Global Perspective on Drug Delivery Submissions – Regulatory

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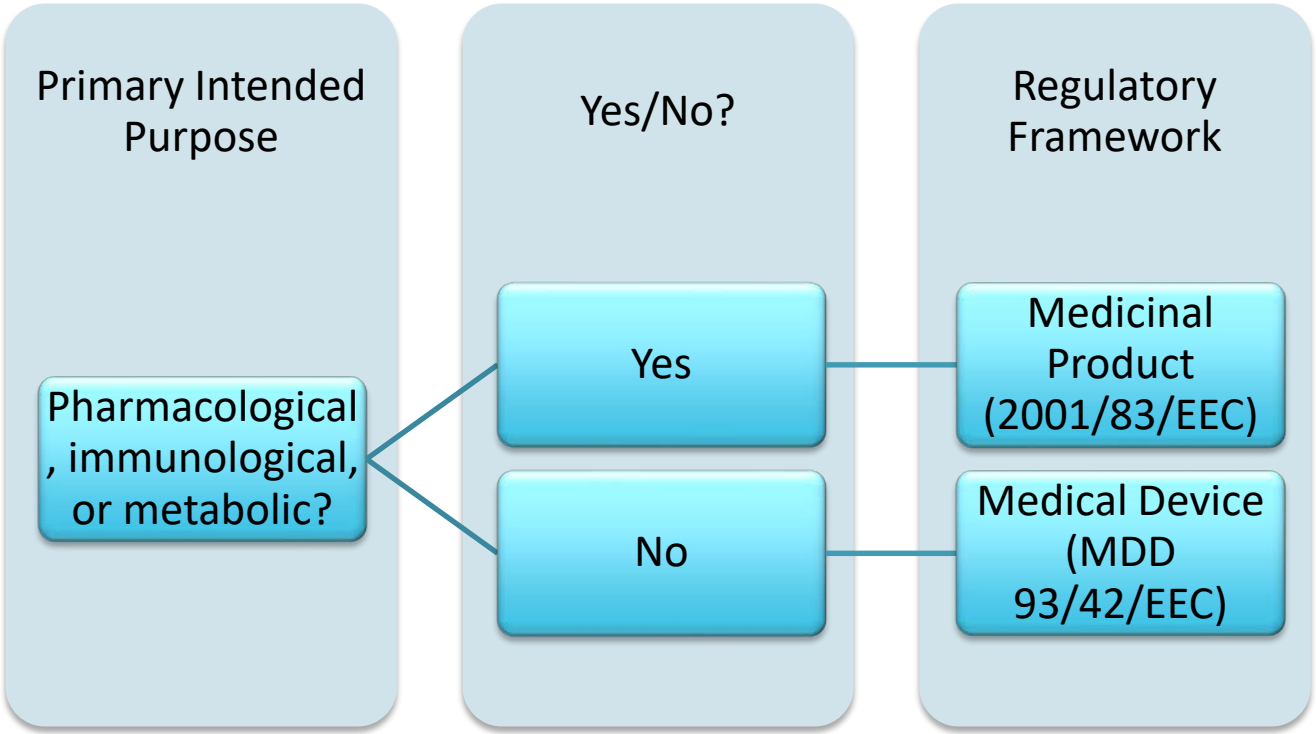
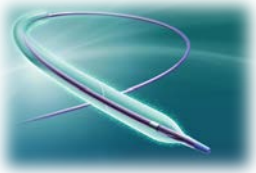
In the EU, a "combination product" is regulated either as a medicinal product or medical device.



Prefilled Syringe (integral, non-reusable) – Medicinal Product



Drug-Coated Balloon (medicinal substance with ancillary action) – Medical Device

In the US, a combination product is defined to include single entity, co-package, or cross-labeled.

Prefilled Syringe

Drug-Coated Balloon

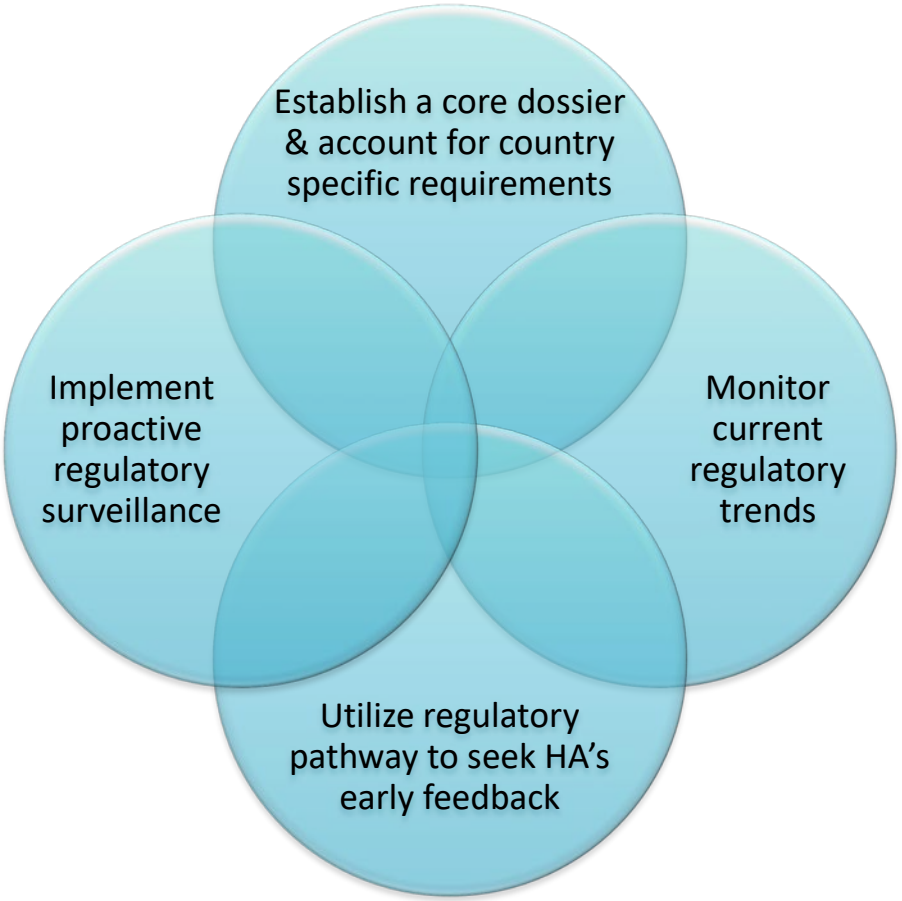
Drug vial and devices

Drug (Cayston) and Nebulizer (Altera) (labels are mutually conforming)

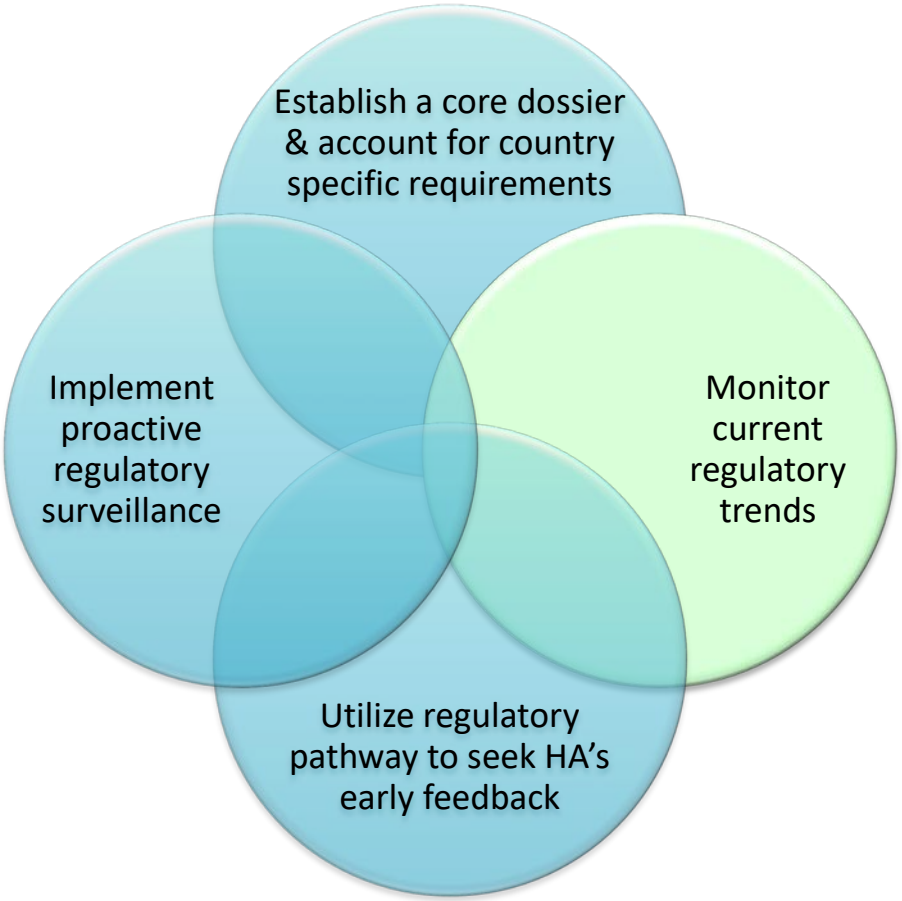
PDA
Parenteral Drug Association

How to achieve effective combination product submissions in a constantly evolving global regulatory environment?

Key success factors *leading to effective combination product submissions in an evolving global regulatory environment*



Key success factors *leading to effective combination product submissions in an evolving global regulatory environment*



Inclusion of an untrained user group in human factors validation studies appears to be an emerging trend, although this may not be consistent

Product	Device	FDA Approval Date	Training is required per PI?	Human Factors Validation Study: Intelligence from the FDA Summary Basis of Approval
Taltz	AI and PFS	22 Mar 2016	Yes	HF validation included: (a) Trained users (b) Untrained users* ***included in the validation study although they were not intended users per the approved Prescribing Information (PI)***
Erelzi	PFS-NSD	30 Aug 2016		
Amjevita	AI and PFS	23 Sep 2016		
Siliq	PFS	15 Feb 2017		
Kevzara	PFS	22 May 2017		
Zinbryta	PFS	27 May 2017		

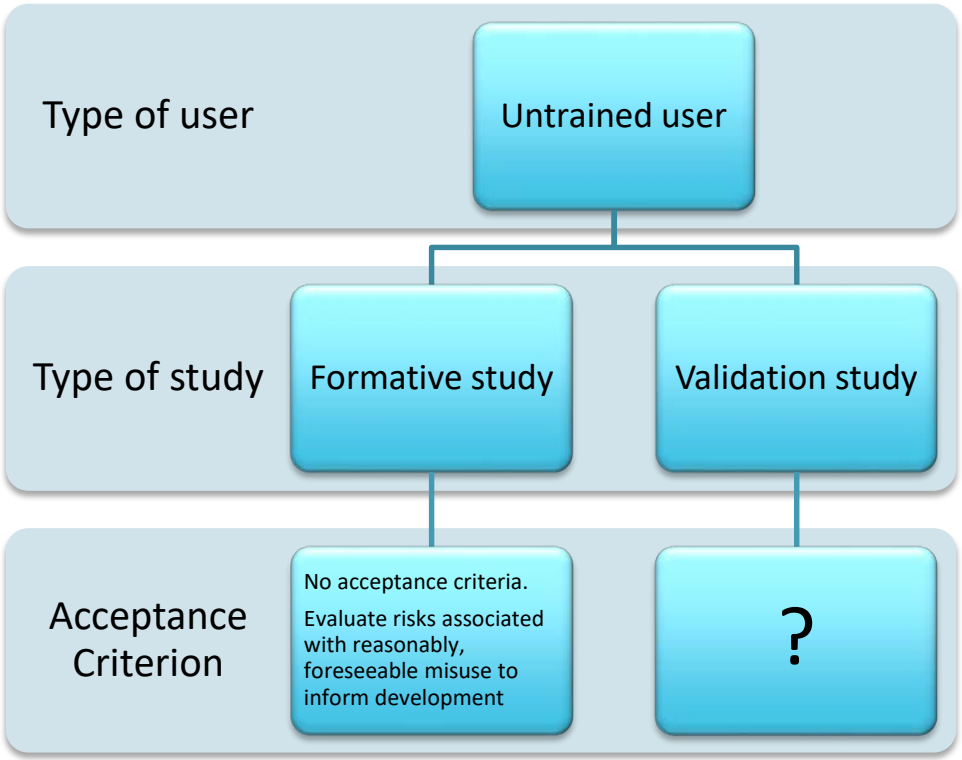
Product	Device	FDA Approval Date	Training is required per PI?	Human Factors Validation Study: Intelligence from the FDA Summary Basis of Approval
Zarxio	PFS-NSD	6 Mar 2015	Yes	No untrained user information is found

If training is required per labeling, inclusion of an untrained user group in HF validation studies is not required.

Validation is intended to ensure safe and effective use of a product. Untrained use does not represent the intended use per labeling.

Reasonably, foreseeable misuse (EN ISO 14971) such as **untrained use can be adequately assessed through formative HF studies and risk analysis.**

The acceptance criterion of untrained use, if included in HF validation studies, is ambiguous



Considerations in analyzing use errors in the untrained group:

- Determine if there is a pattern of use errors that could lead to unacceptable harm
- Understand the root cause of the use errors
- Determine if the use error is self-correcting (user acknowledges the error and has learned from the event)

Acceptance of the HF validation study is based on the overall risk-benefit analysis from use of the device by the intended users.

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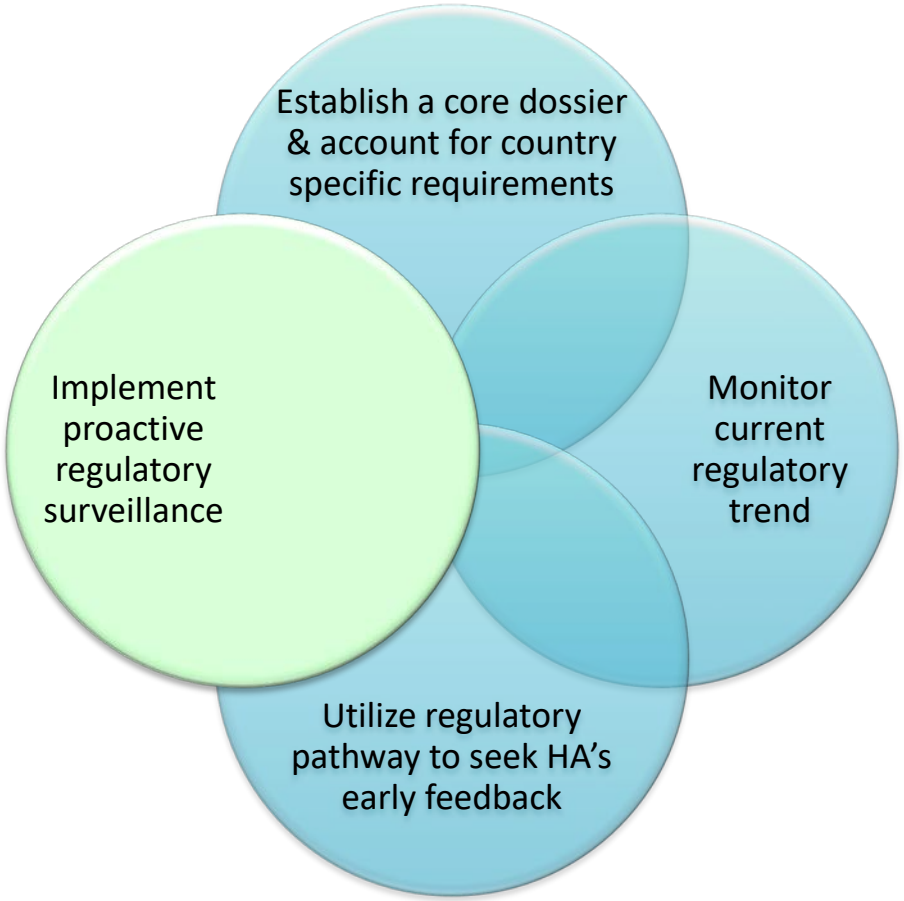


Annex I of the EU Medical Device Regulation (MDR): Safety and performance requirements have increased

Present	26 May 2020
Medical Device Directive (MDD 93/42/EEC)	Medical Device Regulation (MDR 2017/745)
• Annex I (Essential Requirements) – **14 Clauses**	• Annex I (Safety and Performance) – **23 Clauses**

Key changes:

- Greater focus on risk management
  - Post market surveillance requirements
  - Risk-benefit profile
- Enhanced focus on chemical safety and phthalates.
- New focus on the interoperability of devices intended to be used together.

And others…

Article 117 of the EU MDR raises significant regulatory uncertainties and ambiguities

Unclear scope	Involvement of Notified Body (NB) is not clearly defined	Undefined roles and responsibilities
Article 117 covers non-reusable, single integral medicinal products. Delivery device often is not designed to be used separately (*CE mark is not required)*	NB's involvement – when, how, and if – are undefined, presenting a significant degree of regulatory uncertainty	Roles and responsibilities of NB and EMA are undefined, which could result in redundant review

Implementation of Article 117 of the EU MDR must lead to a regulatory system that is least-burdensome and ensure patient safety.

Transparent	Predictable	Efficient	Collaborative
• Clearly define the roles and responsibilities of NB and EMA	• Define the circumstances under which a NB's involvement is recommended	• NB's review, when required, is value-added. • NB's review can be done in parallel (instead of sequential)	• Collaborate with industry, NBs, and other key stakeholders to implement Article 117

Proactively monitor regulatory landscape in emerging markets

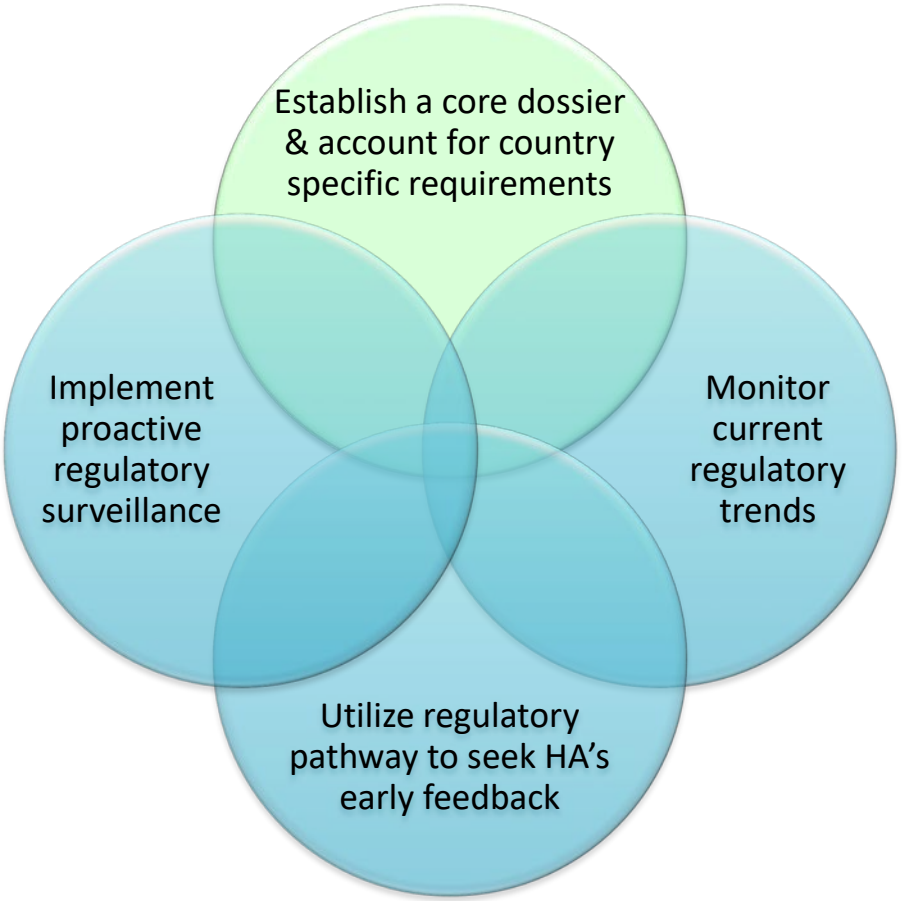
Malaysia

- Primary mode of action determines the regulatory pathway.
  - Drug: Pharmacological, immunological or metabolic action
  - Device: Not pharmacological, immunological or metabolic action
- Combination products will have to meet both the Medical Device Authority (MDA) and the National Pharmaceutical Regulatory Agency (NPRA).
- Will start enforcing the new regulations in July 2018.

China

- No specific regulatory pathway for combination products.
- Per "*Notification on Matters Concerning Registration of Drug and Medical Device Combination Products*" (SFDA, No 16, 2009):
  - Combination products refer to single entity consisting of drugs and medical devices.
- CFDA has the discretion to determine how to regulate other combination products on a case-by-case basis.

Key success factors *leading to effective combination product submissions in an evolving global regulatory environment*



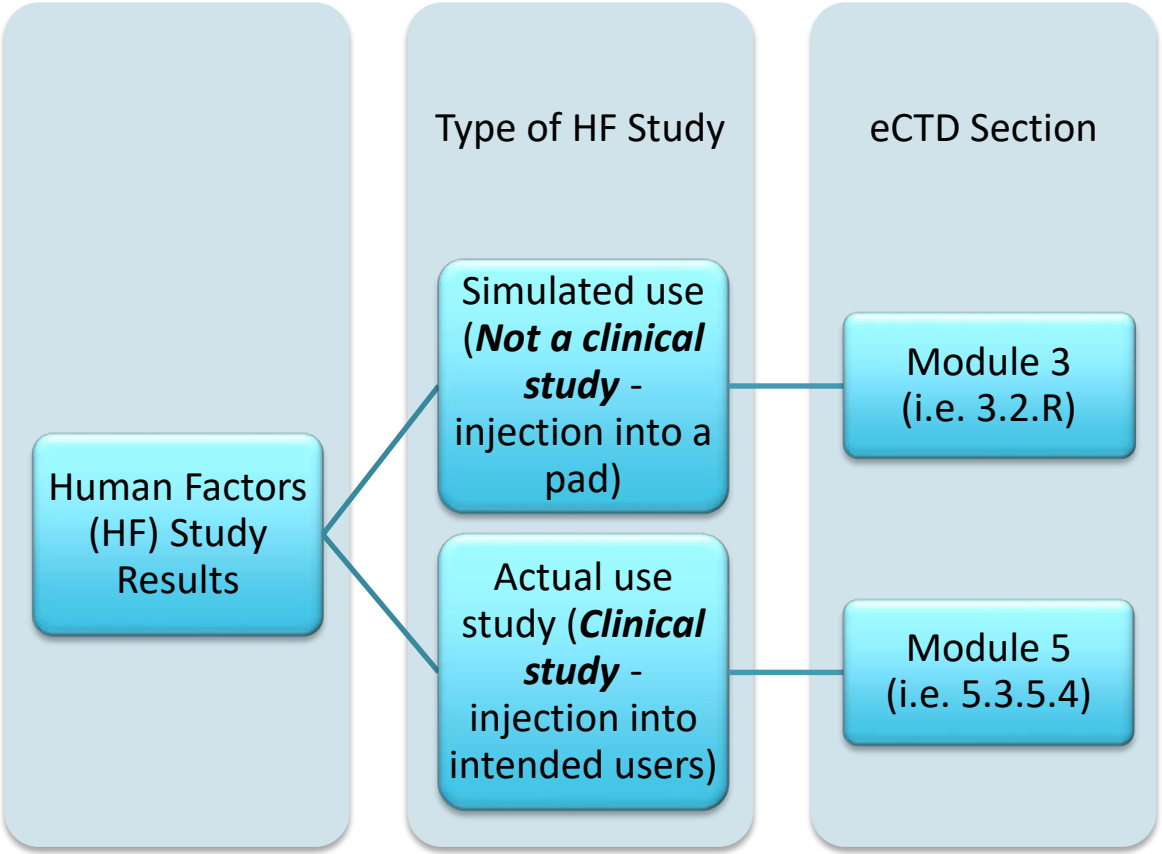
Establish a core "global" dossier – see 3.2.P.5 example for Prefilled Syringe

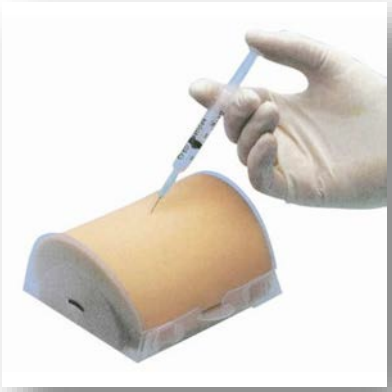
3.2.P.5.1 [Specifications]	• Provide a list of regulatory specifications, including functional tests, if applicable [Note: Functional tests may be controlled upstream (e.g. in-process tests, vendor, etc.), instead of final release, as long as rationales are provided.]
3.2.P.5.2 [Analytical Procedures]	• Describe the analytical procedures for the release specifications, including a brief description of the functional tests
3.2.P.5.3 [Validation of Analytical Procedures]	• Provide the validation of the release tests, including functional performance method validation

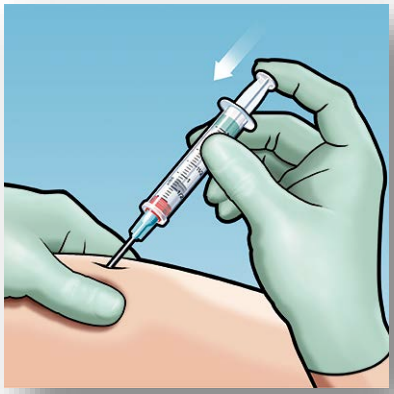
Establish a core "global" dossier – see 3.2.P.5 example for Prefilled Syringe

3.2.P.5.4 [Batch Analysis]	• Provide batch analysis results for the batches (pivotal, bridging, process validation, etc.)
3.2.P.5.5 [Characterization of Impurities]	• Describe characterization of impurities due to contact of drug with the delivery device
3.2.P.5.6 [Justification of Spec]	• Provide the justifications for the functional specifications, if applicable, based on applicable studies, standards, etc.

Human factors validation study results may be described in Module 3 and/or Module 5, depending on the type of the study







Supplement with country-specific regulatory requirement

- Section 3.2.P.3.1 (Manufacturer(s))

Facility	Activity	Quality System
A	• Fill drug into bulk syringe barrel	21 CFR Part 211
B	• Final assembly of PFS • Final CoA release of PFS	Drug-based streamlined quality system (21 CFR 211 + specified provisions from 21 CFR 820)

- Section 3.2.P.3.3 (Description of Manufacturing Process and Process Controls) or 3.2.R (Regional)
  - A **general** description of compliance with 21 CFR 4, subpart A should be sufficient.
    - Negate the need to provide quality system procedures in eCTD.

3.2.R [Regional] – Compliance with Annex I of MDD 93/42/EEC must be clearly documented in the MAH's quality system

3.2.R [Regional]	• Provide a compliance statement that the single, integral (non-reusable) medicinal product meets the applicable sections of Annex I of MDD. • Provide test results associated with design verification, design validation, biocompatibility, risk management, and sterilization (if applicable).

MAH must meet the applicable safety and performance requirements set out in Annex I of Medical Device Regulation (MDR 2017/745) from 26 May 2020.

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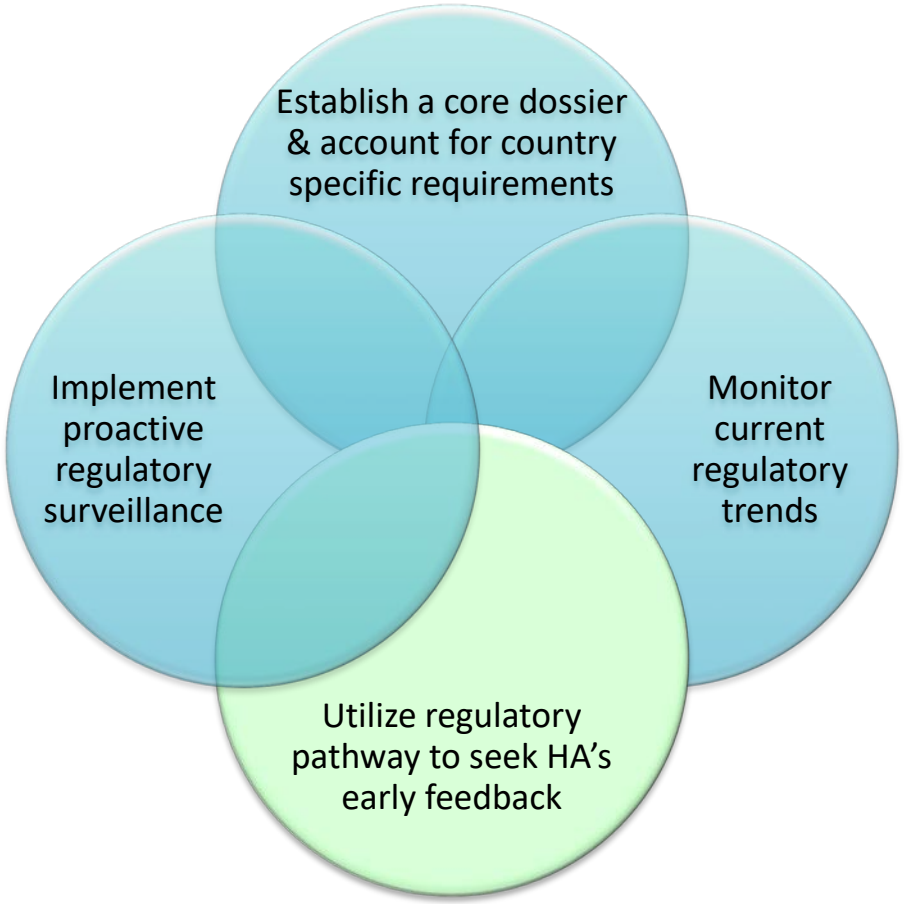
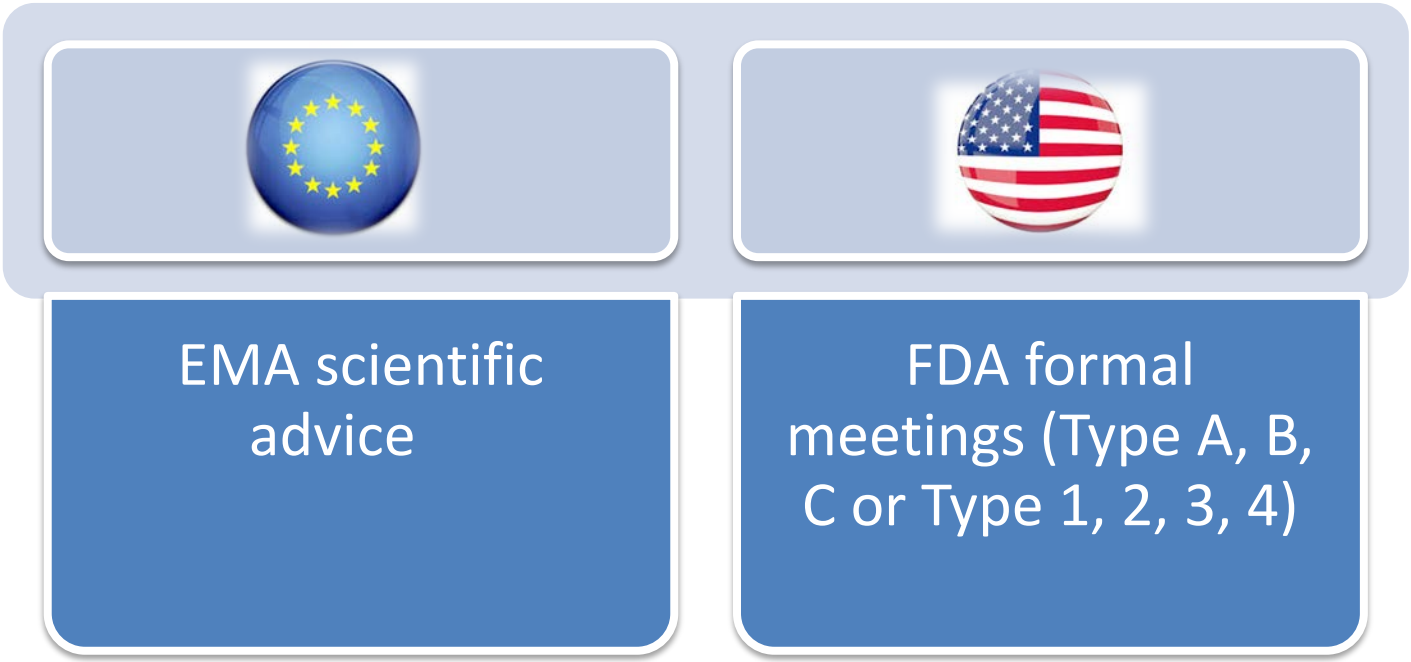


Utilize existing pathways to obtain HA's agreement on key topics



Perform a regulatory risk assessment to determine device topics that would need HA's early agreement.

Acknowledgements

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