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Influence of formulation and lyophilization process variations on protein aggregation and chemical degradation: Impact of scale up

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Statement of the Problem: Currently nearly half of the therapeutic proteins are freeze dried but the freeze-drying does not guarantee stability partly because the product temperature during a freeze drying cycle cannot be directly controlled. Variations in product temperature can significantly impact the product Critical Quality Attributes (CQAs), even for bio-similars having the similar formulations. Therefore, a better understanding of product temperature variations and their impact on meaningful CQAs will enable development of sampling strategies to better assess the influence of distribution in CQAs like protein chemical degradation and aggregation on the probability of releasing out of specification product.

Methodology & Theoretical Orientation: Currently, we are evaluating the variations in CQAs related to protein degradation by: (1) Assessing the variations in key physical properties like phase composition (i.e. phase separation and crystallinity), specific surface area, and glass transition temperature (Tg) in the product vials, as well as levels of product degradation. Attempts are being made to identify the physical properties that are predictive of chemical degradation and aggregation and (2) quantify the position-dependent differences in product temperature history caused by differences in vial heat transfer coefficient (Kv) and assess whether or not these differences are likely to cause differences in stability, particularly aggregation (which can potentially generate adverse immune response).

Results: Preliminary results indicate that temperature history differences due to variations in Kv are not likely to result in significant differences in stability. Significant intra-batch variations in ice nucleation temperature result in modest variations in specific surface area with possible stability consequences, but current results indicate a large difference in ice nucleation temperature between laboratory and manufacturing with likely adverse stability consequences.

Conclusion: Although, the current research focuses on proteins, the general scale-up technology will also apply to generics and vaccine products. An understanding of these variations in CQAs will reduce the probability of releasing out-of-specification product.

Biography

Paritosh Pande is a Research Scientist focusing on formulation and lyo cycle development at IMA Life North America Inc. As a Postdoctoral Fellow at Prof. Mike Pikal's lab at the School of Pharmacy at the University of Connecticut, he investigated the influence of formulation and lyo process on aggregation and degradation of therapeutic and recombinant proteins. He is the author of more than ten original research articles, he has been invited as reviewer for journal manuscripts and fellowship applications for American Chemical Society and Royal Society of Chemistry and is the current Chair of 2019 Gordon Research Seminar on Nucleoside, Nucleotides and Oligonucleotides.

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