Purpose and objective:
This course will highlight the fundamental aspects of crystallization by relating the crystal product quality aspect such as solid form, morphology, crystal size distribution and purity to the processes of nucleation and crystal growth.

Industrial crystallizations are performed on a scale from 1 to multiple cubic meters. The crystalline product from such processes usually has a size of around 1 to 1000 micrometers. The building blocks (molecules, atoms, complexes, proteins) have very specific orientations and positions within the crystal structure of these crystals. Crystal growth typically proceeds by the incorporation of building blocks at kinks of steps on crystal surfaces. So, although crystallization is performed in industrial scales it remains a molecular level process.

An important advantage of crystallization compared to other separation techniques is that generally high purities (>99.9%) can be obtained in a single process step. A crystallization process furthermore results in a particulate product which usually is easy to handle, store, transport and apply. Product quality aspects of a crystalline material such as dissolution rate, stability, taste and colour generally can be related to Solid Form, Crystal Size Distribution, Crystal Shape and Purity. The crystal product quality is in turn determined by the subsequent processes taking place during crystallization: Supersaturation generation, Nucleation, Crystal Growth, Secondary Nucleation and Agglomeration.

Crystallization is a complex collection of processes and fundamental knowledge on the molecular processes that take place during crystallization is needed to come to an optimal crystallization process design or optimal crystalline product quality. Moreover, each compound has different crystallization behaviour resulting from among others the
crystal structure of the solid phase. The crystallization process design is therefore compound specific.

Classical Nucleation Theory is based on sequences of molecular collisions in a supersaturated fluid, which result in the formation of clusters of molecules that may or may not achieve thermodynamic stability. This is referred to as homogeneous primary nucleation. Most primary nucleation in industrial crystallization processes is heterogeneous rather than homogeneous. Heterogeneous nucleation is induced by foreign solid particles that are invariably present in working solutions. Secondary nucleation takes place only if crystals are already present and can have a profound influence on product quality from industrial crystallization processes.

Crystal growth is a two-step process involving mass transport, either by diffusion or convection from the bulk solution to the crystal face, followed by an integration in the lattice of the building units at the crystal surface. Either step may control the overall growth process while several integration mechanisms may play a role, depending on the character of the crystal surface, temperature and the supersaturation.

A theoretical description of both nucleation and growth will be given in the lectures. These processes will be discussed in respect to the prevailing driving force, solution speciation and integration kinetics. The relation between these and the crystal product quality will be exemplified.

**Who should attend:** the workshop is dedicated to PhD students, researchers and industrialists, who are interested in the theory of the fundamental processes involved in crystallization and want to deepen their knowledge.