It is a well-known fact that F&T negatively impacts product quantity and quality. In respect of the marketing of large volumes of protein bulk drug substance (BD), F&T processes have become essential for safe storage and distribution. The total production capacity can be improved to its maximum by means of optimised F&T processing. This is a guarantee for safe global distribution. Safe storage of deep frozen high value proteins minimises the possibility of microbial growth. However, the risk of freeze-induced aggregation, caused by cryoconcentration, crystallisation of solutes or buffer salts, pH changes, and ice-water interface-induced denaturation, influences the success with this unit operation. Freezing reduces risks from mechanical stress during transport and extends stability of valued APIs. Safe storage of deep frozen high value proteins increases the product loss up to a certain point; freezing conditions; increasing the rate of freezing mainly decreases the product loss up to the time point purification. Setting-up a mechanistic process design for F&T increases the product quality and serves the QbD approach. Regarding effects on quality, safety, and efficacy of the finished product are arising with special respect to product quality risk. The F&T process may cause significant product loss. Mechanical stress and phase interaction may even overlay these effects. Negative impacts on product quality offer little for each formulation, thus proper understanding of dependencies are essential!

They conclude that:
- There is a need to define ‘fast’ and ‘slow’ freezing conditions.
- Increasing the rate of freezing usually decreases the product loss up to the time point purification.
- The freezing-induced aggregation, caused by cryoconcentration, crystallisation of solutes or buffer salts, pH changes, and ice-water interface-induced denaturation, influences the success with this unit operation.
- Systematic knowledge-based freezing process for each individual formulation is a must for meeting the QbD approach. There is the need to correlate protein and product analysis all parameters carefully to avoid freezing-induced quality losses.

ZETA Business Activities
- Biomanufacturing 
- Downstream Systems
- Preparation Systems
- Crystallisation Systems
- Magnetic Agitators
- Freeze & Thaw Systems
- Engineering
- Automation

Customer Benefits
- Deep process understanding
- GMP FDA Compliance
- Super-Skid Designs
- Focus on stability
- High process reliability
- Scale-up capabilities
- Experience in complex biologies
- Customised process systems

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Biopharmaceutical Proteins are usually most stable in frozen form. Therefore, freezing and thawing (F&T) is an important step to stabilize the product drug before fill-and-finish for storage and transportation. Debates regarding effects on quality, safety, and efficacy of the finished product are arising with special respect to product quality risk. The F&T process may cause significant product loss. Mechanical stress and phase interaction may even overlay these effects. Negative impacts on product quality offer little for each formulation, thus proper understanding of dependencies are essential! Setting up a mechanistic process design for F&T increases the product quality and serves the QbD approach. Literature bodies such as USP/EP require details of the F&T cycles for product registration.

Advantages for the customer:
- Best in practice risk control
- Best in process product quality
- Reduction of product losses

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STARTER SET

Find suitable formulation buffer for F&T

STARTING-POINT:
- The product formulation is not finalized.
- There is the need to find a suitable formulation buffer for freezing & thawing.

STRATEGY:
The starter service includes F&T studies with a previously determined number of test runs and analysis methods to identify the buffer conditions at various freezing ramps and freezing temperatures.

BENEFITS OF THE FREEZE SERVICES:
- Test runs in a small scale are best suited for identifying the buffer behavior in F&T cycles. The best buffer composition can then be specified as a result.

INTERMEDIATE SERVICES

Develop knowledge on basic product behavior during F&T in formulation buffer

STARTING-POINT:
- The product formulation is finalized, but the freezing process is still unknown.
- There is a need to develop knowledge on basic product behavior during F&T in formulation buffer.

STRATEGY:
The intermediate services offer scientifically approved methods in order to investigate F&T processes with respect to freezing temperatures and F&T ramps. The target is to determine the best homogenous freezing scenario.

BENEFITS OF THE FREEZE SERVICES:
- The systematic process analysis provides knowledge about product behavior during F&T cycles. The best buffer composition can then be specified as a result.

ADVANCED SERVICES

F&T process optimization and scale-up

STARTING-POINT:
- The product formulation buffer is finalized and the F&T process is known.
- There is a need to optimize F&T process and develop scale-up.

STRATEGY:
The advanced services provide the definition of a 3D F&T process. The target is to define scale-up and process parameter for technology transfer to any scale.

BENEFITS OF THE FREEZE SERVICES:
- A 3D system provides systematic and holistic process understanding. Results of the F&T cycles are valid process data and transferable to any scale.