Science-based Development & Licensing of Combination Products – Focus on High Concentration Monoclonal Antibody Solutions in Prefilled Syringes or Prefilled Pens

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Topics

● Module 3 organization for prefilled syringe and prefilled pen presentations

● Location of Device information in Module 3

● Agency questions on device constituent parts - biologics/device combination products (EMA, FDA, PMDA)
Module 3 organization

- Different configurations (e.g., pre-filled syringes, pre-filled pen) of one finished pharmaceutical product intended to be for the same route of administration for the same indication(s) can be bundled in a single marketing application.

- A unique Drug product (DP) section (i.e., leaf in the eCTD) created for each presentation:
  - solution in pre-filled syringe (PFS)
  - solution in pre-filled pen (PFP)

- Non plunger rodded prefilled syringe defined as bulk prefilled syringe (bulk PFS), intermediate for PFS and PFP assembly

- Information pertaining to the bulk-prefilled syringe is presented only in the pre-filled syringe section.

- This information is cross-referenced in the analogous pre-filled pen section, with inter-document electronic link provided to ease the review
  - information on the bulk prefilled syringe reviewed only once as per ICH M4Q requirement
**LEAF 1: Drug Product** INN, solution for injection in prefilled syringe, manufacturing site

P.1

...  

P.3.3 Description of manufacturing process and process controls

Manufacturing of bulk prefilled syringes

Assembly with plunger rod

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**LEAF 2: Drug Product** INN, solution for injection in prefilled syringe, manufacturing site

P.1

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P.3.3 Description of manufacturing process and process controls

Manufacturing of bulk prefilled syringes

Assembly in **prefilled pen/autoinjector**
## Device information in Module 3 TOC (PFP leaf)

<table>
<thead>
<tr>
<th>Items</th>
<th>Location (BLA and EU MAA)</th>
</tr>
</thead>
</table>
| Design and development plan for the prefilled pen                    | BLA and EU MAA: P.2.4 Container Closure System  
BLA: Attachment of design control SOP                                                                 |
| Functional performance testing and dose accuracy - Conformity to ISO 11608-1 (Needle based injection system and -5 (automated functions) | BLA and EU MAA: Summary in P.2.4 Container Closure System  
BLA: MAF for complete report                                                                                                                                 |
| Biocompatibility data according to ISO 10993                         | BLA and EU MAA: P.2.4 Container Closure System (summary)  
BLA: MAF for complete report                                                                                                                     |
| Sharp Injury Prevention Study (in a simulated setting with the PFP (typically 500 devices) | BLA: P.2.4 Container Closure System (summary) and report attached                                                                                   |
| Human Factor Study                                                   | BLA (previously and EU MAA: P.2.4 Container Closure System (summary) BLA: HFS report attached  
**BLA currently: Currently, HF Validation Study 5.3.5.4**  
**Other Study Reports and Related Information (you can cross-reference from Module 5 to Module 3**                                              |
| Summary of technical complaints during clinical trials              | BLA and EU : P.2.4 Container Closure System  
| Change in Prefilled pen over development                             | BLA and EU MAA: P.2.4 Container Closure System  

## Device information in Module 3 TOC (PFP leaf)

<table>
<thead>
<tr>
<th>Items</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assembly process description</td>
<td>BLA and EU MAA P.3.3: including mechanical CPP and CIPC and maximum Time out of Refrigeration (TOR)</td>
</tr>
<tr>
<td>Assembly process and shipping validation</td>
<td>BLA and EU MAA: P.3.5 Batch size independent – done at ~10% scale, TOR validation)</td>
</tr>
<tr>
<td></td>
<td>Critical Functional Performance attribute tested (e.g. 5-6 tests), statistical sampling</td>
</tr>
<tr>
<td>Assembly process controls</td>
<td>BLA and EU MAA: P.3.4 Risk Assessment of CPP and CIPC</td>
</tr>
<tr>
<td>Documentation of the finished combination product to demonstrate compliance with regulatory requirement applicable to 21 CFR Part 4</td>
<td>BLA P.3.3 Quality System summary Purchasing and CAPA SOP’s</td>
</tr>
<tr>
<td>Items</td>
<td>Location</td>
</tr>
<tr>
<td>---------------------</td>
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<tr>
<td>Sterility Assurance</td>
<td>BLA and EU MAA:</td>
</tr>
<tr>
<td></td>
<td>CCIT done as part of assembly process validation, simulated shipping validation and during primary stability testing</td>
</tr>
<tr>
<td></td>
<td>Dye ingress method cross validated with microbial ingress test (P.5.)</td>
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<tr>
<td></td>
<td>P.2.5 Container closure integrity tests by microbial ingress</td>
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<td></td>
<td>P.3.5 Container closure integrity tests by dye ingress for PV lots</td>
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<tr>
<td></td>
<td>P.8 Container closure integrity tests by dye ingress in PFP primary stability program</td>
</tr>
</tbody>
</table>
Device information in Module 3 TOC (PFP leaf)

<table>
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<tbody>
<tr>
<td>PFP Control Strategy</td>
<td>BLA and EU MAA P.5.</td>
</tr>
<tr>
<td></td>
<td>Release specifications include device appearance, id, protein content critical functional performance testing (6 tests, statistical sampling – ISO2859-1) Method validation provided for functional tests in P.5.3</td>
</tr>
<tr>
<td>PFP Stability</td>
<td>BLA and EU MAA P.8</td>
</tr>
<tr>
<td></td>
<td>Leverage « bulk PFS primary stability data for shelf life setting Functional stability testing part of PFP primary stability program Long term, accelerated, stress conditions, temperature excursion + photostability</td>
</tr>
<tr>
<td></td>
<td>BLA: MAF for aging studies (AI components and AI sub-assemblies)</td>
</tr>
<tr>
<td>Identification of the essential requirements of the MDD Annex I applicable to the AI</td>
<td>EU MAA: 3.2.R</td>
</tr>
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</table>
EMA/CHMP: Questions during MAA review Prefilled Pen Assembly process

● The Applicant should justify (and if necessary extend) the current list of CPPs/CIPCs based on an appropriate risk assessment

● What is a PFP Assembly process?
  • Serial production process where all PFP produced following the same sequence of process steps on automatic assembly/packaging lines
  • Assembly/packaging line is a modular construction, built of individual units mechanically and electronically connected, supported or controlled by qualified computer-assisted systems
  • Assembling the auto-injector sub-assemblies with the “bulk” PFS controlled by automatic controls, which monitor the process online and continuously.
  • This comprises cameras as well as a test of the assembled auto-injector to ensure that the pre-filled pens are accurately assembled and that no manufacturing faults adversely affect the correct functioning
EMA/CHMP: Questions during MAA review Prefilled Pen Assembly process

How are set CPP/CIPC?

CPPs/CIPCs

- Defined through comprehensive risk assessment based on the patient hazard, the occurrence and the detectability of the failure.
- Potential process risks identified with failure mode and effect analysis (FMEA) considering e.g. design requirements, experience with similar products, knowledge of potential hazards, etc.
- CPPs: e.g. PFS insertion force, (rear/front sub-assemblies forces)
- CIPCs: e.g. a number of in-line visual controls of correct positioning/assembly
The specification for silicone oil applied to syringes should be included in section 3.2.P.3.4 or another suitable section of the CTD.

Ph. Eur. <520> parenteralia requires the following: Containers for parenteral preparations are made as far as possible from materials that are sufficiently transparent to permit the visual inspection of the contents, except for implants and in other justified and authorised cases. The applicant should substantiate that satisfactory visual inspection of the contents of the PFP is possible.
The combination product developer, is responsible for development of device constituent part requirements and specifications, and the verification and validation of those specifications.

The future marketing application should include all design control information for the final finished combination product.

If some low-level performance tests of the sub-components of the combination product are determined to be unaffected by medication and intended use of the product, are considered to be proprietary to a third party sponsor developing those subcomponents, then it may be acceptable to for them to submit such information in a master file; a letter of authorization (LOA) should be included in the application (e.g. BLA) for cross-reference to the master file.
FDA: Device information in Module 3 TOC
Compliance with 21CFR Part 4

- Design Control SOP in section P.2.4
- SOP Purchasing Control in section P.3.3
- SOP Corrective Action and Preventive Action (CAPA) in section P.3.3
- Document defining the respective responsibilities for the development of the auto-injector and the combination product in P.3.3
- FDA was requesting copies of SOP’s for certain QSR (e.g. design controls, purchasing controls, CAPAs) to ensure that the manufacturer is in compliance with cGMPs in 21 CFR Part 4. Summaries may suffice; however, some reviewers are still requesting SOPs.

➤ If you elect to proactively provide SOPs or if they are requested by a reviewer, make sure that you provide commentary (on the SOP documents) that state that the SOPs are provided for reference only, and not subject to update. In addition, each page should be marked confidential.
FDA: Questions during BLA review

- Provide a complete description of the design input controls in the form of device requirements and specifications, which fully describe the attributes of the system and their acceptability in the context of the intended use of the system and the medication being delivered.

- Provide the risk analysis which characterizes and evaluates the risks to the user or patient both during normal use, reasonable foreseeable mis-use, and potential system failure states. Such an analysis should clearly describe system hazards, mitigations implemented to reduce the risk of those hazards, effectiveness of the mitigation, as well as conclusions of the acceptability of system risks within the final finished system.
The specifications for device performance tests need to be justified and that should include usability aspects. Devices have more established criteria and all should be listed. Be sure to use clinical trials, human factor studies to narrow down the acceptance criteria.

If the final to-be-marketed combination product has not been used in the pivotal clinical trials, please specify what changes were made, when they were made, and how many patients were exposed to each version of the change.

If changes were made to the combination product during the conduct of the clinical trials, what was the incidence of adverse events, such as injection site reactions, device malfunction, etc. before and after the change.
PMDA: Questions during JNDA review

- **Drug Delivery to the patients**
  - impact of shear stress when delivering the drug solution by the syringe or pen has on the quality of the Drug Product to be studied

- With regard to the sterilization of plunger stoppers by gamma radiation, add an explanation on a determination method of sterilization dose, the maximum irradiation dose and the sterility validation criterion in the AF.

- Explain whether the applicant could conclude that a gamma radiation does not cause a degradation of materials with showing examination results.
PMDA: Questions during JNDA review

- Compliance with the pre-filled syringe requirement provided in Medical Devices Notification (JMDN), Syringe for prefilled drug with needle
  - JIS T 3209 Sterile injection needles
  - JIS T 3210 Sterile injection syringe
- If there is non-compliant requirement, explain the rationale that the applicant concluded that there was no problem even if the syringes do not meet the requirements.
  - E.g. compliance with stringent requirements of EP, USP, ISO and FDA guidance for syringes, syringe barrel, needle steel, adhesive using for stacking the needle, silicone fluids inside the barrel and needle shield)

- Specifications for rubbers used for needle shield and plunger stopper
  - At least compliant with JP grade rubbers assured by “JP 7.03 Test for Rubber Closure for Aqueous Infusions
PMDA: Questions during JNDA review (AF)

- Dimensions of syringe and AI to be described as partial change application (PCA) items rather than MCN items.

- Specifications for silicone oil used for needle and syringe barrel to be described in the AF.

- Syringes with staked needle and needle shield sterilized by ethylene oxide and the sterility validation criterion of ethylene oxide to be added in controls performed on syringes in the AF.

- PFP manufacturing process CIPC (Visual test, Verification of assembly and Functional tests) to be added in the AF as PFP performance tests
Concluding Remarks

- **BLA:**
  - Overlap of GMP and Regulatory information in the BLA
  - Unclear whether SOP’s for certain QSR (e.g. design controls, purchasing controls, CAPAs) have to be submitted or if summaries are always acceptable
  - HFS study location – not a clinical study

- **EU MAA**
  - PFP Assembly process considered as manufacturing operations versus packaging operations but Regulatory and GMP expectation (e.g. secondary packaging operation in manufacturing authorization) may differ

- **JNDA**
  - Emphasis on components specifications including dimensions and sterilisation as binding information
  - PFP Assembly process CIPC considered binding information
Thank You!