

# The complex legal and ethical issues related to generic medications. Viral hepatitis: a case study

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## Abstract

The economic impact of medications is significant, with many countries unable to afford the essential medicines listed by the WHO. Generic medications are one strategy to address this issue. Generic medications are similar to but not the same as originator medications. They have a significant cost advantage because they do not require the background research and development studies to support registration. Consequently, they are gaining increased market share in both the developed and developing world. Many new medications are now licensed to generic manufacturers in the developing world. As a result, it is possible for patients to bypass regulatory and cost barriers by importing medications directly from generic producers. Importation of the novel hepatitis C direct-acting antiviral therapy into Australia before it was registered in the country is an illustrative case study. This review will characterise generic medications and some of the legal and ethical issues around their utilisation, focusing on the relevant players, including pharma, government, patients and doctors.

## Background

The WHO has defined essential medications as those that satisfy the needs of the population, and to which all people should have access at all times [1]. According to the most recent WHO World Medicines Situation Report, however, approximately 30% of the world's population does not have access to these essential medications [2]. The economic impact is significant; the poorer the country the larger the proportion of the health budget is required to fund medication. In developing countries the proportion spent on medication has been estimated at between 25–66% of the health budget [1]. Generic medications are one strategy available for addressing lack of access to essential medications as they make medicines more affordable. Even in relatively rich nations, such as the USA, generic medication now accounts for approximately 80% of all medication dispensed, leading to huge cost savings [3]. Over the 10-year period 2003 through 2012, generic drug use has generated more than USD 1.2 trillion in savings to the US health-care system [4].

In a pluralistic and hyper-connected world, it is possible for the linear view of drug development, from drug discovery through to marketing and monitoring, to break down, creating ethical and legal challenges. For instance, countries unable to afford the high prices demanded for some medicines by originator companies are incentivised to ignore patent expiry and produce local copies. The prime example of this is the production of HIV antiretroviral therapies in Brazil throughout the 1990s. In the 21<sup>st</sup> century, individuals in prosperous countries can access medications overseas, circumnavigating access issues related to cost or regulation, either via personal importation or medical tourism – a case in point being Egypt's *Tour n' Cure* initiative with hepatitis C treatments [5]. Due to the ethical demand not to deny patients access to potentially beneficial treatments, most countries have laws permitting the personal importation of medicines to varying extents. These laws, however, create their own challenges as distinguishing between personal importation, and the collaboration of individuals to enable large-scale importation, is not straightforward.

This review will characterise generic medications and some of the legal and ethical issues around utilisation of these medications,

focusing on the relevant players, including pharma, government, patients and doctors. Importation of the novel hepatitis C direct-acting antiviral therapy will be used as an illustrative case study.

## Generic medications: similar not identical

The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have clear definitions of generic medications [6,7]. Generic medications are similar but not identical to originator medications. They are generally only permitted to enter the market when the patent for the originator has lapsed. Globally, this is currently 20 years.

The fundamental appeal of generic medications is the significantly lower cost in comparison to the originator compounds. This is possible because generics can rely on the originator compound's existing data, which streamlines the approval process and limits the need for research and development investment. Consequently, generics need not demonstrate safety and efficacy, but only bioequivalence with the originator medication, which leads to the lower cost of bringing them to the market.

The FDA defines bioequivalence as: 'The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in the appropriately designed study' [8]. This is typically carried out through a comparison of the generic and originator medication in 24–36 healthy controls. Measuring serum levels allows a comparison of the rate and extent of absorption of the medications. Statistically, the generic drug cannot exceed 80–125% of the bioavailability of the originator drug [9].

The risk–benefit calculus of generics is paramount, as the demonstration of bioequivalence still allows for variability. While the bioequivalence range suggests that a 25% variation is acceptable, in practice it appears variability is far less. In the largest study of bioequivalence, Kesselheim and colleagues used 2070 single-dose bioequivalence human studies conducted between 1996 and 2007 to support FDA generic medication registration [10]. Comparison of absorption revealed the average difference in bioavailability between the generic and the brand name was only 3.5%. A number of studies have analysed the efficacy of generic medications. A systematic review of cardiovascular generic

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and branded drugs evaluated the results of 38 published clinical trials and found no difference in efficacy between brand name and generic cardiac medications [11]. Similar results have been demonstrated with other classes of drugs. A large study of clarithromycin showed no difference in outcome in community-acquired pneumonia [12]. Evaluation of generic omeprazole, a proton pump inhibitor, by the FDA revealed no significant differences in performance [13]. However, there has been debate about drugs with a narrow therapeutic range, such as anti-epileptics, with some data suggesting a difference [14]. Other studies have also demonstrated equivalence. Furthermore, there are still issues around highly specific drugs, such as immunosuppressors, or drugs with narrow therapeutic ranges, such as warfarin, and the fact that bioavailability testing can vary by country.

## Regulatory background

To understand the legal and regulatory context in which generic medicines exist it is important to be cognisant of the broad history and reasons behind the regulation of pharmaceuticals [15]. The USA has the clearest history of regulatory development. Following the public outcry to the condition of meat sold at the beginning of the 20<sup>th</sup> century, the US Congress introduced the Pure Drug and Cosmetic Act in 1906 to provide truthful labelling of food and drugs, and prohibited interstate commerce in adulterated and misbranded food and drugs. This was the beginning of the regulatory function of the Food and Drug Administration (FDA). In 1937 more than 100 children were poisoned by diethylene glycol that was a constituent of a medication being sold to treat infection. In response to this catastrophe the Federal Food, Drug and Cosmetic Act was passed in 1938, which required that the safety of new medications be demonstrated. In 1962 the Kefauver–Harris Drug Amendment was passed, which required medications to have proven efficacy for their intended use. Identifying that generics were an important cost-saving measure, the US Congress passed the Hatch–Waxman Act in 1984, which sought to increase utilisation of generic medications. Most recently, in 2009, the Biologics Price Competition and Innovation Act allowed for a more rapid registration pathway for biosimilar drugs, which are copies of large complex molecules as opposed to small molecular medicines, if proven similar to already registered products. The effect of these final two pieces of legislation was reduced spending on pharmaceuticals. Similar pathways have been followed by the European Union [16].

In 1975 the development of the WHO Essential Medication list resulted in the support and development of local generic drug production in the developing world. The potential risk to intellectual property rights was obvious as there were few barriers to importation of these cheaper medicines. Over the next two decades, in part under pressure from the USA, this led to the Trade-related Aspects of Intellectual Property Rights (TRIPS) agreement, which focused on securing protection of intellectual copyright and patents internationally.

The HIV pandemic forced countries such as Brazil to develop and supply cheap generic antiretroviral therapy to help combat the disease. India and other countries have followed and accelerated this trend. Over time, many generic companies have emerged in these developing countries. High-quality generic manufacturers are now supplying medications to many parts of the world, sometimes by bypassing national regulatory systems through personal importation schemes. A current and topical example is the 5000-subject HIV EPIC pre-exposure prophylaxis (PrEP) study in Australia using generic combination tenofovir and emtricitabine

from Mylan, purchased at a fraction of the cost of brand-named Truvada from Gilead [17].

## Hepatitis C direct-acting antiviral generics: a case study

Access to hepatitis C (HCV) treatment provides an excellent illustration of the issues related to generic medication. Worldwide, an estimated 80–150 million people are infected with hepatitis C, with the highest prevalence rates in Africa and Asia. HCV-related liver disease mortality is estimated to be half-a-million per annum [18,19]. Following the long phase of interferon-based HCV treatment, revolutionary new direct-acting antiviral agents (DAAs) were developed, which disrupt replication through inhibition of HCV protease, polymerase and NS5A function [20]. Simple (single daily dosing oral regimens), highly tolerable, short-duration (8–24 weeks) regimens with extremely high efficacy (cure rates above 95%) have been developed and registered internationally. These new DAA therapies clearly mitigate HCV-related liver disease and hepatocellular carcinoma (HCC) risk [21]. The broad implementation of these therapeutic regimens has the potential to dramatically impact HCV-related disease burden globally. Indeed, new HCV treatments have been deemed so important that some (sofosbuvir, daclatasvir) were added to the 2015 WHO Essential Medicines List along with a number of their combinations [22]. However, access to these essential medications is limited by their exceptionally high pricing, up to USD93,000 per 12-week course. In turn this has limited broad implementation in many countries, with restrictions based on liver disease stage generally introduced to reduce budget impact [23].

Australia was late to list the DAAs onto the Pharmaceutical Benefits Scheme (PBS). Prior to the commencement of the Australian government-funded HCV treatment program in March 2016, an estimated 1400 Australian patients had been treated with the assistance of FixHepC, a web-based platform for the importation of HCV therapies [24]. Through importation and compounding of the active pharmaceutical ingredients (APIs) for sofosbuvir, ledipasvir and daclatasvir from India, patients were able to access a course of 12 weeks of therapy for AUD1500–2000 – a fraction of the market price for these treatments. Australia, like many countries, allows for the importation of 12 weeks of unlicensed medication at the patient's own risk. The Australasian Society of HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) supported the importation and treatment with generic DAAs, including purchasing these medicines from overseas or over the internet [25].

The efficacy of the imported generic DAA therapy for HCV was analysed in the Australian REDEMPTION study [26]. This enrolled 412 HCV patients treated with generic DAA therapy accessed through the FixHepC website. The quality of APIs was evaluated using liquid chromatography, nuclear magnetic resonance and mass spectroscopy. The interim week-12 sustained virological response (SVR) for genotype 1 HCV was 95% using imported sofosbuvir and ledipasvir or imported sofosbuvir and daclatasvir. The cohort included 28% of individuals with cirrhosis. Across all genotypes, the SVR was 94%, revealing equivalent clearance rates at 1% of the cost. These outcomes were equivalent to those using branded treatments. Despite this apparent success story, the ethical and legal issues related to such initiatives remain unresolved and led to the FixHepC operation being forced to move to Myanmar after the Australian government warned the website against illegally advertising unlicensed medicines.

## Ethical and legal issues

As the above case illustrates, utilisation of generics, especially unlicensed generics imported from overseas, raises a number of

legal and ethical issues. Broadly, these challenges can be related to the principles of autonomy, beneficence, non-maleficence and justice; and how to balance the individual/society interests with business and corporate interests.

### Enhancing options for patients and physicians (autonomy)

Studies have shown that when patients are forced to pay for their own care, the cost of medicines may lead to patients not filling their scripts, or skipping doses [27]. The financial hardship associated with high-cost medicines is exacerbated and can severely limit the treatment options available to patients [28]. The fact that generic medicines are generally far cheaper than the originator product means they provide additional choices to patients from poorer socio-economic backgrounds, and to patients without insurance coverage. Generic medicines are also important to physicians when they know effective drugs exist but are not available locally, or when the brand name version may be unaffordable to their patients. In this regard, it is worth noting that the large-scale importation of generic unlicensed hepatitis C medicines into Australia was supported by the clinical community, despite controversy relating to illegal pharmaceutical promotion by the importer [29].

The application of the autonomy principle is further complicated for physicians by laws that may be at odds with their values. For instance, the law in the European Union appears to disavow economic-driven prescribing for any reason, which is the primary driver for importing generic medicines [30]. The UK General Medical Council therefore advises that doctors cannot prescribe an unlicensed drug on grounds of cost if a licensed product is available [31]. While in practical terms it is difficult to stop patients from importing medicines, when physicians get involved – and often they will have to when either prescribing or administering medicines – being seen to support such practices can potentially expose doctors to greater liability.

### Evaluation of risks and benefits by regulators (beneficence and non-maleficence)

The ethical principles of beneficence (do good) and non-maleficence (do no harm) can be simplified to clinical risk–benefit when it comes to medications. Medicines regulation and the practice of medicine are above all else about making judgements regarding risks and benefits. Regulators acknowledge this, which is why they demand evidence of efficacy and safety – so that medicines which enter the market do not create unreasonable risk for the benefits gained, or do not prove to be safe but useless.

A long-standing concern in this regard is whether the standards to which generic products are held by regulators is sufficient to justify substitution for brand-name products. Even when studies have demonstrated equivalence, for example the study by Kesselheim and colleagues comparing generic and brand-name cardiovascular drugs discussed previously, the authors noted that editorials published in medical journals cautioned against substitution [10]. Others have argued that the appropriateness of generic substitutions may depend on the clinical condition being treated, with the British National Formulary warning against making assumptions of bioequivalence between different brands of some anticonvulsants [32]. Matters are further complicated in the case of biosimilars since the large and complex molecules are potentially more sensitive to changes in manufacturing processes which are proprietary, and will not be chemically identical to the original product due to different cell lines used [33].

These concerns about bioequivalence are heightened when generic compounds are imported from overseas, as they may have bypassed regulatory controls which ensure the quality of pharmaceutical products. Such concerns can potentially be overcome. For instance, in the case of the Australian FixHepC website and HCV direct-acting antiviral therapies, the active pharmaceutical ingredients (APIs) imported were assessed for quality using liquid chromatography, nuclear magnetic resonance and mass spectroscopy, with the subsequent study, outlined above, revealing equivalent outcomes to the originator medicines [26]. However, the unanswered issue that needs to be addressed in this case is whether we can rely on unregulated third parties to be responsible for ensuring the quality of pharmaceutical products.

Despite the fact there may be hypothetical and/or probabilistic risks associated with use of generic medicines in some instances, it needs to be recognised that these risks may be of little importance to desperate patients who already face certain harm from their illness [34]. Indeed, it is for this very reason that governments and payers are increasingly pressured to accept greater uncertainty in the approval and funding of medicines (many of which subsequently demonstrate no benefits), and promoting one avenue for enhanced access to medicines while debarring the other may appear to be applying double standards.

### Distributing health resources equitably and fairly (justice)

Health-system efficiency (i.e. maximising health outputs per input utilised) is critically important for ensuring an optimally functioning health-care system. The World Health Report published by the World Health Organization in 2010 concluded that 20–40% of all health spending is wasted, impacting on global access to health care [35]. Of the 10 leading sources of inefficiency, the top three related to medicines use. Of these, the main source of inefficiency identified was the underuse of generic medicines or paying higher than necessary prices for medicines. For this reason it has been argued that distributive justice should be a new ethical paradigm that underpins the promotion of generic prescribing by physicians [36].

### When it isn't about protecting the patient

While there are, no doubt, some legitimate clinical concerns relating to the use of generics, particularly when these are imported without regulatory oversight, the ethical and legal issues posed are complicated in cases where the use of brand-name products is driven by commercial rather than patient interests. For instance, pharmaceutical companies have been known to game the system through 'pay for delay' tactics to avoid generic competition for their products, or implementing legal strategies to extend the effective patent life of a product line [37–39]. A new strategy utilised by Turing pharmaceuticals to avoid generic competition for Daraprim took advantage of US legislation requiring generic products to be tested against the original product. Turing implemented a closed distribution system which severely limited the opportunity for generic competitors to source enough product to make meaningful comparisons for registration purposes. This is despite the fact the manufacturing process is simple enough that a group of Sydney high school students was able to manufacture the active ingredient in the classroom. Generics, therefore, bring into sharp focus the tension between the interests of patients and health systems, and the private financial interests of industry.

### The big picture

Despite the appeal of gaining access to generic medicines as soon as possible, the short-term benefits of immediately increasing

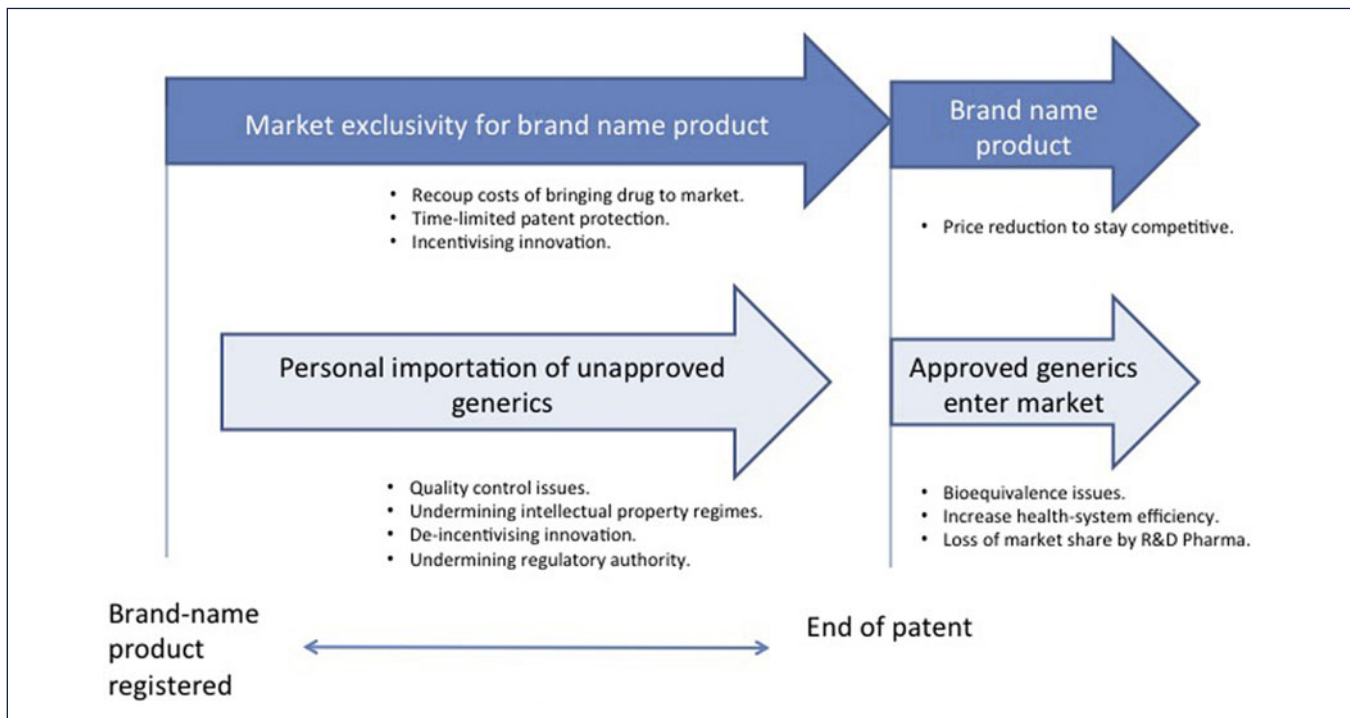


Figure 1. Brand name versus generic medications.

affordability, wider utilisation and health-system efficiency may have longer-term adverse effects, outlined in Figure 1. Intellectual property regimens exist to incentivise innovation, and the marketing exclusivity afforded to pharmaceutical companies for their innovations ensure that private investment continues to be funnelled into drug development and research. In Europe alone, it is estimated that the pharmaceutical industry spent over €30 billion on R&D in 2013, whereas in the United States it was almost US\$ 70 billion in 2010 [40,41]. While critics may argue that the pharmaceutical industry spends a fraction of its revenues on R&D, in a world dominated by capitalist market economics this is irrelevant – the important question is how to incentivise private funds to be directed towards drug development rather than other investment opportunities.

Therefore, theoretically speaking, the greater revenues pharmaceutical companies secure from the public, either by charging high prices or extending patent terms, the more R&D that should take place as investors rush to make lucrative returns. This in turn should lead to the development of new drugs that enhance public health and safety, and while there will always be inequitable access to the newest drugs in the market, over time these medicines will funnel down into the health system benefiting all. On the other hand, the more money that is directed towards generic medicines the less lucrative investment in research-based pharmaceutical companies becomes. When importation of cheap generics before patent expiry is added to the equation, the threat for investors is potentially substantial.

The broader economic benefits of a robust pharmaceutical industry to countries such as the US also cannot be ignored. The pharmaceutical industry group PhRMA declare on their website that the industry employs 854,000 people in the United States, and supports a total of 4.5 million jobs throughout the country [42]. Spending more on generic medicines therefore also has geopolitical consequences as money is redirected from countries which have a strong R&D industry to those that rely on the generic industry.

## Conclusion

Generic medicines provide greater access to treatments due to their greater affordability. They also enhance health-system efficiency. However, utilisation of generic medicines places great pressure on the R&D-driven pharmaceutical industry, which we rely on to develop drugs of the future. Balancing the need to invest in innovation with the need to maximise access to safe and effective drugs, and maximise health system efficiency, is an issue that will never go away and needs to be managed delicately.

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