CPhI Pharma Insights

UBM

Part 1.

Preventing innovation inertia

PANEL MEMBER
Girish Malhotra, President at EPCOT International

Pharma's future is putting innovations in the hands of innovators

Introduction

Pharma's future is putting innovations in the hands of innovators, not regulators – but we need to end the inertia before it's too late

Girish Market Predictions:

- Warns that in the next few years we will lose valuable process advances if regulators don't stop dictating approaches
- We are seeing a 'cultural dogma' in pharma companies where their approach is only to meet regulations and companies become devoid of process advancements
- Foresees that, maybe, if given freedom by forward thinking pharma companies, CDMOs may have the incentives to innovate new process and manufacturing improvements and be a key part of the solution
- Is hopeful that if the regulators are listening in the next few years they will enable a manufacturing technology innovation environment, by shortening approval time to three months. That way commercial and financial considerations can dictate innovations – e.g. continuous manufacturing is an ongoing case in point

Who is Responsible for Manufacturing Technology Innovation: Product Developer/Producer or the Regulator or the Equipment Supplier or the Contract Manufacturer

Sometimes answer to a question exists and everyone is aware of the answer but is ignored for one self's convenience. However, it is good to ask the question again to refresh and reinforce the existing and an established answer. We all know the answer to the question 'Who is responsible for the product quality and manufacturing process technology innovation for any product?' Answer has been in front of us since the Stone Age. It is 'the manufacturer and manufacturing process developer who is the creator of the product'. Other entities can, and do, assist in the process. But, I am revisiting the question and the answer to ensure that we all are on the same page. It is my perspective and not intended to question the creativity and imagination of any individual or entity.

Since the Stone Age humans have innovated and created products and processes that improve life and lifestyle. Time after time human creativity and imagination has delivered and transformed our understanding through the Stone age, the Industrial Age to the Information Age. Remarkable contributions have been made. As the products and processes developed with time, innovators also realized that every useful product and/or process may and may not be safe for the consumers and workers. However, over time product quality, consistency and process safety gained importance. Since many products impact human

life, regulatory bodies were created to safeguard consistent product quality, integrity and safety. They achieve this by using robust and reliable processes, as a result product quality consistency became critical for the survival of businesses. Regulatory bodies were also created to assure environmental preservation for generations.

Product producers even with the best processes and product quality "at times" live at the edge to maximize their profits. This is true for most enterprises. This is not a bad thing, so long as producers can maintain product quality, their safety and profits.

If we focus on the chemical industry – and that includes pharmaceuticals as its subset – the manufacturing philosophy is to maximize profits whilst retaining product quality and their safety. This is economics 101 and the basic building block of every business. Competitive pressures keep companies on their toes for product quality and safety through manufacturing process technology innovations and continuous improvements. Again, every manufacturing technology innovation has to come from the product manufacturing organization (1,2). In addition, their incorporation in every process has to be justified. Companies have to make sure that they do not run afoul of the regulatory requirements. If they do, they deserve to be penalized with no exceptions.

Following entities participate in making sure that each manufacturing process and product follow certain norms. Focus here is on pharmaceuticals.

1. Process Developers, Designers and the Commercializers
2. Equipment suppliers including CMOs (contract manufacturing organization)
3. Regulators

Process Developers, Designers and Commercializers

Design of type of process for chemical synthesis and formulation depends on product demand. Generally manufacturing processes fall in two categories batch or continuous. Their definitions are well established (3,4) and accepted for over two hundred years. Chemists and chemical engineers manipulate chemical synthesis steps, unit processes and unit operations, to create an economically viable process. Same happens for the formulations. Understanding and exploitation of physical and chemical properties of chemicals have a significant role in process development, design and commercial operations (4).

Creativity and imagination play a significant part in selection/manipulation of unit processes and unit operations in development, design and commercialization of an innovative and economic process. The resulting innovations can many a time stump even the equipment manufacturers. They, after justification, may be incorporated in the manufacture and formulation of chemicals; pharmaceuticals being a subset of chemicals. Each process especially continuous processes are chemistry, formulation and demand specific. Thus, the philosophy of batch process, that many products fit the same equipment, does not apply for continuous processes.

In the design of a pharmaceutical process and/or product like in any chemical synthesis or formulation process, chemists and engineers are assigned the task of creating the most economically viable process that produces quality products from the get go using safe processes and practices. Actually, instead of being assigned, it is expected they will create and commercialize such processes. They follow what is normally taught in their curriculum and hands-on training. If the commercialized process does not produce quality product the first time, it suggests all of the necessary process design considerations have not been incorporated in the process. Every "t" has not been crossed and every "i" has not been dotted. It could point to lack of experience and also suggest short comings in their education. If the expected norms are followed, product

quality is built in rather than tested in. Harsh words, but shortcomings ultimately lower profits.

However, if an external enterprise suggests/tells a manufacturing enterprise that it has to build quality in their products, the manufacturing organization is essentially being told that it has failed to do what is expected from them – i.e. design and produce quality products from the start. With this lack of a quality culture, long-term viability of enterprises can be in jeopardy. By having outside guidances/directives on process design, quality and manufacturing methods or technologies, I believe our universities are also being indirectly told that they have failed to teach process developers and designers value of innovation and creativity in process design.

As stated earlier product demand and volume dictates the type of process (batch or continuous) that will be used. Investment and profits of the company depend on the process selected. Process type, batch or continuous, have established definitions (3,4). One cannot and should not ignore these established definitions and misrepresent realities. In addition, one should not, and cannot, create their own definitions to suit their objectives.

Since discussion and use of continuous process pharmaceuticals has become the latest fantasy, it is necessary to acknowledge and differentiate between a batch and a continuous process. Batch processes operate part time during the 8,760 hours that are available per year. Batch campaigns can be done multiple times during the year to satisfy the product(s) demand if the demand is not large enough to operate 8,760 hours per year. A continuous process (5) means an 8,760 hours per year production of a single product with minimal or no downtime. Downtime means the time when the product is not being produced. It includes time for preventive maintenance, generally pre-designated, or time due to fix un-expected process upsets. Downtime for a continuous process is accounted in the product standard cost.

Ironically many drug formulations have the demand to be produced using continuous processes but the producers have opted not to do so. Reasons and rationale are not known. Could it be internal reluctance or tradition? My conjecture "it is the combination". The majority of the APIs, except for less than ten, are produced using batch processes even if they could be produced using a continuous process.

Equipment Supplier and C/DMO (Contract Developer/Manufacturer Organization)

My definition of equipment supplier is much broader than the generally accepted definition. I have included contract/developer manufacturer and the equipment supplier in the same category. My basis is that each is a vendor that loans or sells their equipment to a company that needs to produce a product. CDMO can facilitate process development as discussed earlier.

Equipment suppliers provide relevant machineries for different unit processes and unit operations that are used in a batch or a continuous chemical synthesis or formulation process. Each innovates equipment and associated process methodologies to gain edge over competitors. The process developer (client) has to be sold on the efficacy of the equipment or the process. Process economics plays a vital part in equipment/process selection. Financial justification has to be made by the client. It is to be noted that the same processing equipment can be used in a batch or a continuous process. Determination of how the equipment is used is made by the process developer/designer and is based on product demand and is not made by the vendor or the regulator.

Contract manufacturer (CMO) uses client company's process and fits it in their equipment to produce the desired quality product. CMO personnel can be a facilitator and innovator, but they still have to sell their innovations to the product developer. Again, everything has to have financial justification.

Regulators

It is my understanding that the primary task of the regulators is to assure consistent and repeatable quality product is available independent of type of manufacturing (batch or continuous) process or for that matter any and every manufacturing process. Regulators have established cGMP practice guidelines that need to be followed. They have the obligation to approve the manufacturing process and the final product rather than endorse type of manufacturing method. As indicated earlier, process selection and product quality assurance are the responsibility of the manufacturing company.

Regulator's endorsement or suggestion of type of processes/methods that should be used, in my estimation, is unethical or is tantamount to favoritism for a type of process and is synonymous to interference in manufacturing company's decision-making process or the equipment supplier's business. It is also, as stated earlier, questioning the competence of chemistry and chemical engineering curriculums of our universities who have trained the best of the best worldwide. If the chemists and chemical engineers at the companies are not continuously creative then our universities and companies have not trained them adequately and our educational institutions as well as the companies have not crafted an environment for continuous innovations and improvements.

FDA's recent blog (6) gives the impression that investing in continuous process will lower costs and produce quality products. This could happen if the process meets the demand and operating criterion outlined earlier. Each continuous process design and equipment configuration are product and demand specific. The blog does not recognize that unlike batch process equipment where many products can be produced in the same equipment, continuous process design cannot be used to produce other products unless the chemical synthesis and formulation needs are exactly the same or are similar. It seems that this is a critical differentiation is not understood by the blog author.

Regulators as well as the product producer, developer and equipment supplier cannot change science based established definitions without due process and public review, which applies to create new or change established definitions. Lately this has been done without any explanation.

Since the regulatory bodies are making suggestions about "how and what" of manufacturing processes, a question needs to be asked is "are these suggestions/ recommendations being made by the personnel with actual hands on experience in process development, design, commercialization and operations of chemical or pharmaceutical plants that produce salable products? Have they justified such investments?" If they have not, I wonder about the credibility and authenticity of their suggestions.

I would also like to ask the regulators "how much effort they have made to simplify the drug filing and approval processes which could immensely lower cost to the approval filing costs (7)?" I believe recently some effort has been proposed, but how long it will take to become a reality is anyone's guess.

More than ten years ago regulatory bodies suggested that the companies should move from Quality by Analysis (QbA) to Quality by Design (QbD). Companies should have questioned this suggestion as QbD is the basic building platform for every commercial process. It is ironic that many companies diverted significant attention to this suggestion as if they were not practicing QbD. It is well accepted that to produce a quality product every company has to have repeatable command of the process, which is QbD. My conjecture is that significant monies has been spent by the companies whether they follow QbD practices. It could have been better spent elsewhere. Did the companies get any return on the monies spent? Most likely none.

I equate such regulatory suggestions to like telling a master chef how to slice and dice onions who practices the art to perfection every day. Since quality issues still persist, my conjecture is that the companies still do not have absolute command of the processes or are not following good manufacturing practices. It is interesting to note that with QbD fervor fading and another fervor (continuous manufacturing) as discussed earlier that needs to meet the established definition and has to be economically justified is taking hold. Continuous manufacturing in pharmaceuticals is a long way from reality (8).

How Manufacturing Technology Innovation Can Become Routine?

Brand and generic pharmaceutical companies due to combination of short patent life after new drug discovery, long regulatory approval times and their ability to secure the demanded selling prices have no desire or incentive to innovate manufacturing technologies. They believe and practice well-known and best processes and methods to manufacture their products.

CMOs, CDMOs and equipment manufacturers have a significant manufacturing role in manufacturing technology and method innovation. However, adoption has to be financially justified.

Regulators have to create manufacturing technology innovation environment. One of the ways I see that happening is to shorten the approval time to three months. This will give companies the freedom and the incentive to innovate and compete on cost and quality basis and allow them to capture bigger market. They will have higher profits. Drug affordability will improve and shortages could reduce also. In addition, regulators have to stop suggesting what and how of the methods and processes companies should use. Companies, as stated earlier, have to justify their investment on the basis of product demand, a fundamental of every business.

I also believe that companies are lost in excessive regulatory guidances and directives that are a distraction to the companies. Regulators are suggesting manufacturing companies to practice continuous improvements for what they practice. Question needs to be asked to the regulators "are they practicing 'continuous improvements also'. If they did costs and time associated with dealing with regulators could be significantly lowered.

Regulators will resist and hedge in giving companies the freedom that would come with short approval times. They still have ultimate control over the companies if they do not produce quality products. It is to shut the manufacturing at the facility down if quality deviations exist and cGMP practices are not followed(9). Loss of profits alone should be enough incentive to maintain quality and follow good manufacturing practices.

Girish Malhotra, PE
EPCOT International

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