MEDWIN PUBLISHERS
Committed to create value for Researchers

Pharmaceutical Drug Regulatory Affairs Journal

Generic Drugs: The Landscape is Evolving....So are the Mentalities?

Francois-Xavier Lacasse*

Faculty of Pharmacy, University of Montreal, Canada

***Corresponding author:** Francois-Xavier Lacasse, Faculty of Pharmacy, University of Montreal, Montreal, Quebec, Canada, Tel: (514) 652-1750; Email: pharmfx@videotron.ca

Opinion

Volume 1 Issue 1

Received Date: September 26, 2018

Published Date: October 04, 2018

Opinion

During the last decade, the generic landscape has considerably evolved. The last two waves of several MM$ of off-patented drugs may be held responsible for that change. For example, the amount of money generated by the statins, the proton pump inhibitors (PPIs),.... according to several experts, may now be difficult to reproduce. Other experts will tell you that it is normal since things are evolving, so cannot be reproduced. However, things cannot be seen from a monolithic way of thinking, but should be foresee with a holistic approach. Generic drug prices are getting lower and lower. It is a paradox since at the same time, in parallel, government agencies are increasing their quality standards, making development more and more expensive. The goal is then to try to decrease the cost associated with development, by narrowing the cost in development (raw materials) and the workforce. Furthermore, FDA in December 2016 has released a revision 2 [1] of their Refuse to Receive Standards, for ANDA Submissions. After discussion with several experts in that domain, who have attended several meetings with FDA in that regards, data quality and regulatory operations were at the heart of this new guidance.

By taking a look at the drugs that are becoming out of patent, therefore ready to be genericized, it must be acknowledged that upcoming drugs are not easy ones, since all the easiest have already been marketed. The "druggability" of these soon off-patent drugs making them more difficult to be bioequivalent with the brand. Solid-state chemistry on both the drug substances and the drug products, has become more and more important and requested by the government agencies. By adding to this last complexity, the bulk drug substance providers, that can supply generic firms, with faster and new methods of synthesis at a lower cost, things became more and more attractive to narrow down the cost....yes but at what cost? It should be noted however that the drug master files (DMF) written by these new emerging fine chemical companies gave headaches to generic sponsors since the close parts, more often than not, were directly finger pointed by government agencies, for their lack of clarity and documentation in their close parts. To name but a few, genotoxicity of the starting materials, accuracy of the analytical methods and procedures, represent ones of the redundant highlighted observations raised by the agencies. Furthermore, for the same drug substance, but synthesized differently, new impurity profiles were born that have created a need, in some cases to carry out some toxicological studies according to current good laboratory practices (cGLP), and this is the kind of vocabulary generic companies are not familiar with, but with these new players, they will have to get used to it. There was then a need to convince people that have been working in a generic environment for a long time, that questions on generic submissions that may be coming from the agency, may now deal with unexpected fields, such as deeper characterization of drug substances and drug products, the carrying out of toxicological studies....People had now to adjust their skills based on the agency requirements and how to convince the generic executives of these agency requests.

In a second time, by taking a look at the TOP 50 drug sales, biologics represent more than 50% of the candidates, making them ineligibles to become generic drugs, such as small molecules. Biologics are considered complex molecules that will make them biosimilar drugs once they will be off patented. Thus, the biosimilar pathway cannot be compared with the route that is adopted for genericize small molecule for several reasons, such as:

- That biosimilars are not considered generic drugs, but should be and are considered innovator drug, so should be developed accordingly.
- The complexity of the developing biosimilar drugs. In fact, the chemistry manufacturing and controls (CMC) section represents the bottleneck of a biosimilar dossier. The more the CMC will be exhaustive, the more the biosimilar pathway will be smooth. In other words, the more results will be generated upstream to demonstrate an almost pharmaceutical equivalence: qualitative (Q1), quantitative [2] and structurally and functionally (Q3) [2], the less will have to be performed downstream to demonstrate this similarity.
- Based on the above, on personal experiences and testimonies of many consultants in that domain, the mentality to be adopted to develop a biosimilar drug versus a generic drug is not the same. The working forces in generic companies have not been raised and trained to develop innovator drugs. This may explain why generic companies at the beginning were not as successful as expected. For that reason, the big generic players have decided to go with merger and acquisitions to overpass this kind of problems.

Another point of interest illustrating the current paradigm shift in the generic industry is by questioning contract research organizations (CRO) working in clinical studies. I have been working in drug development for the last 20 years, and I do remember when I was working for a CRO, when statins, proton pump inhibitors, platelet aggregation inhibitors amongst others, used to represent the read and butters of several CROs specialized in bioequivalence studies. Nowadays, most of these CROs are still carrying some bioequivalence studies however the 505b2 [3,4] approach has become more and more attractive and successful, the generic industry taking part of this advantage. As a reminder, a 505 b2 submission, or "truncated brand" submission, or hybrid submission in Europe [5] will not generate a generic drug, (thus cannot be substituted), but a brand drug, that will show differences in the indication, the route of administration of an already marketed drug. Therefore, some cross references of the brand dossiers can be done, making the regulatory pathway faster and at lower costs, and especially this kind of submission will give an exclusivity up to 7 years [6] on the market to the sponsors. Generic leaders had to adopt a new way of thinking, since the know how to develop that pathway. However as mentioned above, the type of development is not the same than a conventional generic development. The need of hiring people with higher scientific and regulatory affairs background was needed and some adjustments were needed and over passed. As an example, by changing the route of administration of an already marketed drug, the gap analysis may tend to the fact that some toxicology studies may be needed to demonstrate the safety of this 505b2 drug product submissions.

Several other items could be part of this short communication to illustrate the paradigm shift in generic drug development. As it can be seen, generic leaders should now face the fact the small molecule pipeline is decreasing, biologics being more and more attractive, that prices are decreasing [7] and agencies are asking for higher standards of quality, making the markups lower, explaining somehow why they are purchasing raw materials from emerging countries and why they are transferring manufacturing drug development technologies somewhere else, in order to globally narrow the cost of goods. They had to face the fact that generic industry is evolving, many of them had no choice than to take the initiative of changing their plan by developing biosimilars, by submitting 505b2 submissions, and this shift has started by hiring dedicated people for these needs.

References

1. https://www.fda.gov/downloads/drugs/guidancecompliance regulatoryinformation/guidances/ucm370352.pdf

2. Krishnaiah YS, Xu X, Rahman Z, Yang Y, Katragadda U, et al. (2014) Development of performance matrix for generic product equivalence of acyclovir topical creams. Int J Pharm 475(1-2): 110-122.

3. https://www.fda.gov/downloads/Drugs/Guidances/ucm079345.pdf

4. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM579751.pdf

5. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004018.pdf

6. https://camargopharma.com/what-is-505b2/

7. (2018) Editorial. Generic drugs: are they the future for affordable medicine? Lancet Oncol 19(2): 149.