PhD in Chemical Engineering

Research Title: Freeze drying of pharmaceuticals: QbD, control and design strategies for development, scale-up from R&D scale to full production level

Funded by	Merck Serono SpA

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Context of the research activity	Merck-Guidonia site is center of excellence for the development of new biological entities (NBEs) and new chemical entities (NCEs) with the purpose to contribute to patient's health. Drug Products (DP) can be delivered as liquid or freeze-dried presentation. Usually the last one is the option preferred when the DP is unstable in the liquid state. The aim of this PhD program, in collaboration with Merck, is to develop a control and design strategy which can be applied to develop freeze-dried presentation of protein based formulations, ensuring a successful scale up from the lab/pilot scale to manufacturing scale, according to the Quality by design approach (QbD). Quality by Design in development and scale-up of Freeze-Dried parenteral products is a new regulatory philosophy aimed to facilitate continuous process improvements and make process robust, thus to reduce amount of work for post-approval change and deviation that can occur during routinely manufacturing operations. During this PhD program it will be investigated how formulations and processes interact to influence critical quality attributes of pharmaceutical products. As per ICH Q9, a risk assessment will be performed to gauge the impact of the lyophilization process parameters on process performance and

	product quality attributes. After the identification of the potential critical process parameters via risk assessment, several studies will be carried out to develop a lyophilization cycle starting from the thermal characterization (i.e. DSC, FDM). Equipment characterization will be considered part of this project to successfully support technology transfer of new freeze-dried cycle from laboratory to Pilot and, lastly, to manufacturing scale. Outcome of the development activities will be also the definition of design space or new innovative approach, propaedeutic to investigate the robustness of freeze-drying cycle. Process analytical Technology (PAT) tools will be promoted to monitor the lyophilization process through in-line measurements, with the goal to improve process knowledge and to ensures consistency between final product and freeze-drying process.

Objectives	**Objective 1.** Application of QbD principles as described in ICH8 and ICH9 in the development of lyophilized formulation at lab scale. o Excipients screening by DoE (conventional and innovative excipients) o Risk management methods and tools application (e.g. FMECA / FTA) o Investigation of the impact of different primary packaging components (vials and stoppers) o Thermal Characterization of the locked formulations (DSC-FDM) o Development of mathematical model o Lyophilization trials and design space determination o Explore controlled nucleation on small scale to reduce lyo-process duration and minimize intra-batch variability **Objective 2.** Fine-tuning of lyo-recipe on Pilot scale o Replicate thermal history of lab scale to pilot plant o Compare results to identify scaling parameters o Verify lyo-cycle robustness o Implementation of innovative PAT tools for pilot scale o H_2O_2 impact evaluation on freeze-dried process **Objective 3.** Develop a strategy for successful technology transfer of lyo recipe from Pilot scale to Manufacturing scale o Equipment characterization at large scale (Kv or innovative approach) o Identify scaling parameters o Validate the resultant parameters in full scale equipment (engineering run or validation batches)

Skills and competencies for the development of the activity	- Chemical engineering background - Knowledge of DSC and FDM, KF - SEM and DVS, X-Ray, Microsoft office, DoE basic knowledge - Flexible to implement other analytical techniques (HPLC) - Knowledge of statistical tools - Literature scouting - Protocol and report issuing