CPhI Pharma Insights

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Industry Expert Panel Submissions

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Part 1.

Quality and regulation

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Manufacturing Processes Require Financial Justification

Introduction

Every business has a mission of making profit, satisfying return on investment expectation of its stakeholders while fulfilling needs of their customers with consistent quality products. In this effort company's investment in product development, manufacturing technology and innovation has to be justified. In a competitive business world many a times process improvements are necessary to meet prevailing regulations and staying competitive. Related costs are either passed on to the customers or counterbalanced by productivity or technology improvements.

In a quasi-competitive world where products are needed to sustain and extend life above norms may or may not apply. Needed new products are created and sold at the highest possible price unless there is governmental price intervention. Justification for high prices is recovery of the R&D efforts. Manufacturing technology innovation is generally not a criterion to sustain such businesses especially when the products have a limited patent life. Innovation might be incorporated to meet regulations. After patents expire company or companies may or may not create or use the most economic processes because the product demand to extend life will be there. This generally prevails in the pharmaceutical world.

At times, I feel that the pharmaceutical industry biggest shortcoming has been in manufacturing technology innovation. It does the minimum for technology innovation or does it under duress because the regulators want them to. Some may disagree with it.

Manufacturing technology innovation in pharmaceuticals is constrained by three factors. In edition to economics they are government regulations and drug dose needed to cure diseases. Why the drug dose? Drug dose (micrograms to milligrams) and patient population heavily influence the needed manufacturing technologies. These nuances are discussed later. All said and done pharmaceutical industry has done a yeoman job in curing diseases.

Government regulations are critical and an essential part of the pharmaceutical landscape for product quality. They assure that the processes are repeatable and the product quality is maintained. Record keeping of manufacturing and test methods are essential. It is expected that once followed diligently, processes will produce repeatable quality products. My conjecture is that companies have to have an excellent understanding and command of the process that they can reproduce any process upset and correct them without much effort. Such knowledge will

shorten processing times and result in optimum processes producing quality products all the time. If done so quality diligence will be ingrained in their overall business.

Regulatory bodies at times are and can be labeled as overbearing and demanding. In the last decade or so the USFDA has been nudging manufacturing companies to innovate manufacturing technologies. They can cajole but cannot force new or better manufacturing technologies or methods. Each company has to have financial justification for their investment in manufacturing technology and methods innovation. Since there are many products each could require their own financial justification.

Manufacturing Methods:

Batch manufacturing methods for the active pharmaceutical ingredients (API) and their formulations have been the norm. Since dose can vary from e.g. from micrograms to as much as 500 milligrams or more low to high volume API might be needed to serve the same population number. Generally the needed APIs are produced using a batch process. Tables 1 and 2 illustrate examples of different process (batch and continuous) possibilities for API and formulations at two different doses. Broader review showing different process possibilities are discussed elsewhere (1,2).

Table 1

Milligrams = **0.112**

Drug use days per yr. = **365**

Population = **5,000,000**

Milligrams/ year	API Kg per year	Tablets per year
204,000,000	**204.4**	**1,825,000,000**

API production batch

Tablets per hour= **~255,000**

Most likely batch but can be produced continuously at one plant

Continuous API manufacturing is limited to products that would exceed yearly production volume of about e.g. 400,000 pounds. There are very few APIs that would meet this volume criterion.

Table

Milligrams = **10**

Drug use days per yr. = **365**

Population = **50,000,000**

API needed Kg per year = **91,250**

Continuous process very possible but financial justification needed. Most likely batch due to many plants

Formulations

Tablet produced per year = **18,250,000,000**

Tablets per hour = **~2,556,000**

Most likely multiple batch operations; Can be produced in two continuous plants

Between batch and continuous processes there is another possibility where products can be campaigned for longer than batch times and less than continuously. Such processes generally would require that their API chemistries and formulations are very similar. Equipment utilization of as much as 80% would be necessary in such campaigns. Such product runs are feasible but will have to be evaluated by each operation. cGMP practices will have to be very carefully monitored.

Industries other than pharmaceutical industry generally use the dictionary definitions in their practice of continuous processes. Recently few pharma companies have claimed to use continuous processes. How they define continuous

is not known. USFDA has indicated that the operation at these are continuous but has not elaborated on details. USFDA has indicated that they would publish guidance for continuous processes in future (3). Based on my conjecture volume of drugs produced at these operations are not large enough to warrant continuous processes and could be easily produced using batch processes. It seems that these companies are labeling their processes to be continuous using a definition that is different from the dictionary and/or industry practiced acknowledged/ established definitions.

Better reactor technologies are evolving for API production but they are expensive and at times are chemistry specific. Thus compared to the existing technologies they might not find widespread use. Their widespread use and financial justification most likely could come from contract manufacturing organizations specializing in similar chemistries. As a substitute much cheaper existing equipment could be used instead efficiently but significant creativity, finesse and imagination are needed.

Continuous formulation processes need their own financial justification. If the equipment is used to produce a single drug and has less than 80% or lower asset utilization, then the plants are no different from the current batch operations. There are unique tableting methods that can improve overall operations. As has been stated earlier drug dose and population dictate the asset utilization.

All said and done each company producing APIs or their formulations has to justify and use the most cost efficient technology (batch, campaigned batch or continuous) to produce products that are economic and deliver the same quality all the time. Regulators can only regulate and assure product quality. They can suggest the technologies and methods companies should consider for their products. However, companies have to justify use of such technologies. Excellence comes from with in the companies rather than outsiders.

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