Roundtable Session 1 – Table 2 - CMC Challenges with Complex Formulations: Excipient Selection and Impact on Product Stability and Process Consistency

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Abstract:

Drug product development of complex formulations requires navigating various challenges to ensure compliance with regulatory requirements. These challenges include 1) selection of excipients compatible with the active ingredient; 2) prevention of degradation to prolong shelf-life and 3) manufacturing process validation to ensure quality, consistency and reproducibility. In addition, comprehensive control and characterization strategies are needed to demonstrate consistency across process changes to ensure no impact to quality, safety or efficacy. Successful development and commercialization of complex formulations require manufacturers to address these CMC challenges to ensure patients receive safe and efficacious medicine.

Discussion Questions:

1. What are the challenges in ensuring the compatibility of excipients with active pharmaceutical ingredients (APIs) in complex formulations?

2. What approaches can be used to ensure the CMC formulation is suitable to limit product degradation to establish shelf-life?

3. What strategies can be used to understand the impact of degradation on safety, efficacy, and quality?

4. How does the manufacturing technology impact formulation development and what needs to be considered to ensure process consistency?

5. What are the regulatory challenges for complex formulations and successful strategies to support development and commercialization?

Notes:

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Case study: Selection of preservatives for multiple dose formulations.

- Preservatives that would be effective but at levels below reg guidance for safety, so ended up with a combination of preservatives. Had impurities that showed up a problem in manufacturing, not development, took a long time to understand what impurities were causing issues and how to work with vendors for purer quality of ingredients, limited to single supplier and custom part numbers.
- Could it be due to different vendors in development vs GMP manufacturing?
- Phenol as a preservative – guidance asks for justification as to why the recommended level of the preservative is being used.

Question: How to choose surfactants? Polysorbate 80 vs 20 vs poloxamer 188? Each has its own issues

- Selection of Poly 20/80 may be determined through formulation screening or platform formulation
- PS20 and 80 are prone to degradation, regulators are aware of degradation, how to establish a control strategy for the surfactant?
- Published an industry consortium paper on polysorbate in 2018. (Considerations for the Use of Polysorbates in Biopharmaceuticals, Research Paper, Pharmaceutical Research, Published: 24 May 2018, Volume 35, article number 148, (2018)
- Significant degradation but no impact on CQA – monitor and supplement with end of shelf-life agitation study (degraded material is still surface active to demonstrate functionality)
- PS20 typically more problematic – when degradation occurs, more poorly soluble fatty acids and therefore particles are formed
- If significant degradation, PS80 is less risky to use, provided functionality is satisfied for the active molecule. PS80 is more oxidation prone
- Poloxamer 188 isnt as protective against interactions with Si oil in syringes or cartridges.
- Safety profile for different surfactants – PS20 or 80 have been very widely used.

General consensus that surfactant is needed beyond manufacturing and during shelf life. How do you put it on specification? Maybe required for release but not for stability? Process control like level of HCPs may impact degradation profile of polysorbates.

What level of degradation is acceptable? Put a justification as to why your product specific development history makes sense e.g. degradation levels are what they are but it doesn't impact product CQAs – clarity upfront in a reg submission will help get feedback on whether the strategy is acceptable. Earlier the better

Some countries consider release and shelf life as the same, so might need wider specifications to accommodate degradation over time

Health authorities ask for at least DP release testing. Stability testing is case by case. EMA challenged sponsor to test polysorbate at DS, but pushed back by claiming testing at DP to demonstrate consistency and was deemed acceptable

Recommendation is to collect polysorbate data during early phase stability studies. Methods for polysorbate measurement have low LOQ and sensitivity. With platform approaches of purification, lipase levels might vary and therefore is important to monitor polysorbate levels

closely. Lipase activity assays can help during development for characterization of the product and process

Platform formulation is hard to justify as polysorbate degradation is related to process and API and not excipients in the formulation

Oxidation due to peroxides, exposure to light and oxygen, and copurification of lipases causing enzymatic degradation are major polysorbate degradation pathways.

Polysorbate degradation might raise questions of patient safety, therefore monitoring through duration of shelf life would be considered necessary

Modelling is being considered as supplemental to real time stability monitoring, get feedback from health authorities as to what is acceptable

Polysorbate degradation – main concern is subvisible and visible particles that impact CQAs. Typically, high conc formulations are more prone to particle generation, but lower conc are more prone to oxidation. Identifying root cause is important to mitigate risk and develop a control strategy. A whole toolbox of assays required for this purpose.

With autoinjectors and higher conc formulation there seems to be an increased scrutiny on polysorbate degradation. FDA seems to be asking sponsors to do additional testing

Different countries have different requirements. In a lot of markets, it’s a checkbox exercise. Major markets FDA, EMA, Japan can typically reach an agreement based on data and scientific justification. Others like China require compliance with Chinese pharmacopoeia excipients and every single requirement must be met.