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Regulatory Affairs: More than Guidance and Guidelines

François-Xavier Lacasse*

Associate professor, Faculty of Pharmacy, University of Montreal, Senior independent consultant, Drug Development, Canada

***Corresponding author:** François-Xavier Lacasse, Email: pharmfx@videotron.ca

Short Communication

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Abbreviations: IND: Investigational New Drug; GMP: Good Manufacturing Practices; GLP: Good Laboratory Practices; NOAEL: No Observed Adverse Event Level; CMO: Contract Manufacturing Organization; PLA: Polylactic Acid; PVP: Polyvinyl Pyrrolidone; GRAS: Generally Recognized As Safe; CMC: Chemistry Manufacturing and Controls; MAD: Multiple Ascending Doses; PK: Pharmacokinetic; CMC: Chemistry Manufacturing and Controls; SAD: Single Ascending Doses; MRSD: Maximum Recommended Starting Dose.

Short Communication

Over the last decade, the drug development landscape evolved sensitively with the increase of virtual companies. Numerous and promising new molecular entities and pharmaceutical technologies coming from universities and research centers were born. The generation of new start-up companies, most of them being virtual, has emerged. A lot of them are managed by brilliant scientists who forgot that science will never be better than regulatory requirements. Indeed, to become investigational new drug (IND) enabling candidates, whether we are talking about a medical device, new molecules or pharmaceutical technologies, these candidates will have to go through several steps that are mandatory prior to be tested in primary clinical studies on human. Furthermore, this observation has been noted in generic industry where some companies tried to become "FDA compliant" only by reading and applying FDA guidelines. Some of them were not successful since reading only guidelines, will not make you FDA compliant… Rome was not built in one day! The author of this short communication has been working in drug development for the last 25 years and more than often had to deal with managers who thought that regulatory affairs are the only rules to follow to become "compliant". It will be illustrated in this communication that regulatory affairs are by far, more than guidelines and reading documents; that some strategies are coming from this specialty, whether it is coming from biotech, generic or innovative companies.

Are Good Manufacturing/Laboratory Practices (GMP and GLP) needed to determine if A New Molecular Entity is an IND Enabling Candidate?

Regulatory affairs really bridge the gap between all specialties that are involved in drug development. This assumption does not sound new for most of the big pharmas. However, as mentioned above, virtual companies are filling the landscape more and more [1] and are not necessarily managed by people who show a proven track record in regulatory filings and strategies. As an example, a lot of preclinical studies can be carried out at a university or research center since the Good Laboratory Practices (GLP) [2] are not mandatory to be followed for these to prove mechanisms. Same things for the determination of the no observed adverse event level (NOAEL) [3], where its determination has not to be performed under GLP. This does not mean that it will not be done properly! Same comments can be addressed for preformulation/formulation. Why would a startup company spend a lot of money in a contract manufacturing organization (CMO) if an academic platform/department specialized in formulation could do the job? In that case Good Manufacturing Practices (GMP) are not mandatory neither. Taken together as an example, the fact the neither GLP nor GMP are mandatory for these steps, the fees associated with the drug development can be narrowed down sensitively for a startup, which is not negligible [4].

Non-Clinical in Vitro and in Vivo Tests: Regulatory Impact of the Indication and its Relevance to Determine the Strategy to Reach the Clinical Development

Regulatory strategies should be considered also for the selection of a new molecular entity or a pharmaceutical technology [5]. As an example, if the choice between two new molecular entities would be an antiviral or an anti-inflammatory drugs, the fastest investigational new drug (IND)-enabling candidate should be the antiviral drug for, amongst others, the following reason: excellent correlation between *in vitro* and *in vivo* tests, even with the clinical study where a drop in the viral charge is the clinical endpoint that can be monitored in few days on a few number of patients. Comparing with anti-inflammatory compound where development should be done by associating the efficacy with a golden standard that is on the market, and from a clinical endpoint efficacy, questionnaire on the quality of life should be part of the assessment that implies an explosion of the sample size, pain being extremely subjective. Moreover, pain killing superiority should be demonstrated in the clinic, versus the golden standard, which is not an easy thing to do. Therefore, entrepreneurs should not be surprised if investors in health sciences are often reluctant to invest in pain killers. For the above reasons, regulatory strategy is more than important prior to selecting any technologies that may enter in pharmaceutical development.

Regulatory Impact of the Dosage form- Time and Cost for Development

This last example was dealing with two different small molecules, but what happens when first investors must face the early development of an oral dosage form versus an injectable delivery system and when will they see the costs associated? From GMP clinical supplies manufacturing standpoint only, the cost will be much higher than for a hard gelatin capsule or a tablet. Now imagine if the drug is a biological, like a monoclonal antibody or DNA, where costs may reach several million dollars only the for the synthesis of these substances and through freeze drying. This must be considered for the first fund raisings. Again, when managers have never faced a drug development, even an early drug development, the amount of first fundings may be quite different when a biologic or a small molecule must be developed and when these entities should be orally or parenterally delivered.

Medical Device or Combination Product?

Some people will decide to invest in medical devices instead, since regulatory requirements are lower, and the literature shows that. However, in a first time, it depends on the type of medical device. If it is invasive, recent guidance [6,7] have been emitted and even though less stringent than for a drug product, they have changed and request much more precaution that was not needed in the past. Many people will also work on compounds thar are identified to be generally recognized as safe (GRAS) by regulatory agencies. Nevertheless, they are working on modified version of these excipients, such as chitosan and modified chitosan, or polylactic acid (PLA) and polyvinyl pyrrolidone (PVP) copolymer, where PLA alone and PVP alone are GRAS and listed in the handbook of pharmaceutical excipients but do not exist under a pharmaceutical grade when they are linked under covalent bonds under PLA-PVP copolymer. On top of that, if the technology is a combination product [8] where, as an example, a drug substance, a biologic is nanoencapsulated in a polymer, is associated with a medical device, and the biotech company would like to get a preIND meeting; in that case, which department will be involved? CDER? CBER [9]? CDRH [10]? Only a person with a strong background and expertise in regulatory submissions would be able to answer that properly and to address valuable questions for the preIND meeting [11].

Shortcut Regulatory Strategy that is Not Well Known: How to Narrow Down the Cost When Possible

Quite recently, some grants [12] emerged allowing the performance of human first clinical studies. Most of the time, grants were extremely useful for preformulation formulation and non-clinical demonstration, for proof of mechanisms on different healthy and knock out animal species. This type of grant could then be very useful for universities and research centers where some new molecules and technologies were born. And again, these people should be surrounded by regulatory persons who will help them for their development pathway by narrowing down the time of development and maximizing the data that may be generated. For the last 5 years costs for clinical development, even for phase I clinical studies have increased sensitively, in all the fields such as chemistry manufacturing and controls (CMC), GLP toxicological and clinical studies. Most of the time, Phase I studies are carried out to determine safety and pharmacokinetic (PK) on healthy volunteers. They are divided in phase IA where single ascending doses (SAD) studies will be done and phase IB where multiple ascending doses (MAD) study will be performed. Hybrid designs allow to use in phase IB more than one cohort of patients to monitor a trend of efficacy. From a GLP toxicological studies, 14- or 28-day repeated dose studies on two animal species (one non-rodent) are most of the time selected to demonstrate and support the safety of the compound and to determine the no observed adverse event level (NOAEL) dose, dose that will be extremely helpful to determine the maximum

recommended starting dose (MRSD) on human for the phase IA [13]. It can be easily imagined that the cost associated for the GLP tox and the phase IA and IB can be several millions, especially if some patients are recruited for phase IB. But some compounds may be monitored for a trend of efficacy in phase 1A on healthy volunteers. Compounds that will have to be taken just one time, such as antifungal, abortive, and sleeping pills to name just a few. As an alternative of a 14-day repeated dose study in the United States of America, the cGLP toxicological studies for a phase IA could be an extended acute study [14] that will be cheaper and shorter in time to do. From an investment standpoint, this cannot be neglected and again, regulatory people should be more than aware of that and the fact that a trend of efficacy can be generated in phase IA in healthy volunteers may sound encouraging for the next funding campaigns.

"Regulatory" Closing Remarks

To conclude, many other examples could be listed to demonstrate the importance of regulatory affairs in drug development, especially at the early stage. Few people are aware that it is possible to carry out a phase I study in Australia with nonGMP drug substance and FDA being aware of that, it is possible then to continue in phase II with GMP material. Still a lot of people think that GMP means that the drug substance will be better, purer, safer… but not at all. GMP also means Generating More Papers! Altogether, the examples exposed in this short communication should have demonstrated that regulatory affairs are not only a question of guidelines but can also be extremely precious when the time comes adding value to a pharmaceutical molecule and/or technologies. It can narrow down cost of drug development and may promote timelier results, which is so important when scientific entrepreneurs face investors.

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