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Early Drug Development: A Lot of NonGMP/GLP Activities can be done to Streamline the Development and Narrow down the Cost as Well as Meet the Timelines

François-Xavier Lacasse*

Associate professor, Faculty of Pharmacy, University of Montreal, Vice President R&D, Hemione Inc, Montreal, Canada

***Corresponding author:** François-Xavier Lacasse, Associate professor, Faculty of Pharmacy, University of Montreal, Vice President R&D, Hemione Inc, Montreal, Canada; E-mail: pharmfx@videotron.ca

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Short Communication

During the last decades, almost all virtual life science start-up companies have rapidly increased their presence in the pharmaceutical landscape. Pharmaceutical development has evolved because of technology (analytical and process development) and clinical development (hybrid design in phase 1, including patients in phase 1B), allowing in certain cases to decrease time of regulatory filings (IND, CTA, NDA, NDA 505 (b)(2),…), which seemed attractive for these new companies.

Furthermore, new molecular entities have become more complex as polypeptides, proteins and monoclonal antibodies drug products take more and more place in many therapeutic areas (plus or less 50% in the 50 best seller drugs) alongside more conventional small molecules. However, it is not the end of small molecules. Research institutes and start-up companies are still busy working hard to develop more powerful small molecules as the physiopathology has also evolved and helped find some new intracellular targets to enhance their efficacy and decrease their lack of selectivity. Start-up companies are mostly driven by high level scientists and business development managers. Few of them are familiar with the drug development process, especially its early phases. There is no doubt that basic research scientists do know their new molecular entities (NMEs) from a scientific point of view. However, they distinguish much less and, sometimes, not at all, in terms of potential drug product candidates (or safety assessment candidate) and of "druggability" and its impact on safety and toxicology (non-clinical development). The author of this short communication cumulates more than 22 years in drug development at various phases with different kind of molecules. He will try to illustrate briefly how why in early drug development, pre-formulation-formulation and non-clinical development steps are closely connected and may narrow down not only the development time, but also the valorization of a NME that is ready to "jump" in the drug development (first GO-NO-GO milestone) process.

With the success of all the biologics, and the generation of new complex macromolecules, such as polymers, monoclonal antibodies and peptides/proteins, the need to have a good idea not only about the administration route, but also of the delivery systems have become tremendously important. This position was not only important in regard to the "druggability" per se, but also to minimize bias, as much as possible, from one species to another, when the transfer is performed on humans.

This last remark is more than often neglected since it may be difficult to get the same delivery system which is irrespective of the species. It is shown in the literature [1] that biologics, including plasmids and DNA/RNA compounds are becoming more and more attractive when locally targeted in the lungs and the gut. Literature also shows that the success of CRISPR technologies [2] has made new treatments possible for a lot of diseases such as cystic fibrosis. With these kinds of therapies, known as "gene therapies", it may be possible to actually cure diseases, not only treat their symptoms. However, for these start-up companies that are always trying to raise money, the challenge became more trying than it was with conventional small molecules. Difficulties arose because the cost and risk associated with the development of a biologic entity is by far more expensive than with a small molecule [3]. Additionally,

the research scientists specialized in the field of gene therapy, are still to date, very different from the pharmaceutical scientists who at least have an idea of the "pharmaceutical way of thinking" and who are better aware of the steps needed for a small molecule to become an IND/CTA-enabling candidate. As a consultant, I had the chance to meet a lot a different start-up companies dealing with different medical technologies, such as medical devices, small molecules, generic, innovative, and biological drugs. Most of them were able to raise money to push the development of their technologies. Nevertheless, one of the highest problems was to try to find the money to bridge the gap between the R&D activities and the GLP/GMP activities needed to reach the clinical trial application submission.

To demonstrate a proof-of mechanism in laboratory is one thing, but to bridge it to the clinic is another. It can be considered like a double edge sword: At this level, there is no need to formulate the molecular entity (biologic or small molecule) according to the current good manufacturing practice (cGMP). However, we have to keep in mind that small molecules have become less and less "druggable" over the time, meaning that formulation has become more and more important to demonstrate a reliability, stability and performance. Therefore, some emphasis must be put in the formulation development, even at its early stage. Done at this stage, the technical transfer to a cGMP facility to generate potent clinical supplies will be streamlined and will perform at a lower cost since neither the formulation development steps nor the stability study will have to be carried out. It will then be possible to not only narrow down the cost, but also be ahead of timelines. The cost can be a higher challenge for biologics, such as CRISPR technologies where, based on the literature, you may need more than the enzyme and the RNA, but some other molecules such as peptides and nucleic acids. Each of these biological compounds has its own stability profile however, it is difficult to have a clear idea of their compatibility once they are mixed, and for how long? Of course, to demonstrate a proof of mechanism, there is no need to obtain a long-term stability profile. However, once the product is in the clinic, clinical supplies will be prepared in advance, not extemporaneously. Moreover, each of these biological compounds may not have the same stability profile. Therefore, what will be the best temperature to store them without a doubt? Enzymes may be stable a -70°C, nucleic acids at -20°C and peptides or other biological compounds at 2-8°C…When mixed, what will be the best temperature? It is not well understood and known that a lot of these experiments can be performed in an academic laboratory, not under cGMP conditions. Most of the young companies are not cGMP compliant, and it is perfectly understandable since this is neither needed nor mandatory. However, this does not mean that they could not generate these kinds of cGMP results. Once again, in order to narrow down the cost (and to be ahead of timelines, such as the example above with small molecules), the nonGMP formulation development of a biological compound should be developed based on the same (or almost) quality attributes than the cGMP drug product that will be tested in the clinic. The technological transfer in a cGMP contract manufacturing organization (CMO) will then be streamlined, and no pitfall may be encountered as it is already forecasted and corrected during nonGMP formulation development. In that specific last case, GMP means Generating More Papers….and does not mean that nonGMP results cannot be reliable. The same kind of comment could be established for toxicological studies carried out according to current good laboratory practices (cGLP). By taking a look at the package required to carry out a phase I clinical trial, some studies need to be done under cGLP and others do not, such as the determination of the maximum tolerated dose (MTD) and the No-observed adverse event level (NOAEL). These two last studies could be performed under a nonGLP environment, in parallel to nonGMP development such as described above, and the results would again be reduction of costs as well as avoidance of undesirable delays which would not need to be explained or exposed to a board of Directors…Furthermore, investors will see that they are in front of people who know what they are talking about, people who have already been through this before. Taken together, the above examples try to show that it is possible to bridge the gap between universities, research centers and the industry, to make discovery compounds viable to become an IND/CTA enabling candidate. It is also possible to reduce costs and to be ahead of timelines during the overall early drug development process. However, since pure science will never be better than regulatory requirements to reach the clinic, we have to keep in mind that people with pharmaceutical development should be part of this process at early as possible…In the end …it is all people related…As Richard Branson said: "Success in business is all about people, people, people. Whatever industry company is in, its employees are its biggest competitive advantage."

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