Roundtable Session 1 – Table 11 - Fix-Dose Co-Formulated Protein Product in Liquid or Solid

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Abstract:

Fixed dose combination (FDC) products are pharmaceutical products that combine two or more active ingredients in a single dosage form, such as a pill, capsule, or injection. FDCs contain a fixed ratio of drug ingredients, which means the dosages of each ingredient are predetermined and standardized. These products are developed and used for various therapeutic purposes, aiming to enhance the treatment's efficacy, convenience, and patient compliance. Each ingredient in the combination targets different aspects of the disease or condition, providing a more comprehensive treatment; however, it's important to design these combinations carefully to ensure optimal dosing and to manage any potential interactions between the combined drugs. FDC products are used for several important reasons, including:

1. Improved Medication Adherence: Combining multiple medications into a single pill can simplify treatment regimens, making it easier for patients to follow their prescribed therapy. Reducing the number of pills a patient needs to take can improve adherence to the treatment.

2. Optimized Drug Synergy: FDCs can offer therapeutic advantages by combining drugs that work through different mechanisms. This can result in enhanced efficacy or a broader spectrum of action for treating complex diseases.

3. Improved Outcomes: By simplifying the treatment protocol and ensuring that patients receive all prescribed medications, FDCs can contribute to better overall treatment outcomes.

Discussion Questions:

Are the active pharmaceutical ingredients (APIs) chemically and physically compatible with each other? How can potential interactions between APIs be minimized?

Is it necessary for DP release and stability methods to monitor molecule-specific attributes from each of the APIs? When can it be acceptable to report product quality attributes that include species from both molecules? When is it not?

What are some control system approaches for FDC products that stretch the limits of analytical capabilities (e.g. highly disproportionate ratio of APIs, highly similar primary sequence or molecular structure, overlapping MoAs, etc.)?

What are some challenges or considerations in the manufacturing process for FDC products in the liquid or solid dosage form?

Are there specific regulatory guidelines or standards that need to be followed for FDC products?

Notes:

Generally, folks are working on the development of doublet or triplet mAb fixed dose combinations (FDC) in liquid form to support clinical studies in oncology. Development of both IV and subcutaneous delivery were discussed. There was also some interest in exploring the analytical development of mAb biosimilar with a commercial mAb and small molecular with mAb combination. Most efforts are focused on developing a fixed dose combination drug product rather than a co-packaged combination. It was noted that some markets may not accept co-packaged drug products as it can been seen as a limit to access.

A common set of analytical challenges in the development of mAb combinations including method development, fixed dose combination characterization and the regulatory strategy seem to exist across development teams.

Defining and approach to analytical method development was discussed and the following were noted as challenges that were still in the process of being overcome in development:

1) Concerns regarding specificity and selectivity of analytical methods when developing purity methods such as SEC-HPLC and cIEF was discussed. When multiple mAbs are combined the sample complexity increases which complicates separation and detection. Several questions were raised as to what extent can DS methods be leveraged in the understanding of these methods and when can profiles be combined. There was discussion about a commercial doublet FDC combined profiles for which the DP release/stability purity methods were approved by the Agencies with combined profiles. There was also discussion around alternative separation and detection methods such as SEC-TOF, MAM and 2D HPLC but this approach could lead to challenges in transferring these methods to a GMP environment for routine testing.
2) Another challenge that was discussed was how to measure protein concentration in a FDC drug product. Two approaches were presented one which used an average extinction coefficient (similar mAbs in a 1;1 ratio), and one presented a separation method for quantitation. It was further discussed if the content method needed to report drug dose ratios to meet label claim. In the commercial FDC only the protein concentration is reported, and the dose ratio is not reported on the label. Teams felt even more challenged if the doses of the API were very different thus requiring the method to be highly sensitivity and capable of detecting a wide range of concentrations.
3) The challenges of purity methods for use in stability studies was discussed. How to manage the method development for complex profiles and ensuring that the degradant peaks are well resolved from the native molecules is a big development challenge. Should the primary intent of the FDC stability methods be to monitor for protein:protein interactions and stability is fully monitored using the DS and FDC methods?
4) Characterization methods were also noted as challenging as the structural elements and sequences are highly similar for mAb mAb combinations. No single solution has been devised.
5) Using a FDC reference material versus multiple reference materials was also discussed. While using multiple RM could work it seems the consensus is that a FDC specific RM is a better route for development.

Some regulatory challenges were also discussed: Most clinical plans started studies as a sequential administration or co-administration, moving to a FDC later in clinical development.

Most development teams are targeting phase 3 studies to introduce the FDC. Early heath authority interaction is recommended to fully understand when the FDC can be introduced and how to demonstrate bio-equivalency. Regulatory authorities will see the FDC as a “new drug”. Most participants were planning to submit multiple INDs/IMPDs for the DS with a single DP module. There are no standard terms identified for sequential administration, co-administration or co-formulation so they must be defined in the registration. The benefits of moving from co-administration to FDC really resides for subcutaneous FDC increasing drug access and reimbursement.