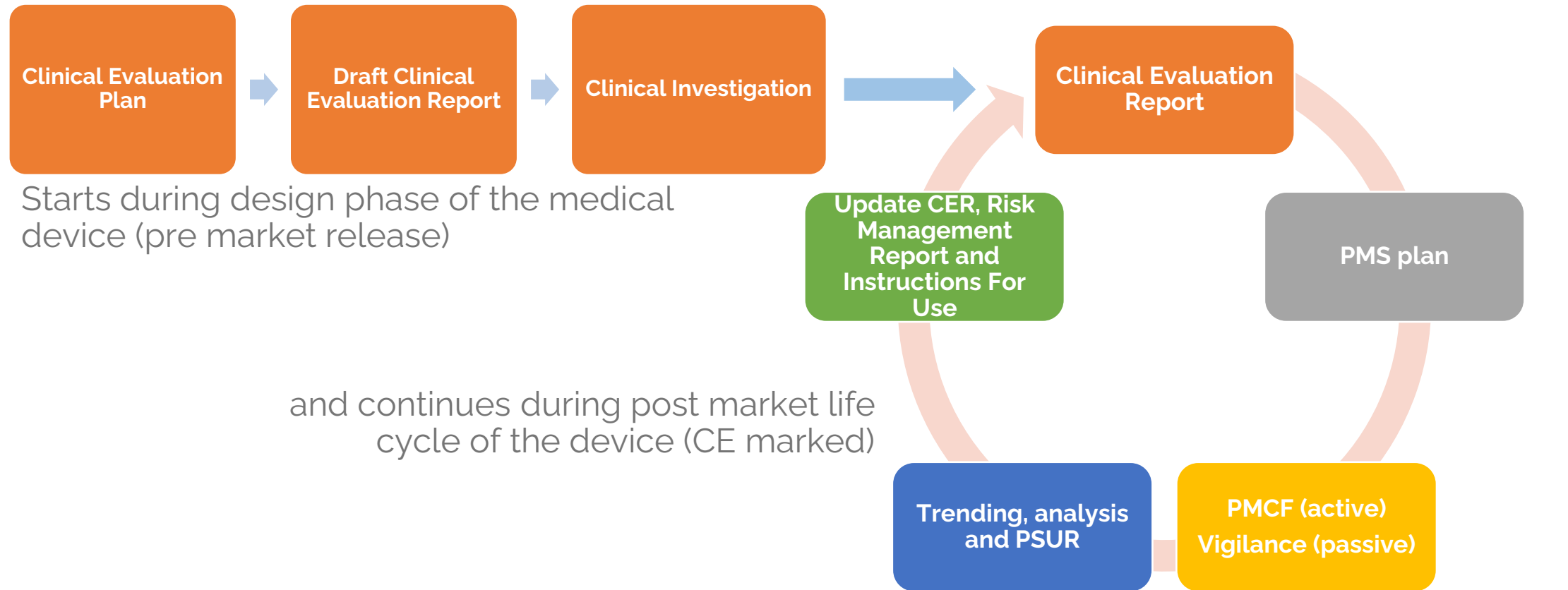
- **No Grandfathering:** all currently certified Medical Devices must be re-certified in accordance with the new requirements.
- Implications:
 - all devices which are currently on the market will need to comply with the new regulations by the end of transition period;
 - requiring new Conformity Assessments under new legislation for all devices currently circulating within the European Union;
 - manufacturers of devices falling under the scope of the new Medical Device Regulation will have to comply latest

Next steps



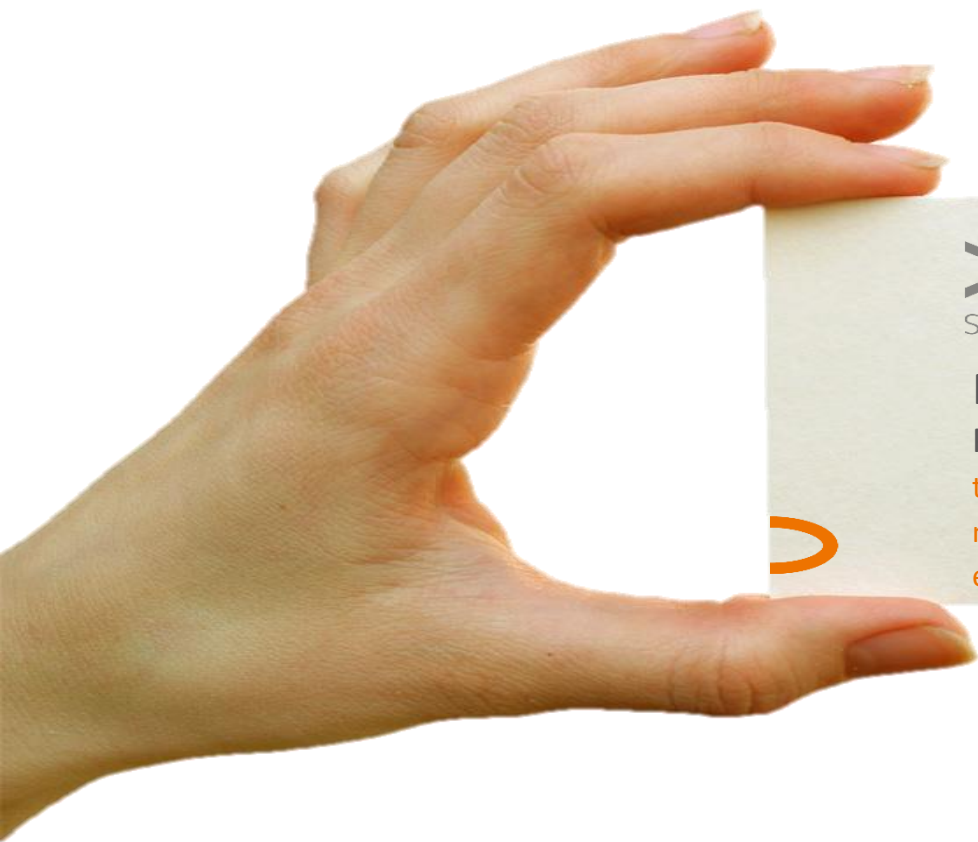
- MDR mandatory per May 2020, recertification required
- No grandfathering
 - It might be wise to check if the clinical strategy also meets the requirements of the MDR to ensure that data is usable also after May 2020.
 - MDD Annex X Clinical Evaluation: 1 page
 - MDR Annex XIV and XV clinical evaluation and investigation: page 164 to 172
- Embedding of clinical data gathering into the clinical evaluation process will be strongly intensified. Integration of investigation activities with Post Market Surveillance activities when product is CE marked.
- Studies that started before May 2020 under the MDD can continue, but product registration after May 2020 must be according to the MDR

Clinical process and deliverables (MDR)



Take home message

1. Combination products and products that are combined make that both MD and MP legislations need to be followed
2. Classification of combination / combined products can be complex and is not always done appropriately



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