Small Volume Parenteral Products as Combination Products in the USA

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Topics

- **Why SVPs are Combination Products in the USA**
- **Regulatory and Testing Expectations in the USA**
  - **Quality Systems/Design Control Expectations**
  - **FDA Testing Expectations**
    - **Safety**
    - **Effectiveness/Performance**
  - **Human Factors/Usability Expectations**
- **Other Challenges**

Why SVPs are Combination Products in the USA

SVPs as Combination Products

- All SVPs must be “Delivered” in some manner - When is it a Combination Product?

- FDA first addressed this subject with regards to Prefilled syringes in 2013, in the preamble to the Combination Product GMP regulation (21 CFR Part 4)

  - “*The Agency will continue to regulate drug containers and closures in accordance with parts 210 and 211. A syringe, however, is not a mere container/closure. A syringe is a device used to deliver another medical product (e.g., a drug) (see, e.g., 21 CFR 880.5860). Accordingly, a prefilled syringe is a combination product and subject to this rule.*”

SVPs as Combination Products

- This was further explained in the Draft Guidance covering GMP Requirements for Combination Products, published in 2015

  - *If the article merely holds the drug, it is only subject to drug CGMPs as a container or closure. An article that holds or contains a drug, but also delivers it, may also be a device subject to the device QS regulation in addition to the requirements relating to drug containers and closures."*

SVPs as Combination Products

- And was ***expanded*** in the Final GMP Requirements for Combination Products published in 2017
  - *"Elements of container closure systems that are device constituent parts include piston syringes, metered dose inhalers (MDIs), and containers for intravenously-administered (IV) fluids (such as IV bags containing saline or anti-coagulants), which both hold and deliver the drugs or biological products they contain. In the case of an IV container, the drug is delivered to the patient via the IV line".*
- *CAUTION: By extrapolating the definition of a Combination Product to the IV container (primary Packaging) via its delivery by a separate, approved medical device, FDA opened all primary packaging for SVPs to consideration as Combination Products.*
  - *Filled Syringes without needles*
  - *Filled Cartridges*
  - *VIALS??*

SVPs as Combination Products

- Recently, FDA has acknowledged that some (parenteral) products that are “delivered” may not be “True” Combination Products as codified in the regulations - 21 CFR Part 3

- They have begun to use the term “Combined Use” Products
  - Combined Use is not defined in any regulation or guidance but has been informally proposed by the Office of Combination Products (OCP) to apply when a drug requires a device to achieve delivery.

Which applies to all SVPs!

SVPs as Combination Products

- Combined Use
  - Proposed to describe
    - two separate finished products (drug and device)
    - that come to the user separately (not packaged together)
    - that are used together to execute delivery
    - but are not “cross-labeled” combination Products per the legal definition
      - e.g.; One-way labeled, Non-exclusive use
  - May **not** require implementation of Medical Device GMPs
  - But **can** have an impact on the testing and controls required to support approval of the SVP

USA Regulatory and Testing Expectations

Quality Systems/Design Controls Expectations

- Quality Systems
  - It is a legal requirement in the USA to comply with 21 CFR Part 4 – "Current Good Manufacturing Practice Requirements for Combination Products"
- This regulation outlines a "Streamline system" to achieve GMP compliance
  - For companies with a drug GMP system (compliant with 21 CFR Pats 210 and 211)
  - Additional compliance with four Sections of the Medical Device GMPs (QSR) are mandatory. These are:
    - 21 CFR Part 820.20 – Management Controls
    - 21 CFR Part 820.30 – Design Controls
    - 21 CFR Part 820.50 – Purchasing Controls
    - 21 CFR Part 820.100 – CAPA
- Although the intent will likely not change, it is not clear how the proposed adoption of ISO 13485 by FDA will impact this requirement.

Quality Systems/Design Controls Expectations

- For a company that has never worked with Medical Device Quality systems, this requirement is a significant challenge

- Design controls are the most difficult
  - First - GMP controls must start **BEFORE** the product is designed or developed
  - Also, for most SVPs, the primary packaging is not “designed”, but chosen and qualified
    - Compliant procedures still must be generated
    - Project must contain all the required elements

Quality Systems/Design Controls Expectations

- Integrated with, and parallel to Design Controls, the company must implement a robust Risk Management System (consistent with ISO 14971)
  - Including “use” risk (Human Factors Engineering)
- The system is to cover the final “combination product” not the components
  - Although some of the requirements can be met by the component or platform supplier

FDA Testing Expectations

FDA Testing Expectations

- FDA will expect the product to fulfill all requirements necessary to “safely” and “effectively” deliver the SVP

FDA Testing Expectations

- Safety
  - Biocompatibility of all direct and indirect patient and user contact materials (per ISO 10993-1)
  - Particulates and Pyrogens delivered to the patient (includes drug contact components that are not part of the primary packaging)
  - Sterility (of drug contact components that are not part of the primary packaging), throughout shipment and storage (can include Package integrity of any sterile barriers other than the primary packaging)
  - Exclusion of some materials (e.g.; phthalates)
  - Needle safety if implied or claimed (per ISO 23908 and FDA Guidance)
  - Basic Electrical and Software Safety must be established, if applicable

FDA Testing Expectations

- Safety includes Medicinal Product (Drug) Compatibility
  - Defined in ISO 11608-3 as - evaluation of the medicinal product quality based on combined use with the needle-based injection system (NBIS)
  - Separate from Primary Packaging testing including standard drug stability
  - Focus is on the quality of the drug that is “delivered”
    - Includes the impact of “conditions of use” (i.e.; temperature and time), the “actions” “experienced by the drug (e.g.; aspiration, reconstitution, manipulation, expulsion) and impact of drug contact with the device material (contact with the fluid path) once the delivery has started.

FDA Testing Expectations

- "Effectiveness" or Performance
  - All functions necessary to deliver the drug will need to be identified and verified or validated
  - FDA will suggest, and then require that the company identify those that are to be considered Essential Performance Requirements (EPRs) for the product
    - No Formal EPR Definition from FDA, although Guidance is promised
      - FDA generally considers EPRs as being the performance attributes responsible for the clinical performance of the device at the point of use (dosing) and include the device's performance attributes relating to the user interactions required to administer the dose.
      - Similar to the concept of "Primary Functions" defined in ISO 11608-1:2022
      - Some relation to Essential Performance as defined in IEC 60601-1 for Medical Electronics

FDA Testing Expectations

- Impact of Essential Performance Requirements (EPRs)
  - FDA requires that these must be verified
    - At all in-use conditions
    - After all preconditioning
    - After Shipping simulations
    - At the end of expiration
    - *Sometimes they expect these are tested at "worst-case" conditions*
  - Also, they need to be established as release specifications for batch release
    - Or you must provide an acceptable "control strategy"

FDA Testing Expectations

- Functions likely to be considered as EPRs (as applicable)
  - Accurate delivery
  - Delivery Rate or Time
  - Location of delivery (needle depth)
  - Force to activate
    - Activation force
    - Injection Force
    - Break-loose and Glide Force
  - End of delivery indication

FDA Testing Expectations

- Other Functions that must be included as part of Design Verification testing (these are only examples)
  - Leakage
  - Burst
  - Connector compatibility (e.g., luer, IV spike)
  - Needle penetration force
  - Adhesion (OBDS)
  - Component separation force
  - Closure removal force (e.g.; Cap, RNS, Tip Cap)
  - Fragmentation
  - resealability

FDA Testing Expectations

- Other Functions and testing conditions for some SVPs
  - For Prefilled Syringe
    - ISO 11040-8 – Prefilled Syringes
    - FDA Guidance, Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4: 2013
  - For Injectors
    - ISO 11608 series – Needle Based Injection Systems
    - All sections (11608-1 though 6) have been updated to be published March/April
  - For IV Bags
    - ISO 15747 - Plastic containers for intravenous injections
  - Emergency Use Products
    - Reliability for Emergency Use Products (FDA Guidance)

Other standards and guidance are included within these standards

- Simulated Shipping Studies (ASTM D4169, ISTA)

Usability Expectations

Usability Requirements

- Guidance and Standards
  - Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development, Draft Guidance, February 2016
  - Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications, Draft Guidance, September 2018
  - IEC 62366-1 and IEC 62366-2

- Information for Clinical studies
  - Use Related Risk Assessment, Threshold analyses, Formative studies and justifications.

Usability Requirements

- Information For Approval
  - Before the NDA Submission
    - FDA requests they review the Summative Testing/Design Validation Protocol before running the study
      - Can be executed after, or in parallel with, a pivotal Clinical Study, but must be completed prior to submission, typically
  - In the NDA submission
    - Submission of HFE/UE Summary Report
      - Per Appendix A of FDA Draft Guidance
      - Full Validation study reports are required if Summary is not sufficiently detailed

Usability Requirements

- The NDA must be supported by an appropriate and complete HF Program
- The program should be consistent with FDA guidance and IEC 62366 standards, including, as appropriate
  - Formative Testing such as:
    - Testing/Feedback from Users to inform design
    - Training Development
    - IFU Comprehension
  - Use Risk Summary with mitigations (URRA)
  - Validation Plan - Summative Testing
    - Safety And Functional Simulated Use Study
  - Usability Engineering Report
    - FDA Guidance – Appendix A
  - Lifecycle Program
    - Design Transfer to Post Marketing

Usability Requirements

- Usability in the USA has become an issue even for PCC and Kits
  - Division of Medication Error (DMEPA) is now the lead review for all Combination Product Human Factors
    - Three Guidance documents from Division of Medication Error on Human Factors requirements
  - Division of Risk Management gets involved in IFU review

Other Challenges

Other Challenges

- **Application of Design Controls to Primary Packaging**
  - **Prefilled Syringes, IV Bags, Ampoules/vials with droppers or applicators, etc.**
- **Complex Generic Products**
  - **Similarity of the Device Constituent**
- **Electronic products**
  - **Software/Cybersecurity**
- **Connected Devices**
  - **APPs – Stand-Alone Software Devices**

Thank You! Questions?