White Paper

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# New Process Engineering Laboratory Combines Advanced Equipment, Risk Management Strategy, and Quality by Design Approach to Support "Right-at-First-Time" Technology Transfer to Commercial Scale

Dr. Ravi Ponnaiah, Shyam B Vispute, Srinivasarao Veedhi

# Introduction

At Neuland, process development begins in the R&D laboratory with the application of rigorous scientific and engineering tools and methodologies, using Quality by Design (QbD) principles, risk management strategies, and Design of Experiments (DoE) software to understand and control processes. Processes that operate in a defined design space will be more consistent, safer, and be less prone to deviations. QbD applied to process development and scale-up focuses on five main issues: safety, environment, health, quality, and economics. The goal is to develop a robust and reliable process and transfer it to the manufacturing plant to ensure that quality product is delivered to the customer every time.

Neuland has expanded its capabilities to support a QbD approach with its new Process Engineering (PE) Laboratory. Equipped with state-of-the-art instrumentation and automation, the PE Lab is staffed by highly qualified engineers and chemists who are trained in the best practices of QbD and DoE. The PE Lab utilizes two DoE software platforms: STAVEX from AICOS Technologies AG, and SigmaTech from Swaroop Tech Services. Based on experiments to identify the critical quality attributes (CQAs) of an active pharmaceutical ingredient (API) and the critical process parameters (CPPs), our scientists create a robust design space with flexibility built in to maximize accuracy and reproducibility on scale-up and transfer to a manufacturing facility. Process monitoring and trend data are collected, analyzed, and used to develop a strategy for continuous process control and improvement in close collaboration with our customers. The PE Lab also has provisions to assess the performance of processes in cylindrical reactors (using scale-down to mimic plant conditions). This can help avoid surprises when scaling up at the manufacturing plant due to potential differences when mixing in cylindrical reactors compared to round-bottomed flasks .

This white paper details the holistic QbD life cycle approach implemented at Neuland and how the new PE Lab supports this effort (See "Implementing a QbD Approach"). It describes how the Lab integrates risk management and process safety studies, particle engineering, QbD and DoE, and process validation/qualification to improve and accelerate process development, optimization, and scale-up to facilitate safe and efficient technology transfer from the laboratory to the manufacturing plant with a right-at-first-time approach. In addition, it speaks to continuous monitoring and the use of flow chemistry, and emphasizes the importance of proactive process improvement.

### *Implementing a QbD Approach*

Successful implementation of a QbD approach requires three fundamental elements:

- A clear understanding of the target product profile - drawn from the knowledge base around the product
- Determination of the CQAs, within an appropriate range limit or distribution to ensure the desired product quality, according to the ICH guideline governing the product
- Design, implementation, and optimization of a process to manufacture the product -- including risk assessment to evaluate the impact of raw material attributes and process parameters on the CQAs; development of an experimental method and design space (using DoE); and creation of a process control strategy that makes efficient use of multivariate analysis and feedback systems.

Successful application of a QbD approach can help advance a product and process from the lab to commercial-scale manufacturing and through the stages of regulatory approval more quickly and cost efficiently. Process optimization should not end with product launch, as a QbD approach incorporates continuous process monitoring and improvements to manage the product life cycle.

We also focus on the equipment and advanced technologies and methodologies used for reaction monitoring and small-scale modeling and simulation of critical processes. A look at problems that can occur during key unit operations such as crystallization and drying and their potential impact on the final drug product highlights how particle engineering can be applied to evaluate and optimize particle size and shape distributions. Finally, the white paper presents examples of the real-world challenges the PE Lab has faced in developing manufacturing processes for customers' APIs and the innovative approaches and solutions Neuland has been able to offer by applying our unique scientific, engineering, and technological capabilities.

# Process Safety

Ensuring process safety refers to the prevention of unintentional release of chemicals, energy, or other potentially dangerous materials during the course of chemical processes that can harm workers, equipment, a manufacturing facility, or the environment. Engineers and scientists in the PE Lab design and conduct process safety studies to understand and assess the potential hazards in processes developed for our Custom Manufacturing Solutions (CMS), Generic Drug Substance (GDS), and Peptides business units. The results of these studies can then guide the design and engineering of process controls and the development of a risk mitigation plan to reduce the chances for runaway reactions and ensure inherently safer processes at commercial scale.

### *Desk Screening*

Preliminary hazard evaluation/desk screening studies of the reactions are performed by estimating bond energies and oxygen balance, using a group contribution method, and applying Cheetah software (ASTM international). Relevant case studies in Bretherick's Handbook of Reactive Chemical Hazards are reviewed and a literature search is conducted.

### *Thermal Screening*

The PE Lab uses a Thermal Screening unit (TSu) to study the thermal stability of molecules at high temperatures (Figure 1). The TSu can assess the effects of elevated temperatures (process temperature + 100oC) on:

- Reaction mixtures
- Distillation residues
- Intermediates/final APIs
- Mother liquors (if recovered)

The TSu uses only approximately 0.5-5g of a sample. Screening studies evaluate the effects of the reaction initiation temperature on molecular stability and of pressure and heat release on chemical decomposition.

### *Reaction Calorimetry*

The reaction calorimeter (HEL ) in the PE Lab assesses the estimated energy released or absorbed during a chemical reaction (Figure 2, overleaf). It measures:

- Rate of energy liberation


*Figure 1. Thermal Screening unit (TSu)*

- Enthalpy
- Specific heat capacity
- Adiabatic temperature rise
- Rate of gas generated
- Overall heat transfer coefficient (U) estimated from UA

This information is useful for understanding the severity of a chemical reaction and, based on the data, Neuland engineers and scientists can recommend control measures to be implemented at plant-scale to ensure inherently safer processes for producing commercial batches.

### *Real-world examples*

Table 1 shows the results of process safety studies conducted for three projects:

- Anti-convulsant O6 -- oxidation reaction on addition of nitric acid
- Antibiotic for treating urinary tract infection-- nitration reaction on simultaneous addition of furfural and nitrating mixture
- Anti-tuberculosis pipeline drug -- electron transfer reaction using magnesium turnings

*Figure 2. Reaction calorimeter*


***Table 1. Process safety study results***

| Project | Reaction | Heat of Reaction (kJ/mol) | Adiabatic Temperature Increase (°C) | Exothermic Severity |
|---|---|---|---|---|
| Anti-convulsant O6- | Addition of nitric acid | 185.7 | 111 | Medium |
| Antibiotic for treating urinary tract infection | Addition of nitrating mixture and furfural | 220.6 | 268 | High |
| Anti-tuberculosis pipeline drug | Charging of Mg turnings | 2,862.9 | 108 | Medium* |

**Note: The earlier process involved dumping all of the reagents and then heating to reaction temperature as this was scale-dependent. After thorough evaluation using the TSU, the reaction initiation temperature was determined. Accordingly, the reagent causing exotherm was added at 2°C above the reaction initiation temperature. The batch was produced at plant scale without any problems; i.e., converted from batch mode to semi-batch mode with provision of automation for controlled addition with respect to process temperature and gas release rate.*

## Particle Engineering

To meet the physicochemical properties required for an API and optimize a process to meet the particle size distribution (PSD) and bulk density requirements of a final drug formulation, engineers and scientists in the PE Lab apply particle engineering techniques and particle size reduction and drying technologies. They also conduct experiments designed to assess the stability of a micronized API at lab scale to be able to predict and, if needed, implement corrective actions to avoid stability-related failure when using a multi-mill, micronizer or fluidized bed dryer to produce commercial batches (Figure 3, below).

### *Real-world examples*

The PE Lab has conducted particle engineering experiments using micronization to meet PSD requirements by customers for products such as ticagrelor (less than 10 microns PSD achieved) and Indacatrol maleate (less than 5 microns PSD achieved). Stability testing of the micronized material under real-time/accelerated conditions assesses the impact of the micronization protocol on impurity profiling. Data generated on experiments with the compound Leveteracetam were used to optimize process conditions to meet the PSD requirement.

## Crystallization and Drying

Variations in crystal formation -- whether due to differences in internal atomic structure or alterations in the external structure -- can impact the porosity and surface area of an API and ultimately the particle size distribution (PSD) and bulk density of the drug product. Polymorphism, which occurs when two or more different crystal forms are present, can compromise API quality. Changes in a drug's physicochemical properties due to polymorphism may affect solvation/hydration, reducing solubility and thereby affecting bioavailability yield.

The PE Lab carries out crystallization studies during the process optimization stage to characterize nucleation and crystal growth and to test process parameters needed to meet the target PSD. These studies employ particle engineering techniques and tools such as focused beam reflectance measurement (FBRM) and particle vision and measurement (PVM) probes that provide data to help understand the impact of process parameters on the size and shape distribution of particles.

The studies are conducted using an automated Poly-block/parallel synthesis reactor (HEL Group), which allows one chemist to perform eight separate

*Figure 3. A) Multi-mill; B) Micronizer; C) FBD*

experiments simultaneously in 100-ml cylindrical reactors. The reactors provide precise stirring and temperature control within a range of stirring speeds and temperature settings spanning -60 to 200oC for each individual reactor.

To optimize the crystallization process it is especially important to conduct lab-scale studies to gather information relevant to:

- The solubility curve (Figure 4)
- Clear and cloud points for different concentrations (using a turbidity probe)
- Metastable Zone Width (MSZW) identification
- Significance of agitation, seeding, holding at cloud point, cooling rate, aging of mass on generation of fine versus coarse PSD
- Importance of seeding in crystallization for consistency in PSD (limiting polymorphism)

The results of solubility studies can be used to optimize processes to improve yield and to determine the best method to achieve super-saturation. Identification of the MSZW, the difference between the saturation temperature and the temperature at which crystals are detected under a constant rate of cooling, also serves as a guide for selecting the optimal rate of super-saturation generation to avoid secondary nucleation. In addition, MSZW helps in defining a seeding regime and establishing a controlled crystallization process.

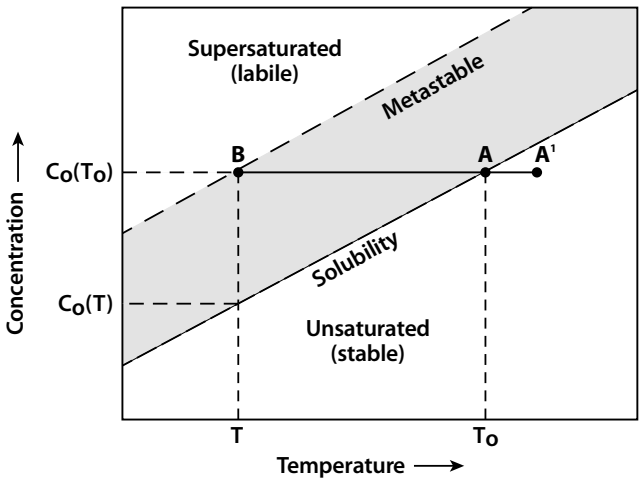


*Figure 4. Solubility Curve*

Drying can sometimes not overcome the problem of residual solvents that become trapped in the lattice structure. A near-infrared (NIR) probe is a valuable tool for online analysis of moisture and residual solvents to ensure that a process meets the limit for residual solvent during drying. This NIR tool is a valuable component of Process Analytical Technology (PAT) and enables real-time analysis of moisture and residual solvents if polymorph is critical.

### *Real-world examples*

Table 2 lists several projects for which Neuland's PE Lab conducted experiments at lab-scale to generate MSZW data to satisfy PSD constraints.

***Table 2. Examples of projects involving lab-scale experiments to meet particle size distribution requirements***

| Project | Constraints |
|---|---|
| Levetiracetam | To make fine or coarser particles |
| Antibiotic for treating urinary tract infection | |
| Entacapone | |
| Olanzapine | |
| Anti-tumor pipeline drug | |
| Anti-fungal pipeline drug | |
| Donepezil HCl | To achieve desired form |
| Ivabradine HCl | |
| Salbutamol Sulphate | To reduce residual solvent |

# QbD

Ultimate product quality depends on having a thorough understanding of the product at lab scale -- identifying and characterizing the CQAs and CPPs and how they might be impacted by the raw materials, reaction and environmental conditions, and other factors. All of this information contributes to a holistic QbD life cycle approach to product development. This approach is built on a solid foundation of product and process knowledge.

The main goal is to assess various parameters and what-if scenarios before taking a process to the manufacturing plant to increase the likelihood of "right-at-first-time technology transfer." A QbD approach to manufacturing process development should include the following elements:

- Systematic evaluation, understanding, and optimization of the manufacturing process based on prior knowledge and data on how material attributes and process parameters affect drug substance CQAs
- Experiments, simulations, and modeling to identify and confirm the relationships between material attributes and process parameters and drug substance CQAs
- Analysis and assessment of the data to establish appropriate ranges, including establishment of a design space if desired.
- Apply DoE to support process development studies, with aim of reducing the number of experiments needed in developmental stage

# DoE

The key to a successful QbD strategy is to apply this knowledge at lab scale, use DoE to develop robust processes that are optimized for safety, efficiency, and yield, and then validate/qualify the process under conditions that can then be transferred to and reproduced at pilot- and commercial-scale. Laboratory analysis of scale-dependent factors in chemical reactions includes studies of heat and mass transfer and mixing conditions. engineers and scientists in the PE Lab use DoE software, such as Dynochem (Scale-up Systems) to simulate scale-up and the effects of these critical factors. Applying Design Space methodology leads to the development of a robust process with sufficient variability built in to avoid surprises and problems during scale-up and technology transfer.

### *Real-world examples*

The PE Lab relies on QbD/DoE to develop robust processes, optimize process parameters, and establish design space, including in the following examples:

- Anti-convulsant O6 -- oxidation reaction: DoE controlling for two variables, reaction temperature and addition of diol/nitric acid, to improve yield and quality. Optimization of the process led to 40% improved yield and easier operation with proper controls at commercial scale compared to a previous campaign.
- Antibiotic for treating urinary tract infection-- macro crystal formation: DoE controlling for two variables, N,N-dimethylformamide (DMF) volumes and cooling rate, contributed to the development of a rugged process that achieved the desired PSD (coarser particles) and a design space to ensure ease of operation during execution at plant scale with proper controls.
- Entacapone -- crystallization: DoE controlling two variables, temperature on addition of hydrogen bromide in acetic acid and cooling rate, with the aim to produce a finer and more consistent PSD prior to micronization that would enhance productivity by avoiding the need for repeated cycles of micronization.
- Olanzapine form I: process developed to achieve acceptable level of chloro methyl impurity and implemented at Unit-1 in Neuland's manufacturing facility; and experiments conducted to achieve positive results using a propeller and seed crystallization to meet required PSD
- Lauric acid purification: process optimization led to20% higher yield and improved quality at increased scale with process validation completed; process to be transferred to commercial plant.

# Process Qualification and Continuous Process Validation

During the process development stage, Neuland carries out scale-up/scale-down studies in cylindrical reactors for process validation/qualification of operations such as mixing. Mimicking and modeling conditions that will be present in the manufacturing plant help process engineers understand the selectivity and effects of factors such as agitation/

tip speed, heating/cooling profiles, crystallization, and filtration characteristics.

Process Analytical Technology (PAT) is applied during process development at lab-scale and implementation in the production plant for process monitoring and the development of trend data to support process validation and qualification. The use of PAT tools enables a shift from Quality by Analysis to Quality by Design and supports continuous process validation at large scale.

The move toward continuous manufacturing will benefit from improvements in novel reactor technology, reaction methods, and continuous monitoring and control strategies. One example is continuous flow chemistry carried out in continuous stirred tank reactors (CSTR). Neuland has filed a patent for a method to carry out the oxidation of a product that releases nitric oxide (NOx) as a gaseous byproduct. We redesigned the process in CSTR in series to enhance the capacity of the oxidation reaction, reduce the batch cycle time, and mitigate the risk at plant scale. Experiments performed at lab-scale with controlled NOx generation results in the desired product yield and quality.

Neuland has also conducted studies with a fixed-bed reactor in continuous processing mode to produce a peptide molecule using solid phase synthesis that involved 33 processing steps. Modification of the process using a continuous fixed-bed catalytic (solid phase) reactor allowed us to reduce the batch cycle time. We have demonstrated the ability to achieve the desired product yield and quality at lab-scale.

# Conclusions

Data and insights generated from the Process Engineering Laboratory help our engineers and scientists develop robust processes at lab-scale for new products, ensure inherently safer processes, and understand the complexities of scale-up to enable right-at-first-time technology transfer, minimizing failures at plant scale. Knowledge and data are essential. Well-designed experiments carried out in batch mode can test for potentially hazardous reactions and suboptimal unit operations, helping to define process parameters and controls to implement at scale. Insufficient process knowledge and inadequate risk management can lead to poor process reliability and a greater likelihood for scaled up processes to be out of specifications , as well as higher production costs and lower profit margins due to the need for more reprocessing.

The technological capabilities of the new PE Lab combined with a team of 25 engineers) and experienced chemists allow Neuland to develop innovative approaches and solutions to the complex challenges in API and drug product manufacturing. We integrate Quality by Design, Design of Experiments, simulation scale-up techniques, and Quality Risk Assessment to develop robust, safe, and validated processes. The successful transfer of this technology is a collaborative effort among the R&D, Manufacturing Technical Operations, Quality, Manufacturing, and other teams of engineers and scientists at Neuland. Together, and working closely with our customers, we can achieve better manufacturing efficiencies with higher yields and improved quality, enhanced process control, and robust design space for enhanced global regulatory flexibility.

## *Glossary of Terms*

API - Active pharmaceutical ingredient
CMS - Custom Manufacturing Solutions
CPPs - Critical process parameters
CQAs - Critical quality attributes
CSTR - Continuous stirred tank reactors
DoE - Design of Experiments
FBRM - Focused beam reflectance measurement
GDS - Generic drug substance
MSZW - Metastable zone width
NIR - near-infrared
PAT - Process Analytical Technology
PSD - Particle size distribution
PVM - Particle vision and measurement
QbD - Quality by Design
R&D - Research & Development
TSu - Thermal screening unit


**Neuland Corporate Office (India):**
Tel: +91 40 3021 1600 | Email: neuland@neulandlabs.com
**Neuland Japan Office:**
Tel: +81 3 3526 5171 | Email: neulandjp@neulandlabs.com
**Neuland USA Office:**
Tel: +1 (888) 617 9587 | Email: neulandusa@neulandlabs.com