

PRO VIEW

The use of generic medications for hepatitis C

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Abstract

Hepatitis C, hepatitis B, HIV, TB and malaria are the five major causes of infectious disease death worldwide. In a breakthrough that rivals the invention of penicillin, drugs that cure hepatitis C, with minimal side effects and high success rates, have reached the market, but, in what must be one of the greatest tragedies of modern times, these life-saving medications are not being deployed on a mass scale. Pharmaceutical patents are gifted to private corporations by governments for the dual purposes of protecting R&D expenditure and encouraging innovation. Unfortunately the monopoly pricing power these patents provision currently lacks adequate checks and balances, is open to abuse, and is quite clearly being abused. The sort of legislative changes required to deliver on the original goals of pharmaceutical patents will take years or even decades to eventuate. Parallel importation of generic medication offers hope to the millions of patients with HCV unable to afford access to vastly overpriced originator medications. Doctors prescribing and monitoring patients taking generics can take comfort from the fact that the REDEMPTION trial results show, like the HIV generics that came before them, that HCV generics deliver robust clinical results.

Keywords

direct-acting antiviral – generic – hepatitis C – REDEMPTION-1

Background

Pharmaceutical companies operate in a highly subsidized and protected market environment. In routine business a company invests in R&D, develops products it then sells at prices consumers can afford, and, if those products are popular, makes handsome profits. Pharmaceutical companies operate largely outside natural price controls producing products that individual consumers cannot afford and are heavily subsidized by communal citizen-funded pools of government tax dollars and medical insurance dollars.

Pharmaceutical patents are a relatively new addition to the landscape of intellectual property protection, and many detailed reports have been written about both

them and the issues around the monopoly powers they provision (1–3).

The rationale for pharmaceutical patents is to encourage high-risk venture capital spending on R&D and thus deliver innovative new products to market secure in the knowledge that the risk capital investment required to do so is protected by a guarantee of exclusive marketing rights and subsequent profits. That is the theory, anyway. A key question is: are we, the citizen payers, getting good value for our hard earned tax and insurance dollars? I contend that pharmaceutical patents, as they currently stand, are failing the world and not delivering what is required.

Many numbers are quoted, in what I refer to as a carefully crafted fiction, to support the current status quo. I am sure you are familiar with them: it takes

Abbreviations

BMJ, British Medical Journal; DAA, direct-acting antiviral agents; EASL, European Association for the Study of the Liver; GMP, Good Manufacturing Practice; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICL, International Liver Congress; NMR, nuclear magnetic resonance; R&D, research and development; SVR, Sustained Virological Response; TB, tuberculosis; TRIPS, Trade Related Aspects of Intellectual Property Rights; WTO, World Trade Organization.

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Key points

- The invention of DAA medication should be a cause for global celebration because it delivers the power to save millions of lives and virtually eliminate one of the five major causes of infectious disease worldwide.
- Sadly, for the majority of patients, these breakthrough medications remain unattainable.
- The evidence for the clinical safety and efficacy of HCV generics is compelling.
- Utilizing parallel importation of generic medications offers an imperfect but pragmatic near term solution while the legislative framework is rebalanced.
- If current pharmaceutical pricing trends are allowed to continue our healthcare system will become increasingly unaffordable.

10–15 years to bring a new drug to market, only 1 in 10 drugs makes it, and the costs of developing new drugs are in excess of \$1 billion.

A landmark article appeared in the *British Medical Journal* in 2012 (4) and contains many myth busting observations.

- 1 Despite assertions that the cost of new drug discovery is now \$1.3 billion, a figure which comes from the industry supported Tufts Center, the real cost is \$90–300 million when the numbers are more appropriately analysed.
- 2 The pharmaceutical business model relies on exploiting government protections against free market competition rather than new drug discovery.
- 3 Pharmaceutical companies spend 19 times more on marketing (25% of revenues) as they do on new drug discovery (1.3% of revenues)
- 4 During the 15-year period from 1995 to 2010, R&D costs rose by \$34.2 billion while revenues increased six times faster by \$200.4 billion.

In short, pharmaceutical companies are now demanding vastly more profits for the same outlay as they were only 20 years ago and this is reflected in the astronomical prices for new breakthrough medications. The problem for society at large is that this greed is strangling the goose that lays the golden eggs, and if current trends continue, our healthcare systems will eventually collapse under the weight of ever increasing costs.

To add insult to injury, pharmaceutical companies are also very efficient at avoiding paying tax. For example, Bloomberg published an article with the title *Gilead Avoids Billions in U.S. Tax on Its \$1,000-a-Pill Drug* (5).

Sofosbuvir as an example

Sofosbuvir is a breakthrough medication and the backbone of the most popular of the new DAA regimens for

HCV. We can get a very accurate assessment of its development cost because sofosbuvir was not actually developed by Gilead Sciences.

Sofosbuvir was developed and proven up through Phase 2 trials by the NASDAQ listed company Pharmasset. Pharmasset's books, from inception in 2001 up until their purchase by Gilead in 2011, are a matter of public record allowing a very precise quantification of the real development costs of this drug.

The development costs at Pharmasset were \$281 million (6). The Phase 3 trials conducted by Gilead carried relatively low risks given the mortality rate of both the disease and the then extant treatments, and would have added less than \$125 million to the total costs, given documented Phase 3 trial sizes of 982 patients for Sovaldi (6), 1952 patients for Harvoni (7) and a cost per patient of \$42 000 (8). In the 3 years since its release, the Sovaldi franchise has returned \$31.5 billion dollars in revenues (9).

While it is not entirely unreasonable that the investors in Pharmasset should enjoy high returns for putting up the risk capital, Gilead is holding the world to ransom over pricing and access, and making more than its \$11 billion dollar investment back every year. It is sad to reflect that more people died of HCV last year, about 500 000 people, than those who received the new treatments (3, 10, 11).

Value-based pricing

Our current system of value-based pricing is also a problem. It was introduced to try and control prices but has been efficiently repurposed by pharmaceutical companies. Gilead's standard response about the extraordinary price of its medications is "*We believe the price of Harvoni reflects the value of the medicine*" (12).

The fundamental problem with this line of thinking is that while it remains, we will see breakthrough medications but we will never see breakthrough pricing. Without breakthrough pricing the net benefit of breakthrough medications will be approximately zero in global health terms. We are paying for it via our tax and insurance dollars and have a right to demand more.

My analogy would be that if Gilead had invented email, a "Gmail" would be priced at \$0.90 based on the fact that it was cheaper than a \$1 stamp, and had tracking and instant delivery. Imagine a world without the breakthrough pricing step change of email.

What does sofosbuvir really cost?

Although the ingredients for a 12-week course of Sovaldi cost less than \$100 (13), the US retail price is a staggering \$84 000 (Fig. 1).

To put that price in perspective, if Apple put the same 100 000% markup on a new iPhone it would cost \$1 million dollars.

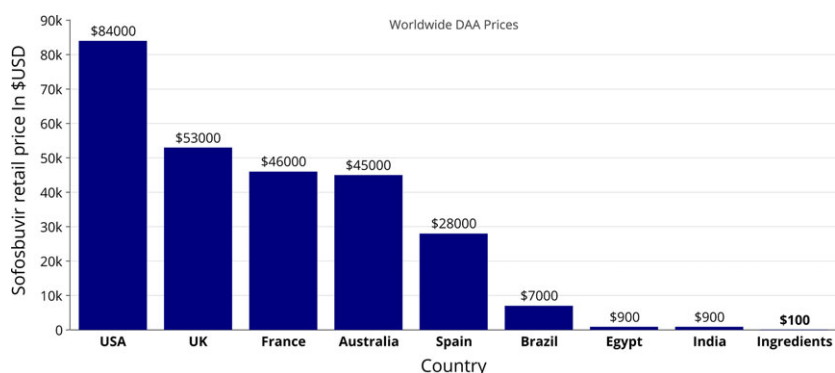


Fig. 1. Retail price for Sofosbuvir in selected countries around the world.

Generics, medication voluntary licenses and compulsory licenses

Generic medications are near identical copies of patented originator drugs and serve many purposes. At the expiry of pharmaceutical patents, the ability to produce generic copies rapidly drives prices down, for example, Viagra[®] was \$20 a pill while it was on patent and is now under \$4 because of price competition with generics.

Lesser Developed Countries (LDCs) are allowed under the provisions of the World Trade Organization (WTO) Trade Related Aspects of Intellectual Property Rights (TRIPS) agreement to produce patented medications for their own internal use, and the use of other LDCs.

Low and Middle Income Countries (LMICS) are sometimes able to negotiate voluntary licenses with the originator, and where that cannot happen, compulsory licensing (in effect ignoring the patent) is an option for medicines on the WHO Model List of Essential Medicines (14), however, the USA in particular is not shy about applying trade sanctions to countries that exercise that right (3,15).

The legality and morality of using generics to bypass patents and excessive prices

I must confess I struggled greatly with this, but resolved it as follows.

Is it morally right to hit somebody over the head with a baseball bat? In isolation no, but: Is it morally right to hit somebody over the head with a baseball bat if they are holding a gun to somebody's head? To me the answer is yes because it is the lesser of two evils.

The world is being held to ransom over pharmaceutical pricing and like the brigands of a bygone era, pharmaceutical companies are demanding 'your money or your life'.

With our health systems buckling under the pressure of ever increasing prices I suggest we need to send a firm message to pharmaceutical companies about our

expectations that reasonable profits and broad patient access are required.

As far as the technical legality goes patents provision monopoly rights that are open to abuse, however, other laws provision other rights.

Article 60 of the World Trade Organization TRIPS agreement makes small consignments exempt, and in line with Article 60 most countries allow some form of personal medication importation.

It is easy to understand why patients will seek out treatment, the question for us, as the medical fraternity, is how we respond.

The safety of generics – supply chain reigns supreme

Despite pharmaceutical company assertions to the contrary, many medications are very cheap and simple to produce. While there is both science and art in delivering drug doses effectively this knowledge is well known and widely dispersed.

I routinely ingest ethanol that was almost certainly not made under complex Good Manufacturing Practice (GMP) inspection requirements. Some of the wine I drink was made from grapes crushed with my own toes, and those of others. Is it as safe, sterile and perfect as factory made wine? Probably not, but it seems to do me no great harm.

In medicine and pharmaceuticals I think we have become a little carried away. Is it sensible to continue to suffer from a 20% fatal disease because I have a 0.1% worry about the provenance of the cure? On balance I think not.

The REDEMPTION-1 (16) trial data presented at European Association for the Study of the Liver (EASL) International Liver Congress (ICL) 2016 clearly demonstrates that the safety and efficacy of generics, at least the generics used in the study, are equivalent to the originator medications and deliver the expected 90%+ Sustained Virological Response (SVR) rates.

Doctors prescribing and monitoring patients taking generics can take comfort from the fact that, like the

HIV generics that came before them, HCV generics deliver robust clinical results.

That is not to suggest we should not be concerned, because great care is required if generics are to be used.

When we as clinicians write medication names on paper we normally depend on a gigantic and well-oiled machine to deliver the correct chemicals into our patient's body. With generics, supply chain integrity is vital. Just as AIDS drugs online has become a trusted conduit to generic HIV medication, FixHepC.com has come to function in the same role and offers an optional \$200 service to test a single tablet with NMR and ensure it contains the expected active ingredients in the correct quantities.

If your patient has HCV, and is in possession of valid generic HCV medications, it stands to reason that the risk benefit equation holds up – the key is ensuring the medications come from trusted sources.

Today, over 1000 of our fellow citizens perished from a disease we have the power to cure.

We have the power to fix hepC.

My question to you, is do we have the will power? The will power to think global, but act local, and see cure deployed on a mass scale?

Or would we rather blindly protect patent rights at the expense of patient lives?

Generics work. Let us deploy them and wipe hepatitis C off the face of the planet like we have done with smallpox and polio.

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