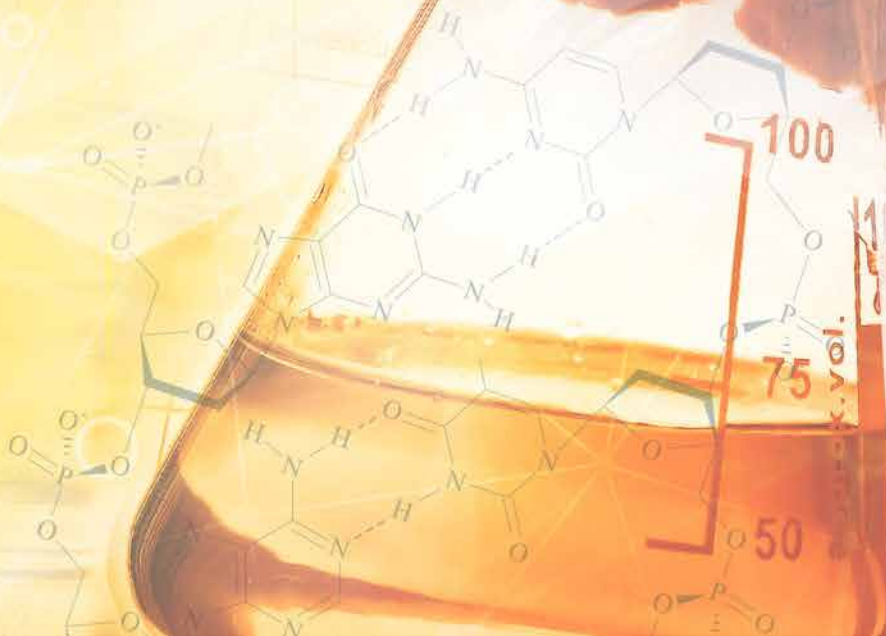


# APIs: Chemistry to Commercialization



# Table of Contents

## Introduction

1

## Chemistry & Innovation

Synthetic Route Scouting: Factors to Improve API Manufacturing

6 Properties of API Synthesis Affecting Yield, Delivery Date & Purity

API Manufacturing of Deuterated Molecules

Peptide Synthesis: Solution Phase, Solid Phase or Hybrid?

Purification of Peptides Using Surrogate Stationary Phases on Reversed-Phase Columns

Disrupting Peptide Aggregation

2-13

## Manufacturing & Commercialization

Common Challenges of Scaling Up an API

Contract API Manufacturing: From Micro-batches to Multi-Tons

API Micronization Techniques for Use in Injectables and Medical Devices

14-19

## Quality & Regulatory

Genotoxic Impurities: Increasing Vigilance, But Still Some Uncertainty

Leveraging QbD for API Scale Up

How to Strengthen Your API Supply Chain Management and Sourcing

20-25





## Introduction



Small molecule APIs and peptides are a story of continuous innovation – from chemistry through to commercialization.

Today – as API development and commercialization has grown more complex – the industry is increasingly demanding faster, simpler, cleaner and more cost-effective manufacturing techniques to address growing drug pricing pressures. For 35 years, from our first API sale in the mid-1980s to our 32nd successful regulatory inspection in 2019, Neuland has invested in and expanded into multiple facilities, broadened our capabilities and built a robust track record of global regulatory excellence. Our customers are at the core of everything we do.

Neuland's expertise in synthetic chemistry and process development provide our customers and partners with confidence that their drug intermediates will meet or exceed standards – on time, every time. We have become a trusted generic and NCE API manufacturing partner & supplier to some of the biggest names in global pharma.

We currently produce 75+ APIs for the customers across 80+ countries in 10 diverse therapeutic segments.

This collection of articles discusses some of the key factors driving the pharmaceutical API industry – from Quality by Design to groundbreaking chemistry advances in the fields of peptides, deuterated molecules and process optimization.

We hope you find these insights helpful! Please visit our website or contact us to learn more about Neuland's capabilities.



Saharsh Davuluri  
Joint Managing Director  
Neuland Laboratories Ltd.

# Chemistry & Innovation



In this section, we present a collection of articles focused on a number of pharmaceutical API chemistry innovations driving change in the drug industry.

At Neuland Labs, our expertise is often called on to provide custom synthesis and route scouting. Demand for these services has continued to grow as more companies realize the cost, efficiency and safety benefits of process optimization. [Synthetic Route Scouting: Factors to Improve API Manufacturing](#) explores some of the top things to consider when devising new routes.

[In 6 Properties of API Synthesis Affecting Yield, Delivery Date & Purity](#) we discuss some of the key synthesis attributes which our team at Neuland have found play a role in the successful manufacture of an API.

[Deuterated compounds](#) – in which drug molecules are modified with deuterium to extend the drug's half-life – continue to show promise in potentially boosting the bioavailability and safety of some drugs. [API Manufacturing of Deuterated Molecules](#) highlights some of the issues involved in this emerging specialized field.

Due to their efficacy and safety, peptide-based therapeutics are increasingly viewed as an extraordinary opportunity for pharmaceutical companies. [In Peptide Synthesis: Solution Phase, Solid Phase or Hybrid?, Disrupting Peptide Aggregation, and Purification of Peptides Using Surrogate Stationary Phases on Reversed-Phase Columns](#), we share some fundamental peptide API principles, along with successful Neuland innovations designed for feasible, cost-effective large-scale manufacturing.

# Synthetic Route Scouting: Factors to Improve API Manufacturing



Synthetic route selection is a crucial element in API manufacturing. While the requirements of the synthetic process of a drug will naturally evolve during its life cycle, scouting alternate routes early in process development provides many benefits. Alternate routes have the potential to help:

- Improve scalability
- Reduce chemical or reagent usage and waste production
- Decrease processing times
- Improve quality and safety profiles
- Reduce the number of processing steps or overall complexity

## Essential Drivers of API Route Scouting

When developing a new synthetic API route, we look for a route that:

- Is cost-effective
- Has the same quality or greater quality than the previously agreed upon route
- Provides reasonable time to market

While meeting the three criteria above would yield the most benefit, focusing on even one or two of these criteria can provide significant process improvements. For niche products, most companies seek to reduce cost by 2-5% through alternate routes; for generics, much greater savings are sought.

In addition to cost, other factors to consider are batch sizes, throughput of the product, lead time and reducing batch cycle. Shortening the route is frequently a goal, as this one change can singlehandedly decrease cost, time, waste and regulatory constraints.

## Ask the Right Questions to Improve Alternate Routes

- When considering a route change, the first question to ask is why. By changing the route, what clear benefits can be gained in terms of cost, time and availability?
- The next point to consider is the availability of raw materials. Are they maximized by your current process, or could an alternate process improve on it? Look at the volume of the product in the market. The higher the volume you need to produce, the more benefit you gain from improving the route.
- Does the manufacturer you work with conduct company product profile matching? This can be very helpful when seeking to make a change. When examining the cost benefit, does it extend to the manufacturer as well as to you?
- Is the process feasible in the manufacturing plants you've selected?
- Lastly, what alternate green reagents could be used for long-term sustainability of the product?

Today, the most innovative routes use the least resources possible and minimize impact on the environment.

## Keys to Getting Route Scouting Right

When considering options, keep these final points in mind to achieve success:

- An alternative route should use a strategically inexpensive starting material. Using an intermediate from an existing process is ideal.
- The process used should be robust and require minimal purification. Stages should be telescoped for maximum efficiency.
- The new route should offer high "atom economy," creating minimal waste via a greener process.
- And finally, the developed route must not infringe on any current patents.

Keeping these factors in mind during the research phase should allow the creation of a new synthetic route that meets expectations and is sustainable across the drug lifecycle.



## 6 Properties of API Synthesis Affecting Yield, Delivery Date & Purity

The ultimate goal is synthesizing an API product with high yields, ease of isolation from impurities, and no off-target hazardous impurities. Final products with these characteristics are more likely to pass stringent FDA and EU GMP requirements.

However, there are a number of properties of API synthesis that can affect the yield, purity, and delivery date of a final product.

### 1 Type of synthesis directly affects yield, delivery date, and purity.

Linear synthesis of the API consistently modifies each step in a sequence. In a multi-step synthesis with yields of 80% at each step, the overall yield drops by 20% for each individual step. Thus, the total yield of a 6-step process is approximately 26.2% and yield for an 8-step process is 16.8% (Table 1).

The unreacted intermediates, B, C, D, E, F, G and H in our example below need to be purified from intermediate(s) or finished products of each reaction.

**Parallel synthesis** reduces the number of steps that are dependent on receiving an intermediate by first preparing each part of the API molecule. The intermediate molecules are then reacted in a predesigned sequence that synthesizes the complete product.

The steps leading to the intermediate molecules dictate the structure of the impurities. The selection of the intermediate molecules and their route steps can minimize the possibility of off-target synthesis of hazardous contaminants.

The intermediates may differ in their charge properties, which allow the intermediates to be easily isolated from impurities with a single column pass. Often complex molecules have mostly positive or mostly negative or mostly neutral (hydrophobic) charges in different regions.

Synthesizing each distinctly charged part separately as intermediates may simplify the isolation strategies and synthetic steps. Intermediates can react at the correct position on a core structure or intermediates can be attached to each other at the correct position until the final product is produced.

**Table 1. Comparison of yields and timing of steps between linear and parallel routes of synthesis**

Linear synthesis			Parallel synthesis		
	Route Steps	80% yield for each step		Route steps	80% yield for each step
1	A → B	80.0%	1	A → B	80.0%
2	B → C	64.0%	1	C' → D'	80.0%
3	C → D	51.2%	1	E' → F'	80.0%
4	D → E	41.0%	1	G' → H'	80.0%
5	E → F	32.8%	2	B + D' → D	64.0%
6	F → G	26.2%	2	F' + H' → J'	64.0%
7	G → H	21.0%	3	D + J' → J	51.2%
8	H → J	16.8%			
	Total yield	16.8%			51.2%

## 2. Proximity

In Table 1, the Proximity or number of steps in the synthesis route directly affects the yield. Since each step has its unreacted components, the number of steps also affects the number of isolation steps and impurities. The number of steps that can be done simultaneously by different chemists can reduce delivery time, whereas downstream steps cannot be started until the intermediate(s) are done and purified.

Generally, manufacturers tend to prefer developing synthetic processes under non-GMP regulations, while manufacturing APIs under current Good Manufacturing Practices (cGMP). This method – which aims to reduce the number of steps – is preferred by manufacturers for three reasons:

- Reduces costly GMP manufacture
- Reduces reporting of process variation and optimization
- Increases flexibility of process and sourcing

Regulators tend to request more steps in the GMP manufacturing process for three main reasons:

- Minimizes quality risks
- Controls impurities from starting material and subsequent steps and to ensure identity and purity of drug substance
- Purges related impurities with multiple purification steps.

## 3. Complexity of structure

Generally, a more complex structure usually involves more synthetic steps for the API.

The manufacturing of some pharmaceuticals results in isomers. Isomers are like a right wrist and a left wrist—the bending of the wrist and its ability to rotate are critical for it to function optimally ... similar to complex molecules. If an intermediate step yields isomers, the active isomer may be more easily isolated in some cases.

Parallel synthesis helps reduce the number of potential isomeric variants. For example, Labetalol has four isomers in its racemic mixture. Two are relatively inactive. The potent alpha blocking activity comes from the (S,R) isomer component and the potent beta blocking activity derives from its (R,R) isomer.

## 4. Cost-efficient synthesis

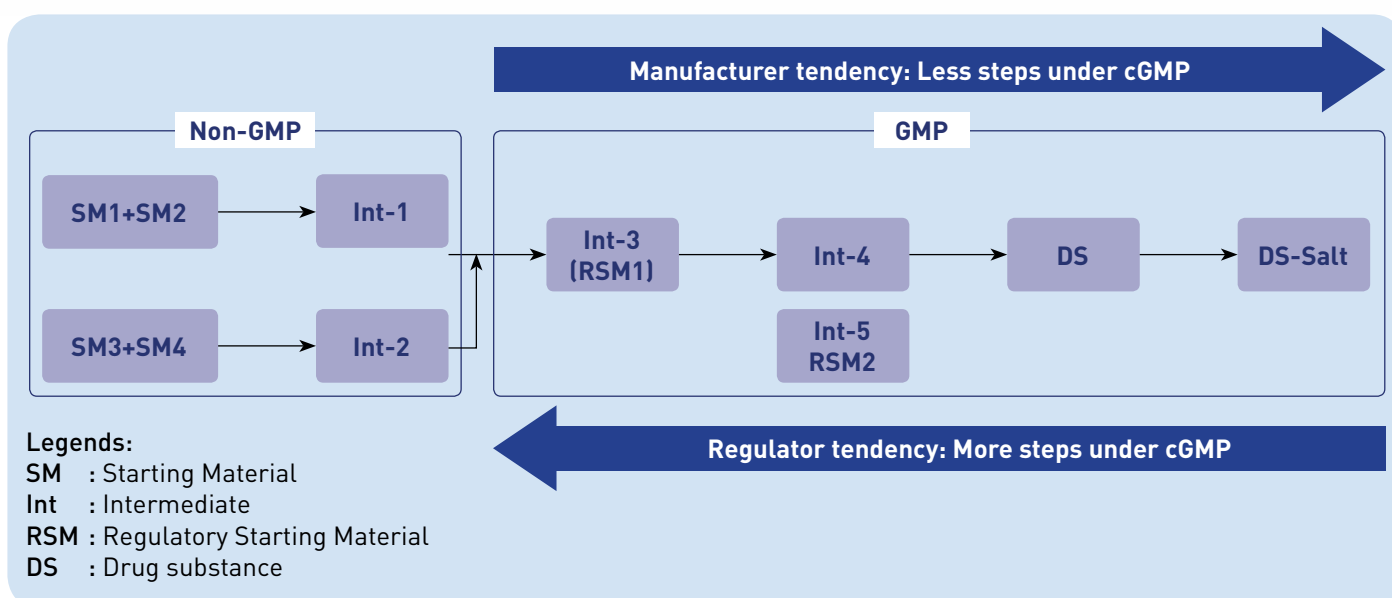
Synthetic route planning is critical to maximizing yields. As shown in Table 1, parallel synthetic strategies overlap the scheduling of the synthesis of intermediates, and can reduce cycle time, and minimize the number of downstream processing steps.

## 5. Carryover of impurities into drug substance

Synthetic routes that minimize or eliminate any potential off-target synthesis of hazardous or unknown impurities should be utilized. Green chemistry has become increasingly important, so routes should be planned to minimize effluent generation. This can reduce the time or even the need to concentrate the intermediates.

## 6. Minimum isolation steps in situ

Typically, synthetic routes are designed to utilize single or two isolation steps for the intermediates. By making intermediates in a parallel manner, certain columns such as specific anion or cation columns can be used more easily for their isolation. Due to efficient stepwise isolation of intermediates, the isolation of the final product is less cumbersome and generally has a very high purity.



# API Manufacturing of Deuterated Molecules

Deuterated compounds – in which a drug molecule’s carbon-hydrogen bond is replaced with a carbon deuterium bond to extend the drug’s half-life – continue to show promise in potentially boosting the bioavailability and safety of some drugs.

The deuterated compound market has attracted many new companies looking to develop and patent deuterated versions of various existing, non-deuterated therapeutic compounds. This is known as the “Deuterium Switch.”

The chart below represents indications and clinical status for deuterated candidates from a number of companies in the space.

Drug Name	Active Indications	Highest Status
deuterated D-serine (oral, schizophrenia), CoNCERT Pharmaceuticals	Schizophrenia	Phase 1 Clinical
PXL-065	Adrenoleukodystrophy; Adrenomyeloneuropathy; Non-alcoholic steatohepatitis	Phase 1 Clinical
ALK-001	Age related macular degeneration; Cone dystrophy; Retinitis pigmentosa; Stargardt disease	Phase 2 Clinical
deuterated S-lisofylline	Necrosis; Radiation sickness	Phase 2 Clinical
deudextromethorphan hydrobromide + ultra-low dose quinidine sulfate	Agitation; Intermittent explosive disorder; Schizophrenia	Phase 3 Clinical
11,11-di-deutero-ethyl linoleate, Retrotope	Brain disease; Friedreich ataxia; Huntingtons chorea; Motor neurone disease; Neurodegenerative disease; Progressive supranuclear palsy; Tay Sachs disease	Phase 3 Clinical
deutivacaftor	Cystic fibrosis	Phase 2 Clinical
deuterium-modified ruxolitinib analog (oral, alopecia areata), CoNCERT Pharmaceuticals	Alopecia areata	Phase 2 Clinical
CTP-730	Inflammatory disease	Phase 1 Clinical
HC-1119	Breast tumor; Hormone refractory prostate cancer; Prostate tumor	Phase 3 Clinical
JZP-386	Narcolepsy	Phase 1 Clinical

## What is a Deuterated Drug?

A deuterated drug is a small molecule with medicinal activity. It is made by replacing one or more of the hydrogen atoms contained in the drug molecule with deuterium – a hydrogen isotope whose nucleus contains one neutron and one proton. As deuterium and hydrogen have nearly the same physical properties, deuterium substitution is the smallest structural change that can be made to a molecule.

## To Deuterate or Not to Deuterate – That’s the Regulatory Question

Developers of deuterium switch compounds must show significant clinical benefits over existing non-deuterated versions to justify why they should replace existing or less expensive therapies. Such a switch can:







- Take advantage of the clinical knowledge concerning the non-deuterated version of the compound.
- Benefit from new patent protections.
- Result in improved therapies and patient outcomes.

Most large pharmaceutical companies today also claim deuterated versions of new molecules in their patent applications.

### **Benefits of Deuterated Versions of Drugs**

Deuterated versions of existing drugs can benefit from improved pharmacokinetic or toxicological properties. Because of the kinetic isotope effect, which is the change in rate of a chemical reaction when one of the atoms in the reactants is substituted with one of the isotopes, drugs that contain deuterium may have significantly lower metabolism rates. As the C-D bond is ten times stronger than the C-H bond, it is much more resistant to chemical or enzymatic cleavage and the difficulty of breaking the bond can decrease the rate of metabolism.

Lower metabolism rates give deuterated drugs a longer half-life, lengthening the timeline for elimination from the body. This reduced metabolism can extend a drug's desired effects, diminish its undesirable effects, and allow less frequent dosing. The replacement may also lower toxicity by reducing toxic metabolite formation.

A major potential advantage of deuterated compounds is the possibility of faster, more efficient, less costly clinical trials, because of the extensive testing the non-deuterated versions have previously undergone. The main reasons compounds fail during clinical trials are lack of efficacy, poor pharmacokinetics or toxicity. With deuterated drugs, efficacy is not in question – allowing the research to focus on pharmacokinetics and toxicity.

Deuterated versions of drugs might also be able to obtain FDA approval via a 505(b)(2) NDA filing, a faster, less expensive route.

### **Manufacturing Deuterium Exchanged APIs**

With our expertise in deuteration technology, Neuland Labs uses a synthetic approach where deuterium-enriched material is combined with the drug to produce deuterated drugs. Another approach, called an exchange approach, uses a catalyst to produce a deuterated molecule.

The most popular process for sourcing deuterium for drugs is extracting D2O from regular water via the Girdler sulfide (also known as the Geib-Spevack) process, which uses a temperature difference and hydrogen sulfide to enrich deuterium in water by up to 20%.

### **Deuterated Molecules Advance in Clinical Trials**

While deuteration has been around for decades, most deuterium chemistry efforts are currently in the pre-formulation stage.

Those deuterated compounds that have advanced are generally performing well in clinical trials. In July of 2016, a deuterated drug reached Phase III testing for the first time, in a study to treat Huntington's disease. Known as deutetrabenazine,

the drug was found to reduce the disease symptoms and the frequency of administration, and it is currently being considered for approval by the FDA.

Recently, another investigational new drug targeting nonalcoholic steatohepatitis & adrenomyeloneuropathy (a deuterium-stabilized [R]-enantiomer of pioglitazone) completed FDA review and appears headed towards a Phase 1 study.

### **Growing Opportunity for Deuterated Drugs**

The current market value of companies specializing in this technology suggests that the value of "deuterium switching" could be more than a \$1 billion, and that the greatest discoveries in the field have yet to occur.



## Peptide Synthesis: Solution Phase, Solid Phase or Hybrid?

Peptides are a complex drug class, and have historically proven challenging from a manufacturing standpoint. They are, however, experiencing a renaissance due to improvements in peptide synthesis, the development of high-throughput approaches and various innovations to overcome some of their traditional limitations, such as stability and half-life. These advances are expected to drive the peptide drug market to over \$48 billion by 2025.

There are three main strategies for synthesizing peptide active pharmaceutical ingredients (APIs):

- Solid Phase
- Liquid Phase
- Hybrid Technology

### Choosing the Right Synthesis Technique for Your Peptide API

Peptide synthesis has roots dating back more than a century. Given its age, it may seem strange that peptide synthesis is currently undergoing a revolution...but it is. A new generation of therapeutics, diagnostics and research tools are emerging on the healthcare scene – a by-product of the industry's turn towards biologics and a greater understanding of the benefits of peptides.

The decision regarding which production technique to use is driven by three pivotal factors:

- The size of peptide (meaning the number of amino acids)
- The quantities needed at the current stage of development

- The ultimate commercial launch quantities & batch sizes that will be required for manufacturing

### Peptides – Different Production Methods

Peptides are produced using one of three synthesis methods: liquid phase, solid phase or a hybrid approach. Each has its advantages and disadvantages.

#### • Liquid Phase: 15 and Fewer Amino Acids

Solution phase synthesis (commonly referred to as 'liquid phase') is regarded as the traditional approach to peptide production. Among its benefits, solution phase synthesis delivers better economies of scale. The technique is much more scalable and produces large quantities of

high-quality peptides at a lower cost point than solid phase or hybrid methods. Solution phase is not well-suited to the production of larger peptides, but it is an ideal strategy for peptides containing less than 15 amino acids and when commercial requirements range from 10+ kilograms to tons.

### • **Solid Phase: 25 Amino Acids & Up**

In solid phase synthesis, the peptide is constructed on resins (e.g., polystyrene, polyacrylamide, PEG). The key advantage with solid phase is the ability to synthesize peptides which don't lend themselves to bacterial expression using solution phase techniques.

One of the major challenges facing solid phase synthesis, however, is yield – as the size of the peptide increases, yields typically decrease due to the challenge of removing closely related impurities from the product. And while some molecules don't lend themselves to bacterial synthesis, others aren't well-adapted to solid phase synthesis – either because of the inherent aggregation encountered during the assembly of longer peptides, or due to the chemicals used to remove them from the resin – which can damage the peptide. Production costs also tend to be substantially higher in solid phase synthesis.

Conventional wisdom suggests using a solid phase approach for peptides containing greater than 25 amino acids for commercial quantities in the 1-10 kg range. Solid phase peptide synthesis utilizes an excess of protected amino acids to ensure as close to a 100% complete reaction as possible.

When larger quantities are needed, this can add considerable cost to the synthesis. However, a significant benefit of solid phase synthesis is the relatively shorter cycle time when compared to liquid phase synthesis. A secondary benefit: liquid phase synthesis of peptides larger than 15 amino acids is labour intensive.

### • **Hybrid Synthesis: More Than 25 Amino Acids & Larger Commercial Quantities**

The hybrid approach brings these two different methodologies together to produce peptides. For example, to

construct a 40-amino acid peptide, small peptides of 5 to 8 amino acid segments would be produced using solid phase methods on resins, and then the segment condensations would occur in solution to construct the full peptide sequence.

Today, a hybrid peptide synthesis strategy is generally chosen for peptides that are greater than 25 amino acids in length, and commercial requirements range from 10 to 200 kilograms. One notable success from hybrid synthesis was the pioneering work on Fuzeon, an approved 36 amino acid therapeutic for HIV-1.

### **Choosing the Right Production Method**

The choice of which method to use is generally guided by a number of factors. A key factor is the desired chiral purity/integrity of the peptide. Pseudoproline can be exploited for racemization-free condensations of segments terminating in a serine or threonine residue. This strategy maintains purity through the various segment synthesis steps – especially with longer (or more difficult to produce) peptides.

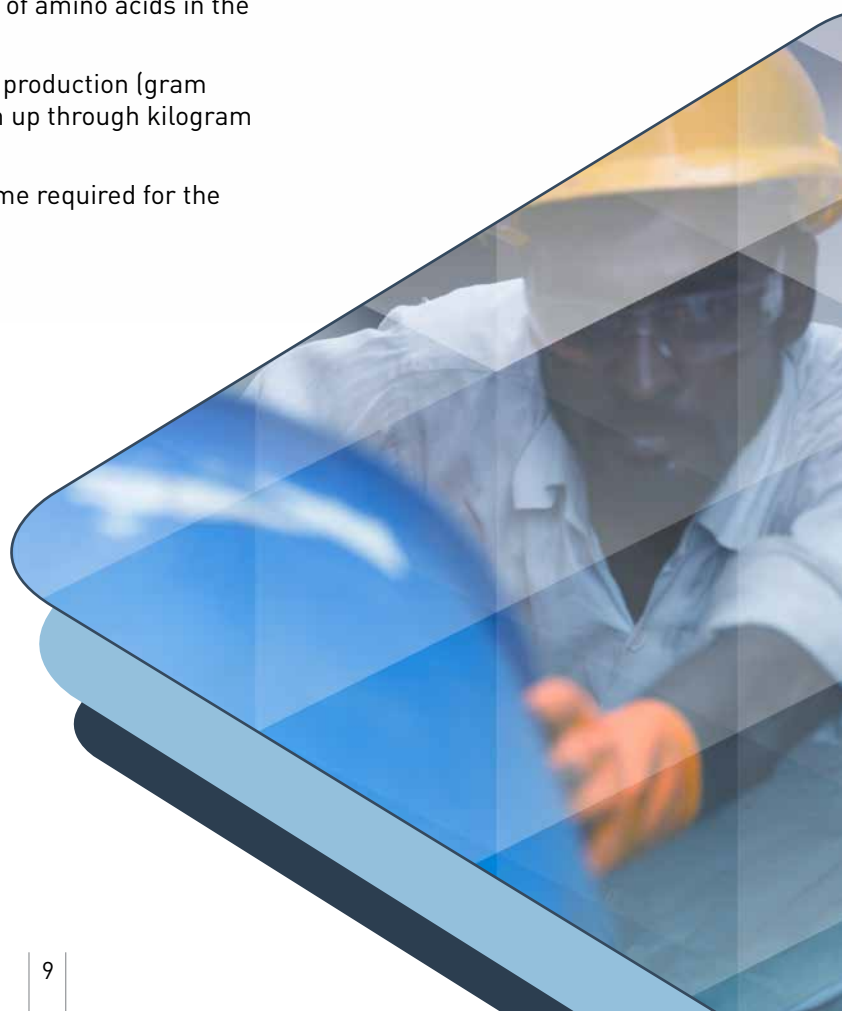
Factors which drive the choice of synthesis method include:

- 1 The number of amino acids in the peptide
- 2 The scale of production (gram or sub-gram up through kilogram quantities)
- 3 The timeframe required for the peptide

### **Liquid Phase & Hybrid Synthesis for Improved API Substance Profiles**

Whenever possible, transitioning from solid phase synthesis to a hybrid – and ultimately liquid phase – methodology is recommended due to the successive improvements in purification. With each change in strategy – from solid to hybrid, and from hybrid to liquid – significant improvements in the substance profile are observed with peptide APIs.

Peptide APIs produced with a solid phase approach contain inherent deletion- and insertion-related substances. These substances decrease progressively with the transition to hybrid or liquid phase techniques. As peptide production progresses across these 3 distinct methods, the intervening purification steps increase – leading to fewer unwanted substances in the peptides.



# Purification of Peptides Using Surrogate Stationary Phases on Reversed-Phase Columns

In recent years, peptides have been acknowledged for their selectivity, efficacy and safety. Combined with new synthesis technologies and advances in peptide science, peptide therapeutics have become a reality – and numerous clinical trials are ongoing.

But while peptides may be safe and effective as drugs, they have never lent themselves to straightforward commercial manufacturing – especially longer-chain, complex peptides.

In a peer-reviewed piece at Pharmaceutical Technology, members of the Neuland team shared a newly-developed strategy to increase sample loading 7-12 fold compared to conventional Prep-HPLC techniques.

Reversed-phase high-performance liquid chromatography (RP-HPLC) is used throughout the pharma industry. Analytical RP-HPLC is used for the release and characterization

of raw materials, intermediates, and APIs. Preparative RP-HPLC is used for the commercial production of peptide APIs and most other complex APIs not suited to crystallization.

Historically, there have been just two ways to increase the amount of sample that could be purified in a single Prep-RP-HPLC run: use a larger column (increase the stationary phase) or use displacement chromatography.

## Advances Have Brought Commercial HPLC Closer

The technological advances in process HPLC instrumentation and the bonded silica supports have made possible commercial production of complex peptides such as Fuzeon, a 36-amino acid peptide, in hundreds of kilos quantities. Unfortunately, large-scale HPLC instruments and the associated column hardware are expensive.

More importantly, none of these improvements have addressed the

loading capacity of a given column, nor have they resulted in a significant increase in the amount of purified product (output/mL of the packed column).

## Using RP-HPLC

In science labs, reversed phase high performance liquid chromatography (RP-HPLC) is used to analyze, characterize, separate, purify, and isolate small organic molecules, natural products, and biologically active molecules such as polypeptides, proteins and nucleotides.

In pharma, analytical RP-HPLC is employed specifically to release and characterize raw materials, intermediates and active pharmaceutical ingredients (APIs). Likewise, preparative RP-HPLC is used to commercially produce peptide APIs, along with most other complex APIs that cannot be crystallized.

Entry	Source/ Operator	Type of Chromatography	Total column volume (ml)	Internal diameter (cm) x length (cm)	Type of stationary phase	Amount of stationary phase	Amount of crude purified	% Loading with respect to total column volume	Relative loading capacity (Standard RP-HPLC = 1)
1	Donald A. Wellings, A Practical Handbook of Preparatory HPLC, Elsevier, UK (2006) [1]	RP-HPLC	4420	15 x 25	C-18	3.5 kg	40 g of crude peptide	0.9%	1.0
2		Self displacement - RP-HPLC	347	4.2 x 25	PLRP-S	Not available	6.2 g of a 25-AA peptide	1.8%	2.0
3		Enantiomers separation	1964	10 x 25	Chiralpak AD	Not available	120 g (6 box-car injections of 20 g each injections)	1.0%	1.0
4		NP-HPLC (normal phase)	196429	100 x 25	Silica	155 kg	15,500 g	7.9%	8.7
5	Neuland: this paper	TBAHS-SSP-RP-HPLC	19.6	1 x 25	Discovery Wide Pore C-18, 5µ 100 A pores, 9.2% C	11 g	1.4 g crude leuprolide	7.1%	7.9
6		TBAHS-SSP-RP-HPLC	14.1	1.9 x 5	Water Symmetry C-8, 5µ 100 A pores, 11.7% C	11 g	1.4 g crude leuprolide	9.9%	11.0



## How the New RP-HPLC Method Works

The new method developed by Neuland uses C-18/C-8 derivatized silica, coated with a hydrophobic quaternary ammonium salt or quaternary phosphonium salt. It increases 7- to 12-fold the sample loading of the crude mixture of organic compounds including synthetic crude peptides. What causes such dramatic results is the additional surrogate stationary phase characteristic of the C-18/C-8 bound quaternary salt.

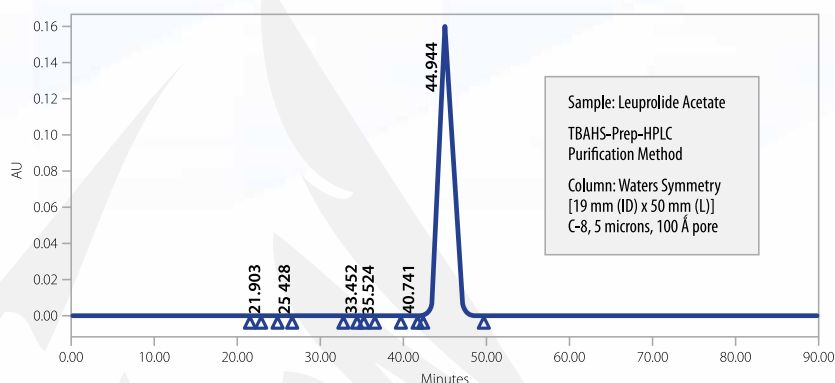
Preparative RP-HPLC in the elution mode is limited by the loading capacity of the analyte. In this mode, however, synthetic peptides typically have a loading capacity of 1-2 mgs per mL of packed column volume (viz., 0.1% to 0.2% with respect to total column volume). Table 1 (found on page 2 of PDF provided at web link) shows how Prep-RP-HPLC aided by a surrogate stationary phase performed compared to standard Prep-RP-HPLC using Leuprolide as an example, and tetra-n-butylammonium hydrogen sulphate (TBAHS) as ASP/SSP.

## Results of Neuland's Prep HPLC Technique

The purified product (Leuprolide) output of the standard Prep-RP-HPLC is 2.45 mg/mL of column volume. In contrast, the purified product output of the Prep-RP-HPLC aided by a surrogate stationary phase is 29.6 mg/mL of the column volume (see Table 1, entry 2, on page 2 at this link) and 16.3 mg/mL of column volume (see Table 1, entry 3, on page 2 at this link). These results demonstrated that the process described enables loadings of 7-12 times the capacity of conventional Prep-RP-HPLC.

To learn more about this novel Prep-RP-HPLC method, view the complete PDF here.

## Analytical RP-HPLC Profile of Leuprolide acetate obtained using the Additional Stationary Phase aided Prep-RP-HPLC



### Peak Results

	RT	Area	% Area	RT Ratio	USP Plate Count
1	21.903	9593	0.05	0.49	5879
2	25.428	5475	0.03	0.57	6217
3	33.452	6803	0.04	0.74	2938
4	35.524	2789	0.02	0.79	6935
5	40.741	12661	0.07	0.91	10954
6	44.944	17743608	99.79	1.00	3829

## Illustrative Example

The C-18/C-8 reversed column is equilibrated with 5 to 10 column volumes (VCS) of 5 to 10% aqueous acetonitrile containing 10 mM TBAHS. The pH of the starting buffer was not adjusted, and was about 1.95 (It is important to keep the concentration of acetonitrile lower than the concentration needed to elute the product on an analytical HPLC column). The crude compound to be purified was dissolved in starting buffer A or aqueous TFA or aqueous HOAc

and loaded on the column. After the loading is complete, the column is equilibrated with with 2 VCS of buffer A. Next, the gradient elution process is started. The buffer B is usually 300 mM to 500 mM TBAHS in 5 to 10% aqueous acetonitrile. A linear gradient of 0%B to 100% Buffer B over 10 VCS is applied. When the product of interest (API) is about to elute, a gradient hold may be applied until all the API has eluted from the column.

# Disrupting Peptide Aggregation

The aggregation of peptide chains caused by intramolecular hydrogen bonds is a common challenge with longer or more complex peptides. It can result in slower and incomplete coupling reactions and incomplete deprotection of the N-amino protecting group – meaning a modified or damaged peptide.

There are a number of steps taken to prevent aggregation during peptide synthesis, including cleavage and deprotection. The most commonly used – and mildest – method is Fmoc – the removal of the Fmoc group to expose the α-amino group. In addition to cleaving under very mild conditions, it is (typically, though not always) stable under acidic conditions as well.

## Fmoc & Orthogonal Approaches to Peptide Synthesis

One of Fmoc's greatest advantages is its ability to work well with other protecting groups (e.g., Boc) – allowing for an orthogonal approach – a common strategy in organic peptide synthesis.

## Common Fmoc Methods for Disrupting Peptide Aggregation

Advances in peptide synthesis methods and ready availability of reagents that disrupt intramolecular hydrogen bonds have made complex syntheses much more practical. There are three Fmoc strategies for disrupting aggregation. The decision to use each one is directly dependent on the type of building block being used.

## • Fmoc-pseudoproline dipeptides

Fmoc-pseudoproline dipeptides are the most common approach for disrupting aggregation. The position of "Serine" or "Threonine" in the sequence of the peptide is identified. Instead of coupling the "Serine" as a single residue (Fmoc-Ser-OH), the dipeptide sequence that includes the next amino acid (Xxx) in the sequence after serine/threonine is coupled as Fmoc- Xxx-Ser/Thr-OH pseudoproline dipeptide. Using this approach, peptides containing over 120 amino acids can (and have been) created.

Research	Intermediates and Peptide Fragments	Manufacturing Services	Analytical and Regulatory Support	Generic Peptide API Manufacturing
Aid in drug design and Analog Synthesis	Novel Routes for Synthesis	Pre-GMP and scale up supply of Clinical Trial Material	Analytical Method Development and Validation	cGMP Manufacturing of Peptide APIs with Regulatory Support
Custom Process Development	Supply of Protected Amino Acids and Building Blocks	Scale up from Lab to Pilot and Commercialisation	Impurity Profiling, Validation	
			Analytical Reference Standards	
			Stability Studies	
			Filing DMFs	
<b>NEULAND'S PEPTIDE WORLD</b>				
From Building Blocks to Commercial Production to Peptide APIs				
<b>Core Expertise:</b>				
<ul style="list-style-type: none"> <li>• Solution Phase Synthesis</li> <li>• Solid Phase Synthesis</li> <li>• Hybrid Technology for Complex Peptides</li> </ul>				

### • Fmoc-isoacyl dipeptides

Fmoc-isoacyl dipeptides are proving themselves to be a remarkable tool for enhancing synthetic efficiency in the Fmoc/ tbutyl based solid phase strategy. Substitution of Xxx-Ser/Thr in a peptide sequence with the corresponding isoacyl dipeptide results in the formation of a depsipeptide analog of the native sequence. This modification results in the disruption of aggregation in a manner similar to pseudoproline or N-Dmb/Hmb-residue.

### • Fmoc-(Dmb)Gly-OH and analogs

The use of Fmoc- Asp(OtBu)-(Dmb)Gly-OH in sequences containing –Asp-Gly- has been shown to suppress formation of b-Aspartyl peptides. Fmoc-Gly-(Dmb)Gly-OH is potentially useful in the synthesis of peptides containing multiple glycines.

# Manufacturing & Commercialization



In this section, Neuland's team highlights some of the challenges and techniques common to the scale-up and manufacture of drug APIs.

From reactions, to crystallization to particle size, Common Challenges Scaling Up an API discusses some of the specific challenges drug companies face when translating bench processes to commercial scale.

Contract API Manufacturing: From Micro-Batches to Multi-Tons explores some of the key challenges which can emerge at larger scales of API production.

API particle size plays a fundamental role in the properties of drugs, directly impacting solubility, efficacy and other characteristics. Advances in particle reduction techniques allow for improvements in API performance. In API Micronization Techniques for Use in Injectables and Medical Devices, the Neuland team examines top techniques used today by pharmaceutical manufacturers.



# Common Challenges of Scaling Up an API

While linear drug scale-up sounds great on paper, the reality is usually much different. In fact, scaling up an API can be challenging even under the best circumstances.

Most scale-up challenges arise from the non-linear nature of shifting from the bench to the manufacturing plant. Not only do chemical reactions function differently at larger scales, but the environmental health & safety (EHS) issues can be enormous. For instance, how do you safely store – and eventually dispose of millions of gallons of potentially highly-toxic chemicals each day?

Here are five common challenges in API scale-up Neuland's scientists frequently confront:

## 1. Reactions

In Unit Processes, reactions may negatively impact product selectivity during scale up if they are not properly understood at the lab scale. This can result in an increase in impurities – impacting both yield and quality. A thorough working knowledge of the chemical reactions includes the effects of scale-dependent factors (such as mixing, mass transfer and heat transfer). Using simulation software (for example, Dynochem or Visimix), the effects of mass, heat transfer and mixing changes can be predicted at larger scales.

Design of Experiment (DoE) should be followed at lab scale to develop a robust process, including the time, temperature and mixing scale criticalities. This exercise will provide adequate Design Space for variability, and avoid surprises during scale up & technology transfer. The lab process validation & qualification to be done in the manufacturing plant should mimic the conditions at the lab scale. For example, switching to cylindrical reactors during manufacturing may mean slowing the addition of reagents, reducing the rates at which heat increases and decreases, and more.

## 2. Safety Data Generation

Runaway reactions are a challenge during scale-up. Generating safety data at lab scale can potentially help in designing the hardware for pilot or commercial scale batches – leading to inherently safer process technology. This typically involves reactions hazards and thermal hazards studies.

These are performed using reactor calorimeters, Thermal Screening units (TSu), or Rapid Screening Devices (RSD) to monitor:

- Reaction heat
- Reaction initiation temp
- Adiabatic temp rise
- Gas evolution rate

## 3. Crystallization

Crystallization often causes problems if the Critical Process Parameters and their impacts on Critical Quality Attributes (CQA) have not been adequately studied. Crystallization can negatively impact solubility and dissolution rates. Changes in crystal habit (the external structure) or the crystal form (polymorphism – in which the internal arrangement of atoms is different) can have wider impacts on ease of filtration, washing and drying.

These changes, in turn, can impact the particle size distribution and bulk density, porosity, surface area or polymorph-pseudo polymorph (solvates/hydrates) to ultimately affect the formulated product's drug activity. Process Analytical Techniques (PAT) can be used during lab development to understand the impact of process parameters on physicochemical properties.

## 4. Drying

Drying APIs at larger scales – much as with crystallization – can be complicated. It is common to use an NIR probe to perform on-line moisture checks. Residual solvents are a frequently-encountered problem during drying, and they are mainly the result of the crystallization process. When crystallization solvent is trapped in the lattice, it is difficult to remove it to a level that meets solvent limits during drying. Crystallization process parameters should be studied at the lab scale,

including the super saturation driving force and its impact of residual solvent.

## 5. Particle Size

An API's particle size has become increasingly important – down to the micron level. Equally as important, however, is the Particle Size Distribution (PSD) – essentially, how wide the range of particle sizes in a given sample. Common size reduction techniques to meet today's small, tightly-banded distributions include multi-milling, micronization or other size reduction (or sometimes enlargement) techniques & systems.

Where particle size matters (and when doesn't it?) Particle Engineering studies should be performed for both drying and crystallization using focused beam reflectance measurement (FBRM) and particle vision and measurement (PVM) probes to understand the impact of process parameters on target particle size and shape distribution.

Determining the proper parameters for API scale-up can be difficult. Using Quality by Design (QbD) and Design of Experiment (DoE) approaches, API manufacturers and CDMOs can reduce unanticipated challenges by developing deep process knowledge at lab scale – which aids in transfer to scale-up.



# Contract API Manufacturing: From Micro-Batches to Multi-Tons

## Different Challenges, Different Scales – The Balancing Act

To some extent, the challenges of commercial API manufacturing vary, based on scale. A large-scale CMO might not necessarily be suited to working in an early stage of development. Applying later-stage standards early on, for example, could waste time and money – ultimately derailing the project timeline and budget.

At the same time, consideration must always be given to later-stage manufacturing processes & requirements during earlier phases of the project to maximize efficiency and minimize cost & time-to-market. It requires striking a balance – maximizing early-stage success while minimizing future challenges.

## Scale Up Gradually to Identify & Solve New Challenges at Each Stage

Many aspects of early-stage production, such as handling and storing raw materials, only become challenging when production is scaled up. Issues with heat generation and dissipation also tend to come to the forefront when production is dramatically increased. In addition, larger volumes often mean longer reaction times. This can be problematic for certain processes.

To detect and resolve these potential issues, production is scaled gradually, going from micro or milligram scale to gram scale, then pilot scale to full production.


## Lifecycle Management Key to Successful Process Scale-Up

When preparing to scale up drug production, it's important to partner with a CMO well-versed in lifecycle management. A contract firm that has the extensive expertise needed to work comfortably at all scales can improve many aspects of the scale-up process in measurable ways, making it smoother, faster, and easier overall.

The issues that arise when shifting from one scale to another can be unpredictable, and because of this, planning and forecasting should be done as early in the R&D process as possible. The more experienced the transfer team, the more streamlined and simplified technology transfer can be.

Several techniques are currently used to make production more





efficient. Scouting alternate synthetic routes to a molecule has become standard, and helps control costs by accelerating production. This can also reduce time spent on regulatory compliance, as there are fewer steps to document, and less analysis to be made throughout the process.

Consider Your Infrastructure: Analyze Processes, Steps, Chemicals & Reagents

At Neuland, we often manage early stage projects in which compounds are produced in small trial batches. With subsequent scale-up steps on the horizon, however, we always advise our earlier stage clients to consider the discharge, infrastructure and cost of the processes used.

We systematically analyze how each process, step, chemical, or reagent can potentially affect the product when it begins manufacture on a larger scale. One solution we

and other API manufacturers are increasingly turning to is green chemistry.

In green chemistry:

- Processes are designed to maximize the amount of raw materials in usable products
- Operations are designed to use less energy and to maximize energy efficiency overall
- Environmentally safe or benign products are used whenever possible
- Waste is avoided as much as possible

By following these principles, the processes used for larger scale API manufacturing can become more efficient.

- Reactions use fewer steps, meaning less resources are consumed to yield more product.
- Operations are simpler, and conducted at ambient temperature and pressure.

- Workplaces become safer overall, housing lower quantities of toxic solvents and hazardous waste products.
- Processes require less heat, pressure and protective equipment.

The reduction in hazardous materials and waste also helps decrease the time spent tracking, managing, and reporting on safety.

While always beneficial for Environmental Health and Safety (EHS) reasons, green chemistry can significantly reduce waste and cost. In addition, it can also be the key element that enables a drug to be manufactured commercially.

Learn more about Green Chemistry at Neuland.



## API Micronization Techniques for Use in Injectables and Medical Devices

Demand is steadily growing for pharmaceutical materials that contain micronized active drug substances (APIs) for inhalation and injectable delivery. These active pharmaceutical ingredients (APIs) are micronized for a number of reasons, generally performance-related.

For injectable drugs and inhalants, particle size distribution typically should be in the range of 2-20 microns, with a steep distribution curve and minimum amount of fine and oversized particles. Depending on the complexity of the formulation, device or inhalation delivery system, the particle size can vary. However, the majority of particles must be between 0.5-8 microns.

With injectable drugs, the particle size is reduced to increase the solubility of the drug, making it

dissolve more quickly, and allowing effective doses to be injected in smaller amounts. Poorly-soluble APIs can be improved by micronization, as it increases surface area and speeds up dissolution. For other dosage forms, micronization can be used to improve homogeneity in addition to increasing solubility.

### Micronization Defined

A particle size of less than 10 microns can be achieved in a number of ways, including controlled precipitation or using an external source of energy. A conventional method of reducing particle size is micronization, in which particles are reduced to a size of less than 10 microns.

Micronization typically refers to processes that use fluid energy to reduce particle size (e.g., jet milling),

compaction using a ball or bead mill, or other non-conventional techniques. Each of these techniques has advantages and disadvantages.

For example, bead mills are suitable for heat sensitive materials, but can also create some problems such as:

- Low productivity
- Reliance on large equipment and typically uses an external medium for grinding
- Potential particulate contamination
- Additional processing requirements.

### Non-Conventional Micronization

Something to keep in mind is conventional micronization may not be suitable for all drug substances. In the last few years, several supercritical fluid-based techniques have been proposed to produce



micron- and nano-sized particles. Three groups of processes used to produce fine and monodisperse powders are:

- Rapid Expansion of Supercritical Solutions (RESS)
- Supercritical Antisolvent (SAS)
- Particles from Gas-Saturated Solutions (PGSS)

These techniques are not without their limitations. By relying on CO<sub>2</sub>, they are held back by its poor solvent power, high cost and the need to use significant amounts. Despite the number of mechanistic studies available, confusion remains concerning how each variable affects the particle morphology and properties.

### **Common Challenges of Micronization**

API Drug Micronization involves many challenges, risks and considerations. Some of the most common are:

- The initial particle size of the API to be micronized – which plays a role in achieving the desired particle size.
- Reducing particle size also carries the risk of altering the morphology of the drug molecule, resulting in different polymorphs, amorphous APIs, or a mixture of crystalline and amorphous APIs.
- Micronized material is charged and may lead to segregation, clumping, and other possible physical instabilities during long term storage or in the formulation if it is not well controlled.

### **API Micronization – Jet Mills Preferred for Inhalation**

Jet mills (or fluidized jet mills) are the preferred method of micronizing an API for use in an inhalation dosage form. Jet milling micronizes drugs using compressed air or inert gas. The desired particle size is achieved by proper control of parameters.

### **Particle Size Distribution (PSD) Trials at Neuland**

Given our experience with inhalation products, Neuland has developed strong micronization capabilities – providing customers with different particle size distributions (3-tier specifications ranging from 2- 5 microns) with a very narrow particle size range, something that can be difficult to accomplish. Another challenge we've overcome is

achieving bulk density and flowability – critical traits for medical devices.

To fine-tune our techniques, Neuland has conducted particle size distribution (PSD) trials using the Design of Experiment model in line with QbD requirements, achieving PSD targets at the outer limit of the specifications. These experiments involved identifying, analyzing and fine-tuning a desired set of parameters to provide accurate, reproducible particle size distributions.

Selecting the appropriate technique for API micronization remains challenging. It is a complex process, reliant on an experienced team well-versed in the advantages and disadvantages of various drug micronization strategies.



# Quality & Regulatory

For more than 30 years, Neuland Labs has maintained regulatory excellence – achieving success in all of our 13 FDA audits and 31 inspections by global regulatory agencies.

Our philosophy is to exceed quality levels defined by our customers, while meeting stringent international standards. We continuously monitor various regulatory bodies worldwide in order to stay ahead of upcoming regulatory changes. This translates into a clear understanding of the possible future direction regulations and standards may take, ensuring that we implement appropriate

policies ahead of legislation.

With complex chemical reactions, quality monitoring takes on an even greater role as products transition across scale-up or are shifted from CROs to CMOs.

Neuland has been at the forefront of research and method development for the detection of genotoxic impurities (GTIs) in drug APIs. Genotoxic Impurities: Increasing Vigilance, But Still Some Uncertainty highlights evolving guidance surrounding the detection and quantification of GTIs, and discusses techniques for avoiding their formation.

We have embraced the rise of new quality approaches such as Design of Experiment (DoE) and Quality by Design (QbD). Our Process Analytical Lab focuses on robust technology development and process transfer to manufacturing.

In Leveraging QbD for API Scale Up, we share how a QbD approach can be used to understand and control processes based on sound science and quality risk management, while How to Strengthen Your API Supply Chain Management and Sourcing examines one of today's most urgent topics (and a key focus of Neuland Labs), supply chain security.



# Genotoxic Impurities: Increasing Vigilance, But Still Some Uncertainty



A genotoxic impurity (GTI) is a chemical substance that can directly or indirectly damage DNA or chromosomes and induce genetic mutations. Fifteen years ago, there were no specific guidelines for them.

In 2007, however, general awareness of the risk and consequences of GTIs surged when Roche's drug Viracept® was accidentally contaminated in a case that quickly became high-profile. Residual ethanol left in a storage tank reacted with acid over a long period of time, creating high levels of ethyl methane sulfonate (EMS) that remained in the product. The EMS levels in the tablets went undetected until patients who took them showed adverse effects.

Since then, vigilance concerning genotoxic impurities has grown, and regulatory standards have emerged. The regulatory standards governing GTIs, however, don't take long-term therapeutic usage (potentially higher, longer-term thresholds) into account, and some uncertainty exists regarding several aspects of the standards.

As some genotoxic impurities cannot be completely eliminated, emphasis is placed on sufficiently controlling them to comply with the impurity limits set by regulatory bodies.

## Threshold of Toxicological Concern

For unusually-potent impurities or those that produce toxic or unexpected pharmacological effects, the detection and quantification limit of the analysis should match the level at which the impurities should be controlled.

The Threshold of Toxicological Concern (TTC) is the level at which someone can be exposed to a genotoxic impurity in most pharmaceuticals with minimal risk, balanced with the therapeutic benefits of taking the drug. The TTC for intake of a genotoxic impurity is 1.5 micrograms per day. Low and high limits are case-specific and based on each compound's toxic potential.

To assess the potential for GTIs to affect drug quality, a proactive,

multidisciplinary approach should be used. A highly conservative limit, the TTC level can only be applied singly to individual GTIs when the impurities are not structurally similar.

With multiple structurally-similar impurities that are expected to act by similar genotoxic or carcinogenic mechanisms, total daily exposure should be evaluated in relation to the TTC. Appropriate individual limits should be applied to the sum of all structurally similar GTIs.

## How to Control GTIs

To best detect and control GTIs, we recommend using a planned set of controls – derived from current product and process understanding – that ensures process performance and product quality. Of paramount importance: selecting a route that doesn't use genotoxic-alerting intermediates or reagents – or a combination with the potential to generate GTIs. Controls include:

- parameters and attributes related to the drug substance and drug

- product materials and components
- facility and equipment operating conditions
- in-process controls
- finished product specifications, and the associated methods
- frequent monitoring and control

In a Pharmaceutical Technology peer-reviewed article, Neuland scientists shared a stability-indicating reverse-phase high-performance liquid chromatographic (RP-HPLC) method for the quantitative determination of potential genotoxic impurities present in pemetrexed disodium (form IV). The method developed was specific in determining the impurities at even lower levels than that of specifications.



# Leveraging QbD for API Scale Up

Using Quality by Design (QbD) and a Design of Experiments (DoE) approach, API manufacturers and CDMOs can reduce unanticipated challenges by developing deep process knowledge at lab scale – which aids in transfer to scale-up. QbD can radically transform the scale-up process, and help companies avoid unforeseen complications.

## Increased Regulatory Scrutiny and the Rise of QbD

Regulatory agencies are emphasizing the need for a more thorough understanding of products and processes prior to validating. This has led to widespread adoption of QbD (Quality by Design) approaches, which emphasize thorough process knowledge to avoid poorly-scaled processes.

QbD approaches typically use a Process Validation Lifecycle Approach, a holistic approach to development, which supports and leverages:

- Robust validation

- Uni/multi variants
- Use of modeling tools
- Use of prior knowledge
- Control strategy implementation
- Proactive process monitoring, including PAT for trending, continuous verification and continuous proactive improvement.

Scale-up is a critical link in this lifecycle. Without enough data, it can also be a 'what if' exercise. Insufficient process knowledge can result in poorly scaled processes. This typically translates into more Out Of Spec (OOS) results, reduced process reliability, as well as higher production costs and a lower profit margin due to increased reprocessing.

With development and transfer to scale-up, the challenges which arise tend to be in a number of different categories: safety, environmental, health, quality and economics.

## QbD Enables Robust Technology Development & Transfer to Manufacturing

With cause & effect analysis of Critical Process Parameters (CPP) on Critical Quality Attributes (CQA), QbD also aids in robust technology development & transfer at manufacturing plants. In order for QbD to improve in scale-up, an appropriate control strategy needs to be in place to ensure a focus on critical points.

## Engineering API Scale-Up

The involvement of engineers in the laboratory during development and optimization of a process is key to trouble-free scale-up and technology transfer. The extent to which engineers need to address scale-up of operations depends very strongly on the interaction between the chemist and the engineer, and the stage at which engineering became involved in the process.

## Drug Safety, Efficacy and Feasibility

This collaboration can mean the difference between a viable drug and one that had great potential, but was not practical from a manufacturing standpoint. It is customary to evaluate drugs on two pillars common to regulatory environments – efficacy and safety. In other words, does the drug perform what it needs to perform, and does it do it safely?

In the real world of drug discovery, development and commercialization, however, there is a third equally important pillar: feasibility.

A product can be determined to be safe and efficacious – but if it isn't feasible to produce (from either an economic or a technical at-scale production standpoint), then it isn't a candidate for success.

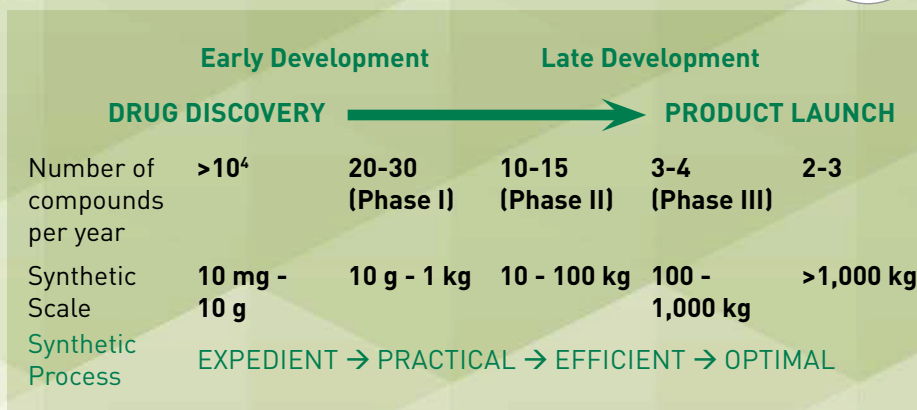
This is especially true since, often before a scalable chemistry process has been fully developed, chromatography (or, more specifically, process chromatography) is used for making materials in early-stage development.





## Collaborating Across Scales

When chemists and engineers work hand-in-hand during process development in R&D, processes tend to progress through scale-up easier. There are considerable differences between producing 10 mg batches and manufacturing 500 kg batches – and numerous engineering-related factors need to be taken into account. This chart describes the increasing scales in terms of the synthetic process employed – from expedient, to practical, to efficient and – ultimately – to optimal.



This is the role played by the collaboration of engineers and chemists (and the beauty of QbD, in general): ensuring the smooth transition from the expedient to the optimal while developing a safer process with optimized yield and quality.

While chemists tend to focus on process optimization, engineers focus on the scale- and hardware-dependent parameters, taking plant conditions under consideration. It is this dual approach that enables a 'Right at First Time' technology transfer. This can be achieved by adopting:

- A scientific statistical approach (QbD-DOE, ICH Q8),
- Simulation scale-up techniques (Dynochem / Visimix) for scale dependent parameters
- Lab validation of process in conditions simulating the plant
- The use of Quality Risk Assessment (ICH Q9) to evaluate each unit process and operations
- Development and manufacturing (ICH Q10, 11) of robust/safe processes

Because chemists and chemical engineers approach each challenge from different perspectives, multiple areas of expertise are needed.

### Chemists:

- leverage expertise in various types of synthetic reactions, based on both literature searches and hands-on experience.
- help select the route of synthesis.
- evaluate the feasibility of the selected route, optimize and validate the process to meet the predefined quality and yield.

- identify and characterize any impurities which have an impact on quality.
- perform generation and qualification of reference/working standards.
- maintain continuous interaction with IP for process infringement with any new process patents.
- perform process and method validation.

### Chemical Engineers:

- generate data on the material balance.
- evaluate energy balances to understand utility requirements for plant scale.
- select equipment for commercial scale for retrofitting or new, per process requirement.
- perform risk assessments (Quality, Safety) of unit operations, powder safety characterization studies, HAZOP & HIRA.
- evaluate particle engineering (particle size, bulk density, surface area & Polymorph).
- forecast potential for new technology implementation considering the volume of products, safety threats, troubleshooting activities related to the commercial products and more.

Some of the tasks in these lists involve collaboration between the two fields. Chemical Engineers, for example, are involved in process development quite early and also play a role in route selection/finalization.

Across the development phase of a project, both chemical engineers & chemists will work together to understand CPPs & CQAs of the process.

More interactions tend to occur once process feasibility has been confirmed and the generated compounds reach a passing level of quality. Once feasibility has been shown, the engineers will evaluate the process from a safety, health and environment standpoint. They then generate process safety data to create inherently safer processes.

Achieving successful technology transfer requires a robust manufacturing process, which – under QbD – is a collaborative effort, comprising Research and Development, Manufacturing Technical Operations, Quality and more.

The benefits of a QbD approach to scale-up are numerous:

- Better manufacturing efficiencies
- Higher yields
- Superior quality
- Enhanced process control
- Higher design space, resulting in global regulatory flexibility
- Fewer deviations and a scientific rationale for strong CAPA

QbD is an effective framework for bringing together a collaborative and inclusive team comprised of both chemists & engineers to ensure a successful API scale-up.

# How to Strengthen Your API Supply Chain Management and Sourcing

## How to Strengthen Your API Supply Chain Management and Sourcing

A pharmaceutical manufacturer is only as good as its supply chain. Supply chain management and strategic sourcing are the key drivers which keep operations running smoothly. Understandably, supply chain security is one of pharma manufacturing's most pressing issues.

## Set the Right Inventory Targets

When planning for the coming quarter, you need to ensure capacities are fully met. Adequate inventory of required items ensures continuous production thereby maximizing manufacturing capacities.

An OTIF – or 'On Time in Full' – calculation with a target of 95% is measured against pre-agreed benchmark lead-times. Timeliness of deliveries is measured against agreed timelines. To achieve a high OTIF score means balancing the cost of non-delivery with the cost of carrying higher inventory.

## Choose Pharma Supplier Sources with Care

It is critical to identify reliable sources that meet all aspects of your company's requirements. When

qualifying API supplier sources, consider these points:

- Synthesis route
- Regulatory standing
- Scalability
- Cost-efficient processes

At each stage of the process, look for sources who meet your expectations for the supply of drug intermediates and key starting materials (KSM) for new products.

## Line Up Multiple Sources

Once you've determined how to seek out and qualify your sources, you can use that same process to secure as many sources as possible for each KSM.

Sources can suddenly be disqualified or lost without warning due to unforeseen issues—anything from pollution and business viability to regulatory issues or other problems which might prompt abrupt closures or supply chain constraints. While being caught in a single-source situation may be unavoidable (due to specific expertise or infrastructure), new alternate suppliers should be continuously sought and added to your source base. Increasing the number of trusted sources you can access ensures your company's reputation (and reliability) is safeguarded.

## Aim High, with First Time Right Approach

With the goal of continuous improvement, employ a First Time Right (FTR) approach. FTR thinking focuses on suppliers and helping them to avoid potential rejections – internally though, it aims to focus and solve whatever gaps exist in specifications, methods and analyses.

By striking a balance between supplier focus and internal accountability, this approach can extend to everything from alignment of test methods including HPLC/GC columns and release procedures to pre-shipment clearance of CoAs. It can also be used to verify the recent manufacture of production batches with select suppliers of your KSM and intermediates, confirming the quality of incoming materials is in line with expectations.

## Ensure Regulatory Compliance of the Supplier Base

A compliance program designed for KSM and intermediate suppliers can keep your supplier base audit-ready. Such a program should emphasize traceability, and clearly demonstrate that all processes are performed in compliance with relevant regulatory standards and the quality agreements made with suppliers.

## Boost Performance

To improve supplier performance on commercial and technical parameters, you can measure and score:

- Supply competitiveness
- Supply quality
- Documentation support
- Compliance
- Speed of supplier response

All of these can be measured on an objective pre-determined scale, plotting supply base performance on two different axes of a Supplier Performance Dashboard. From there, Supplier Improvement Actions can be devised with the goal of moving the suppliers from three different sub-optimal quadrants (Q1, Q2 and Q3) to a more desirable fourth quadrant (Q4) [see image, at right].

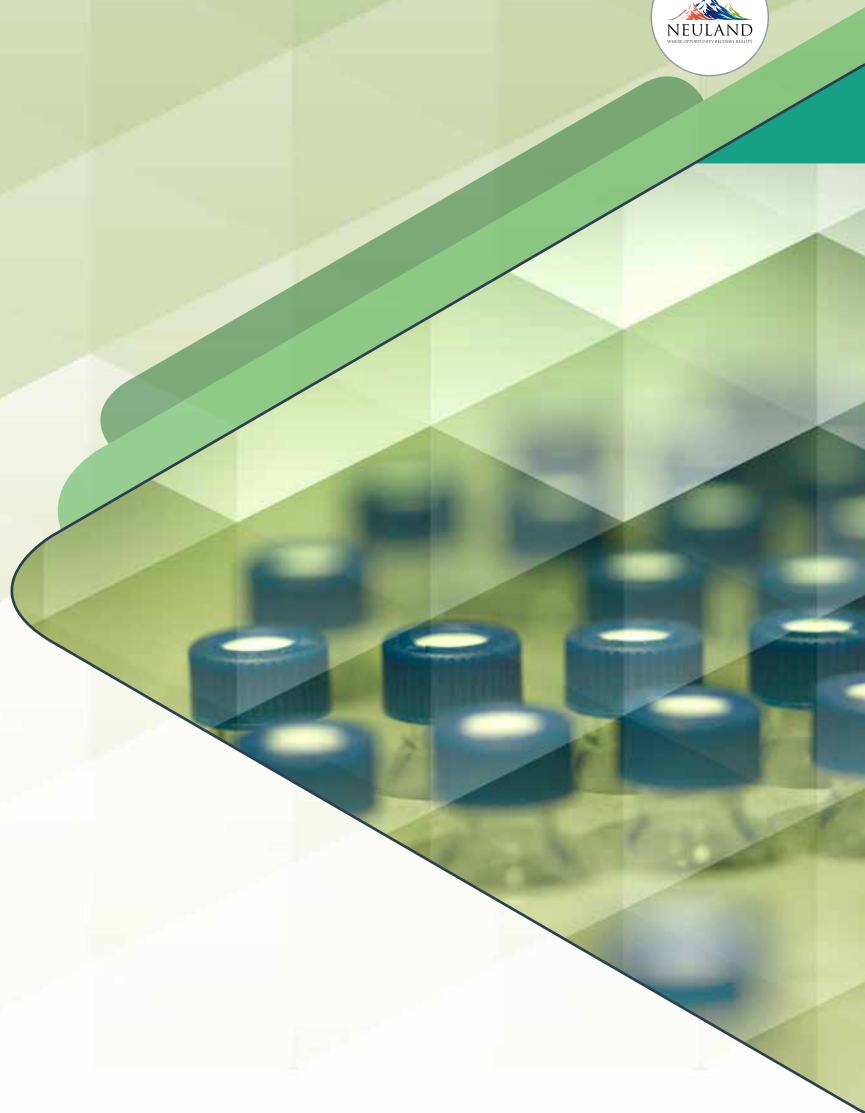
## Check Competitiveness

Buying competitiveness can be measured using relevant benchmarks. Via a transparent RFQ process, you can invite multiple quotes, and then fine-tune the results based on Commodity Price Trends.

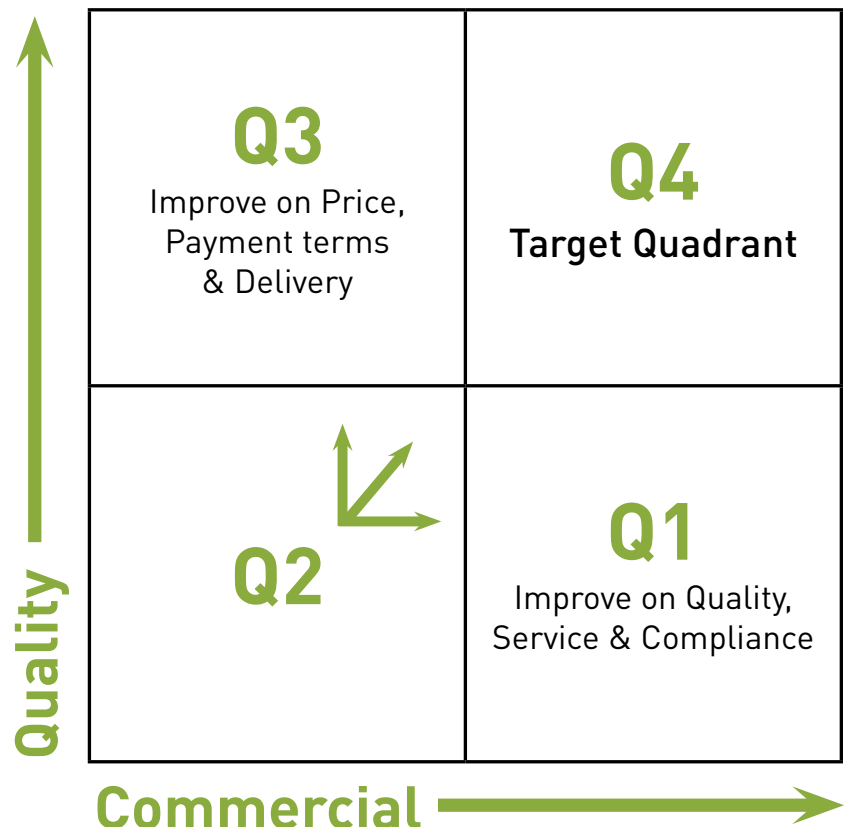
## Deliver On Time

A manual tracking program can be used to track outbound cargo from origin to destination, per delivery terms. The Outbound Delivery OTIF, which is an effectiveness metric, (at Neuland, for example, the target is >=95%) should reflect successful delivery lead-times vis-à-vis pre-determined target lead-times taking into account mode of transport and destination. Good performance in OTIF is a key indicator of an end-to-end supply chain that's working effectively.

By effectively pursuing and gaining visibility of demand to plan inventory, choosing and guiding sources that meet your expectations for quality, and keeping everything on track with an OTIF that makes sense for your business, you can manage your supply chain and sources with greater efficiency – improving your bottom line and benefiting your customers.



## VENDOR PERFORMANCE DASHBOARD





**Neuland Laboratories Limited**

Sanali Info Park, 'A' Block, Ground Floor,  
8-2-120/113, Road No. 2, Banjara Hills,  
Hyderabad, 500034, Telangana, India

**T:** +91 40 3021 1600

**F:** +91 40 3021 1602

**E:** [neuland@neulandlabs.com](mailto:neuland@neulandlabs.com)