

# The Value of Batch Process Design in a Chemical Engineering Education

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## *White Paper*

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<sup>†</sup> I want to thank my colleagues, past and present, for inspiring and adding to the thoughts and ideas presented here.

## Abstract:

Process design for the batch industries, particularly pharmaceutical process design, relies heavily on collaboration across technical functions and across time. Whereas traditional chemical development can occur in just a few months, pharmaceutical development spans many years and has many requirements beyond providing a manufacturable process. This has interesting applications in the education of tomorrow's chemical engineers, particularly with respect to providing guidance on how traditional chemical engineering activities are aligned closely with the larger efforts of the business.

## 1. Background

A batch process is any manufacturing process that runs in short time bursts, where the quantity or scale of manufacture does not justify continuous operation. Nearly all pharmaceutical production is done in batches, for both the active pharmaceutical ingredient (the chemical) and the drug product (the pill). Specialty chemicals, by their nature of being "specialty," are commonly produced in batches. These might be high-performance materials, new chemicals looking for a market, some agricultural chemicals, inks and paints, and many others. Biochemical processes, depending on their scale, are run in batches or semi-continuously. Commercial food production is often done in batches, though there are aspects that appear semi-continuous. Alcohol production is batch wise—even mass produced beers are fermented in large batches.

Chemical engineers learn this from the outset of their education; the cut-off between batch and continuous production is one of the first things discussed in chemical engineering 101 courses, along with the basics of doing material and energy balances. After this discussion, the chemical engineering education—at least when it comes to production-scale—is focused almost entirely on continuous production environments. Given that the vast quantity of chemical production is done via continuous production, this makes sense.

However, chemical engineers have been moving into non-traditional markets, where batch production dominates. A great value of chemical engineering concepts is that the basics apply in non-traditional markets just as they apply in traditional chemical and petroleum endeavors. While engineering schools are adding deeper study of batch processes and biotechnology, there are aspects of the larger business environment that should be included in the education of future engineers. These areas of focus include collaboration, the time it takes to develop manufacturing processes, and regulatory hurdles.

## 2. Batch Process Development

Within the business, the general goal of batch process design is the same as any other process design work: devise a process that is safe, documented, repeatable, efficient, and meets regulatory requirements. The work that goes into a process design happens at various stages throughout the business cycle of bringing a new product to market. *Figure 1* gives a view of where batch process design fits into the larger business flow for process development. None of these boxes are labeled "design" because it happens throughout the development workflow.

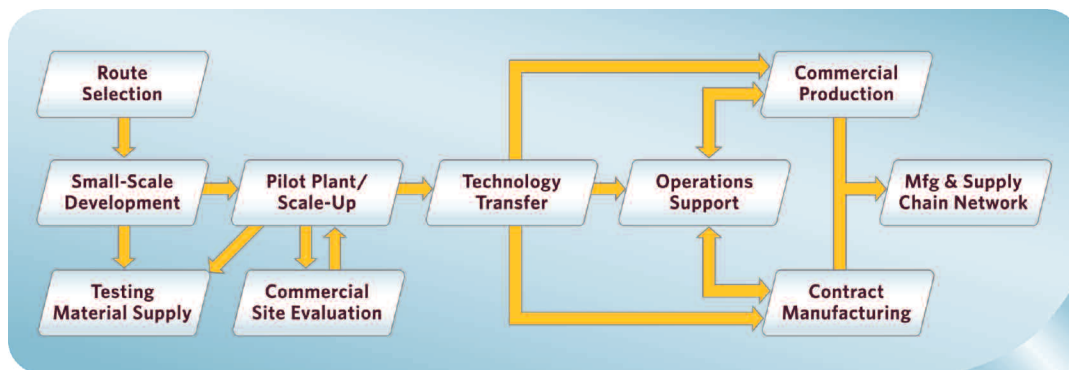


Figure 1: A view of batch process development activities

At the earliest stage, a new product arrives through the research organization (or via contract from partner organizations). The first stage of development, **route selection**, is to design the basic set of chemical/biochemical transformations to make the product at a reasonable scale from the commonly available raw materials. Along with the key bio/chemical expertise, the process of route selection seeks input from process development and production engineers for the kinds of operations that are most easily managed in the available equipment. In addition, the procurement organization will provide estimated costs for raw materials. Even at this early stage, organizations will begin to consider where they intend to do long-term manufacture of the product, and they will start negotiating with suppliers for price on raw materials or key production steps. *Figure 2* is an example of a route view of the process.

With a basic route selected, the process goes through a series of **scale-up** cycles from laboratory scale to kilo labs to a pilot plant and eventually into manufacturing. At each stage, more and more detail is added to the process design and to the know-how for this process. A process that may have been described as a simple sequence of reactions on a single sheet of paper grows to become a recipe in the lab (such as in *Table 1*), and it eventually expands to a full set of operating instructions that can be several hundred pages long. Along with the scale-up activities, the organization must supply materials for testing, formulation studies, packaging trials, market trials, clinical trials, and other needs.

At some point during the process, the business must decide how and where to make the product, the **site evaluation**. The decision depends on how well the process fits into the available plants from both a processing perspective and the anticipated load on the facility. Process fit involves exploring whether the equipment is sufficient to achieve the process conditions of the product. The load question involves demand forecasts for existing and future products that are made in the plant. To handle the highly uncertain nature of new product demand, some companies set aside "launch" facilities, where they plan to manufacture a new product for its first several years and then shift to another facility for long-term manufacture. If no facility will fit the process, decisions may arise about expansion and construction of greenfield sites. Alternatively, a company may decide to use a contract manufacturer to produce some or all of their product. This, of course, raises another set of issues related to managing the process and guaranteeing quality, but contract manufacturing is on the rise as companies focus on their core skills of innovation and marketing.

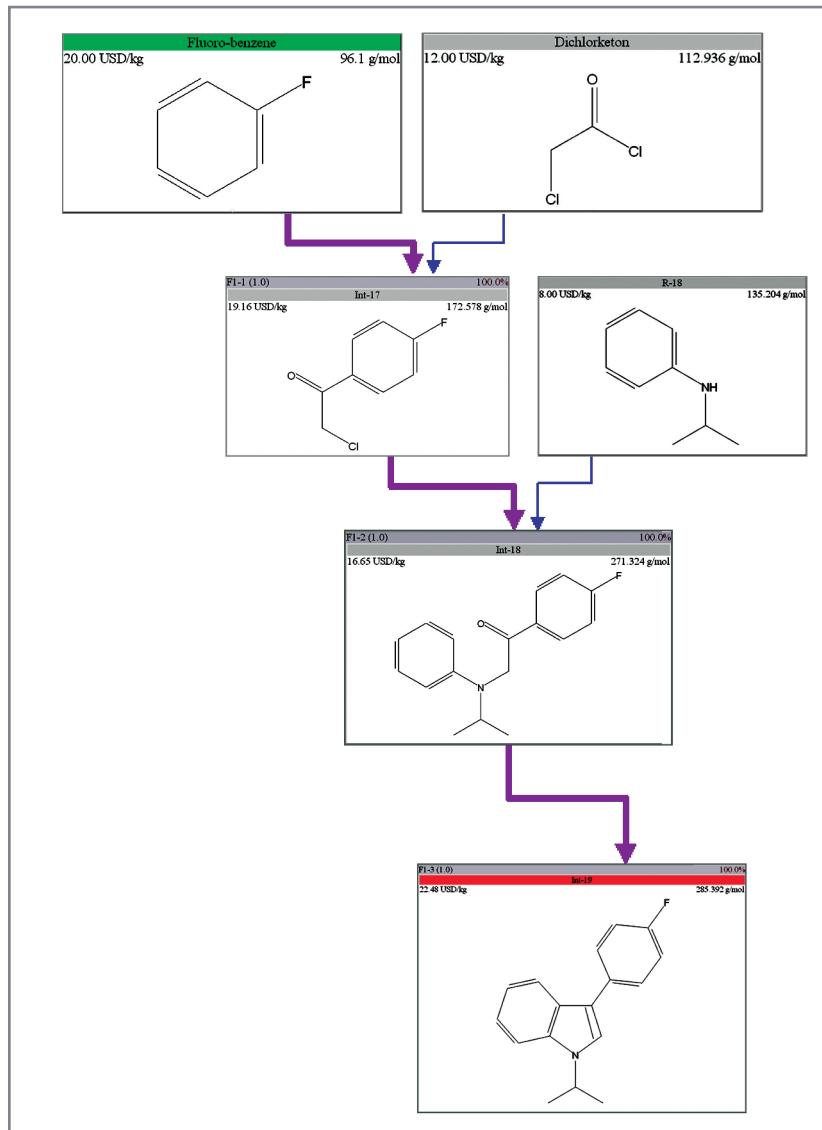


Figure 2: Route view of a process

Aspirin R&D Process
1. Reaction 1.1. Charge Erlenmeyer Flask, 250 ml with 0.003 kg of SALICYLIC-ACID. Dissolve the following components: 100% of SALICYLIC-ACID. 1.2. Charge Erlenmeyer Flask, 250 ml with 0.006 liter of ACETIC-ANHYDRIDE. 1.3. Charge Erlenmeyer Flask, 250 ml with 0.001 liter of 85% $H_3PO_4$ . 1.4. React in unit Erlenmeyer Flask, 250 ml via Aspirin Synthesis. The final temperature of the batch is 75 C.
2. Crystallize 2.1. Charge Erlenmeyer Flask, 250 ml with 0.02 liter of WATER. 2.2. Crystallize the batch in unit Erlenmeyer Flask, 250 ml. The following components are separated in the crystal phase: 100% of ACETYLSALICYLIC-ACID. Ramp the temperature to 25 C.
3. Filtration 3.1. Filter the batch from unit Erlenmeyer Flask, 250 ml in filter Filter Flask, 250 ml. 3.2. Wash the cake in unit Filter Flask, 250 ml. For each wash, use 0.0025 liter of WATER. Spent Wash Stream: The stream belongs to category: Solvent Recovery.
4. Drying 4.1. Transfer contents of unit Filter Flask, 250 ml to Evaporating Dish. 4.2. Dry the batch in unit Evaporating Dish. The drying time is 30 min. The drying temperature is 100 C. Evaporated Solvent: The stream belongs to category: Solvent Recovery.

Table 1: A simple text recipe

At the right time, the development activities shift from scale-up and tweaking the process to transferring the process, knowledge, and responsibility to the manufacturing location. During **technology transfer**, there are many coordinating activities and requirements for a successful transfer, such as validated trial runs that show the manufacturing site can produce within specifications. This is a key requirement in regulated industries, but it is important for many high-value products, as slight deviations can have a detrimental impact on the final quality or performance of the product in the marketplace.

Once settled into manufacturing, organizations have the opportunity (and obligation) to continue monitoring the performance of the process and the quality of the final product. While it is ideal to have the best process in the plant from the outset, that is difficult to achieve in reality, particularly since new technology and new regulatory oversight continue to change expectations. Even without these changes, the manufacturing site is subject to its own changes in product mix and demands from the market, so the manufacturing process must be updated continually and improved to fit the current circumstances.

Depending on the business, this sequence of steps may happen all together over the course of a few months (specialty chemicals), or it may happen over several years (pharmaceuticals), or somewhere in between. On the shorter time scales, the development activity may go right from a new product to designing a process for manufacturing scale, eliminating or reducing a number of activities in *Figure 1*.

While this description focuses on processes that include at least one chemical or biochemical transformation, the general concepts apply to formulation development: creation of the full-scale process that meets the safety and quality requirements, and within the appropriate time-frames.

### 3. How is batch different from continuous?

After understanding the basics behind batch process development, the key elements that are unique to the batch environment begin to surface. Some of them have to do with designing and managing the process itself. Other differences are associated with how process development fits into the larger framework of the business and its goals.

On the process design side, the main difference is on the focus of the design work: the product itself. The typical approach is to design the transformations, find appropriate solvents and anti-solvents for processing, and use fairly standard unit operations to process the materials. At the **pilot plant/scale-up** stage (*Figure 1*), the detailed development of a step looks very similar to traditional conceptual design for chemical engineering, which focuses on designing and optimizing the unit operations, once the transformations have been decided.

Recycle strategies in the batch industries are different. There is no continuous recycle with purge and make-up streams. At best, manufacturing facilities have solvent (and other) recovery systems to provide fresh, to-specification materials for use in subsequent batches, or in other processes. Design for recycle in batch operations focuses on ensuring that impurities can be removed in the recovery operations, so on-specification materials feed back into the next batches.

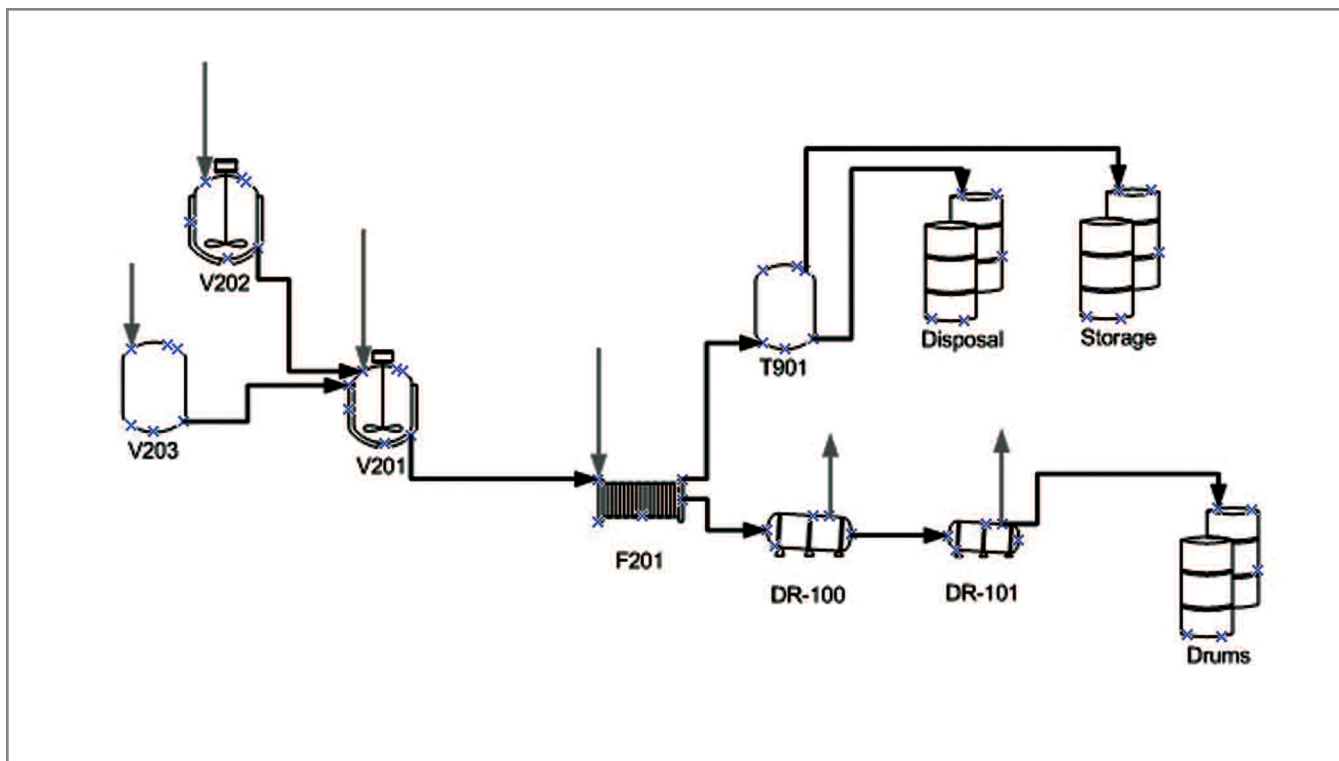


Figure 3: Flowsheet view of a step

Control strategies in the batch industries are at once simpler and more complex. They are simpler in that operations focus on one activity at a time, rather than the entire process. But the complexity arises with the addition of dynamic behavior everywhere. If you need to tweak the last few percentage points out of a fermentation operation, then you need a multivariate, dynamic controller that monitors conditions in the fermenter and keeps the process on the appropriate trajectory while adjusting nutrients, temperature, etc. Multivariate, dynamic control strategies are making their way into many complex batch operations where quality considerations are a must.

Another element is the visualization of batch processes. Depending on the purpose and the level of development, batch processes can be drawn or described many ways:

- *Figure 2* - The basic set of transformations (A -> B -> C -> Product)
- *Table 1* - The text “recipe” or instructions for conducting these transformations
- A block diagram, describing the sequencing of operations
- *Figure 3* - An equipment-centered or plant layout view for process fit and logistics studies
- *Figure 4* - A Gantt-chart view of an individual process or a collection of processes running in a given facility to adjust schedule operations

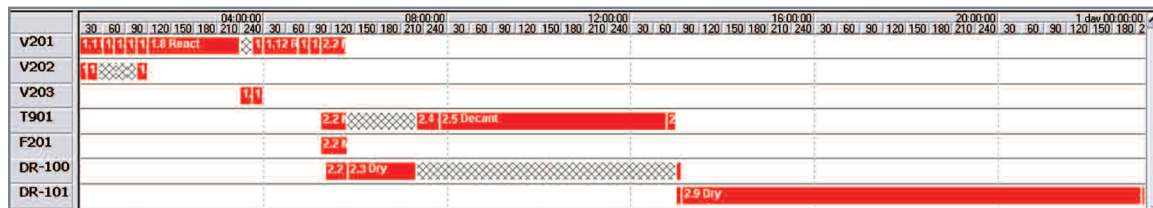


Figure 4: Schedule view (Gantt chart) of a step

There are many other process visualizations, including standard stream reports, materials balances, and cost-of-goods analyses. Note that these all need to represent the time aspect of batch operations in some way. For example, cost-of-goods analyses must account for labor and other operating expenses, based on the time the process consumes.

On the business side, there are a number of interesting aspects of this visualization that offer good educational opportunities—for engineers in particular—in terms of batch process design.

Engineers are not the leaders of many of these businesses. In the pharmaceutical world, it is typically chemists and biochemists who develop the initial process routes and shepherd them through the development cycle, where engineers are more heavily involved. In formulations areas, it is pharmacists or the ink-and-dye experts who design the basic process. As a result, the final process that ends up in manufacturing frequently looks very similar to the process that ran on the lab bench of the original chemist. Another reason why this occurs is that in pharmaceuticals and other regulated industries, the requirement to provide materials for clinical trials locks the business into the basic process quite early in the development cycle. Significant changes to the process require proof that businesses produce the exact same product, and this leads to conservatism in terms of advanced engineering optimization of the process at the later stages. This is a circle-of-influence issue; as awareness about manufacturability rises, the value of engineering input into the Route Selection stage also increases.

Specialty chemical is much closer to familiar territory for chemical engineers, and as a result, many concepts of process optimization have made their way into that arena.

Again in pharmaceuticals and other regulated industries, the level of documentation required is another difference or challenge in batch process design. In fact, most companies call out high-quality documentation as one of the primary deliverables from the development process. This aspect, however, is not taught as part of the standard engineering curriculum - possibly not in any discipline. The FDA and its worldwide counterparts require higher and higher levels of quality and verification throughout the development of new drug products and their processes. It is often quite an education to see the impact of these rules first hand.

Whether the development timeline is measured in months or years, another key element is the required level of collaboration across many disciplines in order to develop a high-quality process, produce trial materials, and create the required documentation. People are involved from many layers of the company as well as every imaginable discipline: chemists, biochemists, lab technicians, chemical & biochemical engineers, pharmacists, formulators, operators, controls engineers, quality control analysts, regulatory filing experts, procurement

specialists, contract manufacturers, and many others. These people must all work together and not just on one project, but across the portfolio of projects over time. In addition, these projects will pass across many desks and lab benches. People must understand the impact of their actions and decisions on the rest of the team and project. Those who have the skills and aptitude to work in a highly interactive environment are bound to do well, and they just may have that ability to influence others outside their formal area of responsibility.

## 4. Where do Chemical Engineers play?

Engineers will continue to play important roles in the traditional areas of skill in scale-up, optimization, and operation of chemical and biochemical processes. Beyond these core competencies, chemical engineers have the opportunity to influence batch process development throughout the batch process lifecycle.

At the earliest stages of development, engineers need to add their voice to the definition of the best route for new products. Ideally, engineers work hand-in-hand with their colleagues to develop robust processes at the outset of route selection. The most influential engineers may also find their influence moving further upstream into discovery operations, leading to selection of the best candidate compounds based on their likely processability, manufacturability, and controllability.

Quality by Design represents an excellent arena for chemical engineers to become involved in pharmaceutical process design. The FDA is asking pharmaceutical companies to provide clear documentation on the “how” and “why” of key process variables. They are looking for proof—whether by experiment, model, or industry practice—that the process by which new drugs are made is under control. From the perspective of chemical engineering, the FDA is asking for a clear definition of the design and operating space for the process. Not only should they know how to run at nominal conditions, but operators should be able to react to process upsets and still produce high-quality product within the design space.

## 5. Educational perspectives

How does all this relate to the education of tomorrow’s chemical engineers? From a basic perspective, schools should continue teaching conceptual design of chemical processes. They should continue expanding the variety of projects under study in the engineering curriculum, while exploring advanced control strategies and their impact on time-varying operations, such as those found in batch operations.

In light of the larger business in which batch process design resides, engineering programs need to expand their reach into how engineers can positively influence the work of their colleagues from all over the sciences and business. Design projects should be set up to include business students, chemists, and other engineers in order to provide early exposure to the variety of perspectives that other disciplines bring to the same set of questions.

Schools should also teach project management; don’t assume that overwhelmed students will figure it out on their own. My experience is that they either do everything at the last minute (Student’s Syndrome) or they create more work for themselves than necessary (Parkinson’s Law).

In addition, schools should offer courses and seminars in the regulatory environment. It is not only the FDA that heavily influences how engineers do their work, but the EPA and many other bodies play a role in engineering activities. They can be looked upon as impediments to growth—or we can view these regulations as opportunities to solve interesting problems in the context of the larger public need. Encourage students to understand why and how these regulations are created, both the scientific view and the political view.

## 6. Batch Process Development

AspenTech has a number of software products that support batch process development activities throughout the development arena. The best AspenTech simulator for teaching the overall batch development approach is probably Aspen Batch Process Developer since it is used by the industry in many aspects of the process development workflow. A number of other products provide solutions that would be valuable in expanding on specific elements of modeling and design courses.

Additional information is available at: <http://www.aspentech.com/corporate/university/index.cfm>

## 7. Conclusion

While batch processes are a common element in chemical engineering education, the larger business context in which batch process development occurs is a key element for growing the engineering curriculum. It's important for schools to grow students' abilities in project management, collaboration, interdisciplinary understanding, and the impact of regulation.