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# Annual Industry Report 2015

Industry Expert Panel Submissions

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# Part 1.

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Calling for change



PANEL MEMBER

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# My perspective for Pharmaceutical Manufacturing Technologies/Processes and Continuous Improvements

## Introduction

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Regulations are necessary for quality assurance of drugs. FDA established 21CFR314.70<sup>(1,2)</sup> and it is a very important rule. It assures that there is no “by manufacturer’s choice” deviation from the manufacturing methods and practices that have been filed for the components involved in the manufacture of any salable drug – the active pharmaceutical ingredient (API) and their formulation – and labeling, packaging etc. Every change has to be reported. Drastic process changes are discouraged.

When there is a discussion about pharmaceutical manufacturing generally only formulations are

considered. API manufacturing is ignored and it should not be. Without API there is no drug.

21 CFR314.70 encourages “continuous improvements” in the processes that will create the best product for clinical trials and that’s the way it should be. However, in my estimation under the current rules all of this has to be done prior to going to clinical trials. QbD (quality by design) becomes a natural part of the process development before a process is commercialized. After the fact process change is difficult.

## Batch processes

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Generally, most APIs and their formulations are produced using batch processes. Existing approved products require annual reporting of improvements/changes. Most of the changes are minor. However, if the processes are to be revamped for process yield, operating parameters and manufacturing methods, they are going to be the biggest challenge as the efficacy of the API and its formulations,

especially prescription drugs could change. In my estimation re-approval would be needed. This can be a monumental task, even for over the counter drugs (OTC) not requiring prescriptions, because new monographs may have to be established. Money and time investment would be necessary. Such changes are major “continuous improvements” and deterrent for prescription drugs.

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<sup>1</sup> Third World Network, 20 April 2015

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## Continuous Manufacturing

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Continuous manufacturing for API and their formulations is pharma's new and least understood buzzword. In the annals of chemical engineering and for that matter in any industry "continuous manufacturing" means 24x7x50 hours of operation per year with pre-established down time. There are few selected APIs (OTC or prescription) that can be converted to continuous processes. (3, 4, 5) Totally different operational thinking/models would be required. The use of existing manufacturing equipment and technologies is very feasible.

Continuous processes for formulations should have been commercialized over sixty years ago. Manufacturing technologies and equipment along with knowledge base for such processes have existed since, but not incorporated. This is due to traditions of business and lack of application of chemical engineering knowledge base to commercialize such processes.

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## Benefits and Challenges of Continuous Improvement

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Benefits of cost reduction, improved profits and larger customer base due to improved manufacturing technologies are huge and well documented. Best of the process technologies have to be created before clinical trials. As we know "after the fact" improvements, under the current regulatory environment, would not happen due to the financial and time elements discussed above.

Only a "maverick company or creative destructionist" can take on the task. Success would completely change the pharma landscape. I am not sure if pharma related components and that includes companies, legislature, vested interest groups, are ready for such an evolution. There will be microscopic examination and doubts raised, forcing many delays even if the companies do the "right" things based on excellent science and engineering.

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## Alternate Proposal

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I would propose the following. I am sure there will be plenty of scrutiny and naysayers – unless we take bold steps not much changes. If there are alternate better ideas, let us discuss those also.

I propose that the pharmaceutical industry be allowed to commercialize process improvements (yield, process/operating conditions, operating parameters, cycle time) in the manufacture of approved APIs and their formulations. The manufacturing company will guarantee that the product efficacy and performance, along with impurities, will be better than the approved product produced by the company. There would be an added stipulation that if for any reason product performance, efficacy, labeling and impurities do not meet or are worse off from the approved product, company proposing improvements

will be barred from making the product using alternate process for the next e.g. two or three years. If they do decide to use the alternate process, they will have to go through the re-approval process. Minor changes that do not change the current filed processing methods etc. would be excluded. This would apply to OTC, brand and generic products also.

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*I propose that the pharmaceutical industry be allowed to commercialize process improvements in the manufacture of approved APIs and their formulations – without reapproval*

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## Conclusion

I admit that my proposal is a bit bold but unless such bold steps are considered, very little will change in the current pharma's manufacturing methodologies or anywhere, for that matter. If incorporated in pharmaceutical manufacturing landscape, continuous improvements and innovation could become a routine and it could be extended to the whole healthcare industry. Wright Brothers did and so was the adventure of sending humans to moon and bringing them back. A successful trek to Pluto would also fit the category. It is time for the pharma industry to be bold. It has an opportunity to add as much as 20% of the global population (~1.4 billion)

to its customer base, an unprecedented opportunity for any industry on the planet. Profits will improve and healthcare costs can come down. It would be a win-win.

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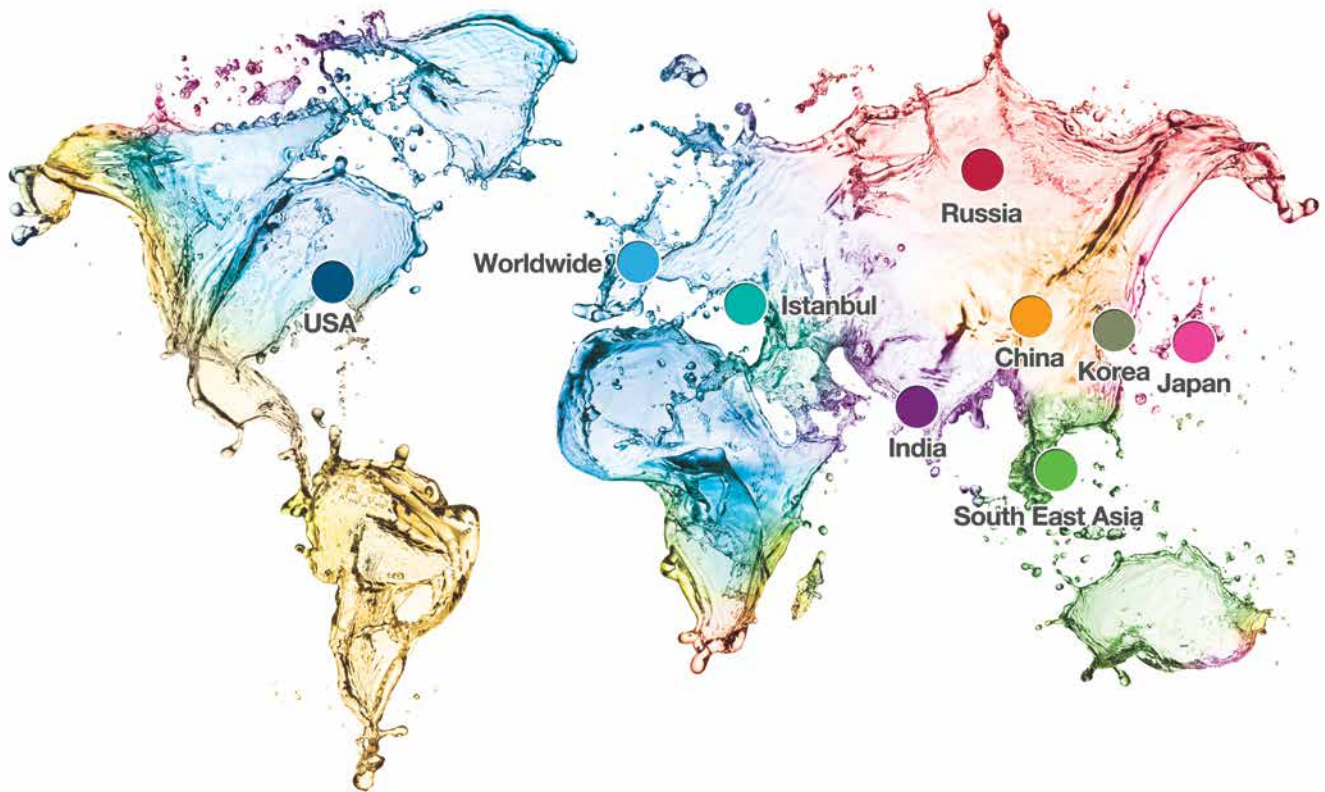
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2. Malhotra, Girish: Impact of 21CFR 314.70 on The Life of a Pharmaceutical Manufacturing Process, Profitability through Simplicity, <http://pharmaceuticalscoatings.blogspot.com/2015/08/impact-of-21cfr-314670-on-life-of.html>
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**CPhI Global Events**

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|-----------------------------|----------------------|
| <b>CPhI South America</b>   | 25 - 27 August 2015  |
| <b>CPhI Korea</b>           | 7 - 9 September 2015 |
| <b>CPhI Worldwide</b>       | 13 - 15 October 2015 |
| <b>CPhI and P-MEC India</b> | 1 - 3 December 2015  |
| <b>CPhI Southeast Asia</b>  | 6 - 8 April 2016     |
| <b>CPhI Russia</b>          | 12 - 14 April 2016   |
| <b>CPhI Japan</b>           | 20 - 22 April 2016   |
| <b>CPhI Conferences</b>     | year round           |

**Addendum**

The statements and figures contained within this release were collected at an early stage of GBR's research. As such, it may not reflect final conclusions on market trends. GBR is finalising its research this May and will be presenting its conclusive findings at the opening conference of CPhI Istanbul 2014