

PDA & West Present: Combination Products Combination Product Hot Topics: Post Approval Device Changes and the New EU MDR Article 117 Requirements

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Disclosures:

- **The following presentation includes the personal views of the presenter and do not necessarily represent the official views of Janssen R&D, LLC.**
- **Regulatory requirements presented may differ from actual regulatory requirements imposed by Health Authorities for specific combination products.**

Hot Topics: Post approval device changes

• How do you determine what device changes are reportable?

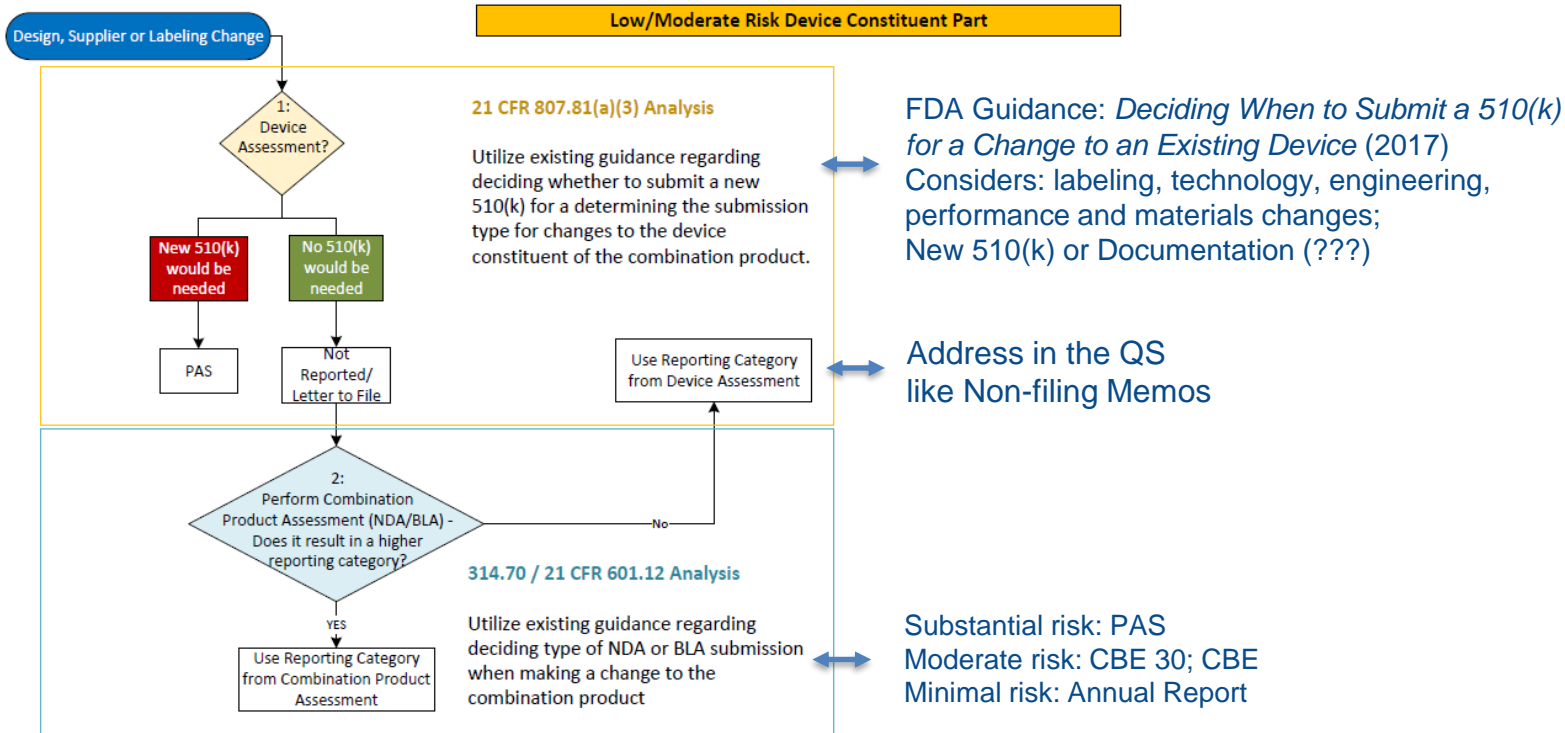
- **Go to: 21 CFR 314.70** “Supplement to an NDA” and interpret: “any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a [substantial/moderate/minimal] potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.”
- **For the EU**, review: *EC Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products*. Also, use option to e-mail queries to EMA.
- **Look in your submissions** - for what details are provided: Delivery device specifications stated in NDA/BLA can be “descriptive” or be registered release and stability specifications. This can create uncertainties. Same with processes and test methods.

Hot Topics: Post-approval device changes

- FDA Draft Guidance: *Guidance for Industry and FDA Staff: Submissions for Post-approval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA* (2013)
 - The Draft proposed submission categories that assumed PMA level risks for a delivery device and its changes
 - Minimal additional considerations for risk-based approaches and delivery devices analogous to Class I or Class II / 510(k) devices and typical device changes [21 CFR 807.81(i)]
- Industry [Combination Products Coalition (CPC)] is advocating a risk-based “Decision Tree” framework in future revisions to the current draft post approval modifications CP guidances
 - Defines path for low/moderate risk devices and constituent part changes
 - A path for Class 3 device constituent part changes
 - Changes to Manufacturing process or control changes
 - Look to be consistent with 21 CFR 314.70 for drug products

Hot Topics: Post approval device changes

Example: Decision Tree Flow Chart



Hot Topics: Post approval device changes

- Internal process for Change Control should include or assess:
 - **Product Risk Analysis:** i.e., Design, Process, and User FMEAs
 - **Regulatory impact:** a review of dossiers content in each market (e.g., NDA/BLA/NDS/MAA/JNDA) to assess the specific content that may be affected; check statements representations made in IR responses too.
- ICH Q12 - Established Conditions: “provide guidance on a framework to facilitate the management of post-approval Chemistry, Manufacturing and Controls (CMC) changes in a more predictable and efficient manner across the product lifecycle”
 - FDA Office of Combination Products and Office of Pharmaceutical Quality (Policy) are working to include Combination Products (delivery devices) in the scope of future Q12 guidance revisions

Hot Topics: Post approval device changes

- Examples that may raise questions about changes to delivery devices - for the potential to impact:
 - Identity, strength, quality, purity, or potency of the drug product
 - A change in technological characteristics or intended use that raises significant new questions of safety and effectiveness.
 - Needle extension (protrusion into SC or IM biospace)
 - Delivery time (theoretical) – e.g., change to spring
 - Volume of dose (for higher volume delivery device line extensions)
 - Introduction of second assembly line for production scale up
 - Alternative release test methods 314.70 (d)(2)(vii) - the addition or revision of an alternative analytical procedure... (for Annual Reporting)

Hot Topics: EU MDR Article 117 Requirements

EU Medical Device Regulation – Summary

- EU MDR replaces the MDD - comes into force on **26 May 2020**
- EU MDR Article 117 contains NEW requirements for medicinal products incorporating a drug delivery device component (i.e., integral, single-use combination products)
 - Device constituent must:
 - Be CE Marked (i.e. have CE certificate or Declaration of Conformity (for Class I devices)) OR
 - Have NB assessment of device's conformity to relevant general safety and performance requirements (GSPR) in EU MDR Annex I, which is provided to EMA during MAA review
- **PRACTICE CHANGE:** Article 117 will now require NB review of device constituent as part of MAA approval
 - Currently it is acceptable to provide an Essential Requirements Checklist in the MAA demonstrating the device's conformity to the relevant GSPR of EU MDD Annex I (CE Mark on device and NB review are not necessary)
- Combination Products developers have raised numerous questions regarding interpretation and implementation of Article 117 with EMA and European Commission
- **EMA Q&A guideline published: Feb 27th 2019**
- **ACTION:** Companies with integral, single-use CPs expecting to file MAAs in 2020 should identify and select a NB to provide conformity assessments for device constituents, inclusive of PFSs

EU Medical Device Regulation (2017/745)

- EU MDR published in May 2017
- Replaces the EU's Medical Device Directive (93/42/EEC) and Active Implantable Medical Devices Directive (90/385/EEC)
- EU MDR will govern how manufacturers of medical devices produce and sell products in the EU
 - Also impacts non-EU countries that leverage the CE (European Conformity) Mark
- EU Directive vs EU Regulation

EU Directive	EU Regulation
EU Directives set certain aims, requirements, or end results that must be achieved by every member state.	EU MDR is an EU regulation (direct form of EU law). Binding legal force throughout every member state, on par with national laws.
National authorities must create or adapt laws to meet the goals of a given directive, but are free to decide how to do so.	National governments do not take action themselves to implement EU regulations, but do ensure their national law does not define the subject matter any further.

Unlike the MDD, MDR will be consistently implemented across the EU and enforced nationally

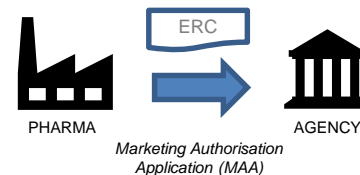
EU MDR Impact on Combination Products

Current EU Regulation:

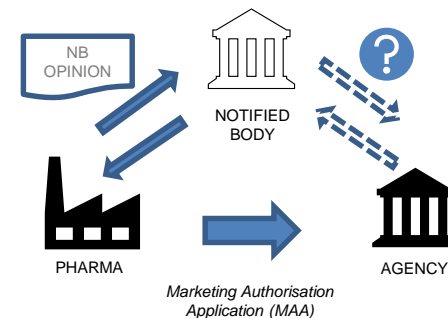
- Directive 93/42/EEC, Article 1.3
- The relevant essential requirements of Annex I to this Directive shall apply as far as safety and performance-related device features are concerned.

Future EU Regulation:

- Regulation 2017/745, Article 117
- Date of Application: 26 MAY 2020**
- ... the marketing authorisation dossier shall include, where available, the results of the assessment of the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation (2017/745) contained in the manufacturer's EU declaration of conformity or the relevant certificate issued by a notified body allowing the manufacturer to affix a CE marking to the medical device.
- If the dossier does not include the results of the conformity assessment ...and where for the conformity assessment of the device, if used separately, the involvement of a notified body is required in accordance ...the authority shall require the applicant to provide an opinion on the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation issued by a notified body...



ERC – Essential Requirements Checklist



EU MDR Impact on Combination Products

Future EU Regulation (cont):

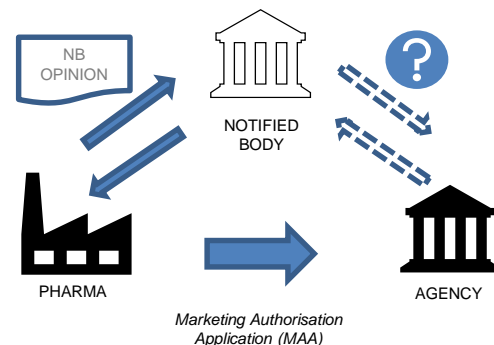
Regulation 2017/745; Article 117

- ... the marketing authorisation dossier shall include, where available, the results of the assessment of the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation (2017/745) contained in the manufacturer's EU declaration of conformity or the relevant certificate issued by a notified body allowing the manufacturer to affix a CE marking to the medical device.

➤ **CE certificate or Declaration of Conformity (for Class I devices) for device constituent of the combination product**

- If the dossier does not include the results of the conformity assessment ...and where for the conformity assessment of the device, if used separately, the involvement of a notified body is required in accordance ...the authority shall require the applicant to provide an opinion on the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation issued by a notified body...

➤ **NEW REQUIREMENT: NB opinion/memo/report confirming compliance with relevant general safety and performance requirements for the device constituent of the medicinal product**



Best practice, implementation and expectations for the regulation for combination products under MDR, impact on MAA

Impact on existing MA for products with a device constituent part i.e. variations

Notified Body Capacity to take on additional assessment work from Pharma Industry

Hot Topics: EMA Q&A on Article 117

Key Points:

- Regulation will encompass all integral, single-use combination products regulated as medicinal products (**PFS**, pre-filled injectors, patches) – including kits with PFS.
- For CE Marked devices that are kitted – these CE Marks must be updated for conformity to MDR (MDD CE Marks will become invalid).
- NB opinion strongly suggested to be included at the time of MAA submission starting May 26th 2020.
- “Substantial” device design changes will require NB opinion – i.e., CPs approved prior to MDR will be grandfathered – but changes to them will not.

Many more questions remain:

- Format for reports to NB – content?; NB prepares an opinion letter or an opinion report?
- What about overlapping review issues: biological compatibility/Leachables/Extractables, CCI?
- What if EMA is not in agreement with NB assessment?
- Note that IMPD’s for integral, single-use Combination Products need to provide a statement as to conformity to Annex 1. Effective March 2018: *EMA Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials*

Hot Topics: What Do Notified Bodies Say?

- Some are just now being authorized to review medical device for CE Marking under the MDR – there will be a backlog of companies/devices needing to be re-certified.
 - NB Authorization to the overall MDR includes special Article 117 reviews.
- May not be taking new clients until Q4 2019.
- No special QS requirement or Clinical Evaluation requirement
- Format/content of submission not determined
- Typically going to be a 90-120 day assessment with clock-stops; Some potential for expedited review>\$\$\$
- Some may do a pre-read gap assessment of a typical device MAA section with Essential Requirements.
- We will have test labs and Authorized Representative in EU (not UK)

Thanks

Questions

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- Jason Lipman
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