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Manufacturing technologies and their part
to achieve future pharmaceutical sales

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Abstract

Global pharma revenue is expected to reach around $1.1-1.3 trillion dollars in the next few years. Even with increasing global effluence affordability remains an issue. High priced drugs can deliver the revenue but very few can afford them even in mutually subsidized systems.
Demand dictates API manufacturing process and formulation technologies. Pharmaceutical companies have to take the lead through use of best technologies to make drugs affordable to larger population. Unless industry takes the lead billions will be spent by very limited patient base.
Pharma has to internalize technology innovation and wider use of drugs. At current pricing strategies less than 1% of the global population will benefit from new the drugs. Regulatory bodies cannot force change and unless pharma takes the lead it will be stuck in "analysis paralysis' mode.

As the world becomes more affluent, need for curing lifestyle diseases will increase. Number of patients taking drugs has and will increase. This is evident by increasing pharma sales. Global sales revenue is predicted to be between $1.07 (2020) (1) to $1.3 (2018) (2) trillion dollars in the next few years.

Pharma's focus has been and is on the money drugs / therapies will generate and profits rather than how many patients can afford the drugs. As the drug needs, due to increasing affluence, increase their sales are still dependent on their price. Significant number of marginally better performing drugs are being discovered and commercialized for common diseases. I wonder how does one justify the related R&D expenditure. It sure would be interesting if a comparative price performance study of drugs for common diseases were done. Inclusion of how many patients (numbers) benefit from different drugs for the same broad class of diseases would be very helpful. Value of such analysis is discussed later. Cancer and orphan drugs that have limited patient base and are the recent focus and the financial driver. Their affordability is being questioned (3-5).

There is no discussion of the efforts to lower drug costs through manufacturing technology innovation. Cost reduction and affordability are not exotica but are generally not part of any pharma related discussion. This paper reviews different options of how the projected global sales would be achieved and which manufacturing technology (batch or continuous) could be used to achieve the results.

A WHO (World Health Organization) 2003 publication (6) suggests "Yet more than 80% of all pharmaceutical products are consumed by the 15% of the world population living in industrialized countries, a figure which reflects a grossly uneven distribution of pharmaceutical consumption across the world". Even though this is an old report my thinking is the conclusions might be still valid. My conjecture is that in overall scheme of things number of people who forgo or curtail drug use over food or healthcare is increasing. This increase is due to higher drug prices. No one knows the number.

One would generally think that due to high priced drugs and drug unaffordability the related death rate should increase. In 2012 death rate was eight per 1,000 compared to nine per thousand in 2000 (7-8). The decline is remarkable considering global population has increased approximately by 1.2 billion in the same period. With rising affluence and increasing population, the rate trend is an anomaly but a good one.

As drug and device prices rise and/or they become unaffordable, patients are increasingly forced to make healthcare choices whether they are part of any healthcare program or pay from their pocket. Part of the selection process is choice between food for the family or well being of

individual/s in the family (9). This observation is applicable worldwide and is not discussed much in press or otherwise, especially in the developed countries as it would be considered a bad publicity. Only explanation I can think of is that the families in such circumstances have accepted their choices and routine of their lives. If death happens, it is rite of passage. Drug affordability is a governmental challenge also.

Till generics came about, brand companies had very little threat with regards to pricing and patents. I have always wondered why innovative manufacturing technologies and methods are not used to make drugs affordable. Better technologies generally improve profits and increase customer base i.e. the sales revenue.

SALES INCREASE

As stated above pharma's sales focus has recently shifted to revenue from limited number of patients rather than serving a larger population base. Using this hypothesis, Table 1 illustrates how many patients at different average price levels would be needed to reach sales of $1.3 trillion by 2018. Subsequent tables give us an excellent indication of the types of manufacturing technologies most likely would be used for the manufacture of APIs and their formulations.
In Tables 2, 3 and 4 single drug price points are used to reverse calculate annual API requirements. Formulation process yield is assumed at 100%. Readers can use their numbers to review alternate "what if scenarios".
Drugs in the Table 2 are priced at $100,000.00 per year.

Year	Yearly Sales, $ Billion	Incremental sales over the previous year, $ Billion	Number Patients needed for $100,000 per year drug	Number Patients needed for $3650 per year drug	Number Patients needed for $365 per year drug
2013	910				
2014	973	63.7	637,000	17,452,055	174,520,548
2015	1,042	68.2	681,590	18,673,699	186,736,986
2016	1,115	72.9	729,301	19,980,858	199,808,575
2017	1,193	78.0	780,352	21,379,518	213,795,176
2018	1,276	83.5	834,977	22,876,084	228,760,838
Population served, % Global population ~7.2 billion			**~0.01**	**0.24-0.32**	**2.4-3.2**

Table 1. Sales, number of patients and drug prices.

Single drug molecule is used for the illustration. Tablet production rate is also for a single drug dose. If multiple drugs at this price point are used in the analysis, API needs and tablets production rate will be equally divided.
Table 2 API requirements are most suited for a batch process. In order to produce API continuously synthesis process, equipment and operating methodology will have to be reconfigured i.e. a different business model would be necessary. Similarly single dose formulation would need batch processes. A continuous operation of 7,140 hours [=350x24x0.85] per year would be difficult to justify. Alternate operating and business model might lead to continuous formulations.

Table 3 is similar to Table 2 and is based on a drug priced at $3,650.00 per year. Compared to Table 2 significantly large number of patients, in millions, would be needed to generate the incremental revenue. If the incremental revenue is based on single drug API, theoretically it could be produced using a continuous process at a single plant. Up to three APIs from Table 3 could be produced by continuous process. Since most likely revenue will come from multiple drugs and that would mean multiple APIs and they all will be produced using batch processes.

Increment over previous year, $ billion	Number of patients needed for $100,000 per year drug	API Kilo needed per yr. @ 100 mg/day dose	Tablets needed per year	Tablets production per hour
63.7	637,000	23,251	232,505,000	32,564
68.2	681,590	24,878	248,780,350	34,843
72.9	729,301	26,619	266,194,975	37,282
78.0	780,352	28,483	284,828,623	39,892
83.5	834,977	30,477	304,766,626	42,684

Table 2. API and formulations requirement for $100,000.00 per year drug.

Increment over previous year, $ billion	Number of patients needed for $3,650 per year drug	API Kilo needed per yr. @dose, 100 mg/day	Tablets needed per year	Tablets production per hour
63.7	17,452,055	637,000	6,370,000,000	892,157
68.2	18,673,699	681,590	6,815,900,000	954,608
72.9	19,980,858	729,301	7,293,013,000	1,021,430
78.0	21,379,518	780,352	7,803,523,910	1,092,931
83.5	22,876,084	834,977	8,349,770,584	1,169,436

Table 3. API and formulations requirement for $3,650.00 per year drug.

Formulations for the drugs (single or multiple) discussed in Table 3 present an opportunity for continuous processes. Volumes are large enough for commercial operations. However, in reality these drugs will be formulated using batch processes at multiple sites. In order to use continuous process, again different business model and operating strategies will have to be used.

Since we are discussing new revenue in above tables, it would come from discovery of new drug/s. With molecule/s being under patent, most likely batch processes would be used. As the product sales ramp up likelihood of them, under the current regulatory environment and operating philosophies, converting to continuous processes for the API and formulation is very unlikely because FDA regulation 21CFR314.70 has to be followed.

LACK OF PROGRESS

What amazes me the most is that the knowledge about formulation process components e.g. blending, compacting, compressing, and coating etc. that are necessary for batch as well as continuous formulation processing have been around for more than fifty years. We all know continuous processes are far more efficient, have lower cost and produce consistently higher quality product than batch processes. Why have the pharmaceutical companies not adopted and used best of the technologies to produce quality products is intriguing? Pharma's answer to this question would be very interesting.

Pharma formulations even after sixty plus years of knowledge and experience are still in QbA (quality by analysis) "analysis paralysis" mode. Again, had the knowledge been truly practiced in commercial operations, continuous formulation processes would have been practiced and we would not be starting to talk about them. I believe that the reason for recent "continuous process" talk is due to regulatory bodies suggesting their incorporation rather than industry taking the lead. I am not sure if everyone, within industry and regulatory bodies, understands what is involved to commercialize a continuous process. Until industry takes the lead, talk will stay talk only.

Engineering curriculums teach fundamentals of chemical engineering. They are used to commercializing batch as well as continuous processes. Continuous manufacturing has been practiced in the chemical industry for more than fifty years. Since we have not considered continuous processes in pharma, does it suggest that our education system and our business processes/methods have failed? Of intrigue is the recent press discussion of adoption (10) and of university research funding (11) for continuous manufacturing. These research projects are fine to educate new generation of chemical engineers but the current practices suggest that we have not incorporated best of the manufacturing technologies and methods in the manufacture of pharmaceuticals. Thorough review would be needed to economically justify continuous processing in API manufacturing and their formulations (12-14).

Regulations are also preventing companies to incorporate continuous process improvements as the efficacy and performance of the drugs has to be re-affirmed [21CFR314.70] with any process change. In their race to get to the market first companies have not spent sufficient time to commercialize best of the process technologies for API manufacture and formulations.

Table 4 is an illustration using low cost drugs. It shows the yearly API need and hourly tablet production rate for a single dose and a single drug. Multiple drugs and dosage can be used for "what if" analysis.

Likelihood of the increased revenue coming from existing molecules, most likely generics, is extremely low. It can only happen if their prices are lower than the current costs and the sales increased exponentially. A continuous process most likely will be necessary. Only a maverick entrepreneur can challenge the existing business model to produce such high volume drugs. New drug molecule/s to deliver the projected revenue would require more than two hundred million patients. Under the current business and pricing scenario this is very unlikely. Two hundred million patients would mean an ongoing global disease epidemics that none of us want.

Revenue generated, $ billion	Number of patients needed for $365.00 per year drug	API Kilo needed per yr. @dose, 100 mg/day	Tablets needed per year	Tablets production per hour
63.7	174,520,548	6,370,000	63,700,000,000	8,921,569
68.2	186,736,986	6,815,900	68,159,000,000	9,546,078
72.9	199,808,575	7,293,013	72,930,130,000	10,214,304
78.0	213,795,176	7,803,524	78,035,239,100	10,929,305
83.5	228,760,838	8,349,771	83,497,705,837	11,694,357

Table 4. Revenue, API and Formulation relationships.

Depending on process chemistry per molecule API need for one or more molecules will have to be high to have continuous processes. Few companies can produce the API using continuous process at a single plant. Logically formulation process would operate continuously. However, to fulfill the patient needs, continuous formulations would have to be done in multiple plants.

WHAT IF ANALYSIS

"What if" analysis can be done for almost any drug. Analysis should include comparison against performance of existing drugs and their degree of efficacy, healthcare value, pricing, affordability and best estimate of number of patients who are benefitting or could. This information along with dosage can be used to determine API and formulation needed for the best costs and pricing. Best of the manufacturing technologies can be selected (12-15). I am sure such analyses are being done internally to discuss and review viability of any and every brand or generic drug. Since I have not seen such comparisons in public domain I just wonder have the companies done such reviews, considered a "good practice" for any business.

PCSK9 (16) class of LDL lowering cholesterol drugs are expected to attain $10 billion dollar sales per year. At about $14,000 per year price and using reverse calculations, less than one million people, a very selective market (0.01% of the global population), will be able to afford these drugs worldwide. Analysis suggests that the APIs and their formulations will be manufactured using batch processes. It is ironic that no one has or wants to quantify number of patients who would benefit from these new or existing high priced drugs. Only discussion is about revenue and profits. If the numbers are being discussed, they are not part of the public domain.

CONCLUSION

Analysis presented suggests that unless the business model and operating strategies along with regulations change (a change will be proposed at CPhI 2015), APIs to achieve 2018 or 2020 revenue will be manufactured using batch processes. Many of the formulations could be done using continuous processes but will require internal desire within the companies and they will also have to tweak their operating strategies.

Would Pharma companies be able to achieve the projected sales? Based on my analysis only high priced orphan or oncology drugs (limited market) or other high priced drugs would be instrumental in meeting the sales projections. High volume drugs at low prices, i.e. millions of patients, could help in achieving the financial projection. However, such drugs would have to have significantly improved performance than the existing drugs or the pharma companies have to create molecules that can serve millions of patients. Likelihood of inventing such large need drug/s in the next year or two is very unlikely.

Views presented are based on API and formulation production volumes and my perspective of operating strategies (12-15) that could be used. Simplification of API batch processes present significant cost reduction and process improvement opportunities and should not be overlooked. These savings are pure profits. Economies of scale can result in as much as 20-25% cost reduction. Since we have the knowledge base, formulation improvements can be achieved much faster but effort is needed. Lower cost drugs can increase revenue but achieving $60-80 billions increase in the next two to three years is unlikely. As I stated earlier it would happen only through high priced for limited population.

I still believe that larger humanity will benefit if drugs can be made affordable and revenues much higher than the projected revenue could be achieved but the business model will have to change. Pharma will have to review its growth options.

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