

# Bioequivalent pharmacokinetics for generic and originator hepatitis C direct-acting antivirals

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## Abstract

Mass production of low-cost, generic direct-acting antivirals (DAAs) will be required to achieve targets of eliminating hepatitis C (HCV) by 2030. The pharmaceutical companies Gilead and Bristol-Myers Squibb have granted voluntary licences (VLs) to generic companies to mass produce the DAAs sofosbuvir and daclatasvir at low cost. However, generic manufacturers need to demonstrate bioequivalent pharmacokinetics for their DAAs, compared to the originator versions, to fulfil World Health Organization standards for prequalification. The aim of this study was to determine whether generic forms of sofosbuvir and daclatasvir had bioequivalent pharmacokinetics to the originator versions.

Generic companies were contacted for results of bioequivalence studies with sofosbuvir and daclatasvir, two of the most widely used DAAs in the developing world. Data on maximum concentration ( $C_{max}$ ) and area under the curve (AUC) were compiled from five generic companies. Pre-specified limits for the 90% confidence intervals were 80–125% of the originator pharmacokinetic concentrations for AUC, and 69–145% for  $C_{max}$ .

The pharmacokinetics of generic sofosbuvir and daclatasvir were shown to be bioequivalent to the originator versions for all five generic companies. This is a crucial step towards securing prequalification of the manufacture of these drugs from these companies. WHO prequalification of bioequivalent generic DAAs could then permit their export to eligible countries for mass-treatment programmes. Mass-treatment with low-cost generic HCV DAAs is the most promising method to achieve the ambitious World Health Organization targets for HCV elimination by 2030.

Keywords: hepatitis C, HCV, direct-acting antivirals, bioequivalence, generics, sofosbuvir, daclatasvir

## Introduction

Mass production of low-cost generic direct-acting antivirals (DAAs) will be required to achieve targets of eliminating hepatitis C (HCV) by 2030. A 12-week course of treatment with sofosbuvir/daclatasvir can be manufactured for under \$50 per person [1]. In the ENDURANCE-3 trial, 12 weeks of sofosbuvir/daclatasvir showed equivalent rates of sustained virological response (SVR) (97%) to 12 weeks of treatment with glaceprevir/pibritensavir (95%), which is a widely accepted standard treatment for HCV. This result was achieved in patients with genotype 3 HCV infection, which is typically the most difficult genotype to treat [2].

The pharmaceutical companies Gilead and Bristol-Myers Squibb have granted voluntary licences (VLs) to generic companies to mass produce the DAAs sofosbuvir and daclatasvir at low cost [3]. Bristol-Myers-Squibb has issued this licence to the Medicines Patent Pool, allowing royalty-free generic manufacture of daclatasvir to 112 low- and middle-income countries [3]. VLs only exist for sofosbuvir, daclatasvir, ledipasvir and velpatasvir. No VLs exist for HCV DAAs produced by Merck, Janssen or AbbVie.

Egypt has used generic sofosbuvir in its national treatment programmes since October 2015, which has contributed to over 2 million people being treated for HCV in the country since the commencement of the programme [4].

WHO prequalification is an assessment process to verify whether medical products meet a global standard of efficacy, safety

and quality. This is undertaken through manufacturer site visits, performance evaluation and a dossier review [5]. Generic manufacturers need to demonstrate bioequivalent pharmacokinetics for their generic DAAs, compared to the originator versions, to fulfil World Health Organization standards for prequalification. In addition, generic manufacturers need to show compliance with standards of good manufacturing practice (GMP) and prove that their products have long-term stability.

Meeting WHO prequalification standards allows global agencies such as UNICEF, the Global Fund and UNITAID to procure medicines from these manufacturers, with the assurance of safe and high-quality medicines [5]. Generic sofosbuvir produced by Mylan Laboratories Ltd and Cipla are, as of October 2017, the only generic pharmaceutical ingredients that have demonstrated bioequivalent pharmacokinetics and are prequalified by the WHO for HCV [6].

Results from the Centres for Disease Analysis (CDA) Foundation show that current treatment levels are insufficient to reach elimination of HCV. During 2016, an estimated 1,512,827 people were cured of HCV worldwide. However, across the same period, there were an estimated 1,597,877 new infections [7]. When deaths of people living with HCV are included, the worldwide HCV epidemic fell by only 2% during 2016 [7]. At current rates, the HCV epidemic will not be eradicated. At least 5 million people will need to be cured each year worldwide with HCV DAAs, to achieve elimination of HCV by 2030 [7].

The aim of the study was to determine whether generic forms of sofosbuvir and daclatasvir had bioequivalent pharmacokinetics to the originator versions.

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## Methods

Companies that manufacture generic HCV DAAs were contacted to see if they had conducted bioequivalence studies of either generic sofosbuvir or daclatasvir. These are the two DAAs used most widely in low- and middle-income countries. Where bioequivalence studies had been conducted, we requested details of each study: sample size, crossover design, duration, location, Good Clinical Practice (GCP) standards and statistical power calculations.

Generics evaluated were from European Egyptian Pharmaceutical Industries (Dawood Pharma and EEPI, Egypt), Beker (Algeria), Hetero (India), Natco (India), Mylan (India) and Virchow (India) versus originator sofosbuvir (Gilead) and daclatasvir (Bristol-Myers Squibb).

Randomised, open label, variable-period pharmacokinetic studies were performed in groups of 22–54 healthy volunteers, to compare generic forms of sofosbuvir and daclatasvir with the originator versions. All studies were conducted under GCP. Plasma concentrations of each DAA were assessed over 24 hours. Maximum concentration ( $C_{max}$ ) and area under the curve (AUC) were calculated for each subject. Geometric mean ratios and associated 90% confidence intervals were used to compare each generic DAA with the originator version. Pre-specified limits for the 90% confidence intervals were 80–125% of the originator pharmacokinetic concentrations for AUC, and 69–145% for  $C_{max}$ . The results for  $C_{max}$  and AUC, along with their corresponding 90% confidence intervals, were provided by each generic company in

bioequivalence reports. These results were compiled for this paper to show the comparison across different generic companies for generic DAAs versus their originator versions.

## Results

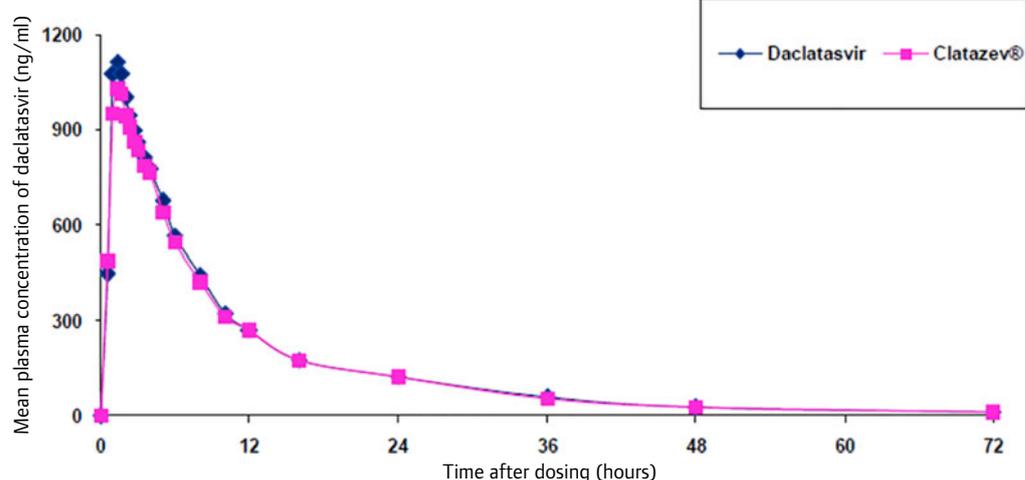
Figure 1 shows the concentration–time curve for generic daclatasvir from the Egyptian company Dawood Pharma, versus the originator version from Bristol-Myers Squibb. Figure 2 shows the concentration–time curve for generic sofosbuvir from the Egyptian company EEPI, versus the originator version from Gilead. Table 1 and Figure 3 show summary geometric mean ratios for each of the generic versus originator versions of sofosbuvir and daclatasvir. All generic forms of sofosbuvir and daclatasvir met prespecified bioequivalence criteria as measured by  $C_{max}$  and AUC.

## Discussion

The pharmacokinetics of generic sofosbuvir and daclatasvir were bioequivalent to the originator versions for all seven generic companies. This is a crucial step towards securing prequalification of the manufacture of these drugs from these companies. WHO prequalification of bioequivalent generic DAAs could then permit their export to eligible countries for mass-treatment programmes. So far, only sofosbuvir from Mylan laboratories has been granted WHO prequalification [8]. Generic versions of sofosbuvir produced by Mylan Laboratories Ltd, Hetero Laboratories Ltd, European Egyptian Pharmaceutical Industries (EEPI) and Strides Shasun Ltd

**Table 1.** Geometric mean ratios (90% confidence intervals)

Drug	Trial type	Company	Number	$C_{max}$	AUC <sub>0–∞</sub>
Sofosbuvir	Four-way, four-period, fully replicated, single oral dose	EEPI	36	101.0 (88.1–115.7)	103.0 (97.6–109.7)
Daclatasvir	Two-way, two-period, single oral dose	Dawood	35	106.9 (100.2–114.0)	103.7 (98.3–109.4)
Sofosbuvir	Three-period, two-treatment, three-sequence, semi-replicate	Beker	35	95.4 (84.7–107.5)	98.5 (91.6–106.0)
Daclatasvir	Three-period, two-treatment, three-sequence, semi-replicate	Beker	35	104.1 (93.1–116.3)	103.0 (94.4–112.4)
Sofosbuvir	Three-period, two-treatment, three-sequence, partial replicate	Hetero	54	95.7 (87.2–105.2)	100.8 (96.2–105.6)
Sofosbuvir	—	Natco	—	96.1 (81.0–114.0)	100.7 (94.2–107.8)
Daclatasvir	—	Natco	—	94.5 (83.1–107.4)	96.5 (87.1–106.8)
Sofosbuvir	Two-period, two-treatment, single dose	Virchow	22	94.8 (83.3–107.9)	95.8 (86.9–105.7)
Sofosbuvir	Two-way, two-period, single oral dose	Mylan	78	103.2 (95.0–112.2)	99.2 (95.4–103.2)
Daclatasvir	Two-way, two-period, single oral dose	Mylan	40	102.1 (94.3–110.5)	99.4 (92.3–106.5)



**Figure 1.** Concentration–time curve for Dawood Pharma daclatasvir against originator daclatasvir

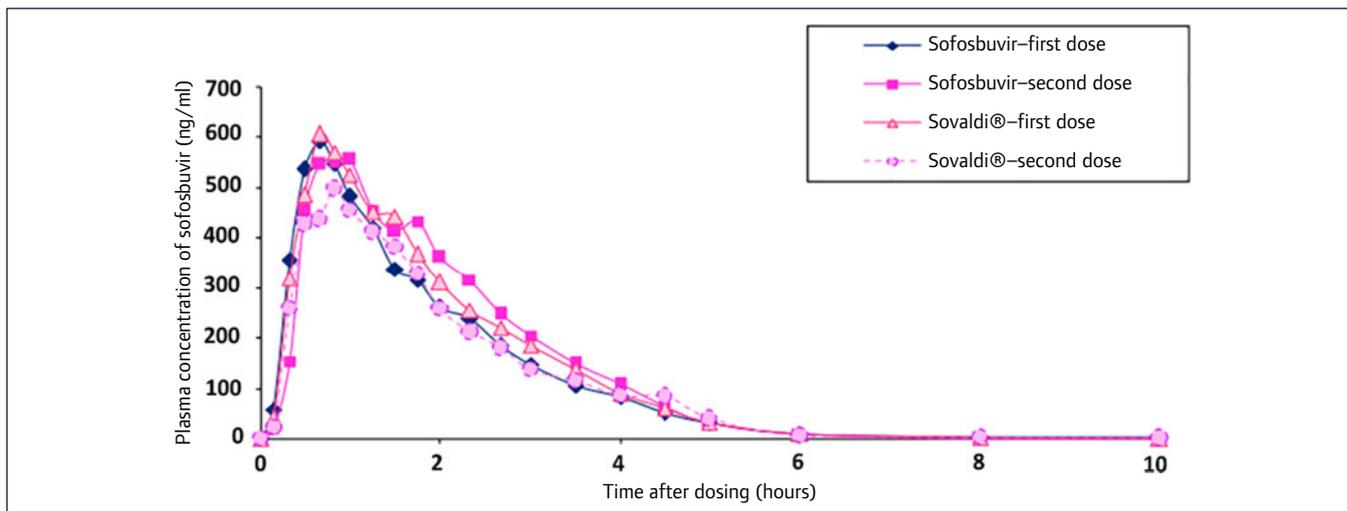


Figure 2. Concentration–time curve for EEPI sofosbuvir against originator sofosbuvir

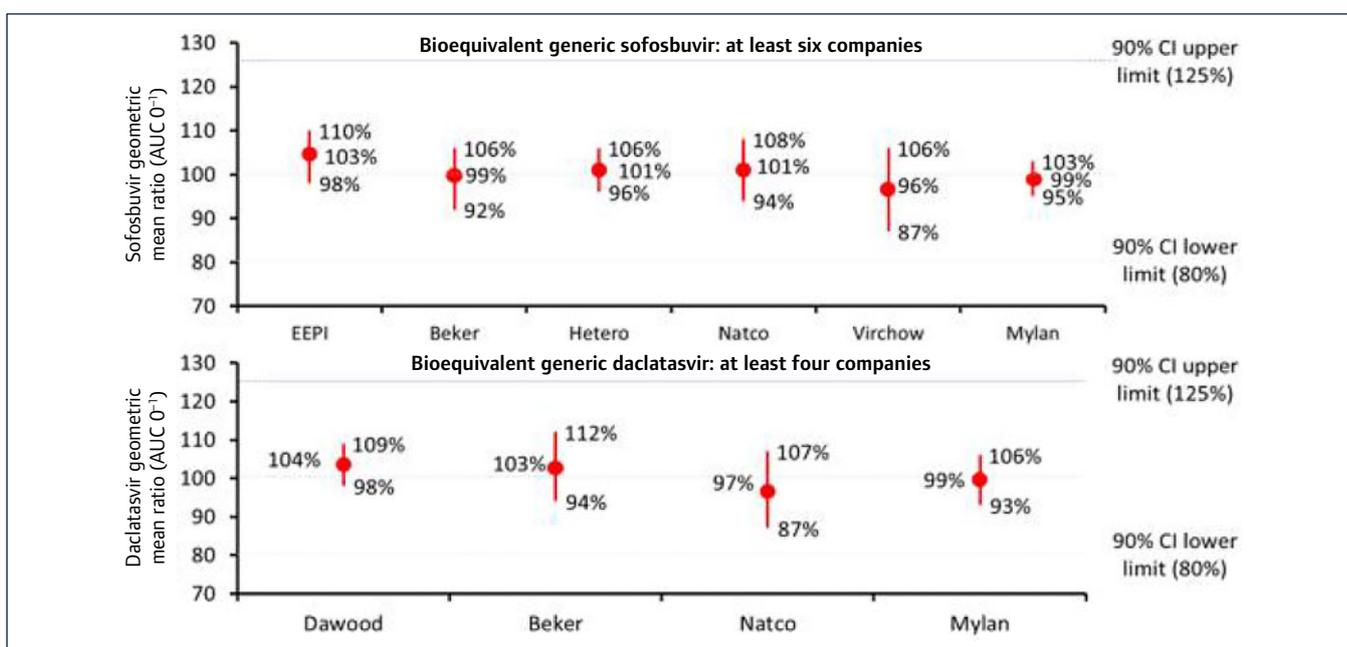


Figure 3. Geometric mean ratio and 90% confidence intervals for AUC of generic and originator versions of sofosbuvir and daclatasvir. CI: confidence interval

have been approved for use through the Global Fund for mass-treatment programmes [6].

However, most countries worldwide cannot benefit from the use of low-cost generic DAAs because they are not included in the list of VL countries, or the DAAs have not been registered with national health authorities. Worldwide, only 49% of the global HCV epidemic is covered by a VL for sofosbuvir [7], while only 29% of the global HCV epidemic is in countries both where sofosbuvir is registered and the country is covered by a VL for sofosbuvir [7]. Although there is a VL granted for daclatasvir, the originator company has not filed regulatory submissions for its approval for use in many low- and middle-income countries. This could limit the ability of generic companies to gain approval for generic versions. In addition, VLs have only been established for four DAAs for HCV treatment: sofosbuvir, ledipasvir, velpatasvir and daclatasvir. Because there are no VLs granted, there is no clear mechanism for access to low-cost generic versions of the DAAs from AbbVie, Merck and Janssen.

Real-world data from clinical practice has shown that generic HCV DAAs show equivalent levels of efficacy to their branded

counterparts [9]. Patients with HCV were able to access generic DAAs for personal use through three buyers’ clubs and their HCV RNA levels were monitored. The results from the studies of buyers’ clubs showed that the cure rate (SVR12) was over 95% [9]. In regions where access to treatment is limited by unaffordable prices, this study provides further evidence to show that treatment with generic DAAs is a safe and effective alternative towards the elimination of HCV.

The limited access to low-cost DAAs is a factor explaining why, since 2016, the annual number of individuals treated for HCV worldwide has fallen behind the WHO target to treat 80% of the total HCV epidemic by 2030. For every person cured of HCV worldwide in 2016, another person was newly infected. The total number of people treated and cured of hepatitis C showed a peak in 2016, although this number now appears to be falling.

Demonstrating that generic HCV DAAs have bioequivalent pharmacokinetics to their originator counterparts is a step towards mass-treatment programmes using low-cost generic DAAs. There are 20 million people taking low-cost antiretrovirals for HIV/AIDS worldwide. This example could be repeated for hepatitis C if

more countries could access high-quality generic HCV DAAs. Mass-treatment with low-cost generic HCV DAAs is the most promising method to achieve the ambitious WHO targets for HCV elimination by 2030.

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