

Pharmaceutical Manufacturing: Is It the Antithesis of Creative Destruction?

PAT and QbD can only move forward if the industry sheds its habit of QbA (i.e., quality by analysis)

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Is the pharmaceutical manufacturing the antithesis of creative destruction? Before we answer the question, it would be worth defining “creative destruction.” In 1942, Joseph A. Schumpeter defined it simply as innovation and new technology that changes the status quo. [1] According to Alan Greenspan: “a market economy will incessantly revitalize itself from within by scrapping old and failing businesses and re-allocating resources to newer, more productive ones.” [2]

Since 2004, FDA has been cajoling pharma manufacturers to incorporate methods that are being practiced by chemical and other manufacturers and to move from “quality by analysis” to “quality by design.” It is interesting that FDA has put forth QbD, PAT, and what I call an “alphabet soup” of acronyms with the hope that the industry would improve its manufacturing technologies. These concepts, along with design of experiments, Six Sigma and Lean Manufacturing have value, if applied properly with the fundamental understanding of reaction kinetics and unit operations. However, in the pull and push between old ways and new ways, the old ways are still winning.

What are the “old ways”? One of the cornerstones of the pharmaceutical industry is quality. The product has to be the same irrespective of the day, the year, or the plant location. With quality being paramount, every effort is made to have repeatability and consistency. The pharmaceutical industry has achieved quality by “analyzing” everything at every step of the manufacturing process. This can be raw materials, intermediates and formulated products. This has been and is the driving culture to achieve quality.

In order to support “quality by analysis,” devices, instruments, analytical tools, and methods are available so that every bit of information produced can be compared against a standard, can be correlated, and used to resolve any deviations. The focus has been analysis of everything, and these tools necessitate that the process be analyzed as it is being conducted. This prolongs the cycle of the batch process. There is nothing wrong with “over-analysis” to ensure consistency as long as the associated costs are covered.

But have we gone so far in our effort to achieve quality by methods that are inefficient that we have forgotten to apply the basic principles of chemistry, physics, math and engineering to the manufacture of specialty chemicals and their formulated products? In the name of quality, it is easy to justify and acquire these expensive tools, which require equally expensive manpower to operate. We should ask ourselves, are there any simpler and less expensive methods that can give us equally good information?

It seems that in the case of pharmaceutical manufacturing we are victims of “analysis paralysis.” We are living in our comfort zone and have not used our creativity and knowledge base to innovate. Other industries use quality by design, but we have overlooked what is happening in the outside world.

Pharmaceutical companies are excellent at inventing new molecules that cure diseases. However, they are not so good at developing commercial processes. Most API processes are multistep (sometimes over 10 steps). If we understand the chemistry and correlate its nuances to commercialize, we can have excellent processes that will deliver quality from onset. We will move away from “quality by analysis” to “quality by design.”

Therefore, what is the relationship of creative destruction to pharmaceutical manufacturing? If one looks at other industries, there is constant evolution of technologies and/or manufacturing methods leading to better, friendlier and greener products and processes. We have seen this in almost everything we touch, use, eat and wear. We have seen the same in the pharmaceuticals as far as new drugs that are used to treat diseases.

However, if one looks at the manufacturing processes for these drugs, technologies are stuck in early 20th-century mode, which is quality by analysis. A majority of API are produced using batch manufacturing methods. In the last few years, there has been considerable discussion of continuous processes for API manufacturing [3-12], but little progress along these lines.

From trade news and other discussions, one can deduce that there is significant apprehension and skepticism about moving from batch to continuous processing. It is being written as if it is a monumental task, as if pharmaceutical manufacturing is going to a different planet. [13] I am sure continuous process development projects like one by Novartis at MIT have been attempted by other pharmaceutical companies, but have been abandoned due to realignment of priorities or lack of champions within. I believe the Novartis/MIT program will succeed as it is being conducted outside the company confines.

We can only conjecture the following reasons for the pharmaceutical industry not looking at newer manufacturing technologies (improved batch or continuous processes):

1. Ethical pharmaceutical companies have been able to get their desired prices in the market because of patent protection on drugs. The companies can charge the highest price the market will bear.
2. Generic companies have developed niches for particular drugs and have divvied up the market. Their drug pricing might be lower than that of ethical drugs but is still based on the highest prices the market can bear.

Since ethical and generic pharmaceutical companies are able to achieve their desired gross margins on individual drugs, they have not had much incentive to change their development and manufacturing technologies and/or business practices.

Many factors are beginning to change the business landscape. With approximately \$100 billion of drugs coming off patent in the next four years and the new drug pipeline sputtering, pressure to retain profit margins is high. With various governments constantly negotiating lower prices, margins are being squeezed. Mass-merchandisers have entered the fray to offer significantly lower prices. With increasing health care costs, drug prices have come under the microscope. There has been discussion of a new national healthcare program, and if this comes to fruition it will affect every pharmaceutical company and its profitability. This begs the question, what can be done to improve profit margins?

Some efforts to preserve profit margins have led to layoffs, off-shoring of R&D and off-shoring of manufacturing. The pace might accelerate as generic companies capture much of the \$100-billion market of drugs coming off patent.

Margins can of course be improved within pharmaceutical manufacturing. For example, inefficient manufacture of APIs influences the total pharmaceutical business. Table 1 illustrates the effect of the inefficiencies. With respect to API manufacture, every effort has to be made to maximize the yield of each process step and the overall yield. If an effort is not put forth to improve the existing batch processes and potentially move to continuous processes, we will see turmoil leading to instability.

Result	Reason	Effect
Poor yield	Lack of understanding of the process chemistry and/or inefficient translation to commercial scale	<ol style="list-style-type: none"> 1. Loss of raw materials 2. Higher investment per unit output 3. Higher waste treatment costs 4. Inefficient business processes 5. Long cycle time 6. High inventories of raw materials, in-process materials and finished goods
Process variability	Same as above	Inability to apply process controls to eliminate/ minimize process variability

In the specialty chemical business, yields above 80% or 85% are considered acceptable. However, in API manufacture, which is also specialty chemicals, yields as low as 50% are acceptable as long as the product cures a disease and there are willing customers.

It is necessary that the process development chemist and engineer develop a process that has the highest yield and is the simplest whether it is a batch or a continuous process. It is not difficult to develop such processes if sound principles of chemistry, physics, math and engineering are applied. We need to take the exotica out and bring simplicity into pharmaceutical manufacturing. We need to get out of the prevailing quagmire. If a bicycle can give us quality results, we do not need to have a Ferrari. Processes based on these principles are simpler to scale up and commercialize. It is also easier to incorporate Lean manufacturing and Six Sigma to have a process that delivers quality as planned rather than quality by trial-and-error method.

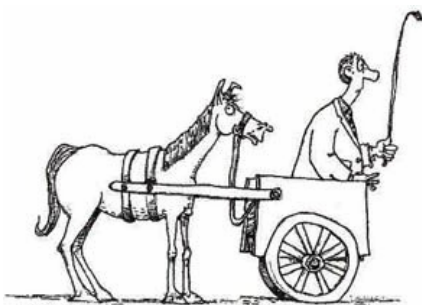
The hot topics in pharmaceuticals for the last few years have been PAT and QBD. However, reading various articles and publications, one gets the impression that it is difficult to justify these improvements and investments. This should not be the case.

What do we need to do to get pharmaceutical technology to the 21st century?

Of PAT and QBD, the first letter of this dynamic duo is “P” and pinpoints the word of which we need to have absolute grasp/control before we address the other five letters. “P” stands for “process” and unless we have an understanding of process, chemistry, and its nuances and understand how to translate these to a simple commercial process, high-priced analytical instruments will not deliver quality. Sometimes one gets the impression that the use of analytical technologies will automatically deliver quality and technology. These instruments just tell what us mistakes we have made but do not cure the mistakes.

Without an understanding of process, we will not be able to pinpoint all of the savings to the whole business process. Thus, we can not justify expenditures. If through process understanding we can improve the API yield by 50%, and improve overall equipment utilization by 50%, and even then we cannot justify revamping the process, then we have serious business issues. When I see low yields and low equipment utilization, it clearly states that we did not understand “P”.

Thus, it is imperative that we put the “P” of PAT before AT; otherwise, it would be like putting the cart before the horse and we will not be able to financially justify and achieve our goals.



I believe that pharmaceutical manufacturing needs to shed its addiction to old ways of manufacturing and implement methods that will improve its profitability beyond the patent term—that is, change its ways of living from one drug to another.

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