

Process Considerations During API Development

This article looks at how the R&D chemist can adopt a systematic and prospective approach in the API development process to achieve documented, controlled synthetic processes. This helps to meet consistent product quality objectives and ease validation and scale-up activities.

The ultimate goal of drug synthesis research is to translate the laboratory method of making milligram amounts to a production process on a kilogram to ton scale while maintaining high quality and reproducibility at the lowest cost.

The term 'process' in the pharmaceutical industry is broad and can apply to the process development work that leads to the efficient, reproducible, economical, safe and environmentally friendly synthesis of the active pharmaceutical ingredient (API) in a regulated environment.

Given the increasingly stringent regulatory requirements and global nature of the pharmaceutical business, the pharmaceutical industry is continuously being challenged, resulting in increased competition and the need to produce high-quality APIs.

The process development of the API, whether it is new or generic, has subsequently gained more attention because of the possibility to establish early control over the process at the R&D stage by identifying and addressing the related issues *a priori*. Thus, a systematic and prospective approach in R&D is

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Because the data generated in the R&D laboratory must be accurate, reproducible and dependable, it is necessary to make and follow standard operating procedures (SOPs) for important activities, for example, the qualification and calibration of equipment such as weighing balances, standard weights, temperature indicators and reference standards.

key to achieving successful prospective API validation and scale-up. These activities are important and are frequently under the scrutiny of FDA investigators.

This article highlights the important process considerations for API development in the R&D laboratory, which can help chemists to understand and adopt a systematic and prospective approach in R&D, and to have documented, controlled synthetic processes. This can encourage consistent product quality and provide a good basis for achieving the goals of prospective validation and scale-up activities in the plant.

Documentation

Because the data generated in the R&D laboratory must be accurate, reproducible and dependable, it is necessary to make and follow standard operating procedures (SOPs) for important activities, for example, the qualification and calibration of equipment such as weighing balances, standard weights, temperature indicators and reference standards. It is also necessary to keep proper detailed records of these qualification/calibration activities, and other laboratory experiments, observations and related analytical data.

API development

It is important to gather all the current literature and possible future developments of the API in question and keep these in the one place. The most important challenges to overcome at the API development stage include

- patent infringement issues
- inconsistency in raw material quality and supply
- hazardous/nonregulated raw materials
- costly raw materials
- unsafe/environmentally hazardous reactions
- lower yields
- difficult-to-achieve level of purity (For example, enantiomers)

- scale-up issues
- difficult-to-handle processes
- polymorphism issues
- stability issues regarding intermediates/products

R&D chemists should devise a route that overcomes as many of these challenges as possible.

Cost

The costs of raw materials, packaging materials, processes and labour are the major cost-factors. R&D chemists can help to reduce the process costs by

- suggesting cheaper alternative reagents/synthetic routes
- reducing raw material consumption (by doing process optimization studies)
- shortening the process time cycles
- recycling the materials whenever possible.

Environmental friendliness

Today, R&D chemists are expected to use environmentally benign ('green') chemistry. Ideally, high yielding processes should be developed so that byproducts are not pollutants or are 'treatable' to eliminate pollution. Further processing of the mother liquor/solvent washes should be attempted to recover the unreacted materials/byproducts/solvents.

For example, a recovered solvent can be treated so that it can again match the desired quality specifications, and thus be recycled in the same process step. The gaseous products should be scrubbed effectively. The final spent materials from the scrubber and other processes should be assessed for its effect on the environment and be handled appropriately causing no environmental damage.

Solvent selection

The International Conference on Harmonization (ICH) guidelines have classified the solvents based on the risk to human health.¹ Class 1

solvents should not be employed in the manufacture of APIs. These include solvents such as

- benzene (carcinogenic)
- carbon tetrachloride (toxic and environmental hazard)
- 1,2-dichloroethane (toxic)
- 1,1-dichloroethane (toxic)
- 1,1,1-trichloroethane (environmental hazard).

The Solvents in Class 2 should be limited because of their inherent toxicity, for example:

- toluene
- dichloromethane
- chloroform
- ethyleneglycol.

Solvents in Class 3 may be regarded as less toxic and of lower risk to human health. These include

- acetone
- ethanol
- 1-butanol
- formic acid.

Process adaptability

R&D chemists should adapt a process to the plant environment. For example, to isolate a product, R&D chemists should avoid evaporating the solvent(s) to 'dryness' because this is not feasible in a plant. Instead, a suitable technique such as crystallization or precipitation should be developed because, in such cases, the product can be isolated by centrifugation or filtration process in the plant. Similarly, the purification of product should be achieved by means of crystallization or selective precipitation, instead of column chromatography as this is not feasible in the plant.

Methods of handling viscous materials in the plant must also be considered because the large surface area of plant equipment and piping can pose problems during material transfer. Solutions include performing a one-pot reaction using a suitable solvent to transfer such materials.

Reactions involving low temperatures or high pressures are difficult to handle in the plant and an alternative route should be considered.

Safety precautions

Material safety. At the time of route finalization, R&D chemists should collect all raw material safety information (normally Material Safety

Data Sheets [MSDS]). The storing and handling risks of such materials should be assessed, and appropriate measures taken to minimize them.

Process safety. During process development, significant consideration should be given to the safety of the chemistry being developed. The majority of industrially useful reactions are exothermic, suggesting the need for risk assessment.

Figure 1 shows the enthalpies of two common reactions to indicate the high degree of process hazard associated with them.²

The magnitude of overall heat release can be influenced by the type of solvents used, concentration, other simultaneous processes taking place, and so on. Together, this can have an enormous destructive power, if not controlled properly. Therefore, all such chemical processes that have the potential to be performed in the pilot plant should be subjected to safety evaluation.

Initially, the thermal stability of the compounds (raw materials, intermediates, etc.) should be screened by differential scanning calorimetry (DSC) to detect endothermic or exothermic behaviour. These results can then be used to decide if more careful measurements are required.

In some scale-up cases, an exothermic reaction can lead to thermal runaway, which begins when the heat produced by the reaction exceeds the heat removed. The rate of heat produced may increase exponentially. Once the control of reaction is lost, the reaction vessel may be at risk from over-pressurization because of violent boiling or rapid gas generation.

The elevated temperatures may initiate secondary, more hazardous runaway or decomposition. The possibility of such a reaction hazard should be assessed in the laboratory by employing methods such as thermal gravimetric analysis (measuring the thermal stability of the reactants or products) and the adiabatic calorimetry (measuring the decomposition and release of gases). A process should not be performed in the pilot plant before such safety assessment.

Other process hazards such as 'dust explosion' during milling or storage may also be assessed at an

early stage, depending on the potential of such risks.

Materials and vendors

To ensure consistent quality and supply of raw materials, packaging materials and other process components (such as the filtration media; gaskets; 'O' rings that may come into contact with the raw materials, process fluids, intermediates or the API) vendor audit/approval has gained importance.

Vendors should be selected using criteria such as their market recognition, past record, ability to supply consistent quality materials in time and customer orientation.

The Certificate of Analysis (CoA) and MSDS of the materials should be obtained from the vendors. Such information is useful while designing the specifications of raw materials and packaging materials, and for recommending storage conditions.

Developing the specifications

The in-house specifications can be developed based on 'user trials' results and the CoA of the vendor's samples.

Process/scale-up issues

It is important for R&D chemists to identify prospectively the potential plant issues and try to address them suitably at the R&D stage itself. Laboratory studies like the ones below can help to address many issues *a priori* to avoid 'surprises' occurring in the plant scale-up batches.

Simulating the R&D plant environment

Once the route is finalized, the plant environment in R&D should be

Figure 1 Enthalpies of two common reactions.

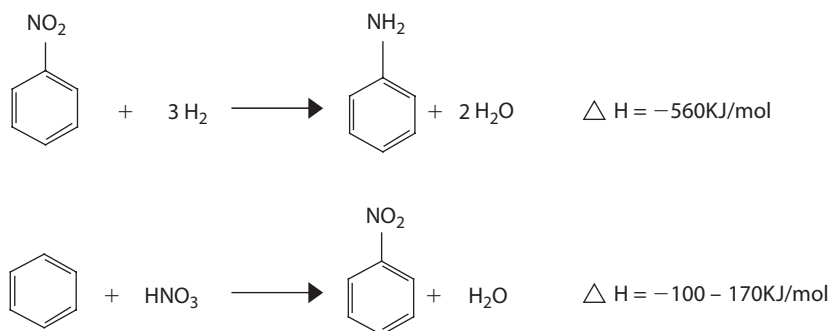
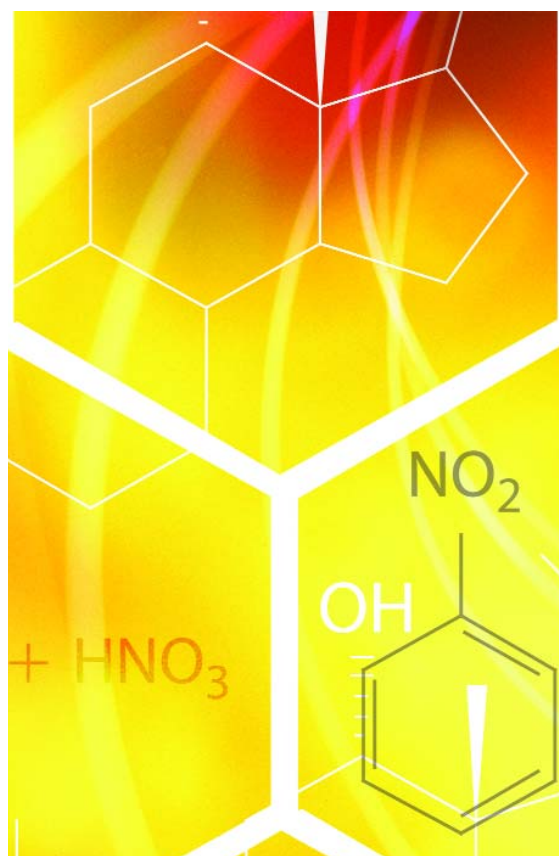
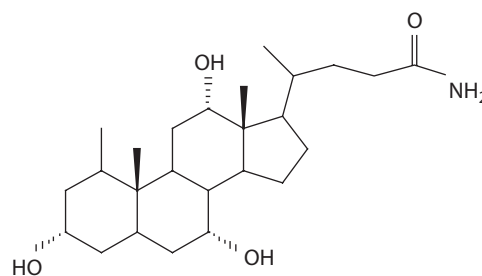


Figure 2 Cholamide produces different polymorphs when recrystallized with different concentrations of acetonitrile:water.



simulated as far as possible by

- Using similar material of construction [MOC]; shape of vessel; type of stirrer; number of baffles; D:L ratio (diameter: length) of vessel and so on.
- Using the same charging sequence of the raw materials.
- Using similar mixing patterns/stirring parameters that are achievable in the plant vessels (similar tip speed, power requirement per unit volume of the

reaction mass, etc. can be maintained in R&D).

- Developing suitable in-process sampling procedures that are feasible in the 'controlled' environment in the good manufacturing practice (GMP) plant.
- Using similar filtration cloth/filtration medium.
- Using a similar type of dryer and drying parameters.

Such simulation experiments can help achieve better reproducibility at

plant scale because the possible deviations can be minimized.

Determining the scale-up factor

Many scale-up operations require more time than laboratory-scale experiments because of the larger volumes of materials. R&D chemists should take into account the scale to which the process can be operated in the plant and the required time cycles for such process steps.

They should then increase the process time cycles to match the plant conditions in a laboratory experiment. The process steps that may be considered for such studies could include the following:

- addition of reactant
- mixing
- filtration
- centrifugation
- drying
- maintaining temperature.

The effect of such 'increased' cycle time on the product quality and yield should be assessed. Thus, a scale-up factor, which the process can be operated without affecting the quality and yield, can be determined prospectively.

Critical process parameters

While performing a laboratory experiment, R&D chemists can test the limits of some operating conditions such as time, temperature and pH, or the quality parameter of a key raw material (For example, water content/impurity level). The effect of such 'challenge' on the product quality and/or yield should be assessed. If a parameter adversely affects either of these, it should be identified as a critical process parameter (CPP) and be documented during the development stage. When scaling up, it is necessary to strictly control such parameters to ensure consistent product quality and yield.

Critical observations

During the R&D experiments, it is important to record observations, such as any signs of exothermic or endothermic activity during reaction, frothing, fuming, sublimation, pressure development, change in colour and change in phase.

Similarly, observations regarding the reaction rate (vigorous/mild), fil-

Table 2 Examples of isomers with different activities.

	Epinephrine (L)-isomer is 10 times more active as a vasoconstrictor than (D)-isomer
	Ketamine The (S)-isomer is anaesthetic. The (R)-isomer has little anaesthetic action, but is a psychotic
	α-Methyldopa The (S)-isomer is a hypertensive drug, but the (R)-isomer is inactive
	Amphetamine The (D)-isomer is a potent central nervous system stimulant, while (L)-isomer has little, if any, effect
	Ascorbic acid The (+)-isomer is a good antiscorbutic, but the (–)-isomer has no such properties
	Propranolol Only the (S)-isomer has the desired adrenergic blocking activity
	Asparagine (D)-asparagine tastes sweet, but the (L)-isomer tastes bitter

*represents a chiral centre.

Table 1 Chemical compatibility data.

Common chemicals	PE	PVC	HDPE	PTFE	Nylon	Ceramic	Viton	Silicon	Neoprene	EPDM	EPM	Epoxy	SS304	SS316	PP
Acetaldehyde	*	X	**	**	**	**	X	**	X	**	**	**	**	**	**
Acetic anhydride	**	X	-	**	X	**	X	*	**	-	**	**	**	**	-
Acetone	*	X	**	**	**	**	X	**	*	-	**	**	**	**	**
Ammonia solution	-	**	-	**	**	**	**	-	**	-	-	**	-	**	-
Ammonium carbonate	-	**	-	**	**	**	**	*	**	-	**	**	**	**	-
Amyl alcohol	**	**	-	**	**	**	**	X	**	-	**	**	**	**	-
Benzaldehyde	X	X	-	**	*	**	X	**	X	X	**	**	**	**	-
Bromine, liquid	X	**	X	**	X	**	**	X	X	X	X	*	X	X	X
Butyl acetate	*	X	*	**	-	**	X	X	X	*	**	**	-	*	*
Calcium chloride	**	**	**	**	**	**	**	**	X	**	**	**	**	X	**
Chloroacetic acid	X	**	-	**	X	**	X	-	X	-	**	**	X	X	-
Chloroform	X	X	X	**	*	**	**	X	X	X	X	**	**	**	X
Cyclohexane	-	-	-	-	-	**	**	X	X	*	X	**	**	-	-
Detergents	**	**	-	-	**	**	**	-	**	-	**	**	**	**	-
Diethylene glycol	**	-	-	-	**	**	**	*	**	-	**	**	**	-	-
Ethyl acetate	*	X	-	**	**	**	X	*	X	-	**	**	**	**	-
Ethylene oxide	-	X	*	**	**	**	X	X	X	*	*	**	-	**	-
Ferric chloride	**	**	-	**	X	**	**	*	**	-	**	**	X	X	-
Formic acid	**	X	-	**	X	**	**	*	X	-	**	**	**	**	-
Hexane	-	*	*	**	**	**	**	**	**	X	X	**	**	**	*
Hydrobromic acid, conc.	**	**	-	**	-	**	**	X	X	-	**	**	X	X	-
Hydrogen peroxide, 10%	**	**	**	**	X	**	-	-	X	-	-	X	*	*	**
Isopropyl acetate	-	-	-	-	-	**	X	-	X	-	**	**	-	**	-
Isopropyl ether	-	-	-	**	-	**	X	-	X	-	X	-	-	**	-
Ketones	X	X	-	**	**	**	X	-	X	-	X	*	**	**	-
Methyl acetate	-	-	-	**	-	**	X	X	**	-	**	-	-	**	-
Methyl bromide	X	-	-	-	-	**	**	-	X	-	X	**	-	-	-
Methyl ethyl ketone	X	X	-	**	**	**	X	*	X	-	**	**	**	**	-
Methylene chloride	X	X	X	**	X	**	X	-	X	X	X	**	**	**	X
Nitric acid, 10%	**	**	**	**	X	**	**	-	X	X	**	**	**	**	**
Oleum	-	X	X	**	-	**	**	X	X	X	X	**	-	**	X
Phenol	X	**	-	**	X	X	**	-	X	-	X	**	**	**	-
Potassium bicarbonate	**	**	**	**	**	**	**	-	**	**	-	**	**	-	**
Potassium cyanide, soln.	**	**	**	**	**	**	**	-	**	**	**	**	**	**	**
Propyl alcohol	-	**	-	**	**	**	**	**	**	**	**	**	**	**	**
Sodium acetate	**	**	**	**	**	**	X	-	*	**	-	**	**	**	**
Sodium bicarbonate	**	**	**	**	**	**	**	*	**	**	**	**	**	**	**
Sodium chloride	**	**	**	**	**	**	**	*	**	**	**	**	**	*	**
Sodium hypochlorite	-	**	X	**	**	X	**	*	**	*	-	**	-	**	X
Sodium sulfite	**	**	**	**	X	**	**	-	**	**	-	**	*	*	**
Sulfur dioxide	*	X	**	**	X	**	X	*	**	-	**	**	**	**	**
Sulfuric acid, 10%	**	**	**	**	X	**	**	-	X	-	X	**	X	*	**
Toluene	X	X	X	**	**	**	X	X	X	X	X	**	**	**	X
Water, fresh	X	**	**	**	**	**	**	-	**	**	**	**	**	**	**
Xylene	X	X	X	**	**	**	**	X	X	-	X	**	**	**	X

Indications: Suitable = ** Fair = * Not suitable = x Not checked = -

There is a need to make enantiomerically pure APIs when one enantiomer does not contribute to efficacy, but may contribute to toxicity.

tration rate, flow characteristics of fluids, nature of product (sticky/fluffy/amorphous/crystalline/semi solid, etc.) should be noted because the appropriate measures can be taken in the plant during scale-up.

Chemical compatibility studies

Certain 'process chemicals', such as process fluids and intermediates, may react chemically with 'plant items' such as process equipment, piping, flexible hoses and filters while in direct contact with them, which can lead to serious quality issues including contamination and impurity formation.

R&D chemists should consider all the process chemicals involved in the synthesis of the API and obtain the data on their compatibility with various MOC of all the plant items that may be involved during the operations (see Table 1 for the illustration of some chemical compatibility data³). In the absence of such data, in-house data should be generated by simulating the exact contact conditions in a laboratory experiment and the observations recorded.

For example, to determine the compatibility of a filter cloth with a process fluid, the sample piece of a filter cloth can be kept in contact with the process fluid for the specified time/temperature/pressure in a laboratory and the effect of the process fluid on the weight/size/shape/colour, and so on, of the sample cloth can be recorded. Such observations can help in deciding the suitability of various plant items involved in the process.

It is recommended that during the purchase of such plant items, an MOC certificate and chemical compatibility information should be obtained from the vendors.

Cleaning procedures

To develop a prospective cleaning method for plant equipment, a suitable cleaning procedure for similar laboratory apparatus should be established. In a typical cleaning

procedure, a similar 'flow pattern' of the cleaning solvent(s) as that in the plant equipment should be followed. The solvent(s) for cleaning, such as acetone, methanol and water, should be selected based on the solubility of the concerned product which is to be 'washed' from the empty apparatus. Cleaning observations and the results of the rinse samples may help to develop a prospective cleaning method for plant equipment during the scale up.

Stability data

The short-term stability data of the critical raw materials and intermediates should be generated in R&D under conditions similar to the plant environment. Based on these data, the packaging and storage conditions for the critical raw materials and intermediates can be established.

'Freezing' of specifications

As the processes are fully developed and optimized, the specifications of the in-process controls, intermediates, API and the packaging materials can be 'frozen'. No change in the process should be allowed without a 'change control' assessment and approval.

Working standards

A 'working standard' is a sample of highest purity that can be synthesized in R&D and purified to the maximum extent by repetitive crystallization/column chromatography. It can then be 'qualified' by comparison with a suitable reference standard, for example, a pharmacopoeal reference standard.

Stability

A representative sample of the R&D batch obtained by a 'frozen' procedure should be kept for stability studies. Therefore, the 'early indications' on the stability profile of future API scale-up batches can be obtained, provided the same process is followed.

Other important challenges

In recent years, API process development has become more challenging because of the need for making APIs with the desired 'enantiomeric purity' and 'polymorphic form'. The following examples justify the need for the stringent regulatory requirements in these areas.

Enantioselective synthesis. More than half of the drugs used in clinical medicine are chiral compounds.⁴ Yet, the majority of these are still prescribed as racemates. There is a need to make enantiomerically pure APIs when one enantiomer does not contribute to efficacy, but may contribute to toxicity. Some interesting examples of isomers with different activities are described in Table 2.⁵

The data indicate that there is a need for enantioselective synthesis in many racemic APIs. In such specific cases, the process must be more thoroughly validated to ensure the formation of only the desired isomer. The other isomer(s) should be considered as an 'impurity'.

Furthermore, it must be ensured that there is no 'epimerization' taking place during formulation, storage or in the human body to avoid adverse side-effects.

Polymorph synthesis.

'Polymorphism' is the ability of a substance to exist in two or more crystalline phases that have a different arrangement and/or conformation of molecules in crystal lattice. Many APIs exist in various polymorphic forms with different properties such as crystallinity, bulk density, solubility and bioavailability. Some interesting cases of product recall as a result of the issue of drug polymorphism are given below.⁶

Abbot Laboratories had to withdraw its HIV protease inhibitory drug Norvir (Ritonavir) from the market because an unwanted polymorph of the drug had been produced (Form II) during shelf life. This form has a different dissolution rate to the known polymorph (Form I), so the bioavailability of the drug was affected.

Chloramphenicol-3-palmitate has 'Form B' as a metastable form having 8-fold higher bioavailability than the other polymorph 'Form A'. This can

create a danger of fatal dosages when the unwanted polymorph is unwittingly administered as a result of alterations in process and/or storage conditions.

These examples suggest the need to identify all the polymorphs of an API at R&D stage. One can establish the polymorphs by determining physico-chemical properties, thermodynamic stabilities and by studying conditions of inter-conversions. Some useful tools for such determinations are Fourier Transform Infrared Spectroscopy (FTIR), X-ray Powder Diffraction (XRPD) and Differential Scanning Calorimetry (DSC).

The formation of a specific polymorph may depend upon the type/composition of the solvent(s), temperature, synthetic route, storage conditions etc.

An interesting example of solvent composition giving different polymorphs is cholestamide⁷, which gives needle-like crystals (Form I) by recrystallization from a solution of 1:1 acetonitrile:water and platelet-like crystals (Form II) by recrystallization

from a solution of 25:1 acetonitrile:water. (Figure 2).

Once the desired polymorph has been identified, the process of the API must be validated to obtain the desired polymorph consistently. Furthermore, the stability protocol of the formulated drug must include some suitable tests to ensure that there is no change in the polymorphic form under these conditions.

Conclusion

The various process considerations mentioned in the article can help the modern-day chemist to understand and adopt a systematic and prospective approach in R&D to achieve documented, controlled synthetic processes. This can help in meeting the product quality objectives consistently and can build a good basis for achieving the goals of prospective validation and scale-up activities in the plant, which are considered to be important and are frequently under the scrutiny of the regulatory authorities such as FDA investigators.

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