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Biowaivers and Biosimilars Reinforcing Intent and Content of Researchers and Regulators

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Over the past two decades, the healthcare costs have swelled exponentially particularly in the developed world. In the USA alone, the annual healthcare budget is estimated at around $ 3 trillion. Addressing this growing burden continues to be their major policy priority. One of the ostensible ways to make healthcare cheaper is the manufacture and use of generic drugs. Consequently today, majority of pharma industrial houses are eyeing on the drug molecules going off-patent and developing their generics. Customarily, these generic dosage forms have to establish their efficacy and cost-efficacy vis-à-vis their branded counterparts. A generic product, however, can solely be considered therapeutically equivalent to the reference listed drug (RLD), if it demonstrates bioequivalence with the RLD. The exceptions can only be a parenteral, ophthalmic or otic solution, inhalations or products intended for topical use. Needless to mention, such bioequivalence trials are known to be quite arduous, expensive and time-consuming. Lately, with the introduction of a vast majority of drug molecules exhibiting highly variable absorption, involvement of hundreds of volunteers is required. Eventually this tends to escalate the overall formulation development expenditure phenomenally, thus calling for biowaivers.

Biowaivers can be obtained through twin pathways; first via a valid *in vitro/in vivo* correlation (IVIVC); second, in limited cases, circumnavigating IVIVC. The latter path can only be undertaken if bioavailability data are available for the highest strength and the lower strength formulations consist of beads in capsules which differ only in the number of beads [1]. For all other formulations, biowaivers can only be sought through the IVIVC path.

Federally, only point-to-point Level A correlation is acceptable for biowaivers. It has been seen that Level A correlations can be rationally developed for ER formulations of BCS Class I drugs and IR formulations of BCS Class II drugs. The IR formulations, however, invariably tend to result in nonlinear *in vitro*/*in vivo* relationships (IVIVR) as the *in vivo* absorption is not able to keep pace with the fast *in vitro* drug release. I personally feel that even if the established relationship by industrial R & D is logarithmic, double-logarithmic, exponential, parabolic (i.e., quadratic) or cubic, a nonlinear IVIVR should be held as valid. The federal agencies, in this regard, need to adopt more lucid guidance. Once a Level A IVIVC is established, the generic can be declared as bioequivalent to the RLD on the basis of comparison of the *in vitro* drug release profiles of the two formulations. Comparing the release profiles of two formulations on the basis of similarity factor (f_2, ranging between 50 and 100) or dissimilarity factor (f_1, ranging between 0 and 15) does not seem to be that credible. There is a dire need of establishing a sound metric which can distinguish the dissolution profiles much more discriminatively before the plateau is achieved. Furthermore, following tremendous advancements in IVIVC for oral products, search for a rational IVIVC/IVIVR for non-oral products like transdermals, buccoadhesives, inhalationals, suppositories and oculars is also a formidable task ahead for the researchers as well as regulators to undertake.

The judicious choice of discriminating biorelevant medium is also a pivotal issue in the establishment of IVIVC. Hence, the federal agencies need to extend their preferences beyond the standard media of intestinal fluids (like FaSSIF and FeSSIF), and gastric fluids (i.e., SGF). The basis of selection of *in vitro* drug release medium should solely be based upon its ability to yield a good IVIVC, as it is extremely difficult to predict the actual *in vivo* scenario of the complex human gastrointestinal milieu. Reports on the successful use of interesting dissolution media like milk are testimony to this fact [2].

With the emergence of biotechnology-based products, the coming era belongs to biosimilars, i.e., "generic" versions of biologicals. Many top pharmaceutical concerns have lately shifted their research interests from the small molecule generics to biosimilars (Europe) or "follow-on" biologics (USA) [3]. Witnessing the heavy flood of biosimilars for commercialization, the USFDA has very recently released its much-awaited draft guidance for approval of the biosimilars on 9th February 2012. While the generic versions of pharmaceuticals are relatively easier to develop, biosimilars pose a lot of hiccups primarily owing to their biological nature. First of all, it is not possible to exactly copy a biotech product the same way as a traditional chemical molecule. As these products originate from the cell cultures or whole living organisms, the degree of variability is bound to be more while attempting to copy them. The method of purification of biologicals is the chief factor affecting its therapeutic performance. As biosimilars are not (bio) generics, their approval process must also not be identical to that of latter. The concept of "switch ability", as applicable to generic drugs, is fastidious with biosimilars, as switching patients from one product to a biosimilar but "not identical" product can have grave implications, esp. on the immune response of body to the changed molecule [4].

The regulatory agencies today have a Herculean task ahead to focus on diminishing the wedge between the performance of innovator products and of biosimilars. On the *in vitro* fronts, efforts have to be made to develop more sensitive analytical techniques, capable of accurately detecting the glycosylation pattern, protein content and conformational properties of these biomolecules. The major challenge, however, lies in identifying apt *in vivo* biological markers

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(i.e., biomarkers) to successfully simulate the pharmacokinetic or pharmacodynamic performance of the biologicals. Post-approval too, biosimilars require extensive surveillance, as the problems of safety of biosimilars may not be visible during pre-approval, when only limited number of patients receives the product over a specified time-span [5].

Notwithstanding the dynamic developments in the domains of biowaivers and biosimilars, the need to fortify their content and intent still remains. The pharmaceutical researchers across the industrial and academic worlds, as well as in the regulatory bodies have to take apt cognizance to that.

References

1. FDA (1997) Guidance for industry: extended release oral dosage forms: development, evaluation, and application of in vitro/in vivo correlations. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER).
2. Jantratid E, Janssen N, Reppas C, Dressman JB (2008) Dissolution media simulating conditions in the proximal human gastrointestinal tract: an update. Pharm Res 25: 1663-1676.
3. Moran N (2012) Biotech innovators jump on biosimilars bandwagon. Nat Biotechnol 30: 297-299.
4. Roger SD, Mikhail A (2007) Biosimilars: opportunity or cause for concern? J Pharm Pharmaceut Sci 10: 405-410.
5. Mellstedt H, Niederwieser D, Ludwig H (2008) The challenge of biosimilars. Ann Oncol 19: 411-419.