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Commentary

The Use of Bioequivalent Pharmacokinetics in the Production of Generic Direct-Acting Antivirals

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DESCRIPTION

To attain the goal of eliminating hepatitis C (HCV) by 2030, mass production of low-cost, generic Direct-Acting Antivirals (DAAs) will be necessary. The pharmaceutical companies Gilead and Bristol-Myers Squibb have awarded generic companies Voluntary Licences (VLs) to mass produce the DAAs sofosbuvir and daclatasvir at a cheap cost. To meet World Health Organization prequalification standards, generic manufacturers must demonstrate bioequivalent pharmacokinetics for their DAAs when compared to the originator versions. The purpose of this evaluation was to see if generic versions of sofosbuvir and daclatasvir exhibited bioequivalent pharmacokinetics to the original forms.

Generic drug companies were approached for the results of bioequivalence tests with sofosbuvir and daclatasvir, two of the most commonly used DAAs in underdeveloped countries. Five generic businesses provided data on maximum concentration (Cmax) and Area Under the Curve (AUC). The pre-specified ranges for the 90% confidence intervals for AUC and Cmax were 80%-125% and 69%-145%, respectively, of the original pharmacokinetic concentrations. For all five generic businesses, the pharmacokinetics of generic sofosbuvir and daclatasvir were proven to be bioequivalent to the originator versions. This is an important step toward obtaining prequalification from these corporations for the manufacture of these pharmaceuticals.

During WHO prequalification, bioequivalent generic DAAs could be exported to qualifying nations for mass-treatment programmes. The most promising strategy for meeting the World Health Organization's aggressive HCV elimination targets by 2030 is mass treatment using low-cost generic HCV DAAs. To attain the goal of eliminating hepatitis C (HCV) by 2030, mass production of low-cost generic direct-acting antivirals (DAAs) will be necessary. A 12-week course of sofosbuvir/daclatasvir medication can be manufactured for less than $50 per individual. In the ENDURANCE-3 trial, 12 weeks of sofosbuvir/daclatasvir treatment resulted in the same rates of sustained virological response (SVR) (97%) as 12 weeks of glaceprevir/pibritensavir treatment (95%), which is a widely recognized standard treatment for HCV. This result was obtained in patients with HCV genotype 3, which is considered the most difficult genotype to treat. Companies that produce generic HCV DAAs were approached to check if they have conducted bioequivalence studies on generic sofosbuvir or daclatasvir. These are the two DAAs that are most commonly used in low- and middle-income nations. Where bioequivalence studies have been done, we asked specifics about each study, such as sample size, crossover design, duration, and so on. Generics compared to originator sofosbuvir (Gilead) and daclatasvir were from European Egyptian Pharmaceutical Industries (Dawood Pharma and EEPI, Egypt), Beker (Algeria), Hetero (India), Natco (India), Mylan (India), and Virchow (India) (Bristol-Myers Squibb).

In groups of 22-54 healthy volunteers, randomised, open label, variable-period pharmacokinetic studies were carried out to compare generic forms of sofosbuvir and daclatasvir with the originator versions. All studies were carried out in accordance with GCP. Over the course of 24 hours, plasma concentrations of each DAA were measured. For each subject, the maximum concentration (Cmax) and Area Under the Curve (AUC) were computed. To compare each generic DAA to the originator version, geometric mean ratios and accompanying 90% confidence intervals were employed.

The pre-specified ranges for the 90% confidence intervals for AUC and Cmax were 80%-125% and 69%-145%, respectively, of the original pharmacokinetic concentrations.

Each generic manufacturer reported the results for Cmax and AUC, together with their respective 90% confidence intervals, in bioequivalence reports. These results were compiled for this paper to highlight the comparison of generic DAAs *vs.* their original equivalents across different generic businesses. The demonstration of bioequivalent pharmacokinetics of generic HCV DAAs to their original counterparts is a step toward mass-treatment programmes using low-cost generic DAAs. Globally, 20 million people are taking low-cost antiretrovirals for HIV/AIDS.

If more nations had access to high-quality generic HCV DAAs, this example may be repeated for hepatitis C. The most promising strategy for meeting the WHO's ambitious HCV elimination targets by 2030 is mass-treatment using low-cost generic HCV DAAs.

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