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Volume 2 • Issue 5 • 2018

Opinion Article

Chronicles of Pharmaceutical Science

ISSN: 2572-7761

Current Opinion on Pharmaceutical Development and Regulatory Perspective on Characterization Parenteral Delivery Systems.

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Received: June 07, 2018; **Published:** June 26, 2018

Volume 2 Issue 5 June 2018
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Over the last decade, numerous new molecular entities (NME, small molecules and biologics) have been formulated under the umbrella of nanomedicine drug delivery technologies. Some of them were submitted through the New Drug Application (NDA) [1], the Biological Legal Application (BLA) [2] while others under the 505b2 [3] pathway. In order to enhance product life cycle management, numerous of these NMEs have been reformulated with the help of nanotechnologies and filed at different regulatory agencies under the 505b2 (for the FDA) and hybrid (EMA) submissions. Nevertheless, the 505B2/hybrid pathways have not only allowed, from a regulatory perspective, to narrow down the time of submission but also from a more scientific standpoint, afforded the generation of "already marketed drug product" presenting a better safety and compliance doubled with a higher efficacy profile. (Bobo., *et al*.) [4] have reported the number of "51 FDA-approved nanomedicines" showing the growing interest of drug formulated with the help of nanotechnology. The authors illustrate that some nanomedicines have been filed and approved 60 years ago (1957: high molecular weight Iron Dextran) and more recently, such as ADYNOVATE (Baxalta), a polymer-protein conjugate (PEGylated factor VIII) where PEG was added to the formulation in order to stabilize the factor VIII protein, enhancing its *in vivo* half-life.

Numerous biologics and small molecules have been filed and classified under the nanomedicine nomenclature because of their ability to generate colloids, or colloidal dispersions when they are solubilized in aqueous medium. However, with the coming of age of the nanoparticle delivery systems such as polymeric nanoparticles, liposomes and micelles, the biopharmaceutical properties of these same molecular entities were enhanced with regards to their half-life excretion, dosing regimen (interferon 1a vs PEG-interferon 1a) [5], cardiotoxicity and nephrotoxicity (liposomal doxorubicin and amphotericin B) [6-7]. From the middle of the 80's till the middle of the 90's, microparticle drug delivery systems attracted a lot of attention and several already marketed drugs have been formulated through microparticulate drug delivery systems. Biodegradable and biocompatible polymers such poly-alpha-esters (PLA, PLGA), polycaprolactone and polyanhydride were of great interest since some of them, such a PLA, had already demonstrated its safety and biocompatible profile, being commercialized through sutures [8] and marketed drugs (octreotide).

Several clinical studies have been initiated and unfortunately were stopped after phase I/II because of poor safety profile and innocuousness through the IV route. Of course, marketed nanodelivery systems are available on the market, such as liposomes and albumin but cannot be classified as solid structures such as polyorthoester nanovectors [9]. Furthermore, when administered through the IV route, a passive targeting through the reticulo-endothelial system because of the particle size, size distribution, and also because of an active or

passive immunological response (opsonization, recognition by macrophages…) was undergoing. These above reasons may explain why current marketed solid micro- and nanoparticulate drug products are administered through intramuscular or subcutaneous injection. Liposomes and micelles are more recognized as colloidal delivery systems, giving them the potential of being administered intravenously (IV). Even if the IV toxicity associated with "solid" polymer particles was then overpassed by using phospholipids, micelles, or more flexible structure allowing their circulation even in the smallest arterioles and venule systems, opsonization and recognition by the reticulo-endothelial system was still occurring. For that reason, in order to enhance the residency time in the blood stream, pegylation was selected to confer stealth behavior to these semi solid vectors (liposomes, lipidic nanoparticles and complex). Even though the literature reports numerous papers describing the positive impact of pegylation on nanosytems' shelf life and toxicity (especially cardiotoxicity for cytotoxic drugs), specific antibodies targeted to the polyethylene glycol have been recently reported [10]. That being said, nanodelivery system developments that were very "academic" during the 80's and 90's became more and more popular in the industry. One of the reason may be explained by the "quest of the nanomolar efficacy". Drug substances became more and more hydrophobic, making them very difficult to formulate, even when developed for the oral route. From 1995 to date [11], almost 50% of the new drug submissions were done with BCS class IV (low solubility, low permeation) molecules. It can be imagined that the development of IV solutions or parenteral drug delivery systems challenge became more and more challenging.

Cyclodextrins became of great interest [12] because of their biocompatibility, lack of toxicity, allowing the formulation of solution with small molecules presenting high log P (above 5). However, according to the handbook of pharmaceutical excipients [13] beta-cyclodextrins, when administered parenterally, are not metabolized and accumulate in the kidneys as insoluble cholesterol complexes, resulting in severe nephrotoxicity [14]. The cholesterol complexes are formed via the competition between cholesterol and the encapsulated hydrophobic molecule inside the cyclodextrin, cholesterol being highly hydrophobic and showing a higher affinity for the cyclodextrin. Furthermore, in 2014, the European Medicines Agency (EMA) published a document entitled Background review for cyclodextrins used as excipients and mentioned that *both α-CD and β-CD showed renal toxicity after parenteral administration and thus are generally not suitable for medicinal products given intravenously. Besides, β-CD has the additional disadvantage of an inherent low solubility, which makes it less suitable for medicines given parenterally* [15].

Furthermore, from a formulation development standpoint, these micro- and nano-drug delivery systems need to be characterized differently than conventional solid oral dosage forms. Then it can be expected that the manufacturing reliability lot after lot becomes more challenging to obtain. For that reason, specific development guides from the bench to commercialization have been proposed and published to maximize chances of commercialization [16]. Besides these efforts, regulatory experts will still defend the point that it is easier to file a new micro-nanoparticulate drug submission than an abbreviated new drug submission, for the one and only reason that the new drug being yours, you will not have to compare yourself with another. This point of view is extremely relevant when a bioequivalence study cannot be carried out. A good example of such situation would be cyclosporin ophthalmic emulsions. The FDA guidance for this drug [17] states that two approaches in vitro or in vivo could be selected for the filing of a generic cyclosporin ophthalmic emulsion. The *in vitro* approach is obviously economically more attractive than the *in vivo* approach, especially for an ophthalmic emulsion for which bioequivalence cannot be assessed by a pharmacokinetic study but only by a clinical endpoint study. First, in vitro tests must be performed, on different batches of both the generic formulation and the innovator, to demonstrate the pharmaceutical physico-chemical equivalence. Several tests that are specific to colloids, such as globule size distribution, viscosity profile as a function of applied shear, pH, zeta potential, osmolality and surface tension must be realized and validated which often discourages formulators and demonstrate that this formulation development is far from a classic qualitative (Q1) and quantitative (Q2) approach used for a conventional sterile product. This may explain why this drug has been very difficult to genericize and is still under development for a lot of generic companies.

To help the industry characterizing more accurately colloidal delivery systems (whether they are administered parenterally or not), academic researchers have become more and more partners of choice. For the first time academic researcher are developing "physico-analytico-chemical" methods with "non-conventional" equipment, or equipment that are not commonly used in the industry. This

approach has become highly dedicated and relevant to enhance and push to the limit the determination of the composition, from both a physical and a chemical standpoint, these micro- and nano drug delivery. The relationship between the industry and the academy has then made a lot of progress since a symbiosis has emerged between them. They realized that they needed to share the same language. By observing what is happening with the biosimilar drugs and the help of the academic sectors to help characterizing as much as possible these biological molecules, it may possible to predict that in a near future biosimilar may become almost equivalent. More especially in Europe in that regards, it became hard not to concede that this symbiotic relationship got more and more successful and for both parts.

It can be expected that regulatory specialists and consultants will proclaim that a face to face meeting, even with the best chemistry-manufacturing and controls (CMC) dossier will, down the road, rise questions from the different government agencies. For instance, a common question asked by agencies is whether or not a micellar structure remains stable post injection in the blood stream. It is easy to understand that these interrogations are extremely difficult to answer even using in vitro settings. Questions like these, if they are not answered appropriately may result in a clinical hold. It becomes therefore challenging to predict to what extent a project can be ahead of timelines or delayed. These kind of questions, that can be qualified as "unwritten laws" may jeopardize all the regulatory submissions, whether they are new or abbreviated.

In summary, even though there is no golden route that will ensure the success of a regulatory drug submission, there is need to share the expertise, the experience form both an academic, a pharmaceutical standpoint. There is a need for complementarity by securing pharmaceutical micro- and nano- drug development as early as possible with subject matter experts.

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