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Scientific and regulatory considerations on manufacturing, process and controls of complex liposomal drug products

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Liposomes are lipid bilayer vesicles that can encapsulate both hydrophilic and lipophilic drugs to protect them from degradation. Liposome-encapsulated drugs have multiple advantages over their non-encapsulated counterparts, including improved pharmacokinetics, selective targeting, reduced side effects and controlled drug release. Ever since their discovery in the mid-1960s, liposomes have been a subject of extensive studies for drug delivery and have been considered to be the most successful nano-carriers for drug deliver. The intense interest in this area has also translated into an increasing number of Investigational New Drug (IND) applications, New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs) for liposomal drug products to the United States Food and Drug Administration (FDA). Currently the FDA has received over 400 liposomal drug product submissions and there are eight FDA-approved liposomal drug products on the US market. While subjected to the same regulatory pathways and the same rigorous regulatory standards as typical drug products approved by FDA, the unique physical and chemical complexity of liposomal drug product may lead to additional scientific and regulatory considerations. In this presentation, we will discuss the current regulatory expectations for complex liposomal drug products including relevant FDA's current guidance, application of Quality by Design principle in liposomal drug product development, physicochemical characterization and commercial manufacturing of liposomal drug products. In addition, some common CMC deficiencies that are relevant to liposomal drug product manufacturing processes will also be discussed.

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Computational model prediction to augment antidepressant efficacy in depressed patients

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Statement of the Problem: Major depressive disorder is prevalent and debilitating and current pharmacological interventions are far from effective. The clinically observed heterogeneity in antidepressant response is not well understood.

Methodology: We present a computational model that represents the antidepressant response to predict novel drug combinations with potentially greater efficacy than currently available treatment options. The model includes the interactions between the monoamine producing brain regions and three non-monoaminergic neurotransmitter systems and simulates homeostatic adaptation to chronic antidepressant administration by adjusting the strengths of eleven receptors that are known to adjust under chronic antidepressant. The model has many ways to adapt to chronic antidepressant and different adapted states are associated with different levels of monoamine production.

Findings: In terms of the percentage of adapted states with therapeutically elevated monoamines, our model agrees closely with the clinically-observed efficacies of 12 antidepressant drugs and combinations, including the low efficacy of selective serotonin reuptake inhibitors (SSRIs; clinical efficacy 25-50%, model 29%). The model also predicts that augmenting SSRIs with Pexacerfont (Pex, a corticotropin releasing factor-1 receptor antagonist), can enhance therapeutic efficacy over SSRI alone by both increasing the percentage of adapted configurations with therapeutic serotonin levels (from 29% with SSRI to 31% with SSRI/Pex) and with elevated dopamine levels (from 0% SSRI to 100% SSRI/Pex).

Conclusion & Significance: The model provides a potential explanation for the heterogeneity in antidepressant response, that the brain can reach similar levels of adaptation in many ways, but not all adapted configurations are associated with therapeutic monoamine levels.

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