

## Quality and Efficacy Concerns with Generics in Treatment of Hepatitis C with Directly Acting Antivirals

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Treating hepatitis C has never been so convenient after the advent of Directly Acting Antivirals (DAA). Convenience is at both ends; for the doctors to prescribe and for patients to comply due to all oral therapy with few adverse effects. Many are already in market, these include, Sofosbuvir, Declastavir & Velpastavir while many others are in pipeline. The SVR success rates with these newer drugs is approaching 99% and they are also showing improvement in fibrosis<sup>1,2</sup>. Cost of innovative brands of DAAs is very high. According to one study Quality-Adjusted Life Years (QALY) with innovator sofosbuvir for short therapy resulted in expense of \$24,000 as compared to no treatment. Pakistan being a poor country with low per capita income, health and innovator brand medicines are not in approach of average patient. With availability of generics there is up to 70% reduction in cost of treatment and they come into the affordability range of most of the patients<sup>4-7</sup>.

Although, generics do bring the prices down and to somewhat within reach of a common patient, but at the same time raises important concerns regarding efficacy of these drugs<sup>8</sup>. Not only doctors but patients receiving these generics are also concerned regarding their efficacy and clinical effects, resulting in their poor acceptance<sup>9,10</sup>. There are major concerns regarding bioequivalence of generics. More over bioequivalence does not translate into therapeutic equivalence. Switching from an innovator drug to generic, or switching from one generic to another generic is not simple as it seems and has important concerns regarding safety, efficacy, tolerability and adverse effects and acceptance<sup>12</sup>.

Standard bioequivalence assessment for regulatory review and approval between a generic and innovator brand drug is well established and widely used in pharmaceutical industry<sup>13-15</sup>. Before a generic can be approved, the sponsor is required to conduct a bioequivalence study to demonstrate that the generic is

bioequivalent to the innovator brand drug in terms of the rate and extent of drug absorption<sup>15</sup>. The basic bioequivalence assumption is that the two drug products are considered therapeutic equivalent if they are bioequivalent in drug absorption profile and achieve 80-120% of efficacy as compared to original brand<sup>16-17</sup>. An approved generic can then be used as a substitute of the brand name drug. The free interchangeability is generally assumed for small-molecule generics, resulting in the substitution of various generics in pharmacies. Because small-molecule drugs are generally safe and effective, these assumptions and practices usually work. However, important exceptions exist.

There are differences among the generics and one cannot be substituted with another. Just consider one generic was at 80% bioequivalence while another was at 120%, substituting the first one with second will result in delivery of excessive drug levels. This will be particularly important with drugs having narrow therapeutic range<sup>8,10,14,18,19</sup>. Different generics will achieve different drug levels although they all have been approved by the regulatory authority. Thus it is responsibility of the treating physician to ascertain which generic to use and the pharmacist, chemist or patient themselves should not change from one generic to another.

The regulations for assessing the quality of generic drugs and their bioequivalence to innovator products are outdated and need updating.

1. Regulations largely remain unchanged since long.
2. Medical therapies have become substantially more & more complex.
3. Pharmaceutical manufacturers acquire ingredients for generics from multiple sources of supply, adding variability in their efficacy & stability.
4. Manufacturers may register with regulatory authority using Active Pharmaceutical Ingredients (API) from one source and they may change the API in next batch.

When these elements are viewed together, they clearly suggest that more transparency of responsible manufacturers in product labels and updated standards

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for bioequivalence are required.

1. Responsibility of regulatory authorities is not limited to registration of product only, it should include continuous monitoring of quality, API source and GMP guide lines implementation.
2. Manufacturers should be restrained from changing their API source and it should be made mandatory to reapply for registration if such a change is done.
3. Batch size is also important in quality assurance, it's easy to maintain quality in small batch as compared to a larger batch. Manufacturers apply to regulatory authority with sample manufactured in small batch purposely manufactured for registration purpose.
4. The batch size for regulatory registration should be sufficient enough to allow process capability to be established. For example, a commercial batch size for solid oral dosage forms should be at least 100,000 units<sup>20</sup>.
5. Product brochure should also include information on API source and batch size and manufacturing date. Responsibility in generics is a combined effort, it includes regulatory authorities, manufacturers, pharmacists, physicians and the patients.

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