API Manufacturing: A Road Map for "Green" API Manufacturing

Tags: API's, Girish Malhotra, green process development, pharmaceutical manufacturing, sustainable manufacturing

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In 1972, while working for a state environmental protection agency, I rejected an operating permit for a chemical plant. The rejection was based on the insufficiency of the plant's emission control equipment and technology. The company submitted a remediation plan and the operating permit was granted.
Fast forward to 1986: I met a chemical company executive and, during the conversation, discovered he had been associated with the chemical plant whose permit I had denied. He told me that the permit denial was the best thing that had happened to the plant, because it forced the company to review its processes and improve its process technology, which resulted in considerably reduced emissions. The investment payoff was much quicker than expected.
The point of the above is to suggest that green chemistry and processes can be simple and have significant financial benefit. Being green requires dedicated thinking and application of fundamentals of science, mathematics and applied sciences, which are taught in most Chemistry and Chemical Engineering curricula.
Active pharmaceutical ingredients (API) are specialty chemicals that have a disease curing value.
Production of any chemical involves two major steps.
* Chemical reaction
* Purification/separation to produce a saleable solid or liquid.
In every chemical reaction, a key raw material is reacted with other chemicals in the presence of solvent to produce the desired chemical. Catalysts are used to expedite the reaction. Solvent used could be water and/or an organic material. Sometimes a reactant participating in the reaction can also act as a solvent. Temperature, pH, heat of reaction, and solvent are an important part of the reaction as they influence the rate of reaction. The physical properties of each chemical used and produced in the chemical reaction are very important as they define the unit process. The combination of unit process and unit operations is used to produce the desired chemical.

Green process development

Green process development begins in the laboratory, when potential chemistries and drug candidates are being considered. The current thinking in pharmaceutical manufacturing is that it's okay to come back and fix the process later. Unfortunately, later rarely happens, or if it does, it's not an easy fix. We have to think that every chemistry and the corresponding process will be a commercial success. If we develop a process with such a mindset, most of the processes will be environmentally friendly.
Every reaction and separation step of a chemical process is crucial. We have to be cognizant of the development work in the laboratory. Every process step in the development of a chemical product has to be simple so that the corresponding unit operation is the simplest and produces the highest yield. It's all right to check the progress of development work by monitoring the conversion of each reaction step using the best analytical instruments. However, this does not mean that we have to use the same or similar instruments to monitor our commercial processes. If we have to rely on analytical instruments at each process step in the commercial operation, it shows that we have not completely understood the process and there are opportunities to improve the process. Previous articles have discussed some of the do's and don'ts of process development and improvement [1-8].

I have outlined a road map for green process development, based upon my experiences in the lab. The fundamentals of the road map will stay the same in most situations, though they can certainly be modified to suit different process development needs.

Reaction steps

My basic rule of thumb is that the majority of non-optimized multiple simple reactions will have a yield of about 60% to 68%. This yield range might seem odd but invariably suggests that it would be quick and easy to improve yields of such processes. Yet most of the time in the pharmaceutical industry, the overall yield is lower. This suggests an opportunity to improve processes and their yields. This also suggests that many processes are overly complex and need revised chemistries, conditions and methods.
Lower yield means that the key raw material and associated reactants are producing undesirable products that have to be properly treated and disposed. In addition, based on stoichiometry, there is excess of some raw materials. Since most APIs are toxic, their disposal becomes important as they can harm the environment.

The reaction steps of a synthesis need to be reviewed individually and collectively to comprise a green process. We can use the items from Table 1 for such a review. These are not necessarily in any order. I use them as guidelines, not as rules.

Table 1

1. Do we have the physical properties of each reactant and intermediate? Collection of this information can be difficult. However, it is necessary to design a unit process and operation.
2. Do we understand the total process feasibility? To do so, each unit process step has to be reviewed individually and collectively.
3. Do we know the solubility of our chemicals? It is an important processing criterion and can influence separation and cycle times significantly.
4. Is the stoichiometry optimized? This can be difficult initially but with experience becomes second nature.
5. Are the heat and mass balance known? Again, this is necessary, as they will be used to design the unit operation. We can use the heat of reaction (exothermic and/or endothermic) in the reaction process and the subsequent unit operation.
6. Are the reaction kinetics understood and applied to simplify the process? Our effort should be to achieve zero-order reaction. It will reduce reaction time and improve conversion yield.
7. Can a single solvent in addition to water be used for the whole process? This economizes solvent recovery and the related investment. Relative physical properties of the solvent and water can facilitate the separation process.
8. Can we eliminate the isolation of intermediates?
9. Are the raw materials to be used easy to handle? Liquids are easy to handle, and if solid raw materials can be solubilized, batch or continuous processing will improve.
10. Are the safety requirements met and is the process safe?
11. Is the process meeting all environmental standards?
12. If the process developers were operating the process, what process modifications and/or additions would be included to have the simplest process? This may seem like a mundane exercise, but it is important. The simplicity of processing is critical and allows us to reduce processing time and have an environmentally friendly process.

Phase separation:

In most reactions, we have to separate the reaction product. The simplest way is to use two liquids of significantly dissimilar densities, with one phase dissolving the desired product and the other withholding the undesirable product. Density difference of the two phases and the lowest mutual miscibility will facilitate the separation. Density and solubility criterion can be an effective tool for proper solvent selection. We should always keep in mind environmental and safety aspects of solvents.
Another method to facilitate the reaction is to azeotrope the solvents and recover/reuse the solvents. Facilitation of the reaction sometimes involves co-distilling the solvents and recycling the desired solvent back to the reactor and removing the reaction by-product with the undesirable solvent.
Unit operation considerations:

The information developed and learned above is used to develop the necessary unit operations for commercial production. This can be a challenge, and the process engineer's creativity comes into play. The selection criterion should be: simplicity, maximum up-time, least use of disposables, and ease of maintenance. Economics, creativity and personal choices lead to the unit operation selection. We can use the following in the selection process.

1. What are the simplest and proper unit operations to achieve the necessary result?
2. Are the necessary steps in place to reduce the cycle time?
3. What is the best unit operation to minimize the process time?

To recap, lower conversion means that there is a potential for raw material loss, which has to be recovered and/or treated in the effluent system or disposed of as hazardous waste. Lower conversion also means that unless the unconverted raw materials or impurities are removed prior to the subsequent reaction steps, additional impurities will be created, adding to the process complexity.

We need to minimize or eliminate rework. Rework is a drain on profit margin. Investment in equipment is needed to reprocess materials to saleable products.

A thorough understanding of every interaction provides a complete grasp of the impact of every process change and its influence on product quality. If the above considerations are followed all the time, Quality by Design becomes a natural part of the development process. In addition to the above considerations, each chemistry and process has its nuances and, if recognized, can be used to simplify manufacturing processes further. Their incorporation also allows one to have complete process control. One can react to any unexpected changes and deliver quality.

If we have done all of the above, then we have a process that will produce quality product by design rather than by analysis.

The following are some examples in which the above-mentioned criteria were used to simplify processes.

In a reaction, two reactants were used in the presence of a catalyst to produce an intermediate. One of the reactants acted as a solvent. The mole ratio of the solvent and the other reactant (key raw material) was about 14 to 1. Due to the nature of the reaction, by-products also formed. The reaction yield was about 50%. Solvent was recovered and reused, but due to the excess use of one reactant and the low yield, overall productivity of the process step was in less than desirable.

Alternate method: The solvent was reduced by 75%. The batch was heated to the boiling point and the key raw material along with the catalyst were added to the vapor stream. The reaction product was removed as soon as it formed as it had a boiling point similar to the solvent boiling point. Since the reaction product was removed, it did not have an opportunity to react with the solvent and produce unwanted product. Yield and productivity improved considerably. Batch productivity improved considerably. These improvements prompted consideration of a continuous process.

U.S. Patent # 6,037,483: This patent describes the preparation of 3-bromomethyl-3-methyloxetane. The process as described in the patent is complex. Preparation of oxetane is completed over two days and involves the isolation of an intermediate and use of a solvent. If this process as described in the patent is commercialized, it will definitely be expensive.

Alternate method: A close examination of the chemistry and reaction kinetics suggests that it is possible to conduct the reaction in about three hours without the use of the solvent and isolation of the intermediate. The yield would be over 85% and productivity much higher compared to the process described. Higher yield and shorter time can be achieved by changing the reaction temperature and order of reactant addition.

U. S. Patent# 7,109,203: This patent, in its first example, describes diazotization of an aniline and subsequent sulfation to produce benzene sulfonyl chloride. The process described is a batch process and if commercialized as described could take a long time. However, diazotization and sulfation are zero-order reactions. A batch process could be completed in a very short time depending on the scale of the process. I have executed similar chemistries by using a continuous process.

In each of three examples above, addition of chemicals and control of the reaction exotherm requires creative addition and applications of unit operations that we have been taught in our chemical engineering curriculum.

One can go on giving examples of how process chemistry can be simplified and improved, and processes can be made eco-friendly. But in the final analysis, each reaction step has its own nuances and they have to be dealt with accordingly. For the development of a great and "green" process, it is necessary to challenge the chemistry and its execution. All this might seem a significant challenge and frustration as we go though

the laboratory and scale-up. However, the rewards after the first few challenges are enormous as the process chemistries become simple to execute.

Not only do such process development techniques provide the lowest-cost product, but they also provide quality product all the time from the start. They minimize raw material use and waste treatment and reduce the plant effluent load. This road map leads us to green processes in comparison to existing processes. Profitability and the whole business process improves.

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