Regulatory Inflation in Pharmaceutical Drug Development?

François-Xavier Lacasse, PhD
Associate professor, Faculty of Pharmacy, University of Montreal, Canada

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*Corresponding author: François-Xavier Lacasse PhD, Associate professor, Faculty of Pharmacy, University of Montreal, Canada, Tel: (514) 652-1750; Email: francois.lacasse@umontreal.ca

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 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 Genera-
tions
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 hased
on audits, or inspections from regulatory agencies sustained by the
states. These entrepreneurs form that generation has been raised
“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
how the development was going, from basic research through
all the steps that were needed to develop a drug, making myself
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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
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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
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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/IP.....
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

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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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