Roundtable Session 2 – Table 2 – CMC Challenges with Complex Formulations

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Abstract:

Developing complex drug formulations involves addressing several key challenges to meet regulatory standards. These include selecting excipients that complement the active ingredient, minimizing degradation to extend shelf life, and validating manufacturing processes to ensure consistent quality. Additionally, robust control and characterization strategies are essential to maintain product integrity during process changes, safeguarding quality, safety, and efficacy. Overcoming these CMC hurdles is crucial for successful formulation development, enabling manufacturers to deliver effective and safe medicines to patients.

Discussion Questions:

- What are the critical challenges in selecting the appropriate excipients (ex. surfactant) for complex drug formulations, considering factors such as compatibility, stability, functionality, and regulatory requirements?
- Which surfactants are most commonly used in pharmaceutical formulations, and what factors make them the preferred choice? Are they 'perfect'?
- If surfactant degradation is unavoidable, how can a comprehensive control strategy be established to manage the interactions and stability of both the surfactant and the protein? What measures can be implemented to mitigate and monitor the impact of degradation?
- Is the degradation of surfactants in a formulation acceptable, and if so, to what extent can it be tolerated without compromising the stability, quality, or efficacy of the product?
- What are the regulatory expectations/ Regulatory frameworks for excipients in pharmaceutical formulations to guide towards decisions?

Notes:

1) LNP/mRNA

Nanomedicine, nanoparticles in general, anticancer research, small molecules, peptides, etc, RNA. Current work is for RNA, LNP, for formulation development is to select the combination of lipids, biophysical characterization to meet CQAs and in cell assays and animal testing. Flow Cytometry and LCMS is a tool to use for LNP potency/characterization as well as PCR for mRNA expression. In the EU to release a batch, there are 3 aspects for char integrity of RNA (CD/LCMS), encapsulation efficacity and the dose of mRNA. Expression of mRNA can be PCR based and there are targeted approaches to load LNP with multiple mRNA to treat multiple conditions in singular treatment. Personalize medicine.

2) Polysorbate 20, Polysorbate 80 and Poloxamer

We know that we need the excipients, PS80 and PS20, P188, and the reason we choose them but we know they have limitations and issues.

No issue with poloxamer, in the past when moving from IV administration to subcutaneous administration, increase in protein concentration and had to pivot to poloxamer due to particulate precipitation on stability.

It worked for the product, however poloxamer is a difficult product to work with and not all are created equal.

P188, from different vendors, lots etc can vary. During raw material testing, there can be completely different elution pattern on the same method. Sometimes it is seen to be more hydrophilic or more hydrophobic. Can others comment on incoming ID or raw material testing when selecting a poloxamer?

Similar issues/challenges, even with PS80 or PS20, where they see differences from vendor to vendor and even same vendor with lot-to-lot variation. Does this lead to the creation of a BCR for PS80? How would that be impacted by process changes?

Not that a BCR would be beneficial but leaning into prior knowledge and possibility a platform formulation. In the early stages you can perform a quick screening to see, PS20, PS80, etc but it can be difficult to find the right concentration and form. As development continues and degradation becomes an issue, it is possible that the wrong form and/or concentration were chosen. One example was selecting PS20 only to have degradation issues where after investigating it was determined that poloxamer at higher concentration would have been better.

We know that PS20/PS80 are prone to degradation, be it enzymatic or oxidation but they are very well known for literature and the regulators.

If well known to have degradation issues, and in literature, we have the rationale not to perform degradation studies to characterize the PS20/PS80 etc. If we can delineate the degradation from literature, do we need to put the reagent on stability or only our product. Particles would indicate degradation, and the worst case is the degradation of the excipient impacts the product and your CQAs reflect that.

Degradation studies – forced degradation conditions.
Agitation, drop shocks, transport, at the end of shelf life as part of characterization.
Agitation (oxidation) as part of forced degradation

If your CQAs are not showing degradation over your stability program, do you need to test the excipient on stability? One approach is if you do not see any molecular indication that it is degrading over time, why would you need to demonstrate the excipient is or isn't degrading within the same stability. Is it expected from regulatory

agencies? If you have cases where you know it is degrading, include it on stability and then it would be an expectation to report.

Recently, there has been more feedback from regulators asking for data for proof that the excipient is not degrading. The FDA at various conferences have been vocal about testing it.

We know what the byproducts of the excipients are, they are not toxic or potent to patients. If that is the case, why are regulators chasing this if end of shelf life is not a problem, then the stability of the excipient is not a problem.

Possible reasons: The appearance of particulates (visible particulates), but that should show within product stability and knowing the root cause and controlling that root cause is desirable. Another reason could be the need to demonstrate the amount of excipient you have in your formulation at the end of shelf life is still sufficient to prevent degradation.

Goes back to if you can prove that the level of excipients you have because it needs to be there for stability. As part of a control strategy, testing homogeneity of product during PPQ lots. Others test routinely, filter binding studies, how much to pass over, filter flush volumes, reduction due to filter binding, filter material, etc.

When we don't see visible or non-visible particles with stability testing of product and no increase in high molecular species what is needed from an excipient's stability standpoint.

It is felt the agencies are concerned about this because there have been products that have all a sudden shown an increase in particulates or some visible particulates. I think they are focused on ensuring drug supply and if there is an increase in visible particulates what is the impact to patients.

Looking into root causes for the degradation, what happened, like with the pre fatty acid. If you have degradation, can you control it? Do you have a method to control, monitor or measure degradation because eventually you can get particles and then you have safety concerns.

Strategy
HCP strategy, downstream and upstream (product quality is fine) at the DS level an in process control. Formulating DS with PS before DP. We go to phase 3 batches and check, they want to put limits at the DS level or in process control to show that it isn't increasing (lipases) Lipase A, or other enzymes. They have agreed with FDA to demonstrate with an assay the reduction by ELISA or other another platform.

It is on characterization but possibly not on release, controlling it so it doesn't get worse. It is a cell line and purification issue not a batch-to-batch issue.

When you talk about controlling for it in the increase of DP concentration (pro A binding or clarification step IEX.CEX) seen improvement form impresa. They have looked at every step of the process to review whether it is a wash etc. Show correlation of the excipient and you use one DS to make one DP and follow it. In the round table yesterday, they had a lot of health authority experience, be open and have a discussion on the issues.

We are indirectly controlling the other CQAs and show all the clinical data and show that they are all fine. Try to ensure that the raw material is same quality from lot to lot, enzyme activity assays, monitoring it but if they see that the activity is below a threshold that is a concern. PS80 degradation and change the parameters downstream to control.

PS 20 is worse than PS 80 in formation of lipases. Increase concentration and if you create fatty acid then the PS20 will keep it soluble.

Price/Concentration is a concern. 0.1 v/v% is the upper end for PS20 or PS80 and tend to keep it the same regardless of the protein concentration. It is a quick and dirty experiment and a screening. FIH you are open to all 3 of them. Some companies have a preferred formulation, and then you must justify why you move away from that preferred formulation.

Build a lot of knowledge for one asset and then as they build, they expand they evaluate all 3 of them. If starting again start looking at them earlier in the process, now they have LLOQ that is good, and you can follow the degradation much closer. They look at the PS to when it degradants to all the species and you have the fast, mid and slow ones. And it is the slow species because they do not go to zero, it is still protecting at various stability.

Experiment: PS20, PS80 and 0.1v/v% max and 0.01v/v% lower end and for poloxamer up to 2%. Compare different concentration and different pH and then determine the surfactant that you selected. 40 c for 3 months, agitation study.

The primary issue many have is that poloxamers are variable, lot to lot, as well as difficult to manage and more costly. You are also using it at a higher percentage than PS20/PS80.

Other excipients.
What if the formulation you get is 20 years old or older and you have excipients that you have never used in the past.

EDTA, DPTA

If it was old technology and stable, can you use as justification. Issue now is knowing that these are metal chelator as well as citrate formulations. Just in a talk today they lean to not using citrate and pivoting towards histidine. Which is also a chelator

No surfactant in the product but is heavily Pegylated. Heavy pegylated as terrible for MS assay and they have to go to MALID-TOF and it is buffer free, PBS, so stable the only degradation is a little bit of free PEG and no control of PEGylation and it was in line with previous but they do not have any way to say only this or that one

Formulation study on a mAb, get to know that oxidation can be provided for serval expectants, guanidine. They did a lot of analysis on the onset of degradation (SEC with light scatter), it looks for worse, but the lcms were good. Certain protein is more stable at a set temperature. Others do not use that technology and lcms are bad for determining aggregates. You want to go beyond the limits of detection and max out the instruments and the lcms can detect dimer information and quantification. It is very poor for anything larger than dimer and the quant between the monomer and dimer without chromatography would be difficult. There would be an overlap and the ion potential. SEC HPLC is good for that. Started using the HPLC for the pegylated, maxed out he cap LCMS

Don't reinvent the wheel!

Product characteristics, not from development or release, may be an investigation. When new technology comes, and this is the next thing but…. Are we going to get an inquiry from Pharma that this will be part of the test.

Huge increase in high MW species, significant increase in dimer and we can control it. But anything about that, dimer and charge variance can destroy your molecule. Predictive stability.

You hope to never have that impact, typically potency doesn't change significantly that quickly. Lyophilized it. Is the problem your molecule or your assay…. naturally to point to the assay. You put crap in you get crap out, had to go and recreate a potency assay CDR impacts the binding, oxidation you also see peptide maps, if an MOS enabling CDR however when seeing your % potency is failing at release and passing at 3M. Generally, potency will drop.

Full characterization we would do that some earlier, are these impurities potent at all. Within potency assay or another platform. Was the tryptophan oxidation on release…. absolutely. Just because you have tryptophan on CDR doesn't mean you have oxidation, and you can show that it doesn't change significantly, and it isn't on control

<u>Wrap up / Take home message</u>

Excipients (PS20/PS80/Poloxamer) should be on stability, but if you have knowledge maybe you should lean on that. Do not go to regulatory with a "shopping list", go with a "narrative"

Once you tell them the story, if they need it they will ask. With that inquiry continue the dialogue….I know you want this, but we didn't see this, we did this and this is why.

If they are asking for it, are they asking for it because others are giving it to them. As an industry, we must be careful what we are giving regulators, if it isn't needed. If we do not believe we need it, we need to justify that.