Understanding Process Safety – Milligram to Tonnage Scale

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Speed to market plays an important role in the success of pharmaceutical organizations and a great deal of efforts are expended to meet desired timelines. Traditionally, the probability of a scale up of a medicinal chemistry route *as is* for a New Chemical Entity (NCE) is low. Most often, a lot of time and resources are directed to develop and optimize a scalable route. In the process, scalability factors and associated risks of the proposed route undergo assessments without compromising its process safety (1).

Typically, alternative routes are evaluated in parallel, where factors such as the commercial availability of raw materials and reduction in the number of synthetic steps with improved yields to control the cost are given prime consideration. However, it is difficult to predict safety hazards for alternate routes since most of the intermediates are novel with scarce information on its physical and chemical properties. Hence, during process development, it is imperative to do a safety assessment to identify potential hazards and operational problems. An assessment is carried through a systematic and efficient investigation that can explain the probabilities and consequences in what might go wrong, during execution.

Of the various important factors that contribute to the successful scale up of a chemical process, it is pivotal to have a robust understanding of the exothermicity of a reaction and its subsequent control. For a new process that moves from the medicinal chemistry lab to a larger scale, a detailed and in-depth safety study should be completed to understand the requirements with regards to the proper handling of a reaction.

Thermal stability studies provide reaction rate data that will be helpful in assessing the conditions of safe handling of materials to avoid runaway reactions. This is important when considering processing, long-term storage, or shipping of a material.

A variety of instruments and tools can be used to characterize the thermal stability of a material such as:

- Differential Scanning Calorimetry (DSC)
- Thermogravimetric Analysis (TGA)
- Advanced Reactive Systems Screening Tool (ARSST)
- Accelerating Rate Calorimetry (ARC)

In general, a process should be operated at 100°C below the onset of a DSC exotherm in order to maintain safe operating conditions on a typical plant scale. Otherwise, further stability testing is required such as the Fall Hammer test and Carius Tube test to ensure that a safe process is developed and transferred to the plant for further scale up.

At the conceptual stage, the following data are gathered and evaluated:

- Proposed equipment's and process flow diagram
- Animal and human toxicology
- Occupational Exposure Limits (OELs)
- Reactivity and stability
- Explosion severity
- Minimum explosive concentration
- Ignition temperature
- Minimum ignition energy

Small-scale laboratory experiments use conventional glassware's (such as round bottom flasks) that suffer from an inability to indicate the release of gases or vapours which may be toxic or flammable. The heat evolved during the reaction is often unnoticed as it may be too small to observe or may get absorbed by the surroundings as it is relatively small scale. Hence, the need for lab experiments to be scaled up in a kilo lab before a commercial scale arises.

Further, laboratory grade chemicals are used for initial screening rather than bulk commercial chemicals.

The presence of unknown impurities in bulk chemicals can lead to unexpected challenges and can be understood only after the batches are executed in pilot scale. Review of the literature presents instances where impurities in traces have been known to catalyse undesirable reactions due to thermal instability (2-4). At the development stage, data collected from the conceptual stage is thoroughly assessed to evaluate and decide the equipment suitability, and mitigation measures needed to ensure safety of the people and assets. These evaluations are crucial to finalize the process design and the operational procedures, which are then captured in batch records, ensuring operational controls are in place.

For implementing an effective process from milligram level to tonnage level, exhaustive information needs to be gathered from the Kilo Lab trials. The identified risks need to be studied before proceeding for a commercial batch.

a) Reactor material of construction challenges, if any.
b) Operational challenges
c) Materials handling and sampling problems
d) Thermal instability and other decomposition phase problems
e) Effluent and waste disposal procedures

Therefore, it is critical that the reactions are well-understood by safety studies for eventual scale-up during production. An in-depth scientific study of the risks associated with pharmaceutical manufacturing operations can thus be mitigated. It is highly recommended to perform appropriate risk assessments and introduce process controls, necessary protective and preventive measures for novel reactions taken forward from lab to commercial scale manufacturing. This will not only ensure safety compliance but also avoid disruptions, cost overruns, potential damage and injuries due to run away reactions in the product life-cycle.

References

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