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Opinion

Regulatory Inflation in Pharmaceutical Drug Development?

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Abbreviations: cGMP: current Good Manufacturing Practices; HC: Health Canada

Opinion

During the last decade, and exponentially over the last three years, numerous pharmaceutical manufacturing plants have closed their doors following current Good Manufacturing Practices (cGMP) audits from various agencies, such as FDA, EMA and Health Canada. Regulatory affairs have been evolving and so should be the audits, auditors and regulations. However, the density and interpretations of regulatory requirements have become increasingly stringent, especially with respect to sterile products, making them more difficult to develop and manufacture within reasonable time and cost. A quick search on Google shows numerous press releases from various pharmaceutical organizations reporting critical/major deficiencies, leading to temporary or permanent closures of manufacturing plants. Furthermore, it seems that this evolving situation has not only impacted drug shortage, but these events have placed the pharmaceutical industry under a permanent state of siege. The negative impacts of regulatory inflation are a center of attention among pharmaceutical professionals.

This article explores four (4) interrelated components of this regulatory inflation phenomenon.

Regulatory Narrative Leading to Global Inadequacy of the Canadian Industry

The Health Canada (HC) website, more precisely the Drug &Health product inspections section [1] is listing 802 pages of cGMP audit results from virtually all Canadian establishment license holders. Even though compliant, the vast majority of them were listed as having inadequate quality systems. Comments such as: *The handling of standard operating procedures for good manufacturing practices was inadequate, the written procedures for recalls were inadequate, the education, experience, and/or oversight of the individual in charge of the quality control department was inadequate*, to name but a few, can be read everywhere across the site.

Compliant CMOs complain privately that labeling them as inadequate on the public domain resulted in drops of direct business revenues and a weakening of their competitiveness. Indeed, foreign clients that would like to export their business in Canada are misinformed through HC website and get the impression that Canadian CMOs are problematic. In contrast FDA and EMA do not publish the same kind of data, through detailed documents and audit reports from compliant organizations. At the FDA cGMP audit reports exist and are on the public domain but recently both EMA and FDA have published the first report from the FDA-EMA pilot program for the parallel assessment of quality-by-design elements of marketing applications [2].

Regulatory Inflation: The Emergence and Growth of the Compliance Industry

Originally, regulatory compliance was an integral part of the pharmaceutical industry. Over the last 20 years compliance has evolved to a separate industry, generating multi-billion dollars of revenues. By definition this new autonomous industry must continue to grow, and this growth is mediated via the creation of new, increasingly sophisticated requirements and guidelines.

Moreover, the costs of compliance audits have all been transferred, directly or indirectly, to the industry. Twenty years ago, regulatory auditors were essentially testing and measuring compliance to operating procedures. Today it is the manufacturers who are paying very competent specialists from the compliance industry to piously prepare risk analysis, gap analysis, trending

analysis, CAPA etc., on all aspects of operations, and present them to public or private regulatory agencies (e.g. ISO system) as proof of compliance. In parallel with this regulatory requirement inflation, there was an emerging of regulatory consulting firms [3].

In an ideal world, the compliance industry must help the manufacturers it regulates because they generate the economy, the profitability, and the taxes that drive the country. Nowadays, it looks like the compliance industry has developed in less than 25 years everything but a symbiotic relationship. And let us be clear, there are no villains or conspiracy here: it is a systemic social problem caused by out-of-control human factors: a form of conflict of interest between two groups that should work together.

Generational Turnover of Inspectors and Auditors

As a professor of drug development, I have been training graduate students in scientific and regulatory affairs for two decades. This training attempts to bridge the gap between the theory of a basic research undergraduate training and the reality that will be faced in the industry. Over the years I have noticed that most of the conformity auditors were people with hands-on experience in the past in their field of expertise, meaning that they had the necessary experience to bridge the gap between theory and reality.

During the last decade, a younger and ambitious auditor profile, showing a lower hands-on experience level, a more reactive than proactive behavior, and an apparent a lack of sustainability taught by seasoned colleagues, has become the conformity auditing landscape. This new generation of regulatory enforcers are highly knowledgeable in regulatory requirements. However, the lack of "hands-on" expertise makes more difficult for them to bridge the gap between theory and practice. Most of my ex-students work in the industry and all their testimonies are pointing in that sense, even though, as described in Costanza and al. [4] meta-analysis showed that "generational differences do exist on work-related outcomes, they are relatively small, and the inconsistent pat-tern of results does not support the hypothesis of systematic difference.

Effect of Regulatory Inflation on the Next Generations

The gravity of regulatory inflation is only beginning to be measured. It used to be relatively easy for a group of young and ambitious entrepreneurs to build, with a reasonable amount of money, a pharmaceutical CMO. The density of regulations was lower, and the way these regulations were managed were based on audits, or inspections from regulatory agencies sustained by the states. These entrepreneurs form that generation has been raised with these inflationist regulatory constraints. Today, the cost of managing compliance has become so disproportionate that there is no young company pushing behind: No succession. Our opinions on this problem are very visceral: the fact that young graduates cannot practically do the same thing as we are doing because of regulatory inflation should be deeply studies, dug and understood. As a professor and consultant in product development, I do think that the primary duty of parents is to keep the context of opportunities they have had and transfer it to their children.

The Canadian federal government has passed the law that recognizes the problem and provides solutions, "the Red Tape Reduction Act" but this law is not retroactive to heal the harm already done [5]. At the light of these comments, it is difficult to see how the wave can be modified, since it has already started to be painful, by looking at all the companies that have already closed. However, it should be extremely clear that the definition of the word "culture" is the following: *Culture is the body of knowledge, know-how, traditions, customs, specific to a human group, to a civilization. It is transmitted socially, from generation to generation and not by genetic inheritance, and largely conditions individual behavior*. It means that people, firms and agencies working directly or indirectly in conformity should be advertised in that regards in order to start a paradigm shift and to make the pharmaceutical industry evolving under a progressive way, where all the actors could benefit of it.

It is interesting to note that this regulatory inflation does not only affect the pharmaceutical industry, but several other industries, such as the aviation [6] and as the article is mentioning: *As the second most geographically vast nation in the world and with a small, open economy, Canada is dependent on air transportation like almost no other country* [7].

Conclusion

The author of this article had the chance to be part of the tail of the "golden age" of the pharmaceutical industry. Indeed, I had the chance, regardless of my "specialty" to share, discuss and see how the development was going, from basic research through all the steps that were needed to develop a drug, making myself "hands on" on all the steps that were, and are still needed to file a new drug product successfully. For that reason, I have been raised "holistically" under a "regulated" way of thinking in non-clinical, clinical, CMC, and regulatory affairs so that it was possible for me to understand, to share the same languages than the auditors, whether they were coming from private firms or government agencies.

Things have changed (and not evolved) in that regards. For example, if current auditors have never had the chance of being part of a blending operation, it will be very difficult for them to realize if a speed of 10,000rpm would be realistic for a blender impeller. On the other side, they will know better than all of us the guidelines saying that this or that should be done according to this or that, as written in the page 5 of the FDA/EMA/EP/JP.... Guidelines. The cost of managing compliance has become such that it has become virtually impossible to start a business without having a lot of money to build large "quality systems" from scratch. Of course, we do not have proximity expertise in all the other highly regulated field such as commercial aviation to assert anything, but according to what we have seen over the past ten years, the trend

is similar, as in other regulated businesses. As a professor teaching drug development, the next steps could be:

i. To conduct a confidential survey in the industry on the effect of this HC website that is showing relatively clearly this regulatory inflation on the Canadian exportation potential of pharmaceutical product and services.

ii. To monitor if there is a correlation between company closures and regulatory affairs and conformity consulting service companies.

Please note that this article strictly represents the point of view of the author based on his expertise and experience.

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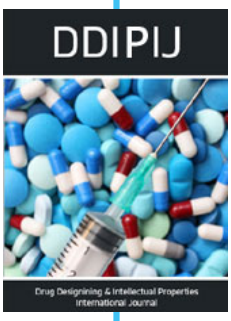

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