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The Secret Life of APIs

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8 comments

Active pharmaceutical ingredients (APIs) make the pharma world go 'round. Without them, any finished drug would be a mere placebo.

So why is it that 99 percent of the discussion taking place about pharmaceutical quality by design (QbD), process analytical technology (PAT), and other “new” methodologies (*actually, there’s nothing new about them, and those of us in the know have been using these methods for at least four decades, but I digress*) focuses on finished drug products, and leaves APIs out entirely?

In this blog series, I’ll try to right this wrong.

My goal is to share my views on the API value chain and the issues affecting their development, manufacture, and distribution. How might we develop and manufacture APIs at minimal cost and optimal quality, the first time and all the time?

In other words, I’ll explore how we can bring a QbD approach to the API world.

First, we have to accept the fact that QbD is not a technology toolkit (I’ve been horrified by the number of articles I see describing QbD as a technology platform!) but, rather, a disciplined way of incorporating the fundamentals of chemistry and chemical engineering. Done right, it will create a process that yields quality product consistently, and despite variations in raw material sources, but will meet established quality specifications.

Through these posts, I’ll present my view of the ideal path to consistently safe and high-quality APIs. Some readers will disagree with my views, and some will have better ideas. I hope that you will share them! My intent is not to challenge, but to review a process that will be required if we are to continue to produce quality products, consistently, at the lowest cost, using sustainable and safe processes.

Surely our creativity, imagination, and ingenuity will allow this to happen. But this process can’t just start at the end of the chain. It must start with the API, which, after all, defines each drug.
First, let’s quickly review API manufacturing. Active content in a tablet ranging from fractions of a milligram to hundreds of milligrams results in variable annual demand for APIs (from a few to more than 100,000 kilograms). In isolation, these numbers might not mean much, but they are critical in process design and production planning.

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Unfortunately, other things get in the way, too, particularly the reliance on “Quality by Analysis,” or the common practice of analyzing every step of a reaction process to ensure that the process is progressing as expected. This “Analysis Paralysis” approach is already inefficient. But it stifles innovation and creates ripples of inefficiency in other business areas, including how we manage our supply chains and use capital equipment and other assets.

Under “AP” mode, our focus is on complying with regulations for safety, health, and the environment, rather than optimizing our processes so that they exceed regulatory expectations and enable continuous improvement.

As engineers, chemists, and other trained scientists, we learn the fundamentals that allow us to use QbD methods to design processes. However, we still don’t incorporate them fully into day-to-day operations. This isn’t because they’re not good ideas, but because business practices blind us to the need to optimize.

At a time when blockbusters (drugs whose annual sales are a billion or more dollars) are coming off patent right and left, why are we are still stuck in the mindset of finding and developing new blockbusters? Some new drugs, recently approved by FDA, serve only 3,000 patients worldwide.

In the early 20th century, demand was focused on the developed nations. Patents could be fully enforced, and there was minimal threat from developing nations.

Since the single API volume per site was generally low, it made sense to manufacture the APIs in batch mode, using the same or similar equipment that was used to produce non-drug products and fine or specialty chemicals. There was minimal consideration about the manufacturing technologies, because the costs related to inefficiency and regulatory compliance could be passed on to the customers. Profits were high, as the pricing was based on need rather than competition. In the early 2000s, the playing field began to change. With patents expiring or being challenged, more countries placing price controls on pharmaceuticals, and new drug pipelines drying out, many companies are scrambling to prop up their balance sheets. One way they do this is through acquisitions, an unproven strategy that often yields only short-term results. Acquisitions are not going to increase pharma's new drug development success rate.

Business realities are changing rapidly today, and pharma must capitalize on opportunities that it has been ignoring for decades. The time has come to bring innovation to both API and finished drug manufacturing, and to bring more jobs back onshore, whether that shore is North America, Europe, or (as costs of doing business there continue to increase) China or India.

Are you with me? We will follow this with a brief questionnaire to help us discuss and shed more light on current practices in the industry. Look for it next week!

Additional Reading:

¥ Neglected Tropical Disease Drugs: What Are They Telling Us About Innovations?
¥ Opportunities vs. Reality

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