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Competition between on-patent medicines in Europe

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ABSTRACT

There is widespread concern regarding the high price of innovative medicines and their impact on the sustainability of healthcare systems. However, the debate rarely accounts for the evolution of prices over the lifetime of the medicine and the impact of competitive forces. This article uses the experience of hepatitis C (HCV), during the years 2010–2017 to examine the impact of in-class competition and implications for policies that enable competition. To study the HCV market, we focused on European countries and applied a two-step approach involving a comprehensive literature review and an analysis of monthly sales data in US$ across seven European countries from July 2011 until July 2017. We find that competition to address the unmet medical need has led to significant treatment improvements to the benefit of patients, payers and the wider healthcare system and society. Competitive launches have led to innovative agreements, lowering the cost per treatment and improving patient access to treatment. For innovators, intense competition does not only impact the price set and their market share but in many cases shortens the economic life of the product to only a fraction of the patented period. This has an impact on future research decisions, focusing efforts on areas where unmet need is greatest. Sustainable innovation requires a well-balanced policy framework that provides the appropriate incentives and encourages competition.

1. Introduction

Over the past few years, there has been continuous focus on the price of innovative medicines with a concern that high prices are not sustainable for the healthcare system. Yet, discussions about the "price of medicines" often fail to acknowledge the difference between the "list price" and the actual final, net price paid by health systems. Rebates and discounts are generally required by national, regional and local purchasers, which lead to lower prices than the "list" or "public" price. Equally overlooked is the fact that innovative medicines almost always face competition from other innovative medicines, as well as from older medicines, affecting the commercial terms, potentially reducing net prices and improving sustainability of healthcare system budgets. The aim of this analysis is to assess whether the existence of competition and flexible agreements mitigate concerns about affordability of innovative medicines. To test this hypothesis, the article uses the experience gained from Hepatitis C (HCV) (a blood-borne and communicable liver disease caused by the hepatitis C virus) during the years 2010–2017. This examines the practical impact of in-class competition, the implications for the policy framework and lessons for other therapy areas.

2. Materials and methods

To understand the dynamics in the HCV market, we applied a two-step approach: a review of the existing literature and evidence and an analysis of sales data in a number of key European countries namely: Austria, Belgium, France, Germany, Italy, Spain and the United Kingdom (UK). As a first step, we undertook a review of existing studies drawing on three main strands of literature: (i) studies providing an overview of the economics of innovation in the pharmaceutical sector, (ii) reports analysing the development of the HCV market and (iii) country-specific evidence and reviews on access and competition in the HCV market. The timeframe for the search included the years from 2011 to 2018 (with a few exceptions for key evidence outside of the time) and targeted literature in English and in local European languages. We used a combination of keywords to identify studies in the three strands mentioned

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above. These included a combination of industry focus: "pharmaceutical", disease area-specific: "hepatitis C" or "HCV", analysis on competition and innovation: "competition", "market development", "trends" and "innovation", debate on price and spending pressures: "cost", "price", "spending" and "expenditure" and tools and solutions applied: "policy", "access", "agreement". The research was conducted in Google Scholar and Pubmed to identify academic peer-review articles (e.g. The Lancet Global Health, Hepatology, Health Affairs etc.) and in Google and other grey literature to capture government publications (e.g. from Ministries of Health and regulator and payer agencies), non-government agencies reports (e.g. World Health Organization) and others (e.g. Financial Times, Bloomberg). This yielded over 60 articles of which around 35 specifically focus on one of the European countries in scope.

As a second step, we examined monthly sales data in US$ across the seven countries.[1] Data was retrieved from July 2011, with the entry of two protease inhibitors followed in 2013 by seven new direct acting antivirals (made up of 2 polymerase inhibitors and 5 N5A inhibitors) and are captured until July 2017, which was the latest available data at the time of undertaking the analysis. Two products launched in 2017, are excluded from the analysis as no sales were made in any of the countries at the time that data was retrieved. We first analysed competition to reach the market with new innovative treatments and then examine the nature of competition in the market after product launch. This includes the impact on market share, prices and costs and "economic" life of an innovative product. Finally, we discuss the extent to which the results can be extrapolated to other therapeutic areas.

3. Results

3.1. The example of HCV

Over the past decades, HCV care has gone through remarkable changes. There have been three major waves of innovation, which have brought multiple benefits to patients and the healthcare system [1]. In the period from the discovery of the virus in 1991 and up to 2010, the only available treatment was PEGylated interferon[2] later combined with ribavirin, the first antiviral launched in 1997. The response rate for the combination varied across HCV genotypes,[3] 42%–46% for genotype (GT) 1 and 76%–82% for GT2/3 patients [2]. Although the most common forms (as illustrated by the prevalence distribution in countries in scope in Figure 5, Appendix 1) were partially addressed, response rates were still low and the remaining genotypes GT4 to GT6 still required treatment [46]. In 2011–2012, the first innovative antiviral agents were approved. These protease inhibitors boceprevir (Victrelis®) and telaprevir (Incivo®), improved cure rates for GT1 patients (increasing to 67% and 88% respectively). In 2014 and 2015, the launch of other direct acting antivirals and combinations, including sofosbuvir (Sovaldi®), daclatasvir (Daklinza®), ledispavir/sofosbuvir (Harvoni®) and, ombitasvir/paritaprevir/ritonavir (Viekirax®) marked a dramatic shift in the treatment of HCV. This class of products targets multiple genotypes and offers a cure to around 92–100% of people treated [3].

The third wave of treatments has delivered substantial benefits to both patients and to the wider healthcare system. This has led to changes in global and national policy. In 2016, the World Health Organization launched a Global Health System Strategy under the title "*Combating Hepatitis B and C to reach elimination by 2030*" [4], which was adopted at the 2016 World Health Assembly. This is being translated into national plans and strategies with the result that policymakers and payers across countries have supported access to treatments with many aiming for disease elimination.

3.2. Competition to bring the best product to the market

Prior to the launch of any new class of medicines, innovative companies compete to bring their product to the market first and for this to have the best product profile offering the greatest benefits to patients. Recent research has examined the 20-year history of companies investigating novel treatments for HCV [5]. For HCV, they find that for each successful launch of a medicine in the market, there should be 30.2 molecules in preclinical development. The overall success rate (which is based on the number of successful launches over the total which includes the success and failures but not ongoing investigations) stands at 2.0% and is less than half of the estimated industry average at 4.1%, as shown in Fig. 1 [5]. This highlights the investment and risk associated to innovation success and need for a system that rewards successful medicines.

The range of new treatments delivered significant benefit over older therapies in terms of clinical efficacy, safety and convenience as shown Fig. 2 (and detail by molecule provided in Table 1 in Appendix 2). It is clear that new waves of medicines delivered value to patients. The investment in research and development (R&D) resulted in the development of injectable interferon in 1991, demonstrating improved cure rates but this was accompanied by debilitating side effects over an extremely long course of treatment [6]. This was followed by the approval of the first HCV antiviral, ribavirin, in 1998 but serious unmet needs persisted, particularly low sustained virologic response (SVR) [2]. Since 2011, NS3/4A protease inhibitor treatments and then the new direct acting antivirals demonstrated substantial progress with respect to addressing unmet needs and transformed the treatment paradigm for HCV patients. More specifically, the following developments are observed.

- *Treatment efficacy has drastically increased with up to 100% SVR response rates observed*: During the past five years the efficacy of new medicines has improved from an SVR at 63% to 80% for protease inhibitors to up to 90% for the new direct acting antivirals to up to 100% in some combination therapies for given genotypes. In addition, it is noted that more treatments have narrower range of responses, showing that even in the lower-response subgroups there is a greater SVR.
- *New medicines deliver to more patient genotypes*: In general, patients are only infected with one genotype, but each genotype is actually a mixture of closely-related viruses which have the ability to become immune to current medicines, which makes their treatment more complex [7]. Treatments in recent years have evolved and expanded in the range of genotypes they deliver positive results for. The earliest treatments, protease inhibitors targeted GT-1 but with the launch of polymerase inhibitors, these expanded targeted genotypes to the most common forms GT1-GT4. More recently, treatments that target all genotypes were launched.
- *Tolerability has significantly improved particularly in interferon-free and ribavirin-free treatments*: In addition to limited efficacy, the earliest treatments caused serious side-effects. The most common of these are hematologic, psychiatric, muscoskeletal, gastrointestinal, metabolic, dermatologic, respiratory, cardiovas-

[1] The data was derived from IQVIA and from GERS DATA for France.

[2] The terms Pegylated interferon and interferon is used interchangeably in this analysis.

[3] The classification of HCV identifies 6 confirmed genotypes (marked GT-1 to GT-6) which have several different subtypes. Globally, GT-1 has the highest prevalence accounting for over 46% of HCV bearers, followed by GT-3 at 30.1% with the rest of the genotypes each affecting less than 10% of the cases. According to the World Health Organization, as of October 2017, at a global level, the disease is prevalent in an estimated 71 million people. The most affected regions are Eastern Mediterranean and European Regions.

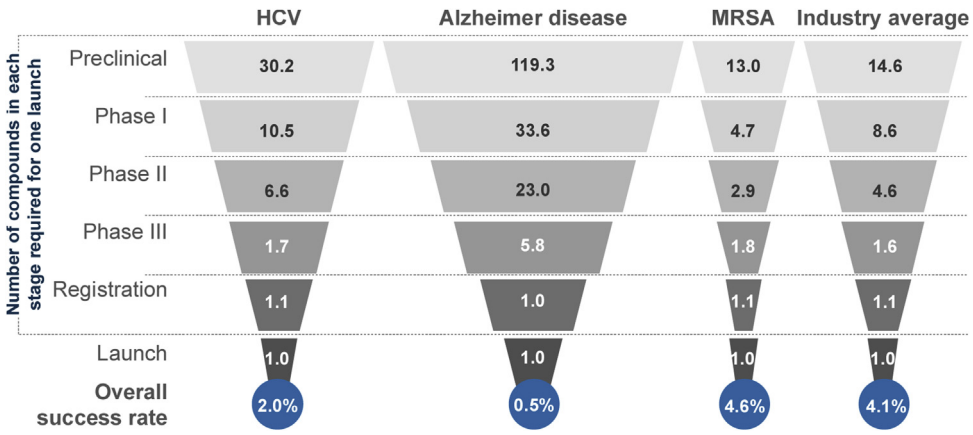

Fig. 1. Attrition profiles across therapeutic areas.
Note: The funnels illustrate the average number of compounds needed at each stage to result in one launched medicine. MRSA refers to an example of an antibacterial i.e. *Staphylococcus aureus*. The success rates are calculated as the number of medicines that have been successfully launched over the total number of past investigations including both successes and failures. This does not account for ongoing studies.
Source: CRA analysis based on Calcoen et al. (2015)

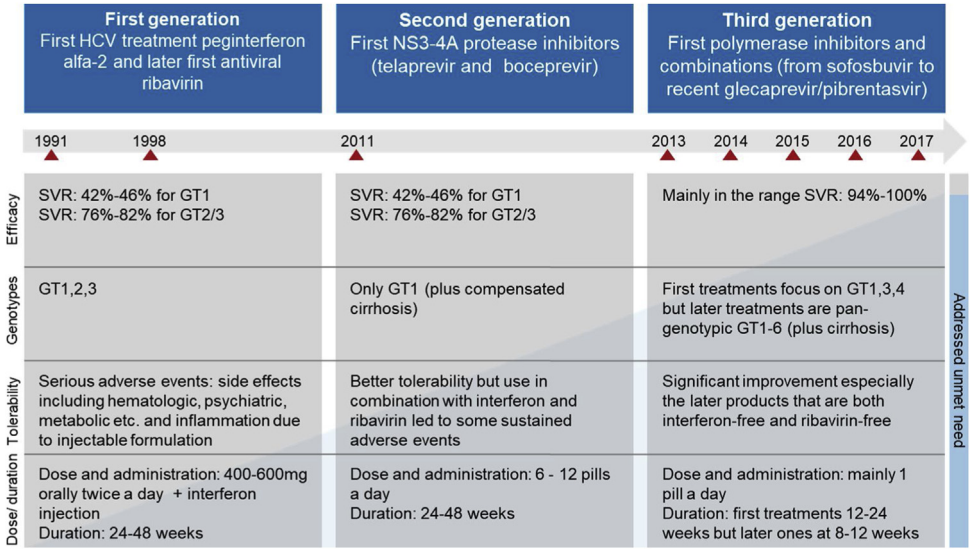

Fig. 2. HCV treatment development and innovation across the years. Note: More detailed information on the individual treatments is provided in Table 1, Appendix 2
Source: CRA analysis based on various public sources provided in the section

cular, ocular and local inflammation of the injection site [8]. These mirrored flu-like symptoms experienced by patients often for many months. Initially, protease inhibitors and the first polymerase inhibitors showed a more positive tolerability profile. This was soon followed by the combination treatment ledispavir/sofosbuvir (Harvoni®) and elbasvir/grazoprevir (Zepatier®) which were the first regimens to market interferon and ribavirin free HCV medicine for specific patient segments (such as HIV co-infected). Finally, the first pan-genotypic interferon-free and ribavirin-free treatments were launched in 2017, providing further tolerability benefits for all patients.

- *Administration is improved as treatments have shorter duration and more favourable dosing regimens*: Convenience of the regimen, defined by the amount and frequency of doses required and the duration of a treatment, is another area where innovators have delivered benefits to patients [9]. HCV treatments have shifted from treatment duration of 24 to 28 weeks requiring daily doses of either 4 tablets 3 times per day or 3 tables 2 times per day to typical treatment duration of 8 to 12 weeks with one pill per day (although could be longer for some genotypes and particular stages of the diseases such as cirrhosis).

3.2.1. *On-going development*

Although there has been significant progress and today's patient population receives largely effective treatment, remaining patients become more difficult to find, diagnose and treat (after the more advanced patients are treated, pro-active efforts are required to target other lower risk populations). This affects the incentive to innovate and is particularly true in the case of a treatment that delivers a cure for the condition. As a consequence, during the past years, we can observe some companies involved in research and development of HCV treatments discontinuing the development of treatments including those in late stages (Phase II and III).[4] Some medicines may have been discontinued as these did not meet their endpoints but more strikingly some of the companies have decided to halt development due to an "increased availability in the number of highly effective therapies that address the medical need in HCV" [10]. A potential medicine could promise great therapeutic value

[4] Based on AdisInsight clinical trial database the number of discontinued HCV medicines in Phase II and III each year is: 2 in 2011, 1 in 2012, 2 in 2013, 3 in 2014, 6 in 2015, 1 in 2016 and 5 in 2017.

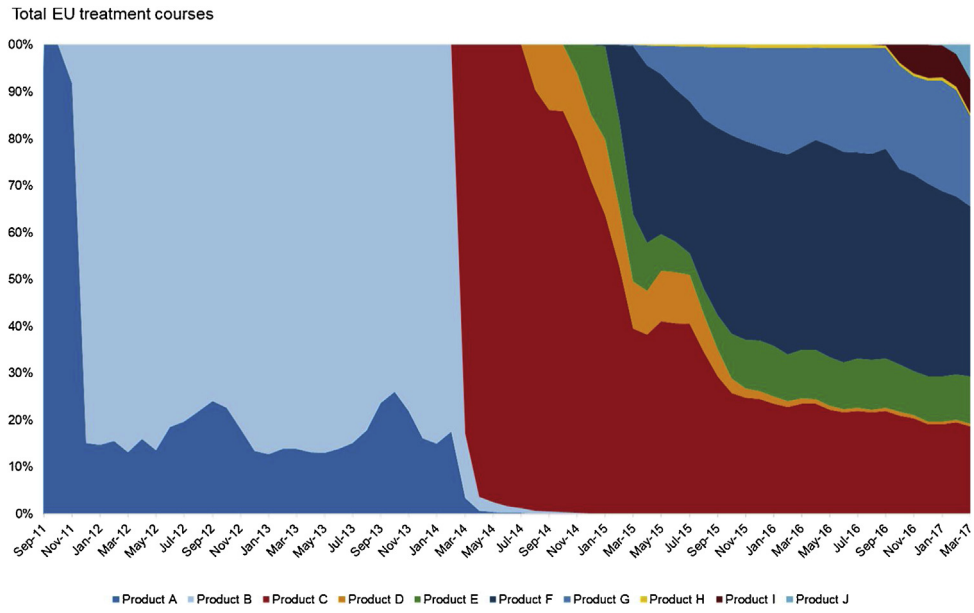

Fig. 3. Total market share of products by treatment course, July 2011 to 2017.
Source: CRA analysis based on data derived from IQVIA and from GERS DATA for France[17]

while it is in development, but if it arrives too late on the market and does not provide any additional benefit to its competitors, it is not a commercially viable investment. While competition in R&D happens in all sectors, pharmaceutical R&D may differ from other sectors due to its long time horizon and respective investments: molecules in Phase II or Phase III have already been in development for 7 to 9 years [11].

3.3. Competition in the innovative medicines market

As for any other pharmaceutical product, the company bringing the first product in a new therapeutic area will need to demonstrate its value and negotiate its price and reimbursement levels. However, even the first product in a new class will be affected by competition. In this section, we investigate how competition works once products have launched onto the market and impacts on the economic life of HCV medicines.

3.3.1. The impact of competitors prior to launch

Given the need to manage limited healthcare resources, some payers monitor the development of medicines and are aware of the pipeline of competing products. Some implement sophisticated approaches to horizon scanning (such as the extensive horizon scanning reviews from public health agencies that are referenced by the National Institute for Health and Care Excellence (NICE) in England – see examples in epilepsy in 2017 [12], corneal disorders in 2016 [13] and for HCV in 2013 [14]). These reviews highlight the prospect that other products will enter the market and the anticipation of competing products will have an impact on the negotiations and outcome for access. Indeed, we can observe the impact of this:

- In England, the National Health Service (NHS) which is responsible for the reimbursement of medicines, delayed coverage of sofosbuvir (Sovaldi®) despite a recommendation by the medicines evaluator i.e. NICE. In an unprecedented move, NHS England requested six months to implement NICE guidance (the mandatory 90 days and three additional months). In addition, NHS England also tried to halt three further HCV treatments undergoing appraisals at NICE [15].
- AIFA in Italy considered new HCV medicines under registration when entering price negotiations [16].
- In France and Belgium, the length of the agreement with the first innovator was set to take into account the timing of future competitors.

3.3.2. Competitors have vied for market share

As new competitor products have launched on the market, there have been big changes in market share. As shown in Fig. 3, in 2011 to 2013 the market in European countries was led by protease inhibitors.[5] Market share is calculated by treatment courses per product calculated as part of all treatments sold at that point in the HCV market. Treatment courses are measured as total standard units (SU) sold per product divided by [treatment length on average (weeks)] times [7 (days a week)] times [daily dose (tables a day). This provides a simplified estimate of the number of treatments and it does not account for different length by genotype or disease progression (such as longer treatment for cirrhotic patients). This could, for example, lead to an overestimation of the treatment courses provided in the initial years when more cirrhotic patients were prioritised. Yet, shifts in market share are clear. Protease inhibitors were initially seen as potential blockbusters, but in practice new advances in HCV treatments replaced the previous generation of products very rapidly. Indeed, the first polymerase inhibitor quickly captured market share and was soon established as a market leader in most countries. Nonetheless, this was also short-lived as new therapies entered the market from 2015 onwards. These shifts offer interesting learnings on the dynamics of the market and the forces behind these changes.

A key observation is that the two leading products in the market in 2011 to 2013, were ultimately programmed for delisting and withdrawal. Despite their recent launch in 2011 as new highly innovative products drastically increasing cure rates from 29% to over 80%, these soon became obsolete with the launch of the first polymerase inhibitor. In fact, the anticipation of the launch of polymerase inhibitors was sufficient to change the dynamics of the

[5] Please note that the analysis does not include revenues for interferon and ribavirin.

market for these products as shown in Figure 6 in the Appendix 3. Since the announcement of clinical trial results, sales started declining and the market shrank in anticipation of the launch of a newer and improved treatment regimen. The older products were ultimately discontinued with their manufacturer arguing that the lower efficacy and tolerability led patients and prescribers to delay treatment until a polymerase inhibitor was launched [18,19]. The early withdrawal meant that these treatments were only on the market from 2011 to early 2014, an 'economic' lifecycle of just over two years. This contrasts with the common perception that patents guarantee exclusivity for a specific product and market exclusivity for many years and this guarantees commercial success (however, in this case the effect was even more drastic due to the curative nature of products to follow). This means that innovators are unlikely to have recouped the investment made in development of these treatments or achieved any rewards for the risk involved in their development. Studies estimate that, on average, it takes medicines from 7 years (medicines with sales revenues in the top decile) up to 19 years (the rest) to be able to recoup R&D investment [20]. Although, in therapy areas of high unmet need, such as oncology and rare indications, recent studies show that this time can be shorter [21].

Since the launch of Product C, we can also observe competition within the class of polymerase inhibitors and combination therapies as illustrated in Fig. 3. The impact from new treatments can be observed after each new product launch. However, we need to recognise that for some of the products this effect is diminished due to two key factors: (i) products do not compete across all genotypes which provides an advantage to treatments targeting unaddressed segments and (ii) some new treatments are used in combination with existing ones, acting as complements rather than substitutes - as shown in Table 1, Appendix 2. An impact is seen at market share by company (calculating market share as the total dollar sales of each company as a percentage of total dollar sales in the HCV market), as illustrated in Figure 7, Appendix 4. Company A and Company B were initially competing between themselves for market share but then experienced a steep decline once Company C entered the market. Company C in turn lost market share when Company D launched its product in 2014, with Company E following close behind in 2016 to gain more sales. Based on the same data, it also emerges that, it has been 0 to 18 months (median = 3 months and average = 4.8 months) between launches. This allows us to take into account that a number of products are being provided by the same company and an analysis looking at the number of products on the market would over-state the extent of competition.

3.3.3. *Competition in the market has led to a range of agreements and lower prices further improving cost-effectiveness for these treatments*

Pricing of HCV medicines has become subject to much debate in the past five years. The launch of the first polymerase inhibitors resulted in increased spending on HCV medicines from healthcare systems [22]. From the innovators' perspective these prices were justified on basis of efficacy as cure rates approached 100% and halved the duration of treatment (from 6 to 3 months). The evidence of the value of these medicines is clear. These curative treatments were demonstrated to be cost-effective based on their initial prices agreed in the market. It was shown that their use would lead to future savings to healthcare costs in analysis conducted across a range of different markets [23]. These treatments provide benefits not only to the patient but also offer healthcare system savings on direct HCV medical costs such as liver transplants [24]. Despite the increased benefits, and although cost-effective, many argue that the price of the products meant the budget impact was too high. These claims are often based on the initial public price (i.e. "list prices"). Evidence suggests that these prices are not the actual prices paid and do not represent the full impact of competition. To investigate this, we first looked at the pattern of publically available list prices.

We have calculated the price per course of treatment to allow for differences in treatment duration, although this might be a modest underestimate as it does not account for duplicative counting due to some use of products in combination.[6] The results of prices across the seven countries are provided in the Appendix 5 in Figure 8. We note that there is no clear trend in the launch price across countries. Despite this, country-level evidence provides important insights on how competition affects prices. We find that in a number of European markets namely Austria, France, Germany and Italy there have been price decreases during the product lifecycle. For example, the first decrease in France is associated to the end of the provision through the Temporary Authorisation for Use (ATU), the early access scheme [25]. The second decrease reflects negotiations between the French Ministry of Social Affairs and Health and the manufacturer [26]. It should be noted, that these are published prices taking into account on-invoice discounts and do not reflect the actual cost per cure that payers in France incurred, given that additional confidential rebates have likely been negotiated.

Initial list prices therefore do not represent the price of the therapy over the life cycle. It also clearly is not the case that prices raise monotonically after the first launch. The data on prices used in the analysis runs up to July 2017, but it should be noted that recently the pan-genotypic and ribavirin-free and interferon-free HCV treatment glecaprevir/pibrentasvir (Maviret®), was launched in some European markets at much lower prices such as £12,994 per course in the UK, which stands significantly lower than the prices of earlier polymerase inhibitors including sofosbuvir (Sovaldi®) at £35,000 per course in 2014 and also of previous generation treatment such as boceprevir (Victrelis®) at £30,800 per 44-week course plus the cost of the interferon and ribavirin at approximately £11,000. This indicates that the launch price of newer cures with more benefits has drastically decreased, as a result of competitive pressures [27,28].

In other markets, the price would appear to be static. Yet, that is a misunderstanding and misinterpretation of how medicine pricing works in Europe. In reality, list prices do not reflect what payers pay for medicines as list prices are subject to negotiations and confidential discounts. Manufacturers and payers have announced on multiple occasions that agreements have been reached to a specific medicine to be provided subject to discounts through direct negotiation or managed entry agreements (MEAs). Although, these discounts are confidential, some net prices have been reported in media reports that were clearly below list prices [29]. Studies have shown that these confidential agreements result in actual prices being 23% below the list price [29]. Nonetheless, anecdotal evidence suggests that in reality actual/net prices can be an even smaller proportion of the visible list price. For example, the Italian national medicine evaluator, AIFA, is one of the agencies that most widely engages with manufacturers in different types of MEAs. In 2014, AIFA agreed to a three-year MEA with Gilead on sofosbuvir (Sovaldi®). The agreement is confidential but unofficial evidence indicates that this is a price-volume and payback type of scheme. It is suggested that initially the Italian payer spent around €40,000 per patient (which was just below the list price). At the end of 2016, the treatment was provided to almost 70,000 patients and the price per treatment for each was down to an estimated €4,000 for this tier of patients [30]. The estimated median price per patients from prior evidence stands at €15,000 per treatment [31]. This is considerably below the visible list price set

[6] This was calculated by the number of Standard Units (SU) per treatment as [treatment length (weeks)] x [7 (days a week)] x [daily dose (times a day). Then we multiplied the price per SU by the number of SU per treatment.

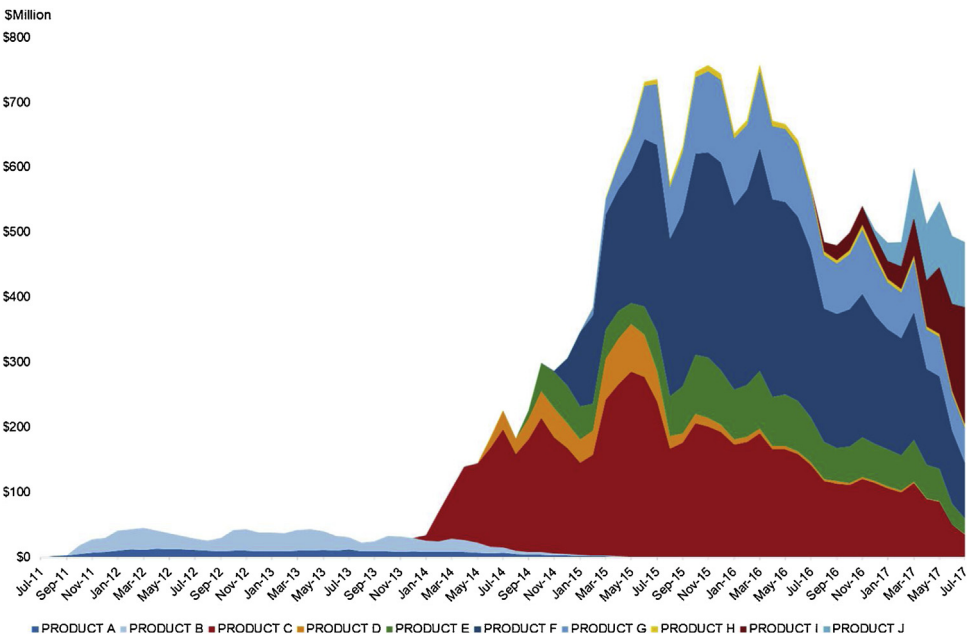

Fig. 4. Total market sales in seven countries by product, July 2011 to 2017.
Source: CRA analysis based data from IQVIA and from GERS DATA for France[17]

at around €45,000 and the associated cost this would indicate [29]. In Spain, a similar price-volume agreement was implemented, with prices decreasing as more patients were provided with ledispavir/sofosbuvir (Harvoni®) and, ombitasvir/paritaprevir/ritonavir (Viekirax®) [32]. In Germany, Spain and France, the government has declared publicly deals they have reached on the list price but without an indication of further discounts that are applied [33,34].

Since the launch of these therapies, despite the agreements reached, pressure on prices has only increased. This has led to novel policy developments. At a national level, in England a new model of therapeutic tendering has been developed, which requires manufacturers to submit prices based on the percentage of market share they could achieve in the given therapeutic class [35]. Also, a number of cross-country initiatives in Europe have emerged during the past three years (although they have not been yet applied to HCV medicines) [36]. It is too early to assess the positive or negative impact of these initiatives onpatent competition.

3.3.4. The impact of competition on spending and overall market size

To understand the dynamics in the total HCV market and impact on total costs, we also need to look at the overall HCV medicines expenditure (overall market sales) across all countries. This was calculated by aggregating the dollar sales of all of the HCV products launched in 2011 onwards across the seven countries. Looking at Fig. 4, we observe that the total market value in sales has increased at the start of the new generation of products launches. The launch of polymerase inhibitors at the beginning of 2014 marked an important shift in the treatment paradigm and expanded the market. As competing products were launched, with more patients being offered a viable treatment, the market continued to expand, reaching a peak in the years 2015 to 2016. However, from January 2016 the market has experienced a significant decline with total market sales in July 2017 35% less than the peak. This may be explained by a combination of factors including competition driving down prices, price-volume agreements and a decline in the number of patients. The fact that "easy to reach" patients (i.e., those with advanced liver disease and presenting themselves in hospital settings) had been treated, while achieving greater treatment rates in the rest of the patient population would require pro-active screening policies at national level or greater focus on at risk populations.

That spending has peaked is also supported by recent statements from public payers. In September 2017, the Spanish Ministry of Health reported on the progress made in their national HCV strategy, stating a decline in spending associated to the acquisition of HCV treatments. According to the source, Spain spent €1.19 billion on HCV treatment in 2015, falling to €412.8 million in 2016 and €177.8 in 2017 [37]. This is not only attributed to the decreasing number of patients being treated. Using the number of treatment courses from IQVIA data, we can estimate the cost per treatment using the budget data from the Spanish Ministry of Health. This shows the cost per treatment displays a significant decrease from 2015.[7] Although, on the face of it, this is inconsistent with Figure 8, it is important to remember that these charts reflect public prices and don't reflect the actual net price or its trajectory (either due to further discounts or price/volume agreements). Looking to the future, forecasts show total market sales is set to continue to decline further [38], even though new products are expected to enter the market as shown in Figure 9 in the Appendix 6. The same situation applies in other countries. For example, in Germany recent reports have shown that the actual spending was much less than the anticipated and shown that spending peaked in 2015 [39].

4. Discussion: implication for other therapy areas

Despite the recognised innovation and benefits, price levels of innovative HCV treatments have been scrutinised and analysed

[7] Using IQVIA data we calculate that the number of treatment courses per year a proxy for patients treated in Spain is 2015 = 65,511, 2016 = 54,107 and in 2017 [Jan-Aug] = 22,710 (assuming August numbers are equal to July numbers). This leads to a cost per patient treated in 2015 = €18,164 (€1.19bn/65,511); 2016 = €7,629 (€412.8 m/54,107); 2017 [Jan-Aug] =€7,829 (€177.8 m/22,710)*. It is important to note two implications: 1) the 2017 estimate may be biased due to incomplete data and assumption of August sales equal to July sales and may lead to a slight increase to 2016 data 2) across the three years the estimated prices may be higher as the treatment number (i.e. volume) is based on an estimate of treatment numbers at product level without accounting for some duplication due to use in combination of some of these products.

by economists, policymakers and the medical community. Prices, combined with the large number of HCV patients who could benefit from new innovative treatments, have led to concerns about affordability even for advanced healthcare systems and payers (even though the medicines have shown themselves to be cost effective). Often, this has been fuelled by estimates of required level of spending based on initial list prices.

Prior studies, (Berndt et al.; Kavanos et al.; Danzon and Chao; Lu and Comanor) have discussed the effectiveness and impact of on-patent and in-class competition in the pharmaceutical market prices [41–44]. To determine the impact of competition various factors must be taken into account, including the number of patients benefiting from effective treatment but also the impact of competition on evolution of the HCV market. In this analysis, we have investigated whether competition has played a role in the market for HCV treatments, both on the development of new treatments and in terms of competition once products are on the market. In line with prior research, we find that there are competitive forces at play in HCV markets and this has had a substantial impact on the development of medicines, the price negotiation at launch, market share and effective economic life of the product, the actual price paid and overall spending and access to medicines.

Due to the curative nature of the medicines, the case of the HCV market is particular in some ways but there are important lessons for the impact of competition in other therapy areas. As shown, each generation of HCV treatments provided a significant improvement for patients. Competition requires innovators to focus on areas of unmet medical need, leading to newer improved treatments and cures to the majority of the patient population. This race to the market was reflected in the number of similar molecules in development, some of them with very brief time differences. These provided higher efficacy, better tolerability and increased convenience in treatment administration and patient adherence. An increasing number of patient groups were provided a cure, granting benefits that go beyond the patient and are positive for the wider society and economy. This race continues to date with remaining sub-groups in the patient population that are not responsive to treatments.

Competition intensifies once products are on the market. The analysis indicates that the prices and costs peaked at the launch of each new class due to the transformative nature and benefits from treatments but decrease after the first wave. Indeed, as new products entered the market, competition for market share was reflected in the intensity of negotiations and commercial agreements with payers. It should be noted that, data on price negotiations and agreements is primarily based on grey literature, which is a limitation as this evidence is not consistent through time and across all the countries. This offers an opportunity to further the research in this area in the future.

For curative treatments, this is particularly challenging as there is an ever-declining number of patients requiring treatment, as more patients are cured. However, this will also apply to other therapy areas. Pressure in the market post-launch, impacts the rewards for innovation. Despite the initial high market share of first in class medicines, this falls quickly as new products are launched on the market, illustrating a considerably short product life-cycle of two to three years. This impact is amplified due to the curative nature of the treatments and will vary between therapy areas but is substantially shorter than the period provided by patent protection. In line with the impact discussed in prior studies (Kanavos et al.; Lu and Comanor), we find the following implications:[41,43]

- For innovators, on-patent competition presents an additional risk (in addition to the risk of R&D). As shown in Fig. 3, protease inhibitors were initially seen as potential blockbusters, but in practice new advances in HCV treatments replaced the previous generation of products very rapidly. As a consequence, protease inhibitors left the market after 2 years despite patent protection.
- For those innovators who enter and remain in the market with treatments offering therapeutic alternatives, competition has an impact on price, which reduces expected return on investment (see Fig. 4). In-class competition means that innovators offering the greatest value are rewarded (rather than all the rewards going to the first entrant in the market). For payers, patients and society on-patent competition has meant more medicines with more benefits but the price has systematically decreased, as a result of competitive pressures primarily within the class of treatments, delivering higher benefits to society.

However, as noted in prior studies (Berndt et al., 2011; Wiggins and Maness, 2004), market conditions and characteristics such as product heterogeneity (or substitutability) and the number of players impact competitive forces [40,44]. It is important to note that in the market for HCV treatments, there is an added complexity in terms of the number of innovators, the different genotypes treated by different products and the use of products in combination. As shown in Table 1 Appendix 2 we need to take into account that products target different genotypes affecting the degree to which they represent direct substitutes.

Competition is generally positive from a societal and payer, and to a certain degree also from an innovator's perspective if used appropriately. According to Berdud et al. (2018) problems can arise if the amount of appropriation – the innovator's capacity to capture or appropriate the added value created by successful innovation – is too low or too high [45]. Competition that results in sufficient appropriation is consistent with dynamic efficiency. Thus, it is key to allow new treatments to compete based on their value proposition (but not trying to engineer price competition that replicates the off-patent market denying innovators a chance to recover the cost of R&D which is called "static efficiency").

5. Conclusions

Based on the HCV market analysis, we draw a number of common lessons for innovative medicines markets. First, having multiple products in development and that compete to reach the market first is valuable to patients and to payers as it addresses medical unmet needs whilst providing competing offers for payers in negotiations. At the same time, anticipating competition through horizon scanning can be a useful tool as it allows payers to plan for budget impact. Second, it is key to contextualise list prices at launch. These do not reflect the actual price paid as innovators and payers engage in sophisticated negotiations and agreements to advance access at a reduced cost. Third, in-market competition has an impact at the launch of the first product and develops over time and improves sustainability of payer budgets and treatment provision, therefore initial budget impact assumptions have to be regarded with caution. Finally, even if different countries adopt different approaches (based on their own pricing and reimbursement regime), all of the countries benefit from competition. Competitive launches have led to innovative agreements, lowering real prices and mitigating the budget impact and improving access to patients. For innovators, intense competition does not only impact the price they receive and their market share but, in many cases, shortens the economic life of the product to only a fraction of the patented period. This has an impact on future research decisions, focusing efforts on areas where unmet need is greatest. Improving health requires a policy framework that balances different objectives. On-patent competition as dynamic efficiency can contribute to this cause.

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7. Conflict of interest statement

Tim Wilsdon and Artes Haderi were commissioned to support this analysis and they assume editorial responsibility as contributors to the study. Charles River Associates is an economic consultancy company with a long-established reputation for independent analysis. The views expressed herein are the views and opinions of the authors and do not reflect or represent the views of Charles River Associates or any of the organizations with which the authors are affiliated.

A. Roediger is an employee of MSD International GmbH

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Appendix A. Supplementary data

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