CASE STUDIES:
Global Regulatory Strategies for Combination Product Registration and Change Management

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Instructions

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- Each table will be assigned a case study and set of questions.
- Participants to choose a table which most interests them and work in the groups for the case study session.
- Speaker faculty will be circulating through the room for during the table discussion portion of the session.
- After table discussions, we will have a readout portion with discussions and questions.
- During readout, the speaker faculty will provide additional thoughts and considerations

Table Assignments

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Orange Tables 1A – Case Study 1 (Prefilled Syringe)

- Q1: development/ compatibility
- Q2: stability/shelf life
- Q3: manufacturing)

Blue Tables 1B – Case Study 1 (Prefilled Syringe)

- Q4: Human Factors
- Q5: EU MDD/MDR
- Q6: Quality System Documentation)

Green Tables 2A – Case Study 2 (Drug-Eluting Stent):

- Q1: Submission pathway
- Q2: development/compatibility
- Q3: stability/shelf-life

Purple Tables 2B – Case Study 2 (Drug-Eluting Stent)

- Q4: Testing and Release for distribution
- Q5: reserve samples
- Q6: post-approval change

Case Study 1 – Pre-filled Syringe

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- Currently approved as vial
- Manufacturer plans to change to a PFS presentation, a single-entity combination product
- Drug-GMP based streamlined quality system
- Combination product manufacturer purchases off-the shelf syringe components
- Manufacturer performs manufacturing processes as separate operations within the same facility:
  - Process 1 – fill/finish
  - Process 2 – Assembly & Label
  - Process 3 – Carton & Label
  - Process 4 – Bulk Carton & Label
- Questions related to development and submission requirements support the post-approval change to the PFS

Case Study 1 Questions

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1. Regarding the development and compatibility of the pre-filled syringe presentation:
   a. What information should be included in the submission? What are the key guidances that you would use as you develop your strategies?
   b. What specific drug/device compatibility issues should be considered for a pre-filled syringe?
   c. What are the device/combination product design related development elements that should be included in the submission (ie., design input requirements, design outputs, device related specifications)? What types of characteristics or features do you focus on? Are there particular instances where you would include this information vs. when you wouldn't?
   d. What are the location options for this development / compatibility data in the CTD? What are the benefits and/or challenges with each option?
   e. Would there be any differences in your strategy for non-US submissions?

Case Study 1 Questions

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2. Regarding stability/shelf life, assuming Manufacturer B provides an expiration date for the syringe components of 5 years
    a. What data sets should Manufacturer A need to establish shelf life?
    b. What is the 'entity' that the testing to establish shelf life should be performed on (e.g., prefilled syringe after fill/finish, labeled prefilled syringe assembled with plunger rod and backstop, finished product in secondary packaging)?
    c. What is the 'entity' that the continuous stability monitoring (e.g., post-approval commitment) should be performed on?
    d. What would be Manufacturer A's options to leverage Manufacturer B's data on the syringe components?
    e. Would there be any differences in your strategy for non-US submissions?

Case Study 1 Questions

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3. Regarding submitting manufacturing information for the prefilled syringe
    a. What different and/or additional information should be included for the prefilled syringe as opposed to the current vial presentation?
    b. What are the location options for each of the processes shown in the figure in the CTD? What are the benefits and/or challenges with each option?
    c. Which processes from the figure would have process validation data included in the submission? Would this change if Process 2 also includes assembly with a needle safety device?
    d. Would there be any differences in your strategy for non-US submissions?

Case Study 1 Questions

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4. Regarding Human Factors

a. When would human factors studies be required for a prefilled syringe? Are there scenarios where Manufacturer A could justify not performing the studies?

b. What would be needed before running your summative validation study?

c. What would be the location options for formative developmental human factors learnings in the CTD? What are the benefits and/or challenges with each option?

d. What are the location options for the summative validation study report in the CTD? What are the benefits and/or challenges with each option?

e. Would there be any differences in your strategy for non-US submissions?

Case Study 1 Questions

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5. Regarding demonstrating conformance with Annex 1 of the EU Medical Device Directive/Medical Device Regulation
    a. What information would be needed to include in your MAA regarding the essential requirements?
    b. Would you submit your essential requirement checklist? Why or why not?
    c. How would you manage changes that impact the essential requirements checklist?
    d. What are the location options in the CTD for including the information regarding the essential requirements? What are the benefits and/or challenges with each option?
    e. How will these strategies change once the MDR is effective?

Case Study 1 Questions

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6. Regarding demonstrating compliance with the specified device QSR sections 21 CFR 820.20 (Management Responsibility), 21 CFR 820.30 (Design Controls), 21 CFR 820.50 (Purchasing Controls) and 21 CFR 820.100 (CAPA)
    a. What information should be included in the filing?
    b. Should procedures be included?
    c. What are the location options for presenting this information in the CTD? What are the benefits and/or challenges with each option?
    d. If this quality system information changed in the future, would Manufacturer A need to submit changes to this information to their NDA/BLA? Are there any strategies that Manufacturer A can incorporate when including this information in the NDA/BLA to minimize the need to file submissions related to changes to this information in the future?
    e. Would there be any differences in your strategy for non-US submissions?

Case Study 2 – Drug Eluting Stent

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- Single Entity combination product
- Combination Product Manufacturer purchases drug substance and polymer and then formulates the drug coating solution and coats the stent its own facility
- GMP base system is device QSR
- Questions related to development and submission requirements to market the DES

Case Study 2 Questions

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1. Regarding submission pathway
   a. What would be the regulatory pathway for this combination product in the US?
   b. What would be the regulatory pathway for the DES in the EU?
   c. What would be Manufacturer A's options to leverage Manufacturer B's data on the API?
   d. How will these strategies change once the MDR is effective?

Case Study 2 Questions

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2. Regarding the development and compatibility of the DES:
   a. What information should be included in the pre-market submission?
   b. What specific drug/device compatibility issues should be considered for the DES?
   c. Are there any differences that Manufacturer A should consider when applying 21 CFR 820.50 purchasing controls to the drug constituent?
   d. What are the device/combination product design related development elements that should be included in the submission?
   e. Would there be any differences in your strategy for non-US submissions?

Case Study 2 Questions

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3. Regarding stability/shelf life,
   a. What data sets should Manufacturer A need to establish shelf life?
   b. What data from Manufacturer B can Manufacturer A leverage? How would this be included in Manufacturer A's filings?

4. Regarding testing and release for distribution,
   a. What data from Manufacturer B can Manufacturer A rely on?
   b. What drug-specific tests should Manufacturer A need to perform to release the DES for distribution?

Case Study 2 Questions

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5. Regarding reserve samples,
   a. What would Manufacturer A's options be for maintaining reserve samples (finished combination product, individual components, other)?
   b. Would Manufacturer A include information related to reserve samples in the submission?

6. 1 year after successfully registering the DES, Manufacturer A is informed by Manufacturer B that they are closing the manufacturing site that the API is manufactured at and transferring the process to another site.
   a. What would be the combination product issues that Manufacturer A should consider as they evaluate this change?
   b. How would Manufacturer A file this change in the US? In the EU?