

**ANALYTICAL DEVELOPMENT, PREFORMULATION/FORMULATION, AND DRUGS' SPECIFICATIONS: WHY THESE STEPS SHOULD BE CLOSELY CONNECTED?**Pascal St-Laurent\*<sup>1</sup> and François-Xavier Lacasse<sup>2</sup><sup>1</sup>DI-Solution Conseil Inc. Canada.<sup>2</sup>Faculty of Pharmacy, University of Montreal, Canada.**\*Corresponding Author: Pascal St-Laurent**

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Each new molecular entity (NME) or active pharmaceutical ingredient (API) is unique. Whether the molecule to be developed is a chemical (small molecule, peptide,...), a polymer, a biologic (polypeptide, protein, immunoglobulin,...) each of this entity will have to be developed under the same lot after lot irrespective of the scale in order to obtain the same physical, chemical and biological behaviors. Over the last decades, with the constant growth of small biotech companies came a paradigm shift in the business model. Since these companies were not necessarily strong enough (money and human resources) to launch a drug product, a new model was adopted to narrow down the risk. To summarize, ideally, the goal was to reach phase IIa clinical trial to generate clinical results (therapeutic exploration) and to license the molecule out to a partner, that would streamline the development through phase 3 and eventually commercialize the NME as a drug product. But, as mentioned, the above represents an ideal scenario. More than often, in the quest of the nanomolar efficiency, these young sponsors forgot the “druggability” and the overall reproducibility of their compounds, the reliability that analytical, preformulation/formulation development and specifications, even though they could have been surrounded by seasoned drug professionals referring to their proven track records, connected with reliable documentations such as pharmacopeia and guidelines. Authors of this short communication combine more than 50 years of drug development and will try to illustrate that science will never be better than regulatory requirements, regardless of drug indication.

According to the international conference on harmonization (ICH), and more precisely ICH Q8 guidance<sup>[1]</sup>: “*The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product*”. This cannot be done without a holistic approach focusing on the physico-chemical characterization of the pure API and over its whole formulation development process. Why? Because the purest and highest characterized API will be mixed with excipients, that may generate solid-solid reactions, liquid-solid reactions, that may generate pseudo polymorphism (hydrate, solvate forms), and will be stressed by the equipment used during granulation, such as high shear granulator, roller compactor that may generate amorphous API structures. Both wet- and solid-state chemistry should be of great interest and very helpful to ensure the reliability, reproducibility and robustness of the API, and the drug product. However, some specific tests may not be part of full compendial release specifications.

When a drug substance (DS) is jumping in drug development, whether the API is a new compound which will be used in the final drug product formulation, or a

generic drug where a lot of information is known about the drug through publications or pharmacopeia; but as mentioned above, there are some basic elements that should be evaluated and considered when establishing specifications for the drug product.

From a physical-chemical standpoint, the API should be well characterized and parameters such as synthetic route, polymorphism, hygroscopic properties, particle size and particle size distribution and solubility will greatly help both the formulators and analytical chemists during the drug development process. The most stable form should be selected when working with an API that has a propensity to exhibit polymorphic changes. It has been noted that since the 1990s, near than 50%<sup>[2]</sup> of new small molecules have been BCS2 and BC4 classified<sup>[3]</sup>, meaning that they showed low solubility profile, and high or low permeability profiles. Companies have then decided to see whether the use of amorphous forms could be viable despite their lower solid-state stability. The need to monitor the chemistry of the solid-state has then become more and more relevant. Over the years, the authors of this communication have experienced ‘surprises’ with polymorphism even if the physical

properties of the API had been well evaluated during the drug development and scale-up process.

As an example, there are quite a few key parameters that should be considered by the analytical chemists before performing intrinsic dissolution studies on different polymorphs or salts, the first question that arises: as the crystal structure of the API been altered by the compression process? Does the compression force have an impact on the crystal structure of the API? As mentioned in the introduction, evaluating a potential polymorphic change is not easy for start-up companies which are typically working with contract development manufacturing organizations (CDMOs). The same rationale applies for the formulators when developing the drug product when the API is usually mixed with excipients. For these two last reasons, it is very important and highly recommended for start-ups and biotech firms to hire relevant people with proven track records in pharmaceutical development. CDMOs will be liable for current good manufacturing practices (cGMPs) however they should not be considered consultants or Subject Matter Experts (SMEs).

The lot-to-lot reproducibility of the API is key and that is why its physical-chemical properties should be evaluated (or available from a certificate of analysis) for all lots received during the drug development process. The same principle applies for an existing API which will be used for the development of a generic product. The route of synthesis for API X might be different between manufacturers; different starting materials, different solvents could be used in the synthesis, different impurities may be present and those need to be identified and ideally characterized. Furthermore, agencies are now asking for a full traceability of the molecule, from the starting materials down to the native API, even though a 100% purity and a very low impurity profile are reached at the release.

The initial characterization of the API can be summarized:

- Is the route of synthesis well known?
- Any potential for polymorphism?
- Residual solvents<sup>[4]</sup> if so, what class (I-IV) as this will impact the specifications?
- What are the process impurities, and have they been identified, from a quantitative standpoint, and if the threshold is above 0,2% per single unit from a qualitative standpoint.<sup>[5,6]</sup>?

The manufacturers of the API should have developed and validated a stability-indicating method, as per ICH Q2.<sup>[7]</sup> The recommendation is that the formulators and analytical chemists should start with this method when developing the method for the drug product. Mixing or dissolving the API with excipients may lead to the formation of degradation products. Degradation products may be formed through exposure to heat, light, acidic, basic and oxidative environments. It is important to

emphasize the difference between process impurities and degradation products; process impurities are inherent to the synthesis of the API and degradation products can be observed during stability studies of both the API and finished dosage form. Furthermore, it should be kept in mind that formulations may change between phase 1 and phase 3 clinical trials, meaning that impurity profiles, degradation products, solid-state chemistry and other physico-chemical characteristics of both API may change accordingly.

Although from different backgrounds, the authors have experienced over the last 25 years, cases where New Drug Applications (NDA) were delayed because the companies did not submit their applications with stability-indicating methods, in other words forced degradation also known as 'stress testing' had not been performed or evaluated adequately. This is first performed on the API itself (the documentation is usually available from the manufacturer or Drug Master File (DMF)), drug excipient compatibility studies where the API is mixed with each excipient on a 1:1 ratio and the prototype of the drug product exposed to light, heat, oxidation, acidic and basic environments. The degradation profile of the API, in all of its possible composition, can then be evaluated and the purity of the API determined using suitable analytical techniques. A mistake commonly made is that if an API has a monograph in any pharmacopeia, it does not mean that the impurities/degradation products assay methods are stability-indicating for the API they are working with. As mentioned earlier, there might be a different synthetic route, different solvents in the synthesis and crystallization (even purification) processes. It is then the responsibility of the analytical chemists to improve the method if needed and validate it.

Protocols describing how these studies will be performed should be written by the formulators and analytical chemists and approved by the quality assurance unit. The results will be then summarized in reports and the data will ultimately determine if the method is stability-indicating or not.

The example which was described not only applies to the assay method. A thorough examination and evaluation of the physico-chemical properties of the API will be very useful for blend and content uniformity studies as well as establishing specifications for a dissolution method if applicable. Additionally, knowing and documenting the properties of the API under stringent requirements will be very useful for any patent litigation issues that may arise after commercialization.

In this expert opinion, the authors tried to illustrate that:

- Analysts and formulators should work together and share the same language to achieve successfully a robust, reliable, and reproducible drug product.

- Care should be taken during all the steps of developments to avoid pitfalls that may occur down the road.
- Over the last years, regulatory inflation has been noticed concerning the overall chemistry, manufacturing, and controls therefore it is highly recommended to do regulatory intelligence to be aware of all the new requirements and guidance that may be raised by all the agencies.

## REFERENCES

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