An Executive Summary

Contributions of Chemical Engineers and Process Engineering Laboratories to Chemical Process Development

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Process engineering laboratories can work with chemists before pilot-plant activity to save time and improve the quality of chemical process development.

Introduction

In today's competitive drug development and manufacturing environment, no one can afford to take unnecessary risks or to waste valuable time, money, or resources. With the integration of highly skilled engineers and a process engineering laboratory, an approach to process design and development can be implemented to improve product quality, accelerate timelines, and support "right the first time" technology transfer to commercial-scale production. The key elements of such an approach include quality-by-design (QbD) principles, design-of-experiments (DoE) approaches, the development of a risk mitigation strategy to guide process development, and design and engineering of process controls at commercial scale.

Chemical Engineering Brings Value to Process Development

The contributions of process engineers and process engineering laboratories are critical for process development through an enhanced QbD approach. For such an approach to be successful, three fundamental requirements must be fulfilled: understanding of the quality target product profile based on prior knowledge; determination of critical quality attributes (CQAs); and design, implementation, and optimization of the manufacturing process (**Figure 1**).

The goals of process development are to develop a safe and robust scalable process, implement engineering controls to ensure quality, optimize each synthetic transformation, demonstrate the chemistry on scale, transfer the technology to manufacturing, evaluate process efficiency, and provide active ingredient for clinical trials.

During the development of a new chemical entity, process development requires a significant amount of time (see **Figure 2**). When an agent is selected for development, it must undergo extensive clinical testing to assess its safety, efficacy, and tolerability. This testing typically occurs over a period of five to seven years and is characterized by a high rate of failure. Only approximately 10% of all agents that enter development actually become marketed drugs.

One challenge of early drug development is that work must progress in an expedient manner as greater supply is needed (from R&D lab to kilo lab to pilot plant to manufacturing), but developers are still researching practical chemical routes and procedures. With batch processing, engineers and the chemists must also investigate whether equipment used for small batches can also be used on a larger scale with some modification. Another challenge is when expensive starting materials are used, and not much sample may be available for testing purposes.

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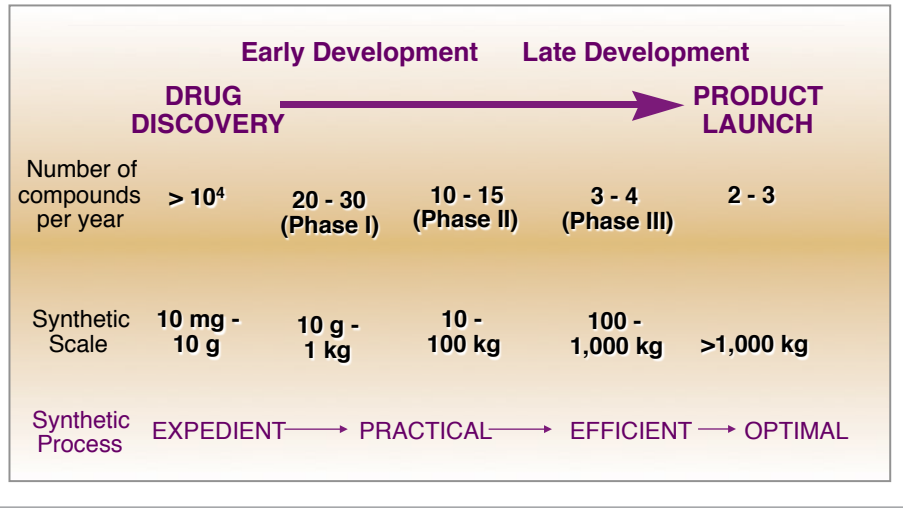
Figure 1: QbD approach: Q8 (R2) and Q11.

Figure 2: Phases of development.



The efficiency of process development (i.e., process intensity) can be measured in several ways such as the number of synthetic transformations, number of process steps, process intensity, suitability to existing equipment, availability/cost of starting materials/reagents, and waste generation. Each chemical step is important, and the fewer the steps, the more efficient the process.

From a chemical engineering point of view, the following key areas are important to pharmaceutical development: reaction engineering, separation and purification, particle engineering, process analytical technology, pharmaceutical engineering, and process hazards evaluation. Reaction engineering laboratories perform reaction kinetics and mechanistic analysis; scale-up diagnostics and troubleshooting; catalyst screening and characterization for hydrogenation; reactor design for productivity, quality, and safety improvement; and process intensification with microreactors and minireactors.

Many times, even before a chemistry is fully developed, chromatography or more specifically process chromatography is used for making materials in early-stage development. Separation and purification laboratories solve challenging issues in process chromatography, membrane, extraction, adsorption, filtration and drying; expedite material delivery for timeline reduction; and design scale-down studies and collect fundamental data. Particle and pharmaceutical engineering can solve complex crystallization issues, generate intrinsic process knowledge, work on designer particles for novel formulations and nanoparticles for drug delivery, and collect fundamental characterization data.

Meanwhile, the process hazards evaluation laboratory focuses on reaction calorimetry and material stability, as well as materials compatibility testing.

Infrastructure and Capabilities of Process Engineering Laboratory

To address, improve, and accelerate process design, the Neuland Laboratories process engineering laboratory has three components: QbD (robust and scalable process development), process safety, and particle engineering.

Throughout the R&D process, teams of qualified scientists and engineers apply the principles of QbD and DOE in the

laboratory. Chemists and chemical engineers work closely together during process development at R&D. DOE studies are performed for all critical reactions and crystallizations using DOE software to ensure that the processes developed are rugged and reproducible at larger scales. An impact assessment is done for critical process parameters on critical quality attributes for different unit processes (reactions) and unit operations (powder processing). Laboratory process qualification/validations are done in cylindrical vessels by mimicking the process in plant-scale equipment set-up. This is done to ensure success at large scale and to avoid surprises during scale-up due to variations in mixing profile from spherical to cylindrical vessels and changing the time, temperature, scales, and other attributes.

The objective of the process safety laboratory is to assess hazards and to suggest engineering controls to develop inherently safer process technology. The approach adopted includes desk screening, thermal studies, hazards studies, and powder safety characterization studies.

Desk screening is a theoretical evaluation of hazards using CHETAH software and literature material safety data sheets, bond energies, or group contribution methods.

Thermal studies using a thermal screening unit (**Figure 3**) provide information regarding the effect of temperature change on reaction/distillation residue and other areas. Information is generated related to reaction initiation temperature, gas generation or pressure rise, and heat release on decomposition or reaction. Data obtained are useful for understanding the process criticalities and for designing the process control philosophies (operation parameters and hardware planning).

Hazards studies using a reaction calorimeter give information about process exothermicity (e.g., heat of reaction), adiabatic temperature rise, and gas generation rate (**Figure 4**). Powder safety characterization studies (e.g., minimum ignition energy, minimum ignition temperature, and powder resistivity) are currently outsourced to qualified laboratories. Data received are used for safer implementation of micronization and multimilling at plant scale.

Case Studies: Process Safety by QbD and Particle Engineering

Several case studies from Neuland illustrate these points.

Case study 1. The active pharmaceutical ingredient (API) of lacosamide was the subject of the first case study, which examined process safety and optimization using a QbD approach. The objective was to develop a safer process with optimized yield and quality for plant process validation (lacosamide). It was a two-stage *in situ* reaction: epichlorohydrin with water was reacted at high temperature to obtain the *in situ* diol, which, on oxidization using nitric acid at high temperature, will yield the desired compound of stage 1 of lacosamide. The approach included thermal and hazards studies for safety and process optimization using a QbD approach.

The old process (diol addition done from the top) at a reaction temperature of 90°C–95°C for 1.0–1.5 hours had a process yield of 27% w/w. There was limited control of gas release, and huge brown fumes seen at the plant were difficult to control. The modified process per DOE (nitric acid addition done from top) at 65°C–70°C for 4–6 hours had a laboratory average yield of 75% w/w. The optimized process was scaled up further to 20 kg (two batches) and 350 kg (three batches) input scale. The yield at the commercial scale of 350 kg ranged from 70% to 77% w/w with purity >90%.

Figure 3: Thermal screening unit.

- Onset of reaction with heat release
- Pressure or gas generated with thermal changes occurring during reaction or degradation.

Figure 4: Reaction calorimeter.

- Provides critical information: heat of reaction and adiabatic temperature rise, Overall heat transfer coefficients, gas release rate etc.
- Used for process development and optimization for plant scale up and safety studies

To conclude, the reaction in this case study fell in a highly exothermic category. The team implemented a semi-batch mode of addition instead of a batch mode. The reaction temperature was optimized at 55 °C to avoid the accumulation of energy and abrupt gas release.

Case study 2. The second case study illustrates particle engineering. The objective of the particle engineering lab is to develop the processes in the laboratory to meet particle size and bulk density of API according to the customer's need, by in process (crystallization) or post process (micronization/compaction). Neuland Laboratories aims to generate stability data of micronized API at laboratory scale and to assess the impact of micronization on stability. If required, corrective actions are planned to avoid stability failures by changing the micronization fluid from air to nitrogen or by changing packaging conditions.

In this case study, the objective was to generate macrocrystals during crystallization of nitrofurantoin. The experimental approach was crystallization process optimization using DOE methods with two variables: solvent volumes and cooling rate.

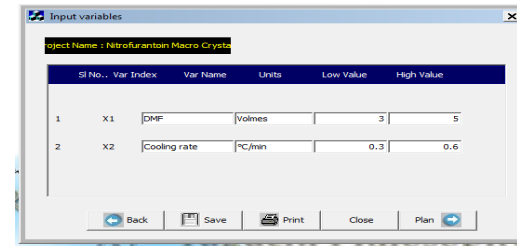
Figure 5: Optimization using by QbD: DoE approach, Part 1.

Variable entry

Response 1: PSD D5

Response 2: PSD D40

Response 3: PSD D80



Experimental plan

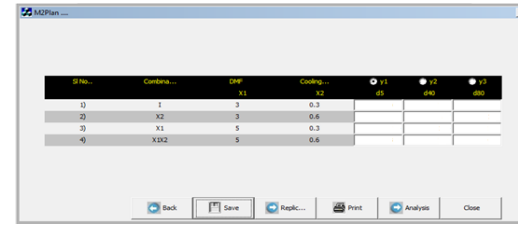
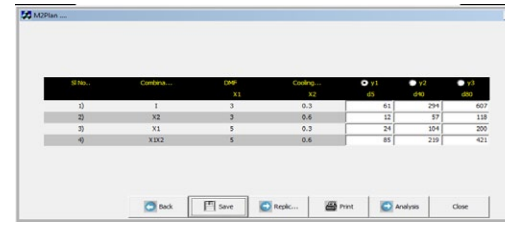
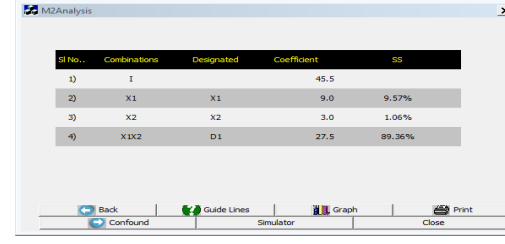


Figure 6: Optimization using by QbD: DoE approach, Part 2.

Entry of experimental results of Response 1 (PSD D5)



Cause Effect & Impact analysis



Based on Cause Effect and Impact analysis, the results of responses 1, 2, and 3 were the same. Percentage significance of interactions between variables were high. Hence, mid-point and second-level experiments were planned and conducted. The desired particle size distribution (PSD) was obtained with mid-point parameters. Size reduction to desired PSD was achieved using a jet mill. Products successfully delivered from the particle engineering laboratory to the plant by high-pressure jet milling included indacaterol maleate (target PSD D90 <5 µm), ticagrelor (target PSD D90 <10 µm), aripiprazole anhydrous (target PSD D90 <10 µm), and an anti-infective API (target PSD D90 NMT 150 µm) (see **Figures 5 and 6**).

Summary

Working together, there are many ways in which chemists and chemical engineers add value to process development by anticipating issues likely to be encountered during scale up and technology transfer. Their activities include studying the critical process parameters and CQAs of processes and unit operations to perform scale up and technology transfer correctly the first time; developing inherently safer process technology that can produce the API with consistent quality at a competitive cost and with an operationally friendly process; and avoiding surprises during scale up at manufacturing plants based on process qualification studies in cylindrical reactors.