Table 2: Combination Products / Therapies: Development of Control Strategies

FACILITATOR:  Pat Rancatore, *Genentech, A Member of the Roche Group*

SCRIBE:  Peter Johnson, *3M Drug Delivery Systems*

SCOPE:

Combination products, as defined in 21CFR3.2(e), are comprised of any combination of drug, device, and/or biologic product. A control strategy for combination products should ensure that a safe and effective product is manufactured and distributed to patients. At the core of this strategy is a systematic risk-based approach to product development and manufacturing - starting with the identification of the product’s critical quality attributes (CQAs) and continuing through development to understand the product functionality and manufacturing process with the detail needed to establish critical design and process specifications. This round table discussion will focus on the control strategy for device- and product-related attributes of a combination product. Specifically, the process for determining device related CQAs will be discussed. The scope of product and process characterization experiments will be reviewed, as well as the final controls implemented – including attributes controlled by suppliers, in-process controls for manufacturing, release test attributes and attributes monitored during stability. Participants are suggested to share health authority feedback on their processes and the controls they have implemented.

QUESTIONS FOR DISCUSSION:

1. The process for determining control strategy for combination products that include a device:
   a. What is the process that manufacturers follow to determine the control strategy for the device component of their combination product? Do they follow a risk-based approach and how is it integrated into their established design controls procedures?
   b. Discuss how manufacturers determine critical quality attributes (design input requirements that are critical to the safe and effective use of the product).
   c. Discuss the product characterization experiments performed to understand the critical design and manufacturing process parameters.
   d. Discuss how these parameters are controlled – are they controlled with the suppliers of those components? Are they controlled in the final assembly process or at release testing? How does a manufacturer decide where the control is needed?
   e. What health authority feedback has been received on control strategy processes?

2. The process for determining control strategy for combination therapies without a device:
   a. Discuss analytical method development challenges for combination therapies without a device – what strategies or unique approaches have been developed?
   b. Discuss approaches to setting specs for drug/biologic-related and process-related impurities.
   c. What is the process used to design the overall control strategy for the individual products as well as their combinations?
NOTES:

Discussion Topic: Content of Applications for Combo Products: Two Approaches:
- Demonstrate compliance for all regulations for drug and device, or
- Streamlined Approach:
  1) Follow the full regulations for a drug product, plus specified regulations for device, or
  2) Follow the full regulations for a device product, plus specified regulations for drug.

Comment: There is new Final Guidance for Combo Products (draft Jan 2015/ final Jan 2017) which addresses Requirements for Combo Products.

Discussion Topic: Contract testing labs are less familiar with device regulations (vs. drug regs). This can impact the way discrepancies are captured, among other things.
- When using contract labs, use “Quality Agreement” to define how Contract Labs handle samples, and data (outliers).

Discussion Topic: for Combo Products, the definition of “Lot” can be confusing.
Reply: A continuous fill operation is a “Lot”

Discussion Topic: How to define combination product stability?
- Discussed commercial combination product stability and whether a manufacturer should place the fully built device on stability or whether it is sufficient to place the primary container on stability.
  o Some participants noted that “stability” implies the entire (fully built) combination product.
  o Other participants noted that since the primary container (e.g. PFS) is the only drug contacting material and since, for example, the autoinjector component will not impact drug stability, it is sufficient to perform commercial stability with the PFS alone. Other participants agreed, noting that for these scenarios, they compare 3 lots of PFS and autoinjector to provide demonstrated evidence that the autoinjector does not impact drug stability as part of their rationale.

Discussion topic: Are you measuring device functionality attributes at release testing
- For prefilled syringe products with needle safety devices, some industry participants are measuring glide force as part of release testing. An FDA participant agreed that this would be typical.
- Two FDA participants noted that would want to see at least one device functionality test as part of release testing with rationale as to why that attribute was chosen. They noted that opinions at FDA are still evolving.

A collection of comments (with little or no discussion):
- It is important to ensure that shelf life of device exceeds the shelf life of the drug since device components can be manufactured and stored in advance of drug manufacturing.
- Quality Agreements with Device Supplier: Ensure that supplier knows the expectations of the device materials and the assembly process.