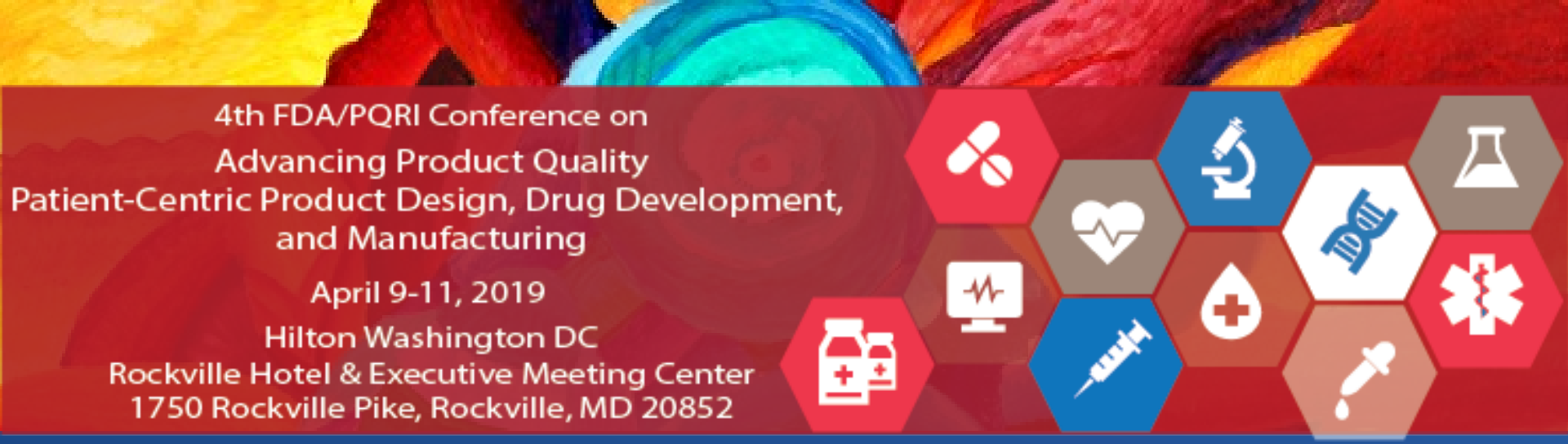

TRACK #3 NOVEL MANUFACTURING TECHNOLOGIES AND CHALLENGES FOR THE PRODUCTION OF PATIENT-CENTRIC DRUG PRODUCTS

SESSION 5: CHALLENGES WITH DRUG DEVICE COMBINATION PRODUCTS POST APPROVAL

Challenges based on Differences in Global Regulatory Filing Requirements

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Post Approval Challenges based on Differences in Global Regulatory Filing Requirements

A “quick” trip around the world on post-approval requirements for Combination Products (CPs) registered as drugs:

- Post approval requirements depend significantly on pre-approval requirements
  - All Combination Product regulations continue to evolve and are becoming increasingly country-specific.
- “Past performance (regulatory success) is no guaranteed of future results (success).”
- What are the hottest markets; the biggest challenges; the greatest uncertainties (?)

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.**

Key principles for all post approval CP submissions for all markets:

- Check for latest country-specific, CP-specific regulations
  - Know how device constituent parts changes can be interpreted as drug product changes under the regulations - where possible.
- Review your submissions - for what details were provided: Delivery device specifications stated in dossiers can be “descriptive”, or be “registered” release and stability specifications. Device assembly processes and test methods may also be registered.
- Apply appropriate device change best practices: Design Controls/Changes (21 CFR 820.30(i); scientific design verification /validation bridging principles; updated risk analyses (ISO 14971)
- Follow Change Control SOPs that include Regulatory Assessments
- Re-connect and rely on your device suppliers - for technical and source document support and latest certifications
- Be transparent – file when required: All CP companies are filing post approval device changes.

What many Health Authorities might be considering:

- Explosive growth in delivery devices: 75 drug-autoinjector combination products are commercially available; amongst these, 30% received marketing approval between 2015 and 2017. Global Autoinjectors Market (2nd Edition), 2018-2030 ResearchAndMarkets.com
- Drug Health Authorities increasingly rely on device SMEs for review of new CP registrations and post-approval assessments (e.g., EC and EMA moving to Notified Body reviews for MAAs, Malaysia approach for MDA reviews for new and registration renewals of CPs)
- Delivery devices are increasingly complex (e.g., connected electronic adherence M-Apps, software controls for delivery from patch pumps; electroporation injection device; iontophoresis devices; battery (active) powered, µ-processor controlled devices)
- Applicable drug regulations and drug-centric guidances (ICH) may not adequately address delivery devices requirements both for new products and changes to them.

What's key under US FDA regulations?

- **Apply 21 CFR 314.70** "Supplement to an NDA" and interpret – for the device: "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."
- Consider 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

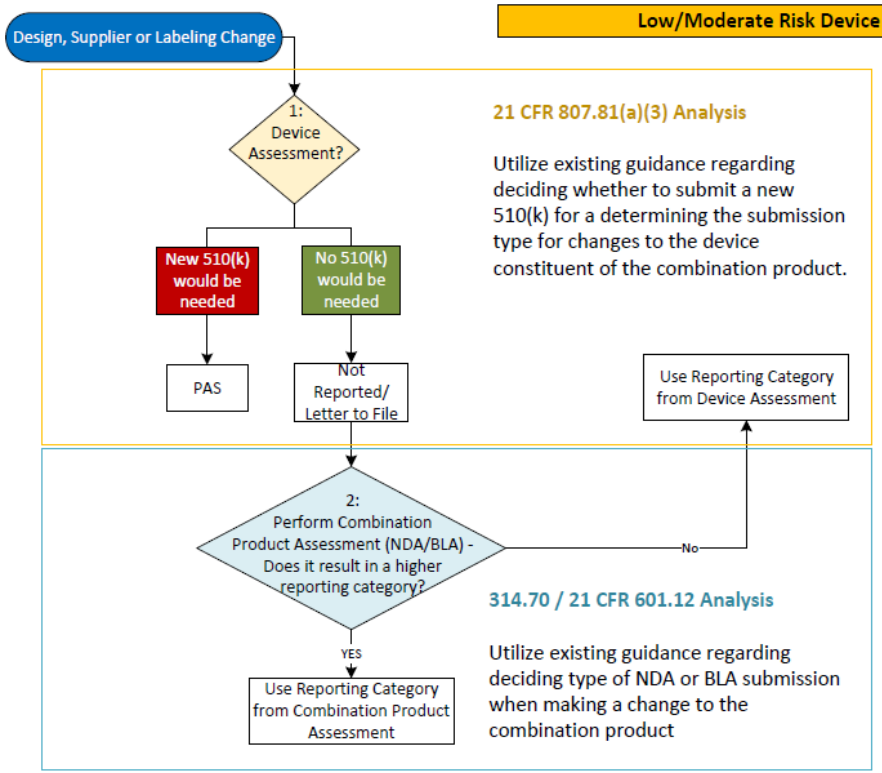
What's specific to Combination Products under US FDA regulations?

- 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 (Class I/II) and constituent part changes
  - A path for Class III device constituent part changes
  - Changes to Manufacturing process or control changes
  - Look to be consistent with 21 CFR 314.70 for drug products

Post Approval Challenges based on Differences in Global Regulatory Filing Requirements

One Example (CPC): Decision Tree Flow Chart for low/moderate risk device changes



↔ FDA Guidance: *Deciding When to Submit a 510(k) for a Change to an Existing Device* (2017) Considers: labeling, technology, engineering, performance and materials changes; New 510(k) or Documentation (???)

↔ Address in the QS like Class II [510(k)] Non-filing Memos

↔ Substantial risk: PAS
Moderate risk: CBE 30; CBE
Minimal risk: Annual Report

Post Approval Challenges based on Differences in Global Regulatory Filing Requirements

Examples that may raise FDA questions about certain changes to delivery devices - for the potential to impact:

- Identity, strength, quality, purity, or potency of the drug product (including the device)
- A change in technological characteristics or intended use for the device (with the drug) that may raise 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)

• [Note that some changes may need to be assessed clinically (e.g., PK comparability) or via Human Factor Studies.

What's happening in the EU for post approval changes?

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.

- Type IA; Type IB, Type II Variations for device changes; eMAAs for line extensions (new doses).
- Reviewed by Drug Competent Authority / Rapporteur

- **But changes are coming** - for post approval changes of a device constituent for:
  - a single-entity, single-use prefilled device (e.g., autoinjector) approved under an MAA
  - For CE Marked devices that are kitted with drugs.
- "Substantial" device changes will require an assessment by a Notified Body for conformance to Annex I of the Medical Device Regulation (MDR) beginning **26 May 2020.**

What are EU MDR Article 117 Requirements?

EU Medical Device Regulation (MDR) – 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 guidelines 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

EMA Q&A Guideline on Article 117 *[Questions & Answers on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746) (27 February 20190]*

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/assessment report?
- What about overlapping review issues: biological compatibility vs Leachables/Extractables, CCI?
- What if EMA is not in agreement with NB assessment?

Note also that IMPD's for integral, single-use Combination Products need to provide a statement as to conformity to MDD Annex 1. Effective March 2018: *EMA Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials*

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 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)

Post Approval Challenges based on Differences in Global Regulatory Filing Requirements

What about post approval changes to approved dossiers in the rest of the world?

- Key point –License/registration renewals can trigger additional device requirements under newly created regulations.

Some Key Markets:

Health Canada

Officially recognizes CPs – Emphasis is on ISO standards - Health Canada: Guidance Document Post-Notice of Compliance (NOC) Changes: Quality Document (2018)

- Level I - Supplements (Major Quality Changes)
- Level II - Notifiable Changes (Moderate Quality Changes)
- Level III - Annual Notification (Minor Quality Changes)
- Level IV Changes - Record of Changes

Japan – Pharmaceuticals and Medical Devices Agency (PMDA)

- Key device specifications are registered in the commitments section of the dossier
  - Dimensions with tolerances; conformity to standards; manufacturing/sterilization sites
- Types: Partial change Application (prior approval for change) [like PAS] Minor change Notification (within 30 days after implementation or shipping) [like CBE 30] (Non-approved matters) [like AR]

Post Approval Challenges based on Differences in Global Regulatory Filing Requirements

What about post approval changes to approved dossiers in the rest of the world?

Some Key Markets:

China CFDA [now National Medical Products Administration (NMPA)] - Medical Device and Pharmaceutical Regulations

- Very few applicable regulations for combination products
- Primarily a negotiation between local operating company and agency

South Korea (KFDA)

- Treats device constituent part as a Medical Device; Typically requires: General information, Photographs, Engineering drawings, Raw material information, Biocompatibility data, Performance data, Physical and chemical data, Manufacturing process related data, Stability data
- Changes to this information typically requires submission (3-5 months)
- License renewals can trigger significant additional device information

Latin America

- Focus has been on post approval device labeling changes – requiring review
- Brazil Anvisa: Can request kitted device specifications – would be regulatory binding – requiring notification if there are changes.
- Mexico COFEPRIS: Devices usually go through 3rd Party evaluation; license renewals can request supplier Quality Certifications (e.g., ISO 13485) legalized, conformity declarations, and sometimes specific device information (needle materials)

Post Approval Challenges based on Differences in Global Regulatory Filing Requirements

Some Key Markets:

Malaysia

Combination products will have to meet requirements of both the Medical Device Authority (MDA) and the National Pharmaceutical Regulatory Agency (NPRA). Deadline extended to 1 July 2019.

- Applicant must first submit dossier to MDA for written endorsement and then make submission to NPRA [Class A device exemption; conformity assessments by Conformity Assessment Bodies (CAB) under review].
- **This requirement is also triggered by registration renewals (5 years duration) .**

MDA Information requirements

An overview which covers an introductory descriptive information on the medical device, the intended uses and indications for use of the medical device, novel features and a synopsis of the content of the CSDT;

Commercial marketing history which covers the list of countries where the medical device is marketed and the dates of introduction into those countries

Intended uses and indications in its label

List of regulatory approval or marketing clearance obtained including the registration status, intended use and indications of the medical device in other countries; copies of certificates or approval letters from each country and declaration on labelling, packaging and instructions for use

Status of any pending applications for regulatory approval or marketing clearance

Summary of reportable adverse events and field corrective actions;

A description of the medical device if the medical device contains animal or human cells, tissues and/or derivatives thereof, rendered non-viable cells, tissues and/or derivatives of microbial or recombinant origin and/or irradiating components, ionising or non-ionising (if applicable)
Relevant essential principles and rule used to demonstrate conformity*

Asian Harmonization Working Party (AHWP): *Guidance on Regulatory Practices for Combination Products* (2016)

Questions

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