LUPINE PUBLISHERS
Open Access

Drug Designing & Intellectual Properties International Journal

DOI: 10.32474/DDIPIJ.2018.02.000144

ISSN: 2637-4706

Opinion

Bioequivalent Drugs: Towards A Needed Holistic Paradigm Shift?

François-Xavier Lacasse*

Faculty of Pharmacy, University of Montreal, Canada

Received: October 17, 2018; **Published:** October 24, 2018

***Corresponding author:** François-Xavier Lacasse, Faculty of Pharmacy, University of Montreal, Canada

Opinion

The author of this short communication has been working in and teaching drug development for the last 20 years. He has been involved in more than 100 drug development projects, including drug delivery, medical device, biologics, innovators and generic drugs. He has also been involved in all the steps that are needed to file properly to different governmental agencies investigational new drug applications (IND), clinical trial applications (CTA), abbreviated and new drug applications/submissions (ANDA\S; NDA/S), 505b2, 510k and biologics legal applications (BLA). After several other interactions with all the other actors, such as Health Canada (HC), the Food and Drug Agency (FDA), the European Medicines Agency (EMA), pharmacovigilance companies and consultants, public relation companies, insurance companies and especially patients, the author has decided to gather all the comments in order to initiate a kind of a new debate on the innovators and generic drugs. However, the goal of this current expert opinion is not to generate conflicts, or to compare generic versus innovator drugs in the sense that one is better than the other. The author has already been involved in several bioequivalence studies, comparing two innovator products where the results showed lack of bioequivalence….or in bioequivalence studies evaluated with clinical endpoint where generic drug products were more potent than the innovators…The goal of this paper should be more based on the following question: are the current methods used to assess bioequivalence are suitable and reliable enough to "stamp" that generic drugs are bioequivalent, are as stable, reliable form a quality, a safety and efficacy standpoints.

Based on the literature generic drugs can be defined as copies of innovator drugs and should contain the same dose strength, the same indication, pharmacodynamical effects, adverse events, safety profile and route of administration than the brand drug. Basically, generic drugs should behave the same than the innovator drugs. To achieve this equivalent profile, drug substance should be formulated and mimic as much as possible the formulation of the brand. It means that drug products ideally should show the same composition from both a chemical but also from a physical point of view. If these last comments are achieved then the biopharmaceutical phase, therefore the phase where the active pharmaceutical ingredient (API) should become available to the body, this phase should be equivalent between the generic and the brand. To help formulators developing bioequivalent formulation, several tools and development methods have been developed over the last decades. The preformulation step represents one of the most crucial steps in order to achieve a reliable, stable and bioequivalent formulation. In the quest of the nanomolar efficacy, small molecules became more and more difficult to formulate, making most of them difficult to solubilize and thus even more difficult to be absorbed because of their low solubilities or bad permeability behavior. Furthermore, all the "easy ones" have already been genericized. The bioavailability and thus the achievement of bioequivalence became then more challenging. In some cases, solid-sate chemistry could be held responsible for this lack of solubility/absorption pattern. Literature has already shown several times that crystalline structure was the most selected structure because sponsors rather have to select a molecule that shows better stability over the time than a higher rate of solubility (by selecting the amorphous structure) for the simple reason of a constant stability, reliability, efficacy over the time. But molecules became more and more insoluble and did not give sponsors the option of working only with the amorphous structure or changing the crystalline structure to amorphous structure (spray-drying, solid dispersion, co-precipitate) in order to get reasonable solubility and then maybe a better bioavailability without changing the stability. This actually represented the highest challenge. The HIV protease inhibitor Ritonavir was one of the best examples [1]. It is a lipophilic molecule with a high molecular weight of 721g.mol-1, that shows low solubility values of 0,001mg/ml at pH 6.8 and 0.4mg/ml in 0.1 N HCl. Because of these last characteristics and its dose of 1,2g per day, it became easy to predict that the absorption would be limited by its poor dissolution profile. It represented than an ideal candidate for solid dispersion. The sponsor then had problems with

Ritonavir and had to stop the solid dosage form manufacturing because of the tendency of the drug substance to recrystallize over the time, generating dissolution and absorption problems [2]. It is then easy to imagine that the monitoring of solid-state chemistry became more popular and preformulation department got more and more equipped with state-of-the-art equipment (such X-Ray powder diffraction, differential scanning calorimetry, Raman, …) to monitor such phenomenon, not only form a preformulation standpoint, but also form a whole formulation/manufacturing development standpoint. But the chemistry of the solid-state became also extremely important from an intellectual property (IP) standpoint. And a lot of people will say that for a brand company, IP represents the "crux of the matter" in formulation development...in other words, how far can it be possible to deviate from the patent (without infringing it) by keeping plus or less the same qualitative and quantitative composition, in order to maintain bioequivalence, stability and reliability over the time. For example, the percentage of crystallinity/amorphous of an API in a formulation could become "patentable" knowing that below or above this threshold, it would become extremely difficult to formulate and to become bioequivalent. Atorvastatin calcium is a good example where both amorphous and crystalline structures coexist [3]. The monitoring of these formulations showing different solid-state characteristics were monitored in the marketed Atorvastatin tablets and as described above such differences may have impacted the stability of these tablets. The author had the chance to be involved in several atorvastatin formulation developments (more than 20) and other drug products showing solid-state chemistry issues to achieve bioequivalence between the brand and the generic (in progress) and in the large majority of cases, solid-state chemistry could be held responsible for not achieving bioequivalence. One of the reasons was that solid-state chemistry was not monitored over the time and formulation development steps, such as wet granulation, blending, roller compacting, grinding may have impacted the chemistry of the solid state and thus change the whole drug product behavior, from both a quality and a pharmacokinetic (PK) standpoint.

Bioequivalence…. What Does It Mean?

The literature [4] is telling that us that bioequivalence is the property wherein two drugs with identical active ingredients or two different dosage forms of the same drug possess similar bioavailability and produce the same effect at the site of physiological activity. Of course, this definition can be challenged, and "purists" are more than invited to argue from a semantic standpoint. In this article the focus on bioequivalence assessment will be on PK parameters, and not on clinical endpoints. Bioequivalence is mostly evaluated with PK parameters, the mains being the API maximum concentration in plasma. (Cmax) and the area under the curve that represents the concentration of API in the body following the dosing of a drug product. From a general standpoint, a generic formulation (or test product) is considered bioequivalent to a brand formulation if the ratio test/reference product for Cmax and AUC 0-t (form time 0 to a time t) are within 80.00-125.00%. For the Food and Drug Agency (FDA) [5] and European Medicines Agency (EMA) [6], the 90% confidence interval (CI) geometric mean ratios is expected for these two PK parameters whereas for Health Canada, the 90% CI is expected for the AUC only [7]. From a physiological standpoint, Cmax is more variable than the AUC therefore it can be predicted that form a biostatistical point of view, if the 90%CI is not requested on the Cmax and only the ratio of 80-125%, a smaller sample size (or volunteers) may be expected to successfully achieve bioequivalence. It does not mean that the generic formulation will be less potent and/or safe but in some cases, for certain class of drug products, but some variability when changing from the brand to a first generic and then to a second generic (and so on) may generate side effects or adverse events. Of course, it is expected that the smallest the difference will be in bioequivalence between the brand and the generic, side effects may not be considered significant form a clinical point of view.

That being said concerning the bioequivalence definitions and how it is evaluated and by going back to all the above in this current short communication, it can be expected that physico-chemical characteristics may impact drastically the bioequivalence between tests and reference products. In order to minimize bias as much as possible it becomes then crucial that chemistry manufacturing and controls (CMC) should not be held responsible for non-achievable bioequivalence. Let's make it clear: a bioequivalence study compares two formulations behavior therefore CMC represents the cornerstone of generic development.

It should be kept in mind that bioequivalence studies are carried out:

a) On healthy volunteers (unless patients are targeted and mandatory according the guidance).

b) On a very small sample size that may not represents the targeted population. It is then difficult to extrapolate on a bigger sample size, on subpopulations. Specialists are relying on phase 4/pharmacovigilance data of the brand (since no such studies are carried out on generic compounds)

c) Most of the time, single doses are evaluated, and even if steady-state is requested by agencies, it will never mimic chronic uses of a drug product (when the drug product is taken over several years). Here again lack of data are available in that regards since such studies are not performed neither.

d) A new generic formulation will always be compared to the reference, and not to the previous generic available in the market. Therefore, for example if the first generic passed on the Cmax with a ratio of 86%, and the second one with a ratio of 117%, some adverse events may be expected. After discussion with worldwide specialists in that domain, most of them will say that

these differences will not affect the patient and will be lost once the steady-state will be achieved. It is clear that pharmacovigilance results are difficult to consult. Hence it is difficult to conclude that differences in terms of safety and efficacy have been monitored, even though a quick survey on the population will show you some interesting results with regards to

i. the perception of generic drugs

ii. whether they have noticed differences by interchanging their brands to generic and

iii. whether they have noticed a difference with regards to safety and efficacy when they have been switched from a first generic to a second generic.

So…Finally Can Generic Drugs Be Considered on the Same Footing Than Innovators?

From an academic standpoint, after several presentations given by the author dealing with drug development in general, the interchangeability, and all the fields plus or less linked with generic and innovator drugs, it has been noted that a lot of healthcare professionals are not aware and are not well trained in that regards. Several of them told the author the following: "we understand what you are saying but we have not been trained accurately in that sense at all". Of course, since the author is teaching it is plus or less true, knowing the propaedeutic of their undergraduate and graduate studies, and the several continuous upgrading trainings they have to follow. Even though the sample size needed for the carrying out of bioequivalence studies, which the author refers, may not be statistically relevant and do not reflect the reality, the goal of this paper was to crystallize an idea about the perception of generic drugs versus innovators that, down the road will hopefully generate a paradigm shift in the perception of these drug products. And then, when new tools may be created and will be helpful to enhance the fact that generic and innovator could be considered equal, from a safety, efficacy, stability and reliability standpoint.

References

1. Geoff GZ Zhang, Devalina Law, Eric A Schmitt, Yihong Qiu (2004) Phase transformation considerations during process development and manufacture of solid oral dosage forms. Advanced Drug Delivery Reviews 56(3): 371-390.
2. James JS (1998) Ritonavir capsule manufacturing problems will require switch to liquid formulation. AIDS Treat News 300(1): 5.
3. Shete G, Puri V, Kumar L, Bansal AK (2010) Solid state characterization of commercial crystalline and amorphous atorvastatin calcium samples. AAPS Pharm Sci Tech 11(2): 598-609.
4. https://www.merriam-webster.com/dictionary/bioequivalence
5. Committee for Proprietary Medicinal Products (2001) Note for Guidance on The Investigation of Bioavailability and Bioequivalence. The European Agency for the Evaluation of Medicinal Products Evaluation of Medicines for Human Use.
6. (2014) Guidance for Industry. Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs -General Considerations. Rockville, USA
7. (2012) What are Bioavailability and Bioequivalence? CADTH Evidence Driven, Canada.

DOI: 10.32474/DDIPIJ.2018.02.000144