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Health Products Regulatory Authority

Drug-Device Combinations: Some Regulatory Considerations

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Introduction

The Current State

The Future State

Conclusions

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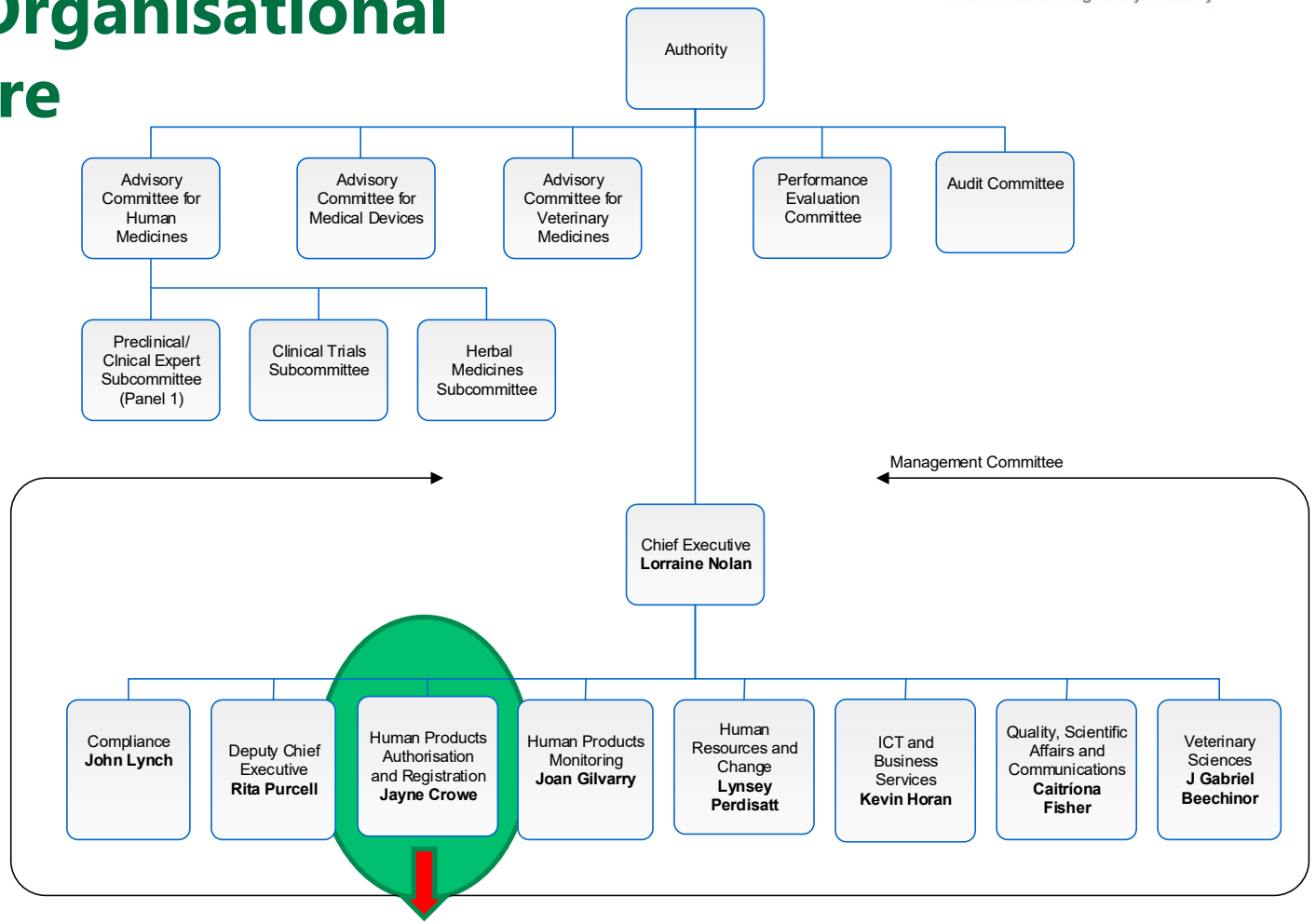
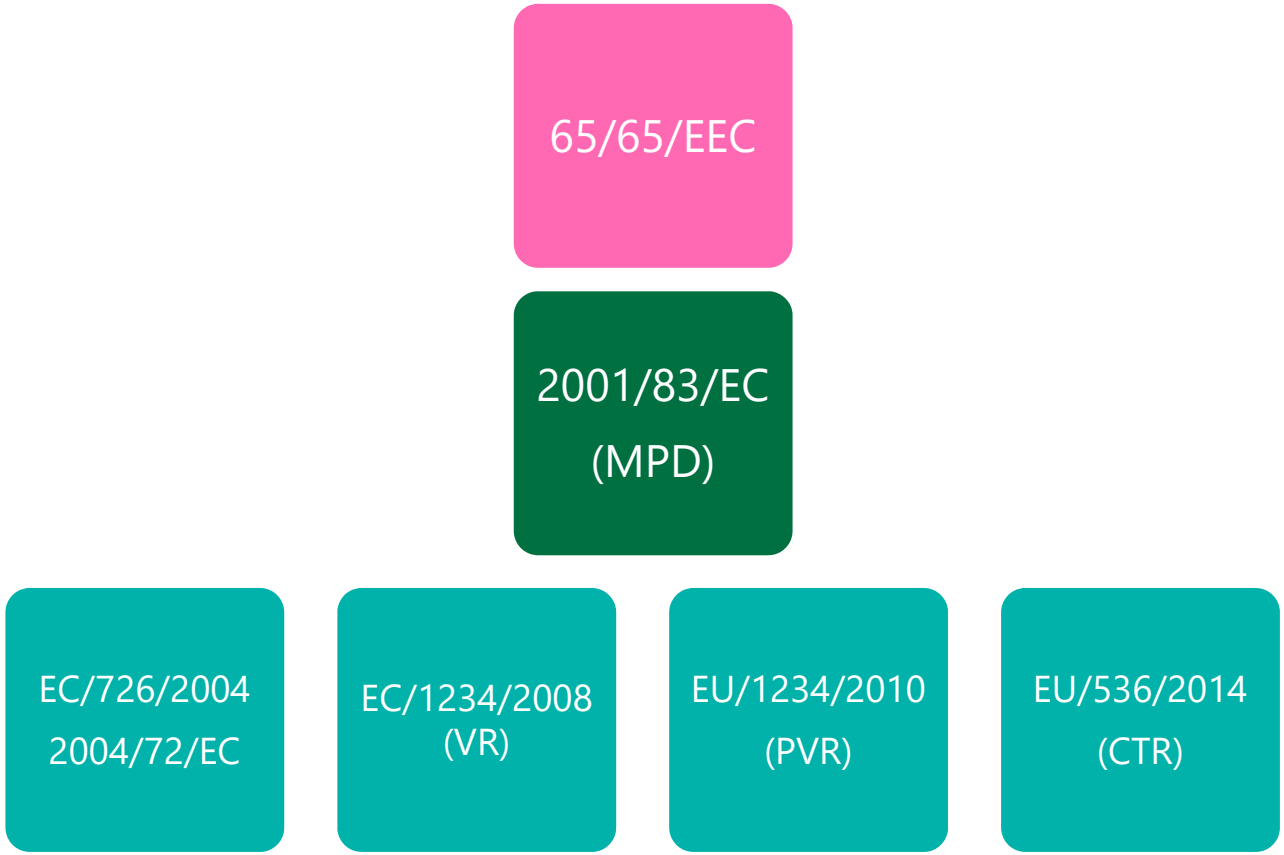
Introduction

HPRA Organisational Structure



Medicines: Clinical, Pre-clinical, Pharmaceutical
Devices: Technical and Clinical

Medicinal Products Legislation



Device Legislation

MDD 93/42/EC	AIDD 90/385/EC	IVDD 98/79/EC
MDR May2020		IVDR May2022

MDD still in effect until 2020

Differences…

	Devices	Medicines
Role	NB verify	NCA assess
Licence to market	No national involvement	National involvement
Basis	Performance/usefulness	Efficacy
	Compliance with ER/ISO	Compliance with Guidelines
	Control = inherent risk	Control = fixed

Scope

Two main classes are considered…

- Non-integral (co-packaged) products, for example…
  - Paracetamol suspension with oral dosing device (“syringe”)
  - Reusable insulin pen
- Integral products, for example…
  - Single-entity combination products, such as a pre-filled syringe

…and these classes are excluded

- ATMPs,
- Blood products,
- Device-drug combination products

<u>MDD is focus of this presentation</u>

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Current State:
Data requirements

Definition…

No specific EU definition of Drug-Device combination product; however, 93/42/EEC, Art 1(3) states…

> *"…if, a device is placed on the market in such a way that the device and the medicinal product form a single integral product which is intended exclusively for use in the given combination and which is not reusable, that single product shall be governed by Directive 2001/83/EC. The relevant essential requirements of Annex I to this Directive shall apply as far as safety and performance-related device features are concerned. In such cases Competent Authorities responsible for the evaluation of the medicinal products in question would consult, if necessary, one of the Competent Authorities or Notified Bodies for medical devices. This consultation would cover the essential requirements of Annex I MDD for the relevant device features"*

So, taking the primacy of the intended use and mechanism of action in account, as well as 2001/83/EC, Art. 8 (which defines the content of an MAA), there are clear signposts regarding data requirements

General considerations

Prior to approval, an integral drug-device product should be demonstrated to meet 93/42/EC, Art 1(3)…otherwise a CE mark is required and the Competent Authority will:

- Require proof of CE marking (EC Certificate/Declaration of Conformity)
- Assess fitness-for-purpose (e.g. performance, compatibility with medicinal product, suitability for intended patient population, etc)
- Assess product information (IFU/PL) to ensure safe and effective use

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Rule of Thumb…

> *The amount of device information included in the MAA should be generally proportionate to complexity and risk, e.g. indication, route of administration, delivery mechanism, "effective" class of the device (Class III > Class IIa/IIb > Class Is/Im > Class I), etc.*

…and because Class II/III devices require either a Technical File or Design Dossier, information should be readily available

General considerations

Confusion? Yes…

- Due to cross-over of responsibilities, different experiences and knowledge of all applicable rules, directives, regulations, etc

Knowledge of both sets of requirements is required

- Medical device ⟷ Medicinal product

In particular, have the most relevant guidelines or standards been referenced? For example…

- "Vol 2B, NtA, presentation and format of the dossier" defines sections in M3 where data should be located
- CPMP/QWP/159/01 (EO residuals limits) has been superseded by ICH M7; however, EO sterilisation should also comply with ISO 11135

General considerations

Changes to device components in the dossier? Variation guideline, Section B.IV.1 devices

B.IV Medical Devices

B.IV.1 Change of a measuring or administration device	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Addition or replacement of a device which is not an integrated part of the primary packaging			
1. Device with CE marking	1, 2, 3	1, 2, 4	IA_{IN}
2. Device without CE marking for veterinary products only		1, 3, 4	IB
3. Spacer device for metered dose inhalers			II
b) Deletion of a device	4, 5	1, 5	IA_{IN}
c) Addition or replacement of a device which is an integrated part of the primary packaging			II

Use of PACMP considered?

General considerations

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Use of PACMP considered?

If in doubt about applicable documents or mechanisms, please ask!

- Regulatory advice is generally free
- Scientific advice (e.g. EMA) or Innovation Offices (e.g. national)

General expectations

In HPRA, Pharmaceutical Assessors and Medical Device Assessors are co-located over two floors. Involvement of both…

- Depends on complexity of the medicinal product/devices
- Depends on the quality and appropriateness of the data

The performance aspects that we assess are focussed on the particular use of the device

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Notified Body

- Is your NB listed in NANDO?
- Is your NB designated to conformity assess your device type/intended use?

Device class should be stated e.g. Class I, self-certified

Where in the MAA?  (M2,M3,CTD)

QoS: include completed ER checklist with data references

Locations include, and are not limited to, the following (for all types):

3.2.P.2, Pharmaceutical Development

- Description of the device, materials used, key functional components; performance dose accuracy; compatibility, leachables/extractables, etc

3.2.P.3: Manufacture

- Detailed information on the assembly of the integral non-CE marked device, integrity testing, component sterilisation, process validation

3.2.P.5: Control of Drug Product

- Test(s) relating to specific functionality of the medicinal product

3.2.P.7: Container Closure

- Proof materials conform to EU requirements, CoAs, diagrams, etc

Where in the MAA?  (M1/M3,CTD)

3.2.P.8: Stability

- In-use stability, microbiological quality

3.2.R: Regional information - Medical Device

- Detailed justification for choice of relevant Essential Requirements, and how these have been met
- Usability study
- Risk assessment for the device component(s)
- IFUs and how they link into Product Information, including training plan
- Detailed data to support equivalence between prototype delivery device used in clinical studies and that intended for marketing

1.3.1, Product Information

- IFU for any device components integrated into PL and/or SmPC

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Current State
Non-integral

Non-integral

Definition… "a drug product presented to include a delivery device that is separate from the medicinal product"

Regulation… each component is regulated in accordance with relevant legislation (including CT/CI)

Directive requirements

Administration devices must be CE marked prior to MA grant (2001/83/EC, Annex I, Part 1, Section 3.2, (12))

- "CE marking which is required by Community legislation on medical devices shall be provided"

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But what if no CE mark?

- Self-assessment is possible where the delivery system represents a Class I device e.g. applicators, where not surgically invasive and for transient use
  - Manufacturers declaration of conformity and NCA number
- Otherwise, CE marked devices must be used

“Bridging” data?

Other expectations regarding 2001/83/EC may apply, taking into account the specific, contextual circumstances of the device and its use

In this case, “bridging” data (as in data to demonstrate suitability of the device in its intended use) is required, e.g.

- Physical (viscosity) and chemical (impact of solvents) (P.2.2), extractables/leachables (P.2.6)
- Device performance criteria (P.2.4/P.7), and when used per SmPC (P.5.1)
- Functional specifications of the delivery system (P.2.4/P.5.1/P.7 as appropriate)
- Device performance criteria over shelf-life (P.8)

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Examples of “bridging” data and possible locations…

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Product information/IFU

- How are the medicinal product and device to be used together?
- Are there specific aspects to be considered when using the device to delivery the medicinal product? If so, how are these presented in a coherent and logical manner e.g. training and/or usability study?

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Product information/IFU

- How are these to be used together?
- Are there specific aspects to be considered when using the device to delivery the medicinal product? If so, how are these presented in a coherent and logical manner e.g. usability study?

Information presented in the dossier should take above aspects into account (in the context of individual, specific circumstances) as to how the device is used to deliver the medicinal product, i.e. a case-by-case basis.

IFUs and Package Leaflet

How are IFUs incorporated into the Package Leaflet, e.g. where procedure/system packs are provided separately?

- Classification of co-packaged devices e.g. what class and under what classification rule have component devices (adaptors, sanitising wipes, pipettes, spacers, etc.) been conformity assessed?
- For each device component, is it CE marked (Annex XII) and is it being used as intended i.e. as per classification class/conformity assessment?
- Has the CE mark been placed visibly and legibly on the product, or if not possible, affixed to packaging/IFU?
- Does the CE mark include the NB number?

IFUs and Package Leaflet (cont.)

- For measuring devices sourced ex-EU, an Authorised Representative is needed, a CE mark should be obtained and correct documentation supplied
- Is manufacturer information, and where appropriate, AR information on the packaging and IFU?
- For each device component, have declarations and certificates of conformity been provided?
- Can all the contents of the pack be kept under same conditions?
- Is there a need to provide (additional) packaging/labelling artwork for device components e.g. identifying each component using a letter or pictogram?

Product Information

What level of information regarding the IFU for each device component can be included in the Product Information without compromising safety/performance/comprehension/readability? How has this been mitigated?

If the medicinal product and particular medical device can only be given in combination to achieve a therapeutic effect…, then:

- SmPC 4.2: describes the device
- SmPC 6.5: includes brief information, e.g. information about the medicinal product and procedure pack
- SmPC 6.6: includes detailed information, e.g. contents of procedure pack, how to prepare, use, store and/or dispose of, the drug product, in-line with IFUs (which should be presented, where possible)

Specific Concerns: Pen Injectors

The following are examples of queries raised:

- Evidence of CE mark e.g. missing EC certificate (NB) and/or Declaration of Conformity (Manufacturer)
- Functionality testing lacks sufficient scope, e.g. repeatability
- Formulation related issues, e.g. syringability and stability/in-use stability studies not adequately discussed and/or justified
- Compliance with ISO deficient, e.g. ISO 11608-series "needle-based systems for medical use"
- Usage by target patient population not adequately demonstrated e.g. training plans deficient
- IFU lacks clarity e.g. no pictograms
- Product information deficient e.g. SmPC sections 4.2, 6.5 and 6.6 not updated, labeling/PIL requirements not met, inadequate disposal instructions in SmPC and PL

Miscellaneous Considerations

Device/medicinal product assembled by the user? Intended to administer multiple doses over a defined period?

- Have all stability, compatibility, leachables, accuracy/precision of dose/delivery, container integrity, etc been assessed for the proposed in-use shelf-life/storage condition of the assembled product?

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Multiple suppliers of the same device are foreseen?

- Has a comprehensive specification been included, along with data to support dose-delivery equivalence (and other ERs, as required) between the different supplier's of the device?

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Device intended for multiple use, with multiple applications of a single integral product until product is exhausted (e.g. aerochamber)?

- Has impact of residues, cleaning etc on the device after use been investigated and, where possible, mitigated, e.g. warnings in the IFU regarding excessive temperature?

Miscellaneous Considerations

Capturing all devices, e.g. no CE mark for cartridges used to filter medicinal product

Where administration of the product requires loading of a container-closure system into the device, this is not considered integral

- CE mark for device is required

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Where assembly or use involves puncturing a seal, have fragmentation studies been performed as per Ph.Eur, or its absence justified? (P.2.4)

Has the application form (Section 2.2.4.3) been completed correctly?

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Current State: Integral

Challenges…

It can be considered that…

- Formulation challenges tend to depend more on active substance (e.g. silicone lubricant, formation of aggregates and impact of shear forces more relevant for biologicals) and method/route of administration (e.g. s/c *vs.* parenteral)
- Device challenges tend to depend on the materials of construction and their suitability for use (e.g. leachables and extractables, impact of sterilisation on physical properties), and
- System challenges tend to reflect in delivery (e.g. accuracy / precision of dosing, usability) and method/route of administration

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Drug production processes conform to the drug regulations, device production process conforms to the device regulations

→ how they overlap can be confusing

Prior Knowledge?

Within a company and for the same use, reference to previous submission should be acceptable; however…

- Indicate that the same container closure system is registered for other products and are providing identical data.
- Understand where the differences are, and…
  - Justify which aspects are identical
  - Provide data for those which are not

Prior Knowledge?

Within a company and for the same use, reference to previous submission should be acceptable; however…

- Indicate that the same container closure system is registered for other products and are providing identical data.
- Understand where the differences are and…
  - Justify which aspects are identical, and
  - Provide data for those which are not

A manufacturer may provide the same platform to multiple clients

- They may understand and/or be aware of regulator expectations

Integral: Product Information

Because the medicinal product can only be given in combination with a particular medical device to achieve a therapeutic effect…, then:

- SmPC 4.2: describes the combination product
- SmPC 6.5: includes brief information, e.g. information about the combination product and any co-packed devices
- SmPC 6.6: includes detailed information, e.g. contents of packs, how to prepare, use, store and/or dispose of, the drug product, in-line with the device IFUs

Product labelling (readability, use, disposal) need to be considered

The product information must ensure that a correct dose can be given by the user

Integral: P.2, PharmDev

P.2.2, Product Development (*"…relevant to drug product performance"*)

Development demonstrates compliance with applicable standards, e.g. Paediatric Development guideline

Suitability of the drug delivery system, e.g.

- Risk to the patient from potential contamination of an adapter surface, in-use, etc)

Integral: P.2, PharmDev

P.2.2, Product Development (*"…relevant to drug product performance"*)

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Suitability of the drug delivery system, e.g.

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Information regarding device design; is the detail presented proportional to complexity, e.g.

- Design and Development Planning, Design Inputs, Design Outputs, Design Review, Verification, Validation, Design Transfer, Design Changes, Summary of the Design History File, etc.
- Summaries are acceptable

Integral: P.2, PharmDev

P.2.3, Manufacturing Process Development

Summary of the comparability study between clinical trial version and commercial product

Derivation of the **drug product control strategy**: does this include relevant aspects of the device?

Integral: P.2, PharmDev

P.2.3, Manufacturing Process Development

Summary of the comparability study between clinical trial version and commercial product

Derivation of the **drug product control strategy**: does this include relevant aspects of the device?

P.2.4, Container Closure System

Dosing accuracy, precision, reproducibility, etc

P.2.5, Microbiological Attributes

Integrity of the product, choice of sterilisation method, etc

P.2.6, Compatibility

Compatibility of the medicinal product with the device, e.g. extractables, leachables, physicochemical properties, etc

Integral: P.3, Manufacture

P.3.5, Process Validation

Comprehensive data should be provided, due to criticality of the manufacturing process with regards to drug product quality.

For example, for a PFS, validation studies should include at a minimum…

- Assembly of the device
- Visual inspection (number of defects)
- Break-loose force
- Glide force
- Fill volume
- Delivery time
- Dose accuracy

Integral: P.5.1, Control

Control of relevant parameters, such that the release specification can identify possible performance failures, e.g.

- Appearance and description
- Glide force, break-loose force
- Closure integrity
- Needle safety device
- Device actuation

Integral: P.5.1, Control

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Note: if the functionality of the device has been appropriately validated (P.3.5), then less functional parameters are required to be controlled on release

Integral: P.7, Container-closure

Reference to previously approved products (prior knowledge)

Component	Description	Supplier	Standard
Syringe barrel	1 ml, colourless borosilicate Type 1 glass, lubricated with silicone oil[A]	X	Ph.Eur 3.2.1
Hypodermic needle	27G * ½" AISI 304 stainless steel, lubricated with silicone oil[A], needle glued to glass syringe body	X	ISO 9626
Plunger stopper	Grey bromobutyl rubber	X[1]	ISO 8871 Ph.Eur 3.2.9
Needle shield	Plastic shell (polypropylene) Rubber (styrene-butadiene) needle shield	X[2] X	n/a
etc..			

A: lubricant <name> complies with Ph.Eur; 1, supplied to X by Y; 2, supplied to X by Z

Description of process by which each component is prepared for use

- Washing, treatment (siliconisation), packing, sterilisation, etc.

Integral: P.7, Container-closure

Relevant specifications for devices

- Critical dimensions, thickness, etc
- Control specifications for components and assembled device, as relevant (e.g. glide force, break-loose force)

(Exploded) diagrams

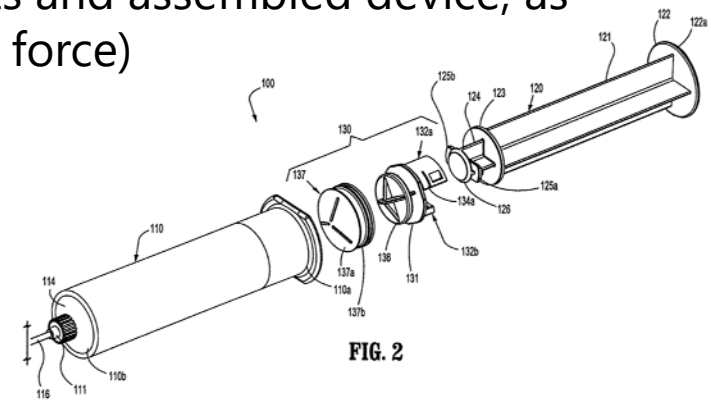

FIG. 2

Pre-use inspections? If so, what tests and why?

Summaries of sterilisation methods

Confirmation that relevant ISO standards were followed and compliance achieved

Integral: 3.2.R

Attribute	CE marked	Not CE marked
Intended use	Specified	Specified
EC Declaration [NB]	Required	n/a
DoC, Annex I MDD [Manufacturer]	Required	Required [detailed information]
Compliance, Annex I MDD [Summary]	Required	n/a
Compliance [ISO standards]	Confirmed	Confirmed
Diagram [components]	n/a	Required
Assembly [components]	n/a	Required
Technical file	n/a	Required
Technical summaries	Depends on Class	Required

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Future State

The future is MDR…

The future is “the Regulation”, with additional requirements in Annex I (phthalates, endocrine disrupting substances, etc.)

The future is MDR…

The future is "the Regulation", with additional requirements in Annex I (phthalates, endocrine disrupting substances, etc.)

However, a guideline is intended, taking into account the general comments on EMA Concept Paper…

- Proposal to develop guidance is welcome; needed across EU
- Alignment with MDR Art. 117
- Engagement with device stakeholders positive; appreciate workshop/training (implementation); address advice for development
- Consistent wording/terminology (ISO), more clarity on scope (e.g. applicability for clinical trials?); global alignment

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Conclusions

Conclusions

Know your regulations, directives, standards, etc. for both medicinal products and medical devices

Be clear in your delineation between medical product and device data, provide signposts in the dossier to where data is located

- Use summaries judiciously!

It is a combination product, clarity around the specific requirements for both areas and the link to performance, safety and efficacy is appreciated

If in doubt, ask!

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