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DRUG DEVELOPMENT: BE A FAN OF THE KISS APPROACH (KEEP IT SUPER SIMPLE AND SAFE OR ...STUPID)

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INTRODUCTION

Drug development is an applied science that should be using a holistic approach. Indeed, several different sciences are involved and could be divided in preclinical sciences, or basic research, and then development research that starts once a safety assessment candidate has been selected and decided to be pushed for clinical development. A lot of departments are involved in the development of a new molecular entity, and it is fair game to see all of them pulling the blanket on their side, claiming that if they were not there, nothing would happen and no drug would reach the market. Of course, this speech may be applied when working in a big pharma, since a list of drug products generate several billions of dollars. However, one must be candid to recognize that this same speech cannot be applied to startups or generics, which, most of the time, have only one product (because of financial constraints) and they do not have the choice to promote it and make it work. Most of the start-ups are made up of several brilliant scientists thinking that science will be better that any regulatory requirements whereas government agencies do not worry about how "wow" the science is since some chemical, safety and efficacy studies will have to be carried out to demonstrate that the drug product can submitted and launched. Large pharmas show a more conservative approach and will go through all the steps that are needed to demonstrate the safety and efficacy of the drug product therefore avoiding surprises without relying on "rocket science". They are more proponents of the KISS method. Authors of this short communication present more than 50 years of experience in drug development and had to chance to work in different companies ranging from start-ups to large pharma. It will then be illustrated that reinventing the wheel is not the best way "to get a short track for submission" and that it is possible to move slowly but surely by following a proven recipe.

Please note that the authors of this opinion do not think that the rise of the biologic molecules will kill medicinal chemistry. Only by looking at the last drugs submitted to the FDA, biologics were highly popular a couple a year ago and now it seems that a kind of steady state has been reached, biologics and small molecules being developed for different and targeted diseases.

Even though the landscape has evolved sensitively during the last decades, the method of developing a drug - the technology - did not…or should not have changed. However, as mentioned in previous opinions, the emergence of startups in life sciences has left room for brilliant scientists and scientific managers. Nevertheless, it seems that for many of them, their time is spent focusing mainly on the science, which is not a bad thing of course, but entrepreneurs should also maintain the flame and passion in their technology. They seem to forget that more than one government agencies, such as FDA, EMA, Health Canada, and the drug development itself are highly conservative and are huge fans of the KISS approach. For that reason, startups and scientific entrepreneurs should be well surrounded by seasoned drug developers. Science will never be better than regulatory requirements.

Drug development starts with understanding as much as possible the physiopathology of the disease to

create a molecule (the key) that will stick to the receptor (the lock) to generate a cascade of biochemical reactions that will give birth to the pharmacodynamics. Most of the time, the way molecules are tested *in vitro*, during high throughput screening, and *in vivo* on animal species, are formulated in solution in DMSO or in aqueous suspension. The goal is to demonstrate a proof of concept, to determine binding affinity, very preliminary toxicological data, therefore there is no need to get a "nice and optimal" formulation at this stage. However, three aspects or approaches must be kept in mind:

1. The route of administration: If the molecule is to be given intravenously, a solution will need to be formulated. If the oral route is targeted, the molecule will need to go through the stomach, the gut, without being altered by either the pH or enzymes and then be absorbed in the small intestine under a molecular state to then travel in the blood stream and be distributed. This means that the molecule's travel to its target will be far more complicated than in vitro testing where the molecule is directly in contact with the targeted cells and receptors.
2. Small molecules are getting more and more hydrophobic, making them more difficult to formulate therefore, the use of specific excipients and/or less classic drug delivery systems will have to be studied during preformulation and analytical development.
3. The analytical development should be as important as the formulation development, which is unfortunately not the case. Drug-excipients compatibility studies and forced degradation are tremendously important and should drive the rationale not only for choosing good excipients but also to help monitor the in-process Quality Control (QC) tests that should be performed during manufacturing, for the determination of the packaging (even though these two steps may change down the road of dug development, until phase 3, or when the biobatches will be manufactured).

Keeping the above three points in mind and applying them to all the next safety assessment candidates would be a good start, avoiding the rocket science and focusing on what is common for all molecules: They are either coming from chemical synthesis or biologics, will make it simple and…stupid.

Medicinal chemistry

One of the main differences between startups and big pharma is that the area of medicinal chemistry. A lot of startups now are choosing their small molecules, based on an indication, in companies that rarely specialized in high throughput chemistry (synthesis and screening). Therefore, when they choose a molecule, they have no other choice than to work with it. If, as an example, the main pharmacokinetic (PK) parameters are not suitable enough to reach a once-a-day dosage, most of the startup will not go back to the bench to modify the lateral groups to enhance the PK parameters, without altering the pharmacophore ring, and will try to generate a controlled release formulation. One of the reasons that may explain this is that most startups do not have a medicinal chemistry group in their company, so the easiest and fastest way to jump in the clinic, for most of the cases, would be to play with the formulation. The example of the drug substance's half-life illustrate better the above. When the half-life of the molecule is near 10 hours, twice a day dosage is recommended (when PK is correlated with the PD). Slow-release formulation may be considered for that case. However, the story may be totally different if the half-life is around 5 hours, especially from an efficacy standpoint: The drug release must be slown or reduced to reach a once-a-day dosage, but the absorption level will be low too, correlated with the low level of release. From a mathematical standpoint this last assumption may be fixed by adding a huge level of drug substance in the delivery system…but who wants to swallow a hockey puck?

Analytical development should not be considered as a support!

The first thing that is needed is an analytical method which will adequately determine the assay and potency of the drug formulation. In early phase, focus should be on the main active. Process impurities should be well known and not ignored during the initial stability studies. The synthesis route should be documented, parameters such as residual solvents used during the synthetic route and crystallization steps should not be neglected. The synthesis path can further be optimized down the line. Forced degradation studies must be performed on the Active Pharmaceutical Ingredient (API). Hence the difference between an impurity and a degradation product. Impurities arise from the synthesis process while degradation products or degradants are generated by stressing the API through acidic, basic, oxidative, heat and light stress conditions. It must be emphasized that an impurity can also be considered a degradant over time once the API is formulated.

From a physical chemistry standpoint, the molecule should be well characterized in terms of chirality, crystal structure and polymorphism. This information could be very helpful once the API is formulated whether in a solid or liquid dosage form. No one can predict how the API will behave once formulated.

The author of this communication's section is not a formulator but has experienced many challenges from an analytical standpoint once an API is formulated. If initial analytical work on the API has been adequately performed, several pitfalls can be avoided

during stability studies of the finished dosage form. It is understood that start up companies do not have the same resources as large pharma and this includes laboratory instrumentation. These four simple steps should have been performed early in the drug development process:

- Physical characterization of the API i.e. solubility, crystal structure and polymorphism. For start up and generic companies, this implies a thorough evaluation of the API coming from their supplier. A review of the Drug Master File (DMF) should be conducted.
- Analytical methods that are easy to use. Methods that should have been developed and semi-validated in early phases using the KISS (Keep It Super Simple) approach. As an example, reviewing the assay method documented in the DMF is a good starting point. Modifications to that method can be made to the method which will be used for the finished dosage form. It is pointless to re-invent the wheel in early stages of drug development.
- Forced degradation studies on both the API and finished dosage form. Excipient compatibility studies are not to be ignored. Although often neglected, the data generated during those studies might become very useful and insightlful during stability studies.
- Initial stability studies where degradants are monitored and reported: This ensures that the degradants, if any, can be trended over time. Retained samples of the API must be available for retest if degradation is observed during the stability study of the finished dosage form.

Once a suitable assay method has been established, other analytical techniques should not be neglected when designing the stability protocols as they might provide very insightful information during the duration of the stability studies.

The reality is quite different between start-up, generic and large pharma companies but it is pointless to do too much in early drug development unless good science and common sense are used throughout the analytical method development process. A dissolution method should be in place, but it will be optimized as the drug development process goes forward. As stated earlier, if the solubility of the API is well determined, then this will be a good starting point for the dissolution chemists to develop a robust and discriminating method.

Needless to say, the analytical chemists and formulators must communicate and work in close cooperation.

Formulation used in toxicological studies and clinical studies

There is a rule of thumb in drug development regarding the purity of the drug substance: Nothing is not written in any guidance or guidelines. Most of the time, it is proposed to use a “dirty” drug substance, around 94-95% in purity to initiate the first GLP toxicological studies. The rational is that if there are no toxicological effects at this level of purity, it won’t be the case at a higher purity. Furthermore, the purity should increase over the time of development and during scale up. It is also highly recommended to use the same (or almost same) formulation over time to be sure that it may not impact any unexpected results. For that reason, seasoned executive people in medicinal chemistry, preformulation-formulation and analytical development, with a proven track record, should be part of the team at the early development stage to give theorical assumption concerning impurities, degradation products, in both drug substance and drug products. This represents a KISS approach, to potentially avoid pitfalls that may come down the road of development.

A special attention should be paid concerning the preformulation-formulation of the drug substance at the early stage. Most companies, especially startups will change the formulation whether they are at the proof-of-concept, the toxicological studies, and the phase 1 clinical trials. Since small molecules are getting less and less soluble, the solid-state chemistry becomes extremely important. Thus, the particle size and particle size distribution, the polymorphism andcrystal structure lead to major differences regarding the PK profiles and the systemic exposure. Early preformulation work could help to streamline the development and to get a high level of confidence that preformulation, formulation, with the precious help of both the wet and the solid-state chemistry, cannot be held responsible of unexpected results.

Packaging

Packaging represents of the most neglected part of drug development, especially for startups. Big pharmas are carrying out what they call probe market container stability study, and the cost can reach a few million dollars. Based on the above example and closely connected with packaging, if the solid-state properties of the API in the formulated drug product are well known and understood, this may minimize the packaging configurations that need be evaluated and tested during the stability studies. In other words, if adequate evaluation is performed upstream, the KISS approach is also achieved. Basically, several types of packaging will be tested to determine in first time which one will be the best but also, depending on countries where the drug will be launched, packaging type may not be the same. As an example, a lot of drug products are dispensed in blisters whereas bottles are part of numerous pharmacies in North America. Authors of these articles often faced problems because of the wrong packaging, thus

generating delays and more fees in the development process. Once again, this packaging example could be easily averted if seasoned scientists and formulators are part of the team at the early stage of development.

CONCLUSION

Several other examples could be listed in this communication. However, authors tried to illustrate as best as possible that the KISS approach should be correlated with human resources. This means that a startup should begin by getting surrounded by seasoned executive developers who have shown a proven track record, will not try to reinvent the wheel, and are aware that science will never be better than regulatory requirements. Of course, no one - even the best drug developers - possesses a crystal ball! However, by not attempting to reinvent the wheel and by applying the steps for a new molecular entity to become a safety assessment candidate ready to jump in the clinic, bad surprises may not occur as frequently as seen when unexperienced people are part of the development process. Moreover, when a drug makes progress in early clinical trials, the one and only thing that can be controlled is the chemistry manufacturing and controls section, since the drug has never been tested on human thus adverse events are based on animals. The KISS approach is easy to understand: Control what can be controlled!