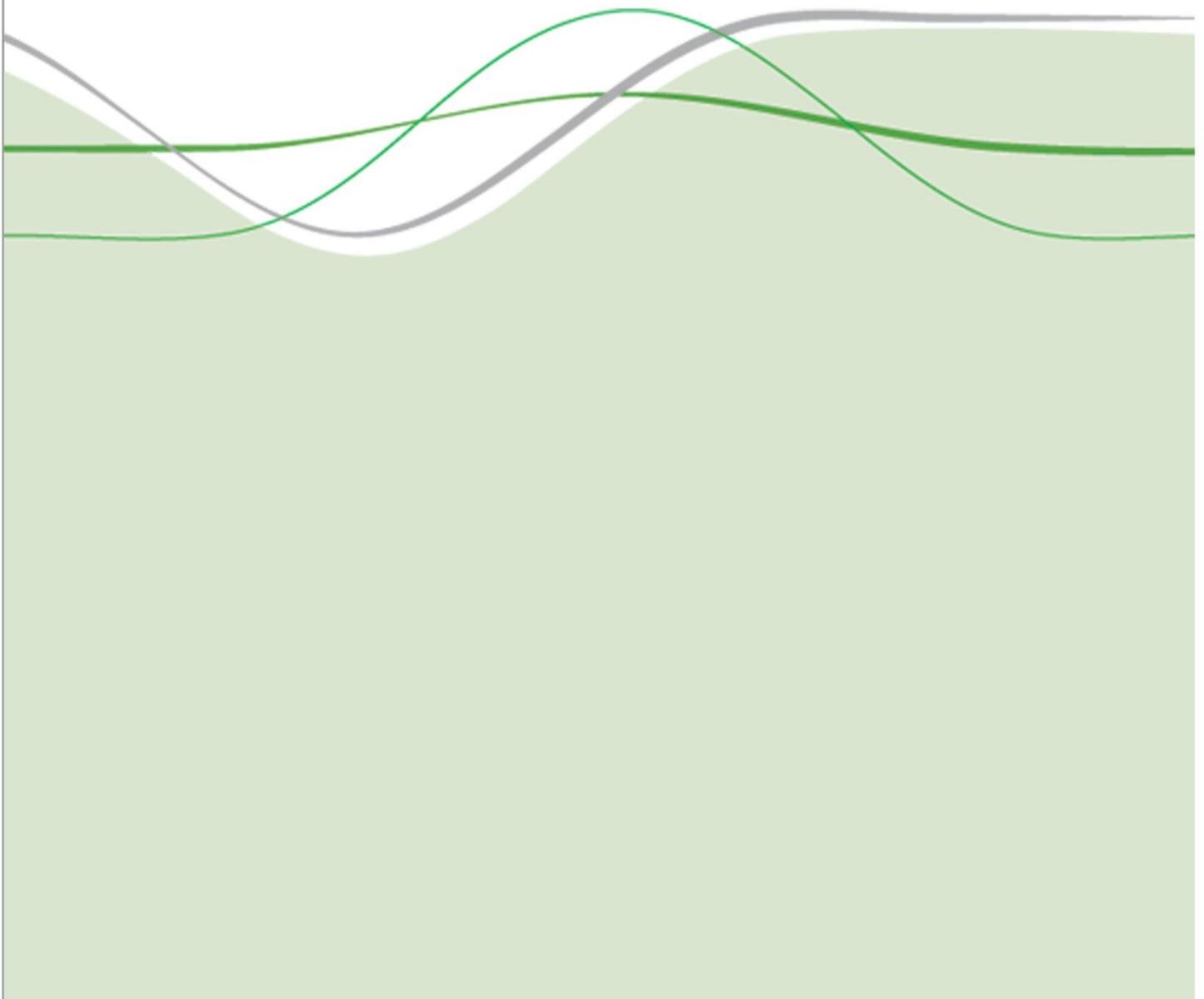


# R&D, Competition and Diffusion of Innovation in the EU: The Case of Hepatitis C

July 2018

Mikel Berdud, Martina Garau, Margherita Neri, Phill  
O'Neill, Chris Sampson, Adrian Towse



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## **ABSTRACT**

**Objective:** We assessed the impact of (i) incentives for R&D based on providing Intellectual Property (IP) rights protection, (ii) market competition, and (iii) other factors including healthcare policies on access to the Direct Acting Antivirals (DAAs) in Europe.

**Methods:** The study combined an economic framework with analyses of market shares and uptake of DAAs and interviews to relevant stakeholders of six European Countries (France, Germany, Italy, Portugal, Spain and the UK) to assess the degree and nature of market competition for DAAs between 2014Q1 and 2017Q2. We performed semi-structured interviews with countries' relevant stakeholders to identify additional factors affecting access to DAAs. We estimated health gains accrued by treated patients in each country, adapting economic modelling performed for the UK.

**Results:** Our stylised framework based on theoretical models shows that current R&D incentives based on IP protection in the EU can encourage in-patent competition. In-patent DAA competition leads to price reductions (making new medicines more affordable). The uptake analyses showed that competition within the DAA class was intense in European markets soon after the launch of the first-in-class treatment. Countries vary as to when they provided access to DAAs but, in all of them (except in Portugal), once several products were marketed and made available, the market was subject to intense in-class competition. Evidence from our interviews suggested that in-class competition improved access and uptake and provided bargaining power to country payers. Other important factors impacting access were: improved characteristics of DAAs from a clinical perspective– in terms of response rate and side effects– compared to interferon-based treatments, as well as their acceptable cost-effectiveness. Our estimates of the health gains showed that countries relying on market competition – providing full access to all DAAs available and negotiating prices –accrue higher QALY gains compared to those, implementing restrictions to control total expenditure on DAAs (such as in the case of the UK until 2016).

**Conclusions:** IP incentives for R&D may have encouraged a high degree of in-class competition of DAAs close to the first entrant launch. In-class competition had a positive impact on uptake and adoption of DAAs in the top-5 European countries. However, in-class competition is a necessary but not sufficient condition for early adoption and fast uptake of innovative medicines as there are other factors related to the performance of the new technology, including the characteristics of the healthcare system and political factors, which have an effect.

## 1. INTRODUCTION AND OBJECTIVES

In the pharmaceutical industry, Intellectual Property (IP) rights protection including patents, Data Exclusivity (DE), and Supplementary Protection Certificates (SPCs), are important due to the high costs of Research and Development (R&D) for new medicines and the issue of *appropriability*, a concept that reflects innovator's capacity to capture or appropriate the added value created by successful innovation (Bader and Gassmann, 2016; Belleflamme, 2008; Cohen, Nelson and Walsh, 2000).

Problems can arise if the amount of appropriation is too low or too high. A low degree of appropriability could result in dynamic inefficiency or a suboptimal (too low) allocation of resources in investment in innovation. In other words, the resulting quantity of innovation would be lower than that maximising the social welfare, which is the total sum of patients', payers' and innovator's surplus (Stiglitz and Jayadev, 2010; Belleflamme, 2008).

However, too much protection might grant the originator excessive market power. An originator can use such market power to charge prices far above manufacturing and distribution cost resulting in static inefficiency, whereby innovative medicines are not used by some patients/countries/systems. Some patients would not access the treatments they need and therefore quantities sold would be lower than the quantity that would maximise social welfare given the existence of the product. As in any other market, the innovator would maximise private profits (surplus) but the total sum of patients', payers' (taxpayers) and innovator's surplus would be suboptimal (Stiglitz and Jayadev, 2010; Belleflamme, 2008).

The economic literature shows that a certain degree of IP protection is necessary to incentivise innovators to invest in pharmaceutical R&D and ensure the dynamic efficiency of pharmaceutical markets. For the duration of the IP protection, price will be above marginal cost as the innovator uses their market power to charge prices that lead to dynamic efficiency, by rewarding R&D investment, but which could result in static inefficiency. In recent times increasing concerns around the current patent and SPC system have emerged. IP critics argue that accessibility to, and affordability of, innovative medicines (static efficiency) is compromised because innovators can impose too high prices for too long periods of time. Extensive economic literature explores the optimal balance between access to medicines (static efficiency) and incentives for innovation (dynamic efficiency) that maximise the social value of new medicines (Danzon, Towse and Mestre-Ferrandiz, 2015; Zeng, Zhang and Fung, 2014; Stiglitz and Jayadev, 2010; Belleflamme, 2008; Vernon, 2005; Finkelstein, 2004; Danzon and Towse, 2003; Philipson and Mechoulam, 2003)<sup>1</sup>. The optimal patent length and breadth is a classic question explored in the literature on economic regulation. Given the evolving nature of biomedical science, pharmaceutical innovation, health systems and health policies, thinking on this needs to be periodically revisited.

This paper contributes to this debate by analysing the functioning of a specific market for innovative treatments, Direct Acting Antivirals (DAAs) for hepatitis C virus (HCV) in six

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<sup>1</sup> For example, Danzon, Towse and Mestre-Ferrandiz, 2015, argue that dynamic efficiency and second best static efficiency is achieved when the willingness of payers to buy QALYs in the form of new treatments reflects the underlying willingness to pay of their enrollees or the citizens covered by the plan. Static efficiency is second best because the mark-up above marginal cost that reflects the value of the innovation inevitably reduces overall demand for and use of the product below the optimal static level.

European countries. The HCV example was selected because the introduction of DAAs challenged countries' ability to pay for highly valuable innovation and initiated a debate around affordability, which for the first time was a bigger issue than cost-effectiveness. In such a context IP protection were questioned as a factor allowing developers to insist on high prices, so restricting payers willingness and ability to give patients' access.

Our particular interest was the potential impact of in-class competition for DAAs. In-class competition refers to competition between medicines within their patent term in the same therapeutic area or category that provide some overlapping effects, i.e. are substitutes for some patients<sup>2</sup>. A market characterised by high degree of in-class competition whilst products still on patent, would improve the affordability of medicines for governments and facilitate access and uptake to patients via prices. Whether IP incentives may have fostered in-class competition for DAAs and whether in-class competition may have facilitated adoption, access and uptake, are two of the main questions for this research.

We adopt a multidisciplinary approach combining a theoretical economic framework with quantitative and qualitative analyses. Using the economic framework, we firstly assess theoretically whether IP protection (i.e. patents) may foster in-class competition. We also assess whether in-class competition may justify the use of SPCs to extend effective patent protection. Secondly, we analyse quantitatively the markets for DAAs of a sample of six European countries, including the five largest EU markets (France, Germany, Italy, Spain and the UK) and a small market (Portugal). Using market statistics and uptake modelling, we assess market competition by measuring volumes and market shares of available DAAs.

Finally, we report on a series of interviews with clinical and Pricing & Reimbursement (P&R) experts from the six countries of the study to help identify key factors that have influenced (positively or negatively) access and uptake of DAAs in the selected countries. Factors will potentially include healthcare system capacity and national health policies and processes (e.g. P&R, HTA assessment).

The objective of this study was to explore whether:

- a. Existing Intellectual Protection (IP) incentives – including SPCs – allow, or didn't prevent, or may have increased, in-class competition in European markets for DAAs;
- b. In-class competition led to price decreases, hence facilitated patient access to and uptake of DAAs in European markets;
- c. Other factors related to the characteristics of the healthcare system and of the condition played an important role in determining prices and access to DAAs.

The paper is organised as follows: Section 2 discusses the economic framework; Section 3 discusses our methods; Section 4 presents the results; Section 5 discusses the results and outline limitations of the study; Section 6 provides main conclusions.

## **2. ECONOMIC FRAMEWORK**

The pharmaceutical sector relies on IP protection such as patents to solve the problem of appropriability (Bader and Gassmann, 2016; Stiglitz and Jayadev, 2010; Belleflamme, 2008). Patents allow innovators (in theory) to sell new medicines at a price above

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<sup>2</sup> Over time, some in-class competition will come from off-patent medicines.

marginal cost during the protection period potentially providing a sufficient rate of return to recoup R&D investments. The duration of a patent is fixed at 20 years from the date the patent application is filed<sup>3</sup>. For pharmaceuticals, this coincides with the preclinical discovery stage, when the active ingredient has been found.

Fixed patent terms may therefore become less effective in incentivising R&D in situations where the process from Phase 1 trial to regulatory approval is lengthening (Schuhmacher, Gassmann and Hinder, 2016; DiMasi, Grabowski and Hansen, 2016; Scannell et al., 2012; Pammolli, Magazzini and Riccaboni, 2011). This period of time reduces the effective patent period, i.e. the time available to earn a return on a product prior to patent expiry. To address this issue, governments have implemented additional IP protection policies and/or amendments. In the EU for instance, policies like Market Exclusivity, SPCs, Data Exclusivity and Paediatric Extensions have been introduced (Acquah, 2014; Kesselheim, 2010; Yin, 2008; Grabowski, 2002).

The focus of this Section is to assess, firstly, how SPCs can in theory restore incentives to invest in pharmaceutical R&D and innovation (dynamic efficiency) and, secondly, how SPCs can allow or even foster in-class competition in pharmaceutical markets and hence make innovative treatment options more affordable for health systems and more accessible for patients (static efficiency).

Figure 1 shows how SPCs can improve incentives to invest in R&D when the development times are relatively long. To help interpret Figure 1 and the discussion, some basic definitions and notation are needed:

- *Invention*. The development of the basic idea for a product to the point where it is patentable.
- *Commercialisation*. All R&D processes necessary to bring the patented innovation to the market.
- *Year of invention*. The year when the patent is filed. We refer to this as  $t_{inv} = 0$  (assumed to be period 0).
- *Year of commercialization*. The year when the invention is granted marketing authorisation. We refer to this as  $t_{co}$ .
- *Commercialization lag*. This is the total number of years between the year of invention and the year of commercialisation. We refer to this as  $t_{lag} = t_{co} - t_{inv}$ . If invention time is assumed to be period 0, then  $t_{lag} = t_{co}$
- *Patent term*. Amount of time of exclusivity that patents (and other forms of IP protection) grant to the innovator. We refer to this as  $t_{pat}$  and as  $t_{SPC}$  when an SPC is added.
- *Effective patent life*. The actual number of years of patent protection an innovator can enjoy. We refer to this as  $t_{eff}$ , which is the patent life net of the commercialization lag, i.e.  $t_{eff} = t_{pat} - t_{co}$ .
- *Full-value price*. The price  $p^v$  the innovator can charge per unit of medicine sold during the effective patent life if no other competitor (therapeutic substitute) enters in the market. It is set at WTP threshold value for the drug.
- *Competitive multi-source post-patent price*. The price  $p^*$  (usually at marginal cost level) that competitors can charge per unit of medicine sold after patent expiration.

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<sup>3</sup>See the WTO TRIPS agreement on intellectual property rights protection: [https://www.wto.org/english/tratop\\_e/trips\\_e/intel2\\_e.htm](https://www.wto.org/english/tratop_e/trips_e/intel2_e.htm)



Consider the case now that an SPC is granted which gives the innovator additional protection years until its expiration time  $t_{SPC}$ . Let assume that the SPC extends the effective patent term up to  $t_{eff} = t_{pat} - t_{co}^S$ . Assume also that the new effective patent term is long enough to ensure a total revenue of  $R_L + R_{SPC}$  large enough to restore innovator's incentives to commercialise the new drug  $R_L + R_{SPC} \geq C_S + C_L$ . This third case shows how SPCs may restore the incentive for the innovator to continue the project. In particular, it may promote dynamic efficiency by rescuing new drug projects that are close to the profitability threshold and which will generate social value in excess of the private cost of development.

To answer the broader question about whether the SPCs may contribute positively to the in-class competition before patent expiry, and consequently to static efficiency, we need first to assume that competition between therapeutic substitutes decrease prices in line with findings in the literature (Berndt, McGuire and Newhouse, 2011; Kanavos, Font and McGuire, 2007; Bhattacharya and Vogt, 2003; Wiggins and Maness, 2004; Danzon and Chao, 2000; Lu and Comanor, 1998; Weston, 1982; Reekie, 1978). Additionally, it is necessary to incorporate an in-class competitor to the framework as well as the health system (or the payer). Let consider:

- Two innovators: 1 and 2
- Single time of invention:  $t_{inv}$
- Two commercialisation times:  $t_{co}^1$  and  $t_{co}^2$
- Two commercialisation lags:  $t_{co}^1 - t_{inv}$  and  $t_{co}^2 - t_{inv}$
- Single patent expiration period for both firms:  $t_{pat}$  (first generic competes with both)
- Two effective patent lives:  $t_{eff}^1 = t_{pat} - t_{co}^1$  and  $t_{eff}^2 = t_{pat} - t_{co}^2$
- Two different costs of R&D:  $C_1$  for firm 1 and  $C_1 + C_2$  for firm 2
- Price effect/payer savings: HS, total expenditure/revenue reduction caused by the price decline due to therapeutic class competition
- Firm 1's total revenue:  $R_1$  which will be lower than that achieved as a monopolist for two reasons, price decline and the market share of the competing innovator
- Firm 2's total revenue:  $R_2$
- Total cost of the medicine for the payer after generic entry: G

Figure 2 shows how SPCs can affect in-class competition, innovators' expected rates of returns and the health system's expenditure (savings). In Figure 2, the two firms start to develop the drug at the same time. Firm 1 is the first entrant at time  $t_{co}^1$ , and firm 2 is the follower at time  $t_{co}^2$ . In principle, both drugs benefit from independent patent terms but, as in reality they could be substitute therapies, the first drug in the market can be taken to determine the effective patent length  $t_{pat}$  for the therapeutic substitute arriving later. This is because the first generic in the market – for the product of firm 1 – will be a low-price competitor to the product of firm 2. We analyse two different cases shown in Figure 2.

**Competition without SPCs and no incentives for the follower.** Firm 2 faces a longer commercialisation time  $t_{co}^2 > t_{co}^1$ , larger R&D costs  $C_1 + C_2 > C_1$  and smaller revenue  $R_2 < R_1$ . Let us assume that in absence of an SPC, firm 2 has no incentives to develop the new drug as  $R_2 < C_1 + C_2$ . Then, firm 1 is able to price up to the full-value price and gets a

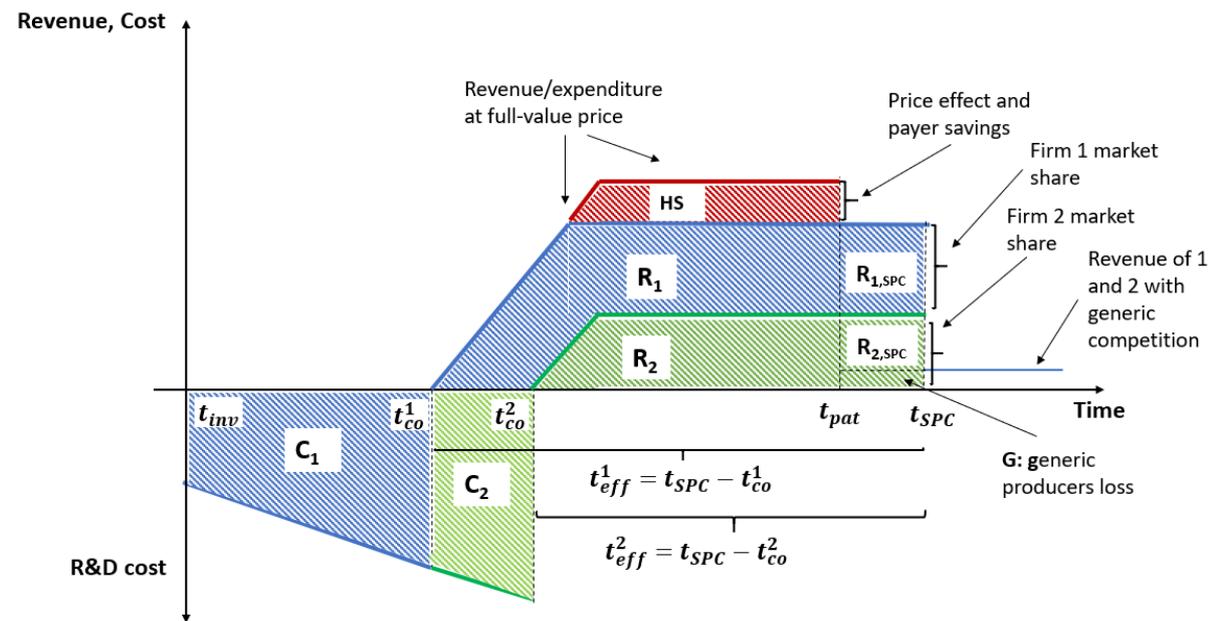
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to the expected commercial value of the innovation before making major (e.g. phase 3) investments.

total revenue of  $R_1+HS>C_1$ . The health system then faces a total cost of  $R_1+HS$  to provide the medicines to patients.

**Competition with SPCs and incentives for the follower.** Can the health system benefit financially from granting firms an SPC? Let us assume that both firm 1 and firm 2 are granted SPCs that lengthen both patent terms to  $t_{SPC}$  extending the effective patent term of both competitors by the length of the SPC. Additional revenue of  $R_{1,SPC}$  (firm 1) and  $R_{2,SPC}$  (firm 2) is generated. Therefore, an SPC not only affects incentives for the first entrant, but also affects other potential competitors' decisions to invest in R&D and enter the market.

**Figure 2. Two competitor framework of therapeutic class competition with and without SPCs**



Source: OHE research

Assume now that this additional revenue restores firm's 2 incentives to develop the new drug  $R_2+R_{2,SPC} \geq C_1+C_2$ . Then, firm 2 competes in the market with firm 1 and as a result prices decrease (increased the bargaining power of the health system)<sup>5</sup>. The price decline generates a cost saving to the health system represented by the area HS in Figure 2.

The introduction of the SPC involves an additional cost  $(R_{1,SPC} + R_{2,SPC})-G$  for the payer (where G represents the cost of the drug under generic competition during the SPC period). The optimal decision (looking only at costs) therefore depends on the magnitude of HS compared to  $(R_{1,SPC} + R_{2,SPC})-G$ . Put in other words, for payers, having a system that implements SPCs is optimal if  $HS>(R_{1,SPC} + R_{2,SPC})-G$ . The optimal length of the SPC is, from a cost point of view, determined by the minimum extension required to maintain an incentive for the second entrant to enter the market ( $R_2+R_{2,SPC}=C_1+C_2$ ). However, making an estimate of a typical case would be difficult and very uncertain and additional entry often brings additional health gains as some patient groups are better served by subsequent entrants.

It is important to note that these results rest on the behaviour of potential entrants for which an SPC can change the decision as to whether to go ahead with the development

<sup>5</sup> We assume that firm 2 anticipates the effect of price competition in estimating  $R_2+R_{2,SPC}$

of the new drug. We acknowledge that for developers expecting extremely negative (or positive) commercial results from the development of a new molecule, the SPC might not have any impact. Overall, we can conclude that if any, the effect of an SPC on in-class and in-patent competition can only be positive. Such a positive impact will happen when there exist potential entrants to the market (developers of substitute therapies still in the R&D process) for which a SPC restores the economic incentives (commercial value) of their projects so avoiding project termination. Although it will delay generic competition, it will still contribute towards achieving static efficiency by decreasing price and improving patient access before the patent expiry of the first entrant. Whether (second best) static efficiency is finally achieved or not, will depend on whether the condition  $HS > (R_{1,SPC} + R_{2,SPC}) - G$  is met. Not meeting the condition would move the outcome away from static efficiency.

### **3. METHODS**

We conducted three empirical exercises to address our research questions:

- (i) Combining market statistics (e.g. volume of sales by treatment option) with data about prevalence and patients treated, we performed an analysis of the uptake and market shares from January 2014 to June 2017;
- (ii) Second, we interviewed a sample of national experts to explore key factors influencing uptake of DAAs.
- (iii) Finally, we estimated the impact on health-related outcomes from the introduction of DAAs in the six countries.

The study was conducted under the oversight of a multi-disciplinary Steering Group which monitored progress, validated methods and results of the analyses, and reviewed an initial draft of the paper.

The country selection was driven by size, hence the inclusion of the five largest markets, with the addition of one small market (Portugal) which had more reliable data than other similar countries.

#### **3.1. Uptake and market share analysis**

We converted drug volume data into the number of patients treated with each medicine to compare usage between medicines using a like for like measure. This approach is aligned with the one used to populate the disease progression models generating baseline estimates of treated patients prior to the launch of DAAs, reported in the Polaris Observatory<sup>6</sup> and related references (Bruggmann et al., 2014; Razavi et al., 2014).

Volume data by countries were obtained from IQVIA<sup>7</sup> using the measure of packs or counting units<sup>8</sup>, and monthly data covering the period 2014 Q1 - 2017 Q2.

Converting volume usage data to estimate patients treated requires the application of assumptions concerning the characteristics of the treatment population and the posology of individual treatments. A feature of HCV prevalence are the differences in the distribution of genotypes between countries. Accounting for these differences is required when converting volume usage into patients as different genotypes are associated with

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<sup>6</sup> See: [http://www.polarisobservatory.org/polaris\\_view/process.htm](http://www.polarisobservatory.org/polaris_view/process.htm).

<sup>7</sup> See: <https://www.iqvia.com/>

<sup>8</sup> "Counting units" is a volume measure approximating to "dose". For all DAA's this is a single tablet taken daily.

specific choices of medicines and courses. Furthermore, liver condition influences treatment options as patients with cirrhosis receive longer courses of treatment. For posology we have adhered to Summary of Product Characteristics (SPC) mandated doses<sup>9</sup>.

For each country, we combine patient characteristics with posology to create an initial set of assumptions which can be used to apportion volume usage and estimate patients treated per annum. The Excel file used for our calculations is part of the supplementary material (available on request).

### 3.2. Interviews with experts

Semi-structured interviews were conducted to identify what factors may have influenced uptake of DAAs in the six selected countries, both positively and negatively.

We designed an interview guide<sup>10</sup> to elicit experts' views with respect to three broad subjects: i) the health care system capacity for the treatment of HCV, ii) societal factors relating to the treatment of HCV, and iii) HTA, pricing and reimbursement (P&R) processes and funding mechanisms introduced for DAAs.

For each country, we recruited interviewees with expertise in HCV or decision making on the provision of treatments. They were either clinicians, HTA experts, or payers. We secured interviews with 12 experts, two experts in each country except France, as summarised in Table 1 and one pan-European HCV expert.

**Table 1. Distribution of the interviewees by country and expertise**

	Clinicians	HTA experts/ payers representatives
France		x
Germany	x	x
Italy	x	x
UK	x	x
Spain	x	x
Portugal	x	x
Pan-European expert	x	

Source: OHE Research

Interviews were conducted by telephone with at least two researchers (MN & CJS) and were recorded. Interviewees were given the opportunity to review interview notes.

Interview notes and recordings were used to identify themes relating to uptake onset, size of the market, and speed of adoption (as characterised in the data analysis). We distinguish between "P&R and funding mechanisms" and "other factors".

### 3.3. Health gains estimation

We generated estimates of the 'global' and genotype-specific health gains associated with the use of DAAs for patients affected by HCV. We combined estimates on health

<sup>9</sup> Information about mandated doses for different genotypes and stages of liver disease is available at <https://www.medicines.org.uk/emc/>.

<sup>10</sup> A detailed interview guide is available as supplementary material to this paper.

gains per patient, as measured by incremental quality-adjusted life years (QALYs), with the number of patients initiating treatment each year in each country.

Data on incremental QALYs for each DAA were extracted from the National Institute for Health and Care Excellence (NICE) technology appraisal (TA) (NICE, 2015a; b; c; d; e; 2016; 2017). Due to country-specific estimates being unavailable, we used per-patient QALY gains estimated for the UK, making the assumption that the QALY gains are similar to those generated from the treatment of patients from other European countries.

We estimated health gains separately for each country, according to the medicine uptake trends over time. Specifically, we used two distinct approaches to estimate the health gains (Approach 1 and Approach 2). Approach 1 is based on apportioning QALY gains 'fractions' to the number of patients receiving each treatment. For Approach 2, we estimated the number of patients completing treatment over the whole period of analysis and combined this information with the correspondent QALY gains.

A more detailed explanation of the estimation of health gains is available in the Supplemental Material.

## **4. RESULTS**

### **4.1. Quantitative analysis**

We collected evidence of sales in all countries for all DAAs launched until June 2017. They were: sofosbuvir (SOF), Daclatasvir (DAC), simeprevir (SIM), ledipasvir and sofosbuvir (LED/SOF), ombitasvir, paritaprevir and ritonavir (OMB/PAR/RIT), dasabuvir (DAS), elbasvir and grazoprevir (ELB/GRA), and sofosbuvir and velpatasvir (SOF/VEL)<sup>11</sup>. Each country had the same entrants for the period under consideration, albeit the timing of entry was different.

As shown in Table 2 each DAA is indicated for specific genotypes of the virus<sup>12</sup>. Some genotypes, particularly those less prevalent, have fewer treatment options. Table 3 reports the distribution of patients by genotype by country for 2015. Genotypes 1, 3 and 4 jointly cover more than 90% of patients in all countries and there are at least 4 options addressing them.

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<sup>11</sup> Glecaprevir/pibrentasvir (Maviret), a new DAA developed by AbbVie, was granted with marketing authorization for the treatment all HCV genotypes by the EMA in August 2017. See product's European public assessment report at: [http://www.ema.europa.eu/ema/in-dex.jsp?curl=pages/medicines/human/medicines/004430/human\\_med\\_002151.jsp&mid=WC0b01ac058001d124](http://www.ema.europa.eu/ema/in-dex.jsp?curl=pages/medicines/human/medicines/004430/human_med_002151.jsp&mid=WC0b01ac058001d124)

<sup>12</sup> As well as genotypes further specification of subgroups of patients may be stated based on further factors including liver condition, co-morbidities notably HIV, and tolerance to peginterferon. For the purposes of this study we have used genotypes to establish substitutability.

**Table 2. Genotypes covered by each DAA**

Genotype	SOF	DAC	SIM	LED/SOF	OMB/PAR/RIT	DAS	ELB/GRA	SOF/VEL
1	X	X	X	X	X	X	X	X
2	X							X
3	X	X		X				X
4	X	X	X	X	X		X	X
5	X			X				X
6	X			X				X
Company	GIL	BMS	JC	GIL	ABB	ABB	MSD	GIL

Source: OHE Research; electronic Medicines Compendium (emc) <https://www.medicines.org.uk/emc/>  
Abbreviations: Sofosbuvir, SOF; Daclastavir, DAC; Simeprevir, SIM; Ledipasvir-Sofosbuvir, LED/SOF; Ombitasvir-Paritaprevir-Ritonavir, OMB/PAR/RIT; Dasabuvir, DAS; Elbasvir-grazoprevir, ELB/GRA; Sofosbuvir-Velpatasvir, SOF/VEL; Gilead Sciences, GIL; Bristol-Myers Squibb, BMS; Janssen-Cilag, JC; AbbVie, ABB; Merck Sharp & Dohme, MSD.

**Table 3. Prevalence by genotype and country (2015)**

Genotype	DAA options (June 2017)	Pt	Ger	UK	Sp	Fr	It
1	8	68.3%	62%	45.3%	78.5%	59.8%	68%
2	2	1.5%	6.4%	7.3%	2%	6.4%	15%
3	4	17.9%	27.4%	43.8%	8.2%	27.4%	10%
4	7	12.5%	3.3%	3.8%	9.7%	3.3%	7%
5	3	0%	0%	0%	0%	0.2%	0%
6	3	0%	0%	0%	0%	0.2%	0%

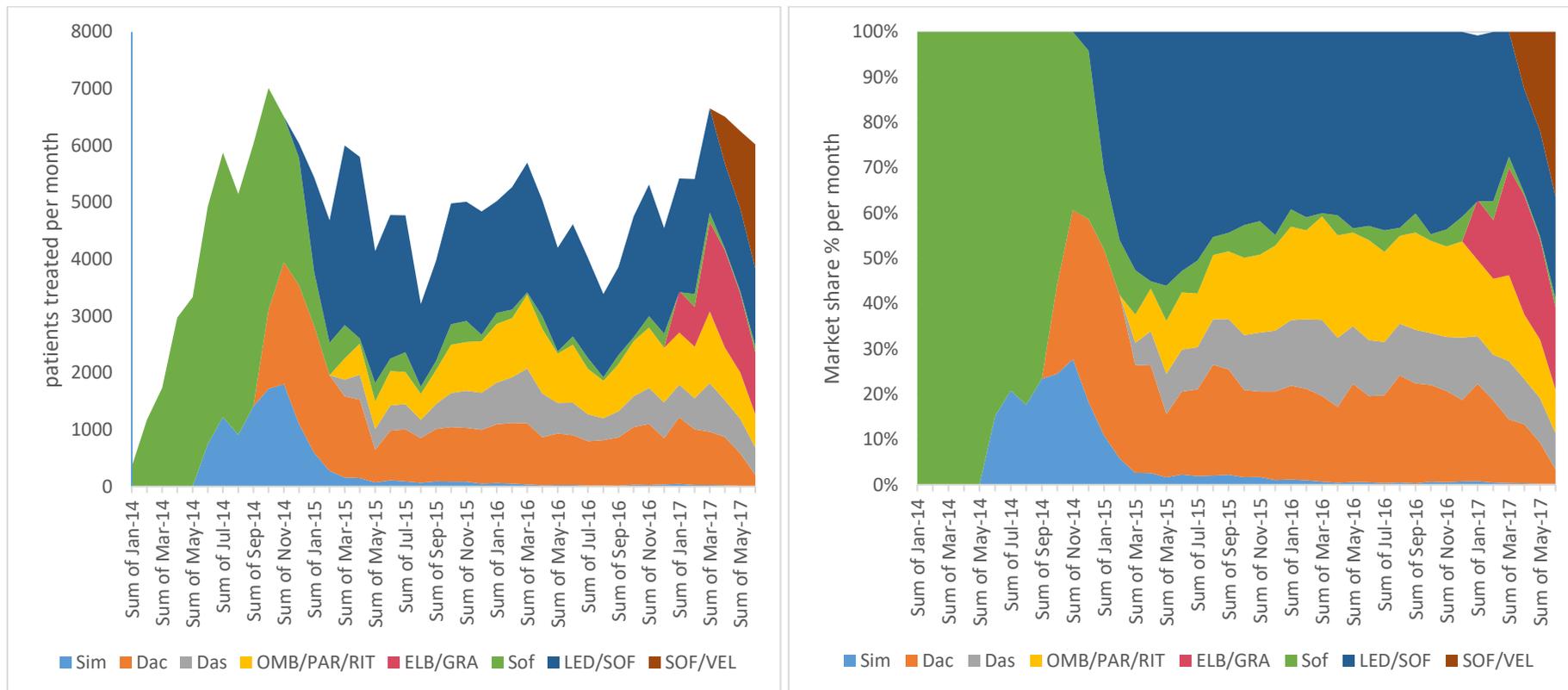
Source: Blach et al. (2017)

Note: Genotype 1 prevalence covers *genotypes 1a-1c plus genotype 1(other)*, and *mixed or other*.  
Abbreviations: Portugal, Pt; Germany, Ger; United Kingdom, UK; Spain, Sp; France, Fr; Italy, It.

All DAA's included were subject to the European Medicines Agency central procedure for marketing authorisation. This is EU-wide and means that all products could have been launched in each specific market at the same time. Differences in the first month of reported sales might be a consequence of country-specific pricing and reimbursement arrangements, demand-side policies in each country, or commercial decisions made by the company of around the launch or supply of each medicine.

Figures 3a to 3f show for each country, the total number of patients treated and market share per month by medicine for all genotypes.

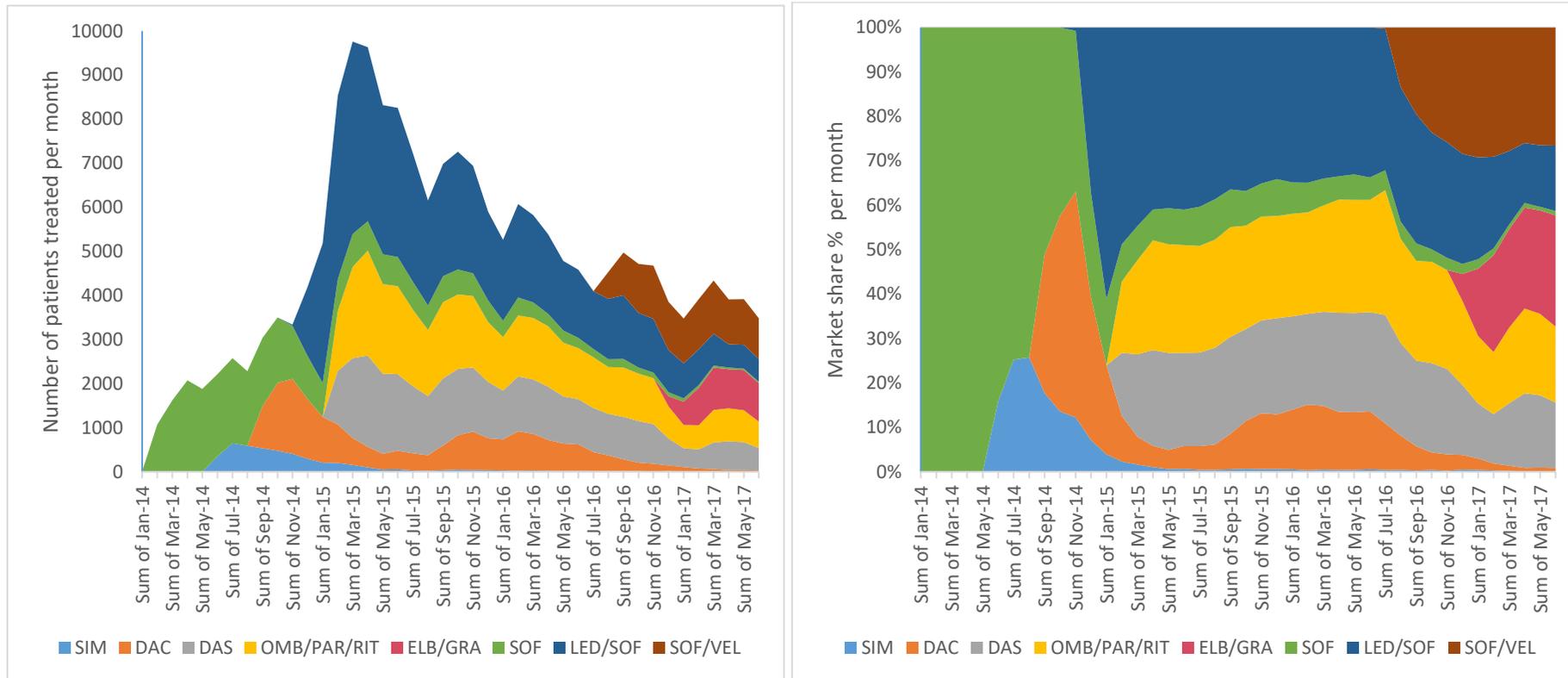
**Figure 3a. total number of patients treated and market share by DAA for all genotypes (Jan 2014-Jun 2017) - FRANCE**



Source: OHE Research

Abbreviations: Simeprevir, SIM; Daclastavir, DAC; Dasabuvir, DAS; Ombitasvir-Paritaprevir-Ritonavir, OMB/PAR/RIT; Elbasvir-grazoprevir, ELB/GRA; Sofosbuvir, SOF; Ledipasvir-Sofosbuvir, LED/SOF; Sofosbuvir-Velpatasvir, SOF/VEL.

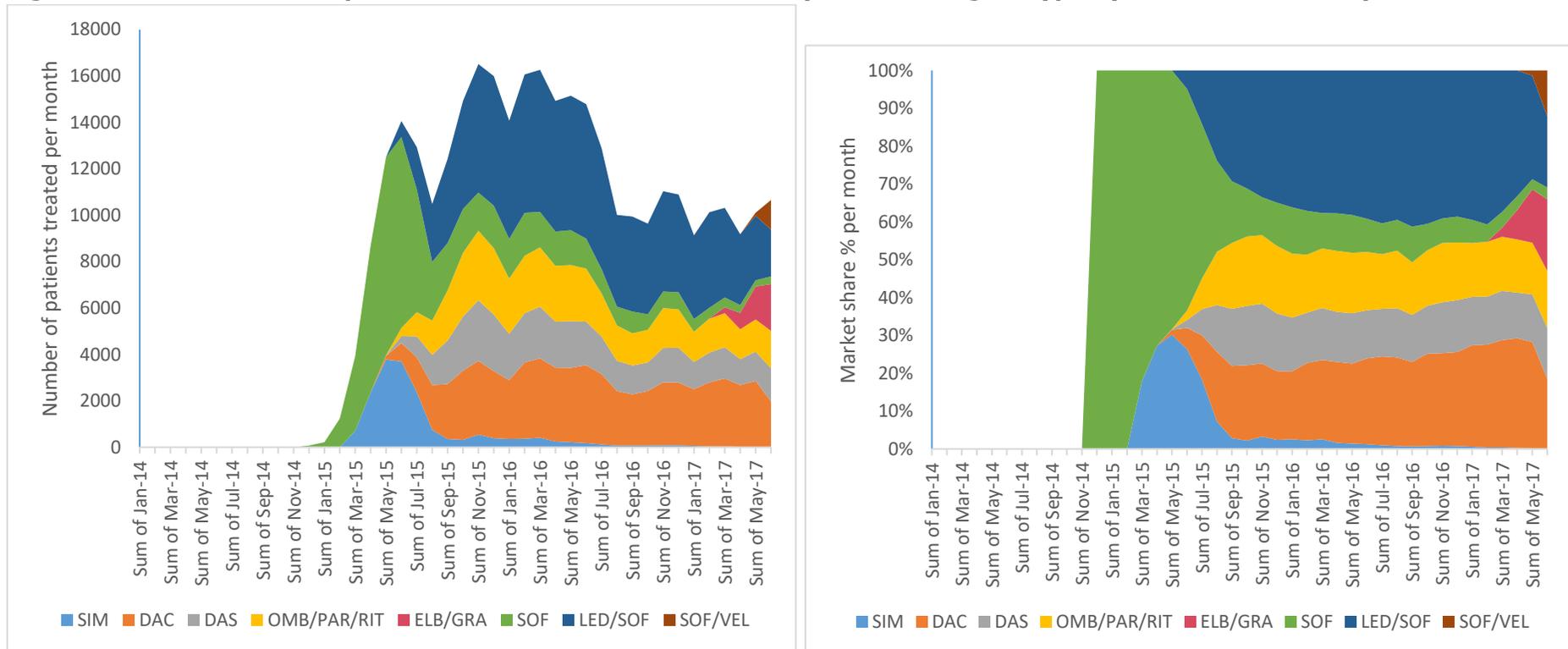
**Figure 3b. total number of patients treated and market share by DAA for all genotypes (Jan 2014-Jun 2017) - GERMANY**



Source: OHE Research

Abbreviations: Simeprevir, SIM; Daclastavir, DAC; Dasabuvir, DAS; Ombitasvir-Paritaprevir-Ritonavir, OMB/PAR/RIT; Elbasvir-grazoprevir, ELB/GRA; Sofosbuvir, SOF; Ledipasvir-Sofosbuvir, LED/SOF; Sofosbuvir-Velpatasvir, SOF/VEL.

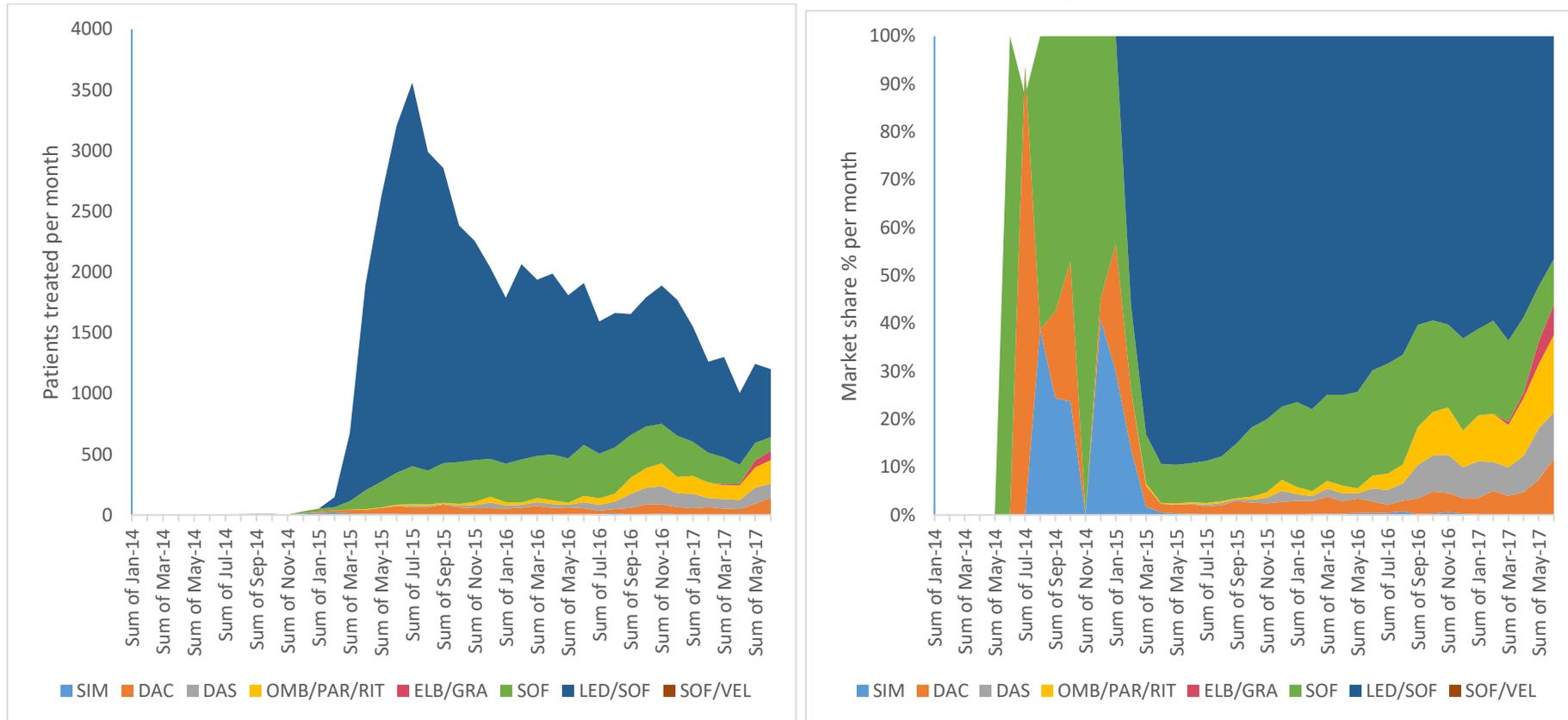
**Figure 3c. total number of patients treated and market share by DAA for all genotypes (Jan 2014-Jun 2017) – ITALY**



Source: OHE Research

Abbreviations: Simeprevir, SIM; Daclastavir, DAC; Dasabuvir, DAS; Ombitasvir-Paritaprevir-Ritonavir, OMB/PAR/RIT; Elbasvir-grazoprevir, ELB/GRA; Sofosbuvir, SOF; Ledipasvir-Sofosbuvir, LED/SOF; Sofosbuvir-Velpatasvir, SOF/VEL.

**Figure 3d. total number of patients treated and market share by DAA for all genotypes (Jan 2014-Jun 2017) – PORTUGAL**

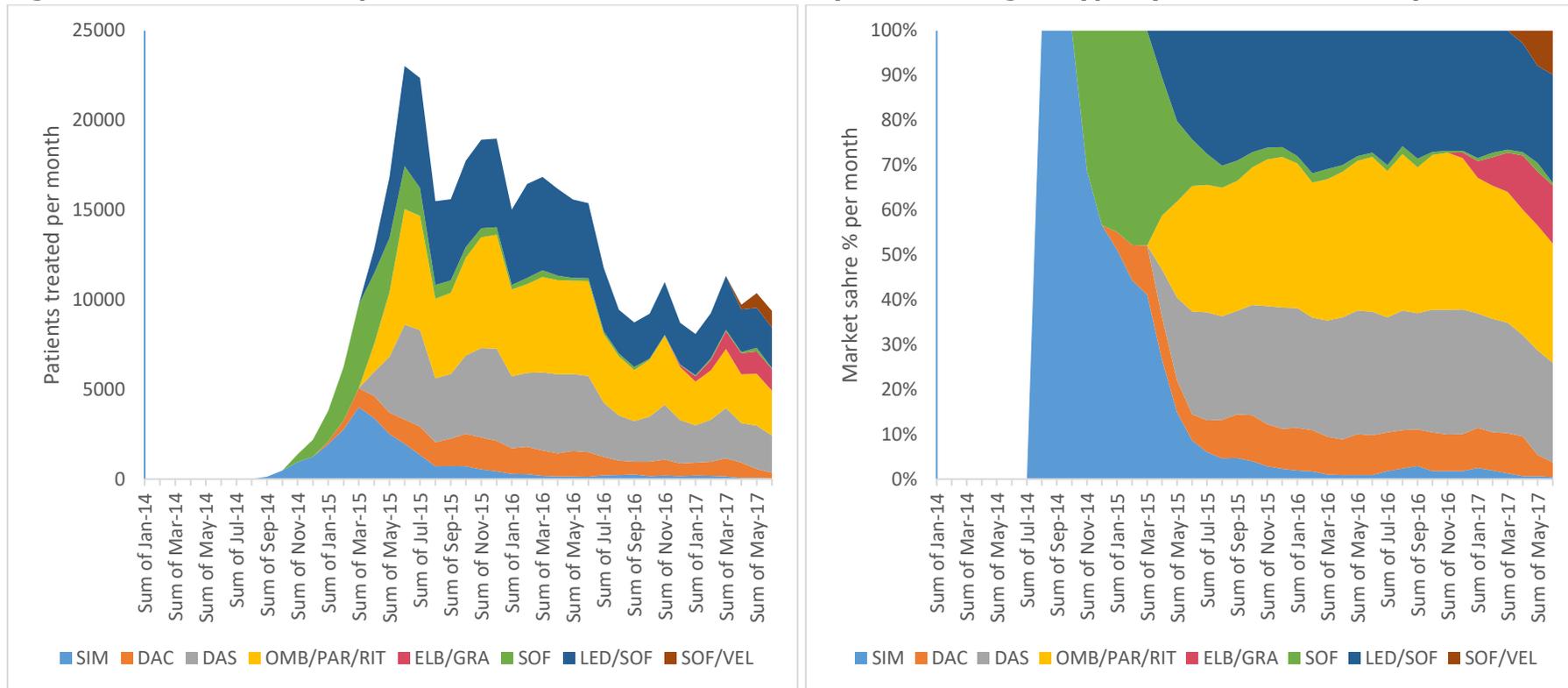


Source: OHE Research

Abbreviations: Simeprevir, SIM; Daclastavir, DAC; Dasabuvir, DAS; Ombitasvir-Paritaprevir-Ritonavir, OMB/PAR/RIT; Elbasvir-grazoprevir, ELB/GRA; Sofosbuvir, SOF; Ledipasvir-Sofosbuvir, LED/SOF; Sofosbuvir-Velpatasvir, SOF/VEL.

Note: negative market shares in early months are due to the assumptions introduced to avoid double counting of DAAs prescribed as combinations

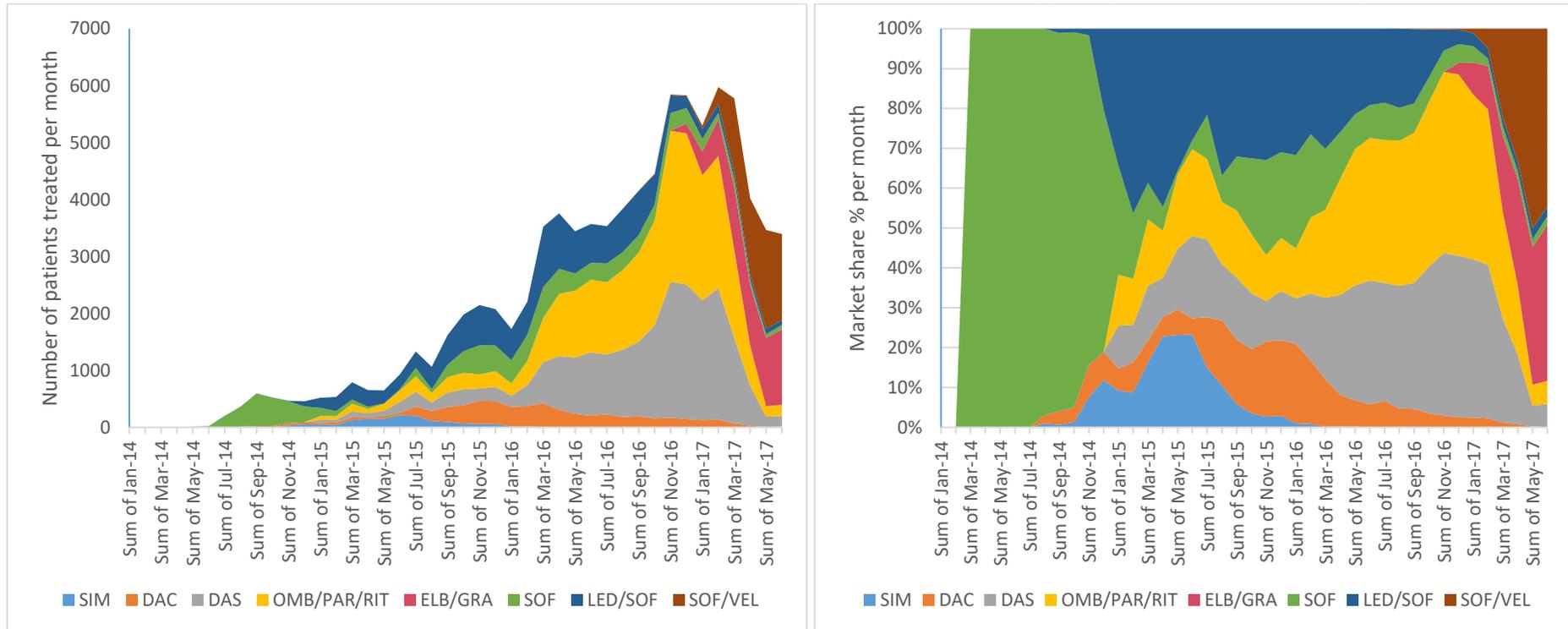
**Figure 3e. total number of patients treated and market share by DAA for all genotypes (Jan 2014-Jun 2017) – SPAIN**



Source: OHE Research

Abbreviations: Simeprevir, SIM; Daclastavir, DAC; Dasabuvir, DAS; Ombitasvir-Paritaprevir-Ritonavir, OMB/PAR/RIT; Elbasvir-grazoprevir, ELB/GRA; Sofosbuvir, SOF; Ledipasvir-Sofosbuvir, LED/SOF; Sofosbuvir-Velpatasvir, SOF/VEL.

**Figure 3f. total number of patients treated and market share by DAA for all genotypes (Jan 2014-Jun 2017) – UK**



Source: OHE Research

Abbreviations: Simeprevir, SIM; Daclastavir, DAC; Dasabuvir, DAS; Ombitasvir-Paritaprevir-Ritonavir, OMB/PAR/RIT; Elbasvir-grazoprevir, ELB/GRA; Sofosbuvir, SOF; Ledipasvir-Sofosbuvir, LED/SOF; Sofosbuvir-Velpatasvir, SOF/VEL.

Based on the evidence for the date of entry, the speed of uptake, the total number of patients treated, and market share distribution, we categorised the six countries as follows:

- Early and fast adopter / large / shared market: Germany and France
- Late and fast adopter / large / shared market: Spain and Italy
- Early and slow adopter / large / shared market: United Kingdom
- Late and fast adopter / small / non-shared market: Portugal

Early adopters (i.e. France, Germany and the UK) provided access to DAAs within the first quarter of 2014. Late adopters (i.e. Italy, Portugal, Spain) provided access to DAAs in the third quarter of 2014 or later.

Fast adopters experienced a high speed of uptake following the date of the first entry. That means reaching a peak in the number of treated patients within the following year after the date of the first entry (i.e. France, Germany<sup>13</sup>, Italy, Portugal, and Spain).

Large markets have a monthly number of patients treated consistently above 5,000 (i.e. France, Germany, Italy, Spain, and the UK<sup>14</sup>). Countries with a monthly number of patients consistently below 5,000 were considered small (i.e. Portugal).

Shared markets had no single treatment taking more than 50% of the market at any month after several options are available (i.e. France, Germany, Italy, Spain, and the UK).

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Large markets have a monthly number of patients treated consistently above 5,000 (i.e. France, Germany, Italy, Spain, and the UK<sup>16</sup>). Countries with a monthly number of patients consistently below 5,000 were considered small (i.e. Portugal).

Shared markets had no single treatment taking more than 50% of the market at any month after several options are available (i.e. France, Germany, Italy, Spain, and the UK).

To some extent, all markets show a 'staged competition'. We identified three stages of the competition within the five 'shared' markets:

- In the first stage, the market is shared between SOF, DAC, and SIM.

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<sup>13</sup> Germany reached the peak in a period slightly longer than one year, but we have included into the fast adopter category as the uptake speeded up significantly after the entry of LED/SOF (Dec-2014) reaching the peak within the next four months (March-2014).

<sup>14</sup> Although the UK was slow reaching numbers above 5,000 patients per month, it consistently peaked around 6,000 patients between October-2016 and March-2017.

<sup>15</sup> Germany reached the peak in a period slightly longer than one year, but we have included into the fast adopter category as the uptake speeded up significantly after the entry of LED/SOF (Dec-2014) reaching the peak within the next four months (March-2014).

<sup>16</sup> Although the UK was slow reaching numbers above 5,000 patients per month, it consistently peaked around 6,000 patients between October-2016 and March-2017.

- In the second stage, LED/SOF, DAS, and OMB/PAR/RIT replace the products of the first stage to a large extent.
- In the third stage, ELB/GRA and SOF/VEL gains substantial market share compared to the products of stage 2, although this trend is only starting in some countries.

Finally, it is important to note these treatments are either prescribed in combinations, mostly with those firstly appearing in the market or they are by itself combinations of two (or three) antivirals. Table 4 shows combinations of DAAs and companies that commercialise each of the 8 DAAs available up to June 2017.

**Table 4. Combination therapies in DAAs**

DAA	Daily dose	Combination <sup>a</sup>	Genotypes <sup>b,c</sup>	Firm
<b>SOF</b>	400mg of sofosbuvir	No combination	1, 2, 3, 4, 5 and 6	Gilead Sciences
<b>DAC</b>	60mg of daclatasvir	400mg sofosbuvir	1,3 and 4	Bristol-Myers Squibb Pharm.
<b>SIM</b>	150mg of simeprevir	400mg sofosbuvir/no combination <sup>d</sup>	1 and 4	Janssen-Cilag
<b>DAS</b>	250mg of dasabuvir	Ombitasvir(12.5mg)/ Paritaprevir(75mg)/ Ritonavir(50mg)	1	AbbVie
<b>LED/SOF</b>	90mg of ledipasvir/ 400mg of sofosbuvir	No combination	1, 3, 4, 5 and 6	Gilead Sciences
<b>OMB/PAR/RIT</b>	12.5 mg of Ombitasvir / 75mg of Paritaprevir/ 50mg of Ritonavir	250mg of dasabuvir/ no combination <sup>e</sup>	1 and 4	AbbVie
<b>ELB/GRA</b>	50mg of elbasvir/ 100mg of grazoprevir	No combination	1 and 4	Merck Sharp & Dohme
<b>SOF/VEL</b>	400mg of sofosbuvir/ 100mg of velpatasvir	No combination	1, 2, 3, 4, 5 and 6	Gilead Sciences

Source: electronic medicines compendium (EMC) <https://www.medicines.org.uk/emc/>

Notes: <sup>a</sup>combination means that the product in the row, which can also be a combination of two or more molecules in a single tablet, is prescribed in combination with other product; <sup>b</sup>genotypes within cells are those for which the combination is prescribed, or all genotypes for which the DAA is recommended when no combination is used; <sup>c</sup>note that genotypes 1, 3 and 4 together represent around the 90% of the market in all countries. The prevalence of genotypes 5 and 6 is negligible (see Table 2); <sup>d</sup>simeprevir is also prescribed alone for genotype 1 but we assume combination with sofosbuvir is prescribed to patients non-eligible for peginterferon; <sup>e</sup> OMB/PAR/RIT is prescribed in combination with DAS for genotype 1 and alone for genotype 4.

In terms of the stages of competition Figures 3a-3f show that:

- SOF, DAC and SIM were the first three launched DAAs (first stage of competition). Given that DAC is indicated in combination with SOF (genotypes 1, 3 and 4) and SIM is also indicated in combination with SOF (genotype 1), competition only takes place between these two products (assuming they are therapeutically superior to SOF alone) and the market can be considered “competitive”, at least to some extent.
- In the second stage of competition, there are three DAAs marketed by two companies competing for the market: LED/SOF (Gilead), DAS (AbbVie) and

OMB/PAR/RIT (AbbVie). DAS and OMB/PAR/RIT are indicated in combination (genotype 1). OMB/PAR/RIT is indicated alone (genotype 4) and LED/SOF is indicated alone (genotypes 1, 3, 4, 5 and 6). Competition is for genotype 1 and 4 between these three options in stage two of competition. For Genotype 3 LED/SOF competes with DAC in this second stage. Excluding Portugal (Figure 1d) graphs of the remaining confirm this pattern of competition with large market shares of LED/SOF, DAS, OMB/PAR/RIT, and significant presence of DAC in countries with high prevalence of genotype 3 (i.e. France, Germany, UK, Italy).

- Stage three of competition is characterised by the entry of SOF/VEL (Gilead) for all genotypes and ELB/GRA (Merck Sharp & Dohme) for genotypes 1 and 4. Where these products were marketed first, around 2016 Q3 in countries classified as early adopters (UK, Germany, France), they have gained market share very fast. They were adopted around 2017 Q3 by all late adopters (i.e. Spain, Italy) except Portugal where almost all the market share continues to be covered by SOF and LED/SOF.

## 4.2. Interviews with experts

### 4.2.1. P&R and funding factors

Countries adopted P&R and funding arrangements to supply DAAs and manage DAAs budget impact. We identified strategies aimed at controlling the volume of patients treated and prices paid, raising funds or controlling expenditure, accelerating market entries of competitors to facilitate price reductions.

No concern related to the effectiveness and cost-effectiveness of DAAs from the HTA/payer decision-makers perspective was raised in the interviews; therefore, this aspect is not explored as a factor impacting uptake. The budget impact was very large and represented a challenge for all countries. Therefore, efforts were focused on controlling patient numbers and/or reducing unit price.

**Controlling patient population treated.** Particularly in the first years of the introduction of DAAs, eligibility criteria were introduced to prioritise treatment of the most severe HCV patients:

- In the UK<sup>17</sup>, NHS England (NHSE) – the central commissioning body in England - first authorised 12-week treatments for compassionate use (i.e. patients at significant risk of death, irreversible hepatic damage or who require a liver transplant) and then introduced annual patient quotas (10,000 patients per year). While quotas have increased over the years, UK uptake was slow compared to other countries.
- Italy established seven eligibility criteria (extended to 11 in 2017), which nonetheless enabled the treatment of many HCV patients. The high prevalence of HCV in Italy (daCosta DiBonaventura et al., 2012) was seen as an asset in the negotiations rather than a challenge by the buyers.
- In Spain, restrictions on patient eligibility were set. Priority was given to patients with liver fibrosis followed by patients on a waiting list for transplant (liver or non-

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<sup>17</sup> Although the uptake analysis is based on UK-wide data, our interviewees provided insights only around HTA and commissioning processes in England. This is an acceptable approximation given that the English market represent around 80% of the UK one.

liver) and liver transplanted patients with relapse of the infection in the liver graft.<sup>18</sup>

- Until 2016, the use of DAAs in France was limited to HCV patients with fibrosis scores of 3 and 4, and 2 when doctors deemed it necessary.
- In Portugal, the strategy was to treat the highest number of patients possible and reduce price<sup>19</sup>.

**Funding arrangements.** Some countries set budget caps to control expenditures:

- In the UK, NHSE required an extension of the three-month period to comply with NICE recommendations (NICE, 2015b). The budget for HCV was increased to £190 million in 2015 from £40 million the year before (NHS England, 2015).
- France set annual caps on HCV total spending, the so-called 'W rate': €450 million in 2014, €700 million in 2015 and €600 million in 2016 and 2017. The spending cap was not reached in 2016 because of the joint effect of restrictions on eligibility for treatment and the DAAs price decrease (the final price was €28,700 per treatment). In the rest of the years, companies were required to pay rebates when the annual spending on HCV exceeded the cap set by the 'W rate', and the growth rate of spending on HCV from the previous year was also larger than 10%. The rebated amount was proportional to the company's revenue up to a 15% ceiling (Mouterde et al., 2016).
- Some countries such as Portugal, Italy and Spain set specific budgets for funding DAAs and chose other mechanisms to limit total expenditures, such as price-volume agreements and budget caps.

**Commercial agreements impacting price.** Countries negotiated deals to directly restrict the prices of DAAs:

- The UK, Portugal and Germany achieved direct discounts on list price (as a percentage of the unit price)<sup>20</sup>. In Germany, discounts are negotiated by insurers, and price deals can influence doctors' prescribing decisions.

Italy and Spain used price-volume agreements, whereby manufacturers provide rebates for revenue beyond an agreed volume, which in effect reduces the average prices per treatment<sup>21</sup>. In 2015, Italy negotiated financial deals with different price levels for consecutive groups of patients receiving treatment. In 2015, the average price per treatment was €15,000 (Gardini, 2017). The implementation of the schemes was supported by registries monitoring DAAs prescriptions and allowing prompt reimbursement from the companies. However, the success of the schemes was variable depending on the regions and the ability of hospitals to claim the refunds. Another

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<sup>18</sup> For a more detailed description of the prioritised patients in Spain see the Ministry of Health, Social Services and Equality's "Strategic Plan for Tackling Hepatitis-C in the Spanish Health National System" available at: [http://www.easl.eu/medias/files/eu/PEAHC\\_v2\\_eng.pdf](http://www.easl.eu/medias/files/eu/PEAHC_v2_eng.pdf).

<sup>19</sup> Eligibility is regulated by the Order 1824-B/ 2015 (INFARMED, 2015), which was updated in 2017

<sup>20</sup> List price is the original selling price a manufacturer establishes for a product before discounts and rebates are applied.

<sup>21</sup> Further information about price-volume agreements between Spanish government and companies commercialising LED/SOF, DAS and OMB/PAR/RIT are also available at: [http://www.easl.eu/medias/files/eu/PEAHC\\_v2\\_eng.pdf](http://www.easl.eu/medias/files/eu/PEAHC_v2_eng.pdf). Italy negotiated price-volume agreements for Ledipasvir/Sofosbuvir <http://www.hepbccppa.org/wp-content/uploads/2015/04/April-newsletter-v3.pdf>

approach used to reduce the effective average price was outcome-based agreements, usually in the form of payment for cures:

- These were used in Portugal, but this type of commercial agreement was not always deemed effective in lowering the price paid by buyers due to poor monitoring infrastructures (for observation of patient outcomes) and high cures rates for DAAs (exceeding 90%).
- In the UK (England) a pay for cure scheme was applied only to the most recently launched product which is not included in our analysis (glecaprevir/pibrentasvir) (Foster G. and Huskinson P., 2018).

The impact of price reductions might be twofold. It may improve uptake, but it can also discourage new entrants by decreasing the value of a market. Evidence on market shares shows that in countries like Italy and Spain commercial agreements leading to price reductions did not deter new entrants.

**Encouraging market forces.** Some countries sought to facilitate price reductions by supporting market forces. Countries like Italy, and Spain, accelerated their HTA or P&R processes to foster the access of new entrants;

In the UK, NHSE runs biannual tendering processes for a variety of therapy areas including HCV, whereby prices are revisited on a regular basis and access is provided to the treatment associated with the lowest price bid. This might have impacted on product market shares, which, in the case of DAS and OMB/PAR/RIT, increase a lot in 2016 for example.

According to the interviewees, efforts to accelerate market entries of competitors had a positive impact on uptake.

**Enabling early access.** Some countries have reimbursed or allowed the use of new drugs within the national health system before marketing authorisation:

- In France, SOF was reimbursed through a temporary authorisation for market use (ATU), linked to rebates to be paid by manufacturers in case the price agreed in the subsequent P&R process was lower than the ATU price.
- In the UK, the NICE process followed standard timelines except for one of the most recently launched DAAs (glecaprevir/pibrentasvir) which met the requirements for the Early Access to Medicines Scheme (EAMs) and was made available to patients with no other treatment option (NHS England, 2018).

#### **4.2.2. Other factors**

In this section, we analyse factors associated with the nature of the condition and its treatments, and the health system capacity to tackle HCV.

**Nature of treatment.** Compared to the previous standard of care (i.e. interferon-based treatment), DAAs expanded patient population suitable for treatment, improved side effects profile, and facilitated administration mode. The attitude of patients and clinicians changed, such that diagnosis and treatment were seen as worthwhile and effective.

**Service delivery.** The introduction of DAAs presented an opportunity to simplify the model of care through a decentralised and localised system of prescribing driven by addiction centres and general practitioners (GPs) rather than by specialists' centres. Such a model of care could be more effective at reaching 'vulnerable' patient groups including people who inject drugs (PWID), who represent a significant portion of the HCV

patient population. However, this transition appears not to have taken place yet in the countries considered.

In the short term, the opposite trend seemed to be predominant because prescription rules for DAAs were stricter and more complex than for older treatments, particularly in the first years of introduction. In Germany and the UK, for example, nurses do not prescribe new treatments for HCV.

**Health system capacity.** Testing for HCV is routinely performed in specific patient groups and settings:

- In France, Germany and Spain, testing is performed in high-risk groups such as pregnant women, patients entering haemodialysis, with HIV, haemophilia or hepatic dysfunction.
- Testing is also performed in drug and alcohol clinics (UK, Germany, Portugal) and, to a certain extent, in prisons (UK, France, Germany).
- Testing is performed in high-risk groups also in Italy. However, the lack of systematic screening programmes may result in a shortage of patients to treat, while a sizable fraction of the HCV patient population remains unidentified.

Testing among high-risk groups is common and, now that DAAs offer an opportunity for cure, testing is considered more ethical. However, in the UK and Spain, testing was restricted during the introduction of DAAs due to concerns about budget impact. More recently, the effort to identify new patients has increased in response to the availability of budgets for treatment and lower prices. Nonetheless, some interviewees considered current testing strategies still patchy.

The capacity of health systems to prescribe and administer treatments for HCV varied across countries:

- The distribution and number of HCV treatment centres in Germany, Spain and the UK seem appropriate to the demand for care. In Germany, only specialist doctors can treat HCV and while this may limit the ability to treat patients promptly, waiting lists did not appear to be an issue.
- In Italy and France, treatment centres faced capacity constraints resulting in some instances in waiting lists. In Italy, treatment centres are geographically well distributed, but healthcare infrastructure was not adapted to accommodate the large population accessing treatment.
- Health system capacity in Portugal was deemed adequate but inefficiently organised.

### **4.3. Health gains**

Health gains estimates were obtained using two approaches, so they are presented in the form of intervals rather than as point estimates.

Table 5 shows the health gains, in the form of incremental QALYs, by country and estimation strategy. The total health gains accrued by patients in all countries, between 2014 and 2017, was estimated to be between 535,418 and 588,694 QALYs.

Approach 1 provided higher QALY gains estimates than Approach 2. This may be due to the assumption in Approach 1 that all patients complete the treatment course successfully (drop rate is zero). Conversely, in Approach 2 we estimated the number of

patients completing treatment over the whole period of analysis using an assumption on drop rates.

**Table 5. Health gains in QALYs by country**

	France	Germany	Italy	Portugal	Spain	UK	Total
<b>Approach 1</b>	96,442	93,762	173,138	33,826	159,038	32,487	588,694
<b>Approach 2</b>	79,715	81,734	160,799	31,809	152,633	28,727	535,418

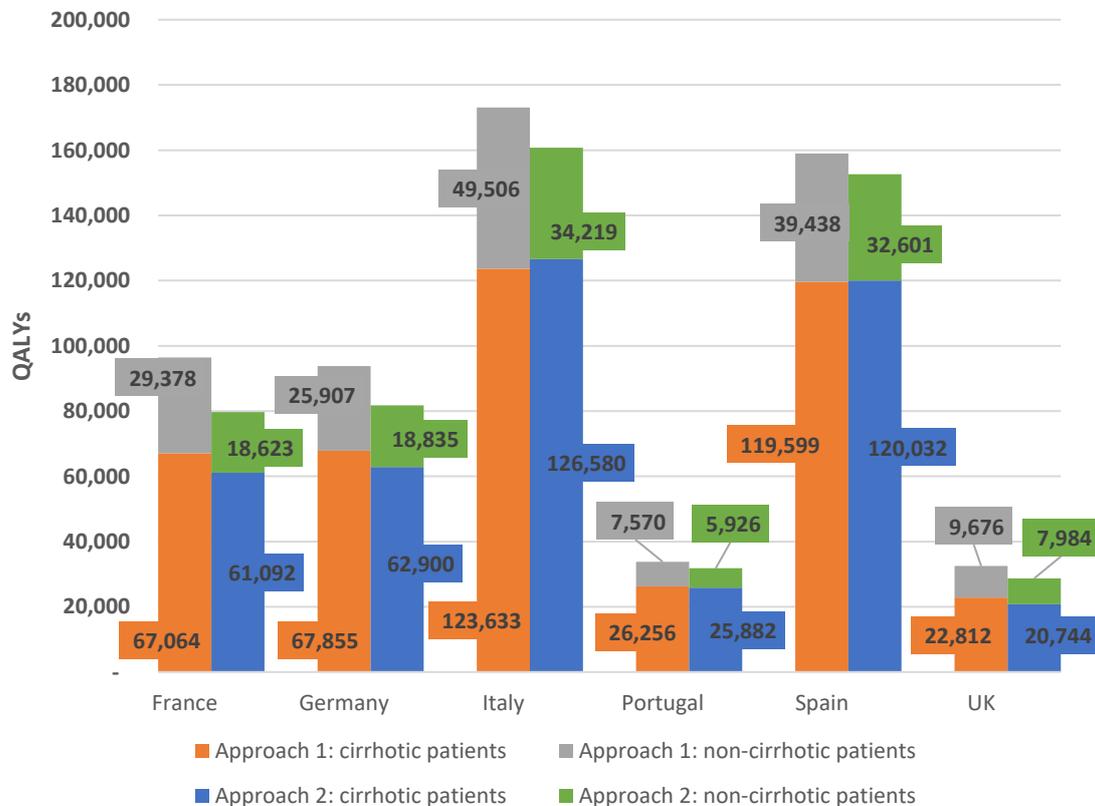
Source: OHE Research

Our estimates take into account differential QALY gains by cirrhosis status (e.g. with cirrhosis, without cirrhosis), as well as of the prevalence distribution of cirrhosis among HCV patients.

Figure 4 shows a breakdown of the QALY gains of each country by cirrhosis status. According to both Approach 1 and Approach 2, the total QALY gains accrued by patients with cirrhosis are larger than those of patients without cirrhosis. This may be due to greater health gains accruing to HCV patients with cirrhosis, as well as high cirrhosis prevalence among HCV patients.

Figure 4 also shows that the two fast adopter countries (Italy and Spain) generated the largest health gains in the years 2014-2017 by treating the largest number of patients. This might be due to the high prevalence, which in Italy is the highest of the countries in the study, with Spain being the second highest (Razavi, 2017).

**Figure 4. QALY gains by cirrhosis status**



Source: OHE Research

## 5. DISCUSSION

Based on the uptake and market shares analyses we identified four typologies of countries based on: time of adoption (access), speed of adoption (uptake), market size and degree of competition (market share distribution).

To answer our original research questions, we assess how the market for DAAs functioned in the six countries belonging to our four typologies.

### **a) Existing IP incentives allow, or didn't prevent, or may have increased in-class competition whilst on-patent in European markets for DAAs**

To assess the role of IP incentives we need to assume that the effective patent term for all DAAs will terminate when the patents of the first DAAs (i.e. SOF, SIM, DAC) expire. First generics which are substitutes for SOF, SIM and DAC will access the European markets and will compete with the other (still in patent) DAAs<sup>22</sup>.

All countries except Portugal showed a high degree of competition as all DAAs eventually secured a significant market share. It is important to note that second entrants (i.e. LED/SOF, DAS, OMB/PAR/RIT) were adopted relatively soon after the first entrants (i.e. SOF, SIM, DAC). SIM and OMB/PAR/RIT were marketed within a range of a lag of five to 13 months after SOF, for Italy and Germany respectively.

The arrival of the third wave of competitors (i.e. SOF/VEL, ELB/GRA) had a longer lag. They were marketed within a range of 20 (in Germany and Spain) to 23 months (in Italy and the UK) after LED/SOF.

This evidence of robust market entry confirms that the IP protection of the first entrants didn't compromise the effective functioning of the market by allowing the development of more options to compete in the DAAs markets in Europe. This is in line with what our economic framework predicts (Figure 2) where IP protection including the addition of an SPC has a positive impact on in-class competition.

### **b) In-class competition facilitated patient access to and uptake of DAAs in European markets**

The five highly competitive markets (i.e. France, Germany, Spain, Italy, UK) showed evenly distributed market shares between DAC, LED/SOF, DAS and OMB/PAR/RIT most of the time during stage 2 of competition until the third wave of entrants came into the market. This reflects an intense level of competition over the second stage (between January 2015 and December 2016). SOF/VEL and ELB/GRA only took significant market share in the UK, replacing DAA options already in the market. In Germany and France, these newest options also took market share rapidly although market shares of all options still remained evenly distributed. In Spain, Italy and Portugal, all later adopters, the newest products had not gained significant shares by the date of 2017 Q2. Our economic framework indicates that in-class competition can decrease prices which should facilitate access to new medicines.

To test whether this was the case in the HCV market, we used information about budget caps, maximum numbers of patients to treat, and average annual cost per patient across countries for 2015, available in the public domain or via our interviews (Gardini, 2017;

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<sup>22</sup>The sustained Viral Response (SVR) of SOF alone (combined with peginterferon and ribavirin, or ribavirin alone) is around 90% for genotypes 1, 2, 4, 5 and 6. The combination of SOF+DAC has also a SVR of around 90% for genotype 3 (information available at electronic Medicines Compendium: <https://www.medicines.org.uk/emc/>).

Mouterde et al., 2016; NHS England, 2015; MHSSE, 2015; Gardini and Aghemo, 2018). These estimates were compared to the weighted average list price of a DAA treatment for 2015 based on IQVIA sales value data. We conducted this exercise for Spain, the UK, France and Italy (details are provided in our supplementary material).

The price-volume agreements in Spain for LED/SOF, DAS and OMB/PAR/RIT established a maximum potential discount of around 64%. For France, we calculated a discount of around 31% and in Italy of around 65%. For the UK, we were unable to estimate the discount levels, as the average price resulting from the budget cap and estimated number of treatments sold is higher than the weighted average list price for a DAA treatment. This suggests – although we have not been able to gather evidence proving it – that UK did not spend the whole budget allocated to DAA treatments.

This suggests that the combination of large volumes (of highly prevalent countries such as Italy) and competition worked in the desired direction in three countries by decreasing prices and enabling access to and fast adoption of treatments, for which restrictions to subpopulations were removed speedily. The UK did not show this pattern, maybe because of the initial focus on meeting patient quotas rather than encouraging market competition and using increasing volume to lead to price reductions. The lack of reliable data does not allow us to draw a robust conclusion on the UK.

The reader should take our estimates of price discounts with caution as they are not based on official or actual data and they are only indicative of real price discounts happening in the countries. More robust estimations of these discounts remain a future research question.

Portugal was the only country where one product (LED/SOF) dominated the market. This might be linked to the small size of the market, which attracted fewer competitors and provided all the reward to the first in class.

This is in line with evidence from our interviews.

- In Spain and Italy, competition was encouraged by accelerating HTA or P&R timelines of new entrants. In addition, both countries struck effective price-volume agreements with the manufacturers which is predictable in highly competitive environments with multiple treatment options available. This allows governments to extract some surplus from producers and facilitate uptake. The Spanish government, for instance, defined price-volume agreements with the two companies (Gilead and AbbVie) commercialising the three main DAAs of the second stage of competition (i.e. LED/SOF, SIM, OMB/PAR/RIT) (MHSSE, 2015).
- On the other hand, in the UK, a tendering process was introduced in 2016. Tenders encourage low price bids awarding them with large (although temporary) market shares. This might explain why market shares in the UK are volatile and not evenly distributed. Tenders can potentially permit more patients to be treated with limited additional budget via competitive prices. This would explain why uptake speed increased after 2016 but was slow in the earlier pre-2016 period when the focus of the UK access policy was to constrain the number of patients to treat certain prioritised categories.

Overall, we observe that the combination of multiple treatment options and large market sizes have contributed to increasing the bargaining power of buyers (healthcare systems) which were able to set (in different degrees and with different mechanisms) prices largely below monopoly price. However (i) whether the area HS in Figure 2 was

larger than  $(R1,SPC + R2,SPC)-G$ , and (ii) whether SPC has contributed to increasing competition remains an empirical question.

Spain and Italy show the highest estimates of QALY gains. Both are characterised by fast uptake, large numbers of patients treated, and a high degree of market share distribution, which suggest that competition works in favour of maximising health gains. But both countries are also characterised by late entry. This suggests that depending on how fast later entrants become available, access policies relying on competition may result in a loss of health gains for those patients unable to access in early periods just after the first launches.

Total health gains in the UK were close to the Portugal total health gains, although the latter had a much smaller population of infected people (Razavi et al., 2017). The UK provided early access, but restrictions applied to patient numbers and budget caps resulted in a slow uptake until tenders were introduced.

In summary, competition may help to maximise health gains through the positive effect of price discounts although, to take advantage of competition, payers need to wait until new entrants come to the market. In this way, they give up earlier health gains. Finally, implementing constraints over the number of patients treated and maximum expenditure may help to get early access but will not maximise health gains from treating that disease unless it is complemented with strategies to increase volume and decrease price in presence of competition.

### **c. Other factors related to the characteristics of the healthcare system and of the condition played a role in determining prices and access to DAAs**

The six countries in our study were categorised by their degree of adoption of new DAAs. Germany, France and the UK were early adopters. In France and Germany, early adoption was facilitated by existing regulatory arrangements that prioritise early access to medicines. In France for instance, the early and large share of SOF may be linked to the ATU policy allowing the product to be available before EMA authorisation and prior to price negotiations. In Germany, all products gain access after EMA approval and subsequently undertake an HTA review. The UK, like Germany, is traditionally an early-launch country in the EU. In the case of DAAs early adoption might have been facilitated by compassionate use. Overall, (a) some features of the healthcare system and its decision-making processes for medicines coverage, which are not necessarily related to HCV, and (b) companies' decisions around launch sequence, might have played a role in the speed of adoption.

As evidence from interviews showed, in all countries except the UK, uptake following adoption was fast. This was facilitated by DAAs improved characteristics compared with interferon-based treatments and their cost-effectiveness.

Challenges associated with training in the use of new medicines, and changes to prescribing guidelines, may have slowed uptake, though this was not a dominant feature in any country.

- In France and Italy, restrictions on patient eligibility and bottlenecks arising due to health system capacity constraints (given the high prevalence of the condition) may also have limited the speed of uptake. This may explain why in both countries the uptake curve is not showing a peak followed by an immediate and clear decreasing trend in the number of patients treated, which is the common

pattern in the other countries characterised by fast uptake (i.e. Portugal, Germany, Spain).

- In the UK, which had the slowest rate of uptake, annual treatment quotas were used by the NHSE to restrict the size of the population receiving treatment. Initially, the quotas ranged between 10-12,000 patients per year. The patient target has increased over time as a result of lower prices and the introduction of an eradication target.

Considering all the evidence collected through the quantitative and qualitative approaches, as well as the predictions of the economic framework we can conclude that:

- IP protection and SPCs did not prevent a high degree of competition in the market of DAAs. According to our theoretical framework, IP including SPCs can increase the degree of in-class competition due to the longer effective patent terms that subsequent entrants in the market could benefit from.
- The high degree of competition combined with the large size of some markets facilitated price reductions and consequently the uptake of DAAs through effective negotiations and increased bargaining power of payers. Examples of price-volume agreements explicitly pointed out as a way to decrease prices in countries like Italy or Spain with evenly distributed market shares have reinforced this conclusion.

Other factors related to the regulatory framework, characteristics of new treatments, the health system capacity, funding arrangements, eligibility criteria, have had some impact on the adoption and the uptake (both positive and negative, and of different degree depending on the country).

### **5.1. Limitations of the study**

The three approaches used in this study present a number of limitations and caveats.

Our economic framework theoretically establishes a positive relationship between IP rights (specifically SPCs) and both pharmaceutical innovation and in-class competition. However, this holds if potential entrants' decision to stay in the race is, at the margin, based on the commercial incentives that SPCs offer to them. This relationship also relies on the assumption that the first drug in the market and new entrants are, for at least some groups of patients, therapeutic substitutes.

Our framework does not capture all the peculiarities of the treatments offering a cure which alter the disease prevalence, diminish market size and decrease the incentives to continue future R&D projects in the disease area. Therefore, the size of the impact of SPCs in incentivising later entrants might be lower and should be subject to further research.

The uptake and market share analyses should ideally be undertaken using registry data, capturing actual volumes of medicines used by each patient. In the absence of such data available systematically and equally in each country, we applied assumptions about medicines usage and patients' characteristics to volume sales data supplied by IQVIA. We note here two key assumptions we had to use:

- To estimate the number of patients we relied on country epidemiological characteristics, notably distribution of patients by genotype (Razavi, 2017), which was mapped onto volume data.

- The conversion of volume usage to a number of patients is also sensitive to the assumptions relating to course duration. We have used licensed course duration in our modelling but recognise a trend in clinical practice is to adopt shorter durations of treatment, which would mean a higher number of actual patients treated.

Uptake analyses would benefit from a comparison with other therapeutic classes to understand to what extent the market evolution observed in HCV is similar in other areas.

The information collected in the interviews was based on a sample of 12 interviews. Although we covered most relevant expertise in most countries, a larger sample including both national and regional (or local) payers and HTA bodies could increase the accuracy of the evidence.

We were not able to collect information with the same level of detail and consistency for all countries. Specifically, information on price agreements was confidential or not readily available in certain countries (in Germany and Portugal for instance), therefore we could not infer the impact of specific price arrangements on competition and health outcomes and present a complete comparative analysis.

The health gains estimation relied on a number of assumptions that we outline in detail in the supplemental material. Main assumptions are on the QALY gains of DAAs for which the NICE technology appraisals do not provide information, and on the estimation of the net number of patients who were treated during the period of the analysis. We are not able to determine to what extent these assumptions led to underestimates or overestimates of the health gains. However, the fact that we used two different approaches which produced similar estimates for all countries suggests that the QALY gains estimates are reasonably robust.

## **6. CONCLUSION**

This paper addresses three questions related to the production of innovation and its diffusion in pharmaceutical markets by analysing the evolution of a set of European markets for DAAs for the treatment of HCV in the period 2014-2017.

The research concludes that IP incentives for R&D (including SPCs) did not prevent markets for DAAs from having a high degree of in-class competition before patent expiry. Although further research is recommended to show to what extent IP protection may generate in-class competition, in particular in the context of cures, our study suggested that the use of SPCs can potentially be a win-win strategy for payers and developers. This holds when savings determined by lower prices due to competition exceed the higher expenditure the health systems pay during the SPC term, when generic entry is delayed.

In-class and in-patent competition had a positive impact on adoption and uptake of the DAAs in the top-5 European countries. This is shown by the fast uptake and evenly distributed market shares characterising some of these large markets (with more than 5,000 patients treated each month). In these highly competitive markets, effective commercial arrangements pushing prices down and favouring the uptake were agreed in some countries (Italy and Spain). However, it is also true that some countries, concerned by the exceptionally large budget impact, imposed restrictions (e.g. UK) on patient numbers which had a negative impact on the speed of uptake. Some countries

(Spain, Italy) faced delays in providing full access to all patients until competition and ability to negotiate lower prices pushed the uptake up when new entrants marketed their drugs.

Finally, it is important to note that efficient market functioning with a high degree of in-class competition does not guarantee by itself the early adoption and fast uptake of pharmaceutical innovation. In economic terms, functioning markets are a necessary but not sufficient condition for the diffusion of innovation. As our interviews indicated, there are other factors related to the characteristics of the healthcare system (such as infrastructures to tackle HCV and the way patients are identified and followed through the system), political and institutional factors not related to the condition, which can affect (positively and negatively) the adoption of innovative medicines.

## REFERENCES

- Acquah, D., 2014. Extending the Limits of Protection of Pharmaceutical Patents and Data Outside the EU–Is There a Need to Rebalance? *IIC-International Review of Intellectual Property and Competition Law*, 45 (3), 256-286.
- Bader, M. A. and Gassmann, O. (eds.) 2016. *Patent Management Throughout the Innovation Life Cycle1*: WILEY-VCH.
- Belleflamme, P., 2008. How efficient is the Patent System? A general appraisal and an application to the pharmaceutical sector. *Intellectual property and theories of justice*. Springer.
- Berndt, E. R., McGuire, T. and Newhouse, J. P., A primer on the economics of prescription pharmaceutical pricing in health insurance markets. *Forum for Health Economics & Policy*, 2011. De Gruyter.
- Bhattacharya, J. and Vogt, W. B., 2003. A simple model of pharmaceutical price dynamics. *The Journal of Law and Economics*, 46 (2), 599-626.
- Blach, S., Zeuzem, S., Manns, M., Altraif, I., Duberg, A.-S., Muljono, D. H., Waked, I., Alavian, S. M., Lee, M.-H. and Negro, F., 2017. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. *The Lancet Gastroenterology & Hepatology*, 2 (3), 161-176.
- Bruggmann, P., Berg, T., Øvrehus, A., Moreno, C., Brandao Mello, C., Roudot-Thoraval, F., Marinho, R., Sherman, M., Ryder, S. and Sperl, J., 2014. Historical epidemiology of hepatitis C virus (HCV) in selected countries. *Journal of viral hepatitis*, 21 (s1), 5-33.
- Cohen, W. M., Nelson, R. R. and Walsh, J. P., 2000. *Protecting their intellectual assets: Appropriability conditions and why US manufacturing firms patent (or not)*. National Bureau of Economic Research.
- daCosta DiBonaventura, M., Yuan, Y., Wagner, J.-S., Gilbert, J., Lescauwat, B. and Langley, P., 2012. The burden of viral hepatitis C in Europe: a propensity analysis of patient outcomes. *European journal of gastroenterology & hepatology*, 24 (8), 869-877.
- Danzon, P., Towse, A. and Mestre-Ferrandiz, J., 2015. Value-Based Differential Pricing: Efficient Prices for Drugs in a Global Context. *Health economics*, 24 (3), 294-301.
- Danzon, P. M. and Chao, L.-W., 2000. Does regulation drive out competition in pharmaceutical markets? *The Journal of Law and Economics*, 43 (2), 311-358.
- Danzon, P. M. and Towse, A., 2003. Differential pricing for pharmaceuticals: reconciling access, R&D and patents. *International journal of health care finance and economics*, 3 (3), 183-205.
- DiMasi, J. A., Grabowski, H. G. and Hansen, R. W., 2016. Innovation in the pharmaceutical industry: new estimates of R&D costs. *Journal of health economics*, 47 20-33.
- Finkelstein, A., 2004. Static and dynamic effects of health policy: Evidence from the vaccine industry. *The Quarterly Journal of Economics*, 119 (2), 527-564.
- Foster G. and Huskinson P., 2018. 25,000 Hepatitis C patients receive new treatments. Available from: <https://www.england.nhs.uk/blog/25000-hepatitis-c-patients-receive-new-treatments/>.

Gardini, I., 2017. Epatite C: chiarezza sui numeri, evitando allarmi infondati. Available from: [http://www.quotidianosanita.it/lettere-al-direttore/articolo.php?articolo\\_id=56928](http://www.quotidianosanita.it/lettere-al-direttore/articolo.php?articolo_id=56928) [2018].

Gardini, I. and Aghemo, A. M., 2018. Treatment of HCV with Direct Acting Antivirals in Italy. *Newsletter*.

Grabowski, H., 2002. Patents, innovation and access to new pharmaceuticals. *Journal of International Economic Law*, 5 (4), 849-860.

INFARMED, 2015. Define os critérios clínicos de doentes no acesso a medicamentos para o tratamento da Hepatite C e a assunção de garantias de cumprimento de prazos e critérios que assegurem equidade de acesso dos doentes aos respetivos tratamentos e por consequência a integração no Formulário Nacional de Medicamentos. In: Contencioso, G. J. e. (ed.). *Legislação Farmacêutica Compilada*.

IQVIA, *Analysis Manager - total market* [Online]. [Accessed 17/04/2018].

Kanavos, P., Font, J. C. and McGuire, A., 2007. Product differentiation, competition and regulation of new drugs: the case of statins in four European countries. *Managerial and Decision Economics*, 28 (4-5), 455-465.

Kesselheim, A. S., 2010. Using market-exclusivity incentives to promote pharmaceutical innovation. *Mass Medical Soc.*

Kondili, L. A., Romano, F., Rolli, F. R., Ruggeri, M., Rosato, S., Brunetto, M. R., Zignego, A. L., Ciancio, A., Di Leo, A. and Raimondo, G., 2017. Modelling cost-effectiveness and health gains of a "universal" vs. "prioritized" HCV treatment policy in a real-life cohort. *Hepatology*.

Lu, Z. J. and Comanor, W. S., 1998. Strategic pricing of new pharmaceuticals. *Review of economics and statistics*, 80 (1), 108-118.

MHSSE, 2015. *Strategic Plan for Tackling Hepatitis C in the Spanish National Health System*. Spain.

Mouterde, A.-L., Bocquet, F., Fusier, I. and Paubel, P., 2016. *Hepatitis C: how has France limited the expenses related to new treatments?* : Taylor & Francis.

National Institute for Health and Care Excellence, 2015a. *Daclatasvir for treating chronic hepatitis C. Technology appraisal guidance [TA364]*. [Online]. Available: <https://www.nice.org.uk/guidance/ta364>.

National Institute for Health and Care Excellence, 2015b. *Ledipasvir–sofosbuvir for treating chronic hepatitis C. Technology appraisal guidance [TA363]* [Online]. Available: <https://www.nice.org.uk/guidance/ta363>.

National Institute for Health and Care Excellence, 2015c. *Ombitasvir–paritaprevir–ritonavir with or without dasabuvir for treating chronic hepatitis C. Technology appraisal guidance [TA365]*. [Online]. Available: <https://www.nice.org.uk/guidance/ta365>.

National Institute for Health and Care Excellence, 2015d. *Simeprevir in combination with peginterferon alfa and ribavirin for treating genotypes 1 and 4 chronic hepatitis C. Technology appraisal guidance [TA331]*. [Online]. Available: <https://www.nice.org.uk/guidance/ta331>.

National Institute for Health and Care Excellence, 2015e. *Sofosbuvir for treating chronic hepatitis C. Technology appraisal guidance [TA330]* [Online]. Available: <https://www.nice.org.uk/guidance/ta330>.

National Institute for Health and Care Excellence, 2016. *Elbasvir–grazoprevir for treating chronic hepatitis C. Technology appraisal guidance [TA413]*. [Online]. Available: <https://www.nice.org.uk/guidance/ta413>.

National Institute for Health and Care Excellence, 2017. *Sofosbuvir–velpatasvir for treating chronic hepatitis C. Technology appraisal guidance [TA430]*. [Online]. Available: <https://www.nice.org.uk/guidance/ta430>.

NHS England, 2015. *Thousands more patients to be cured of hepatitis C* [Online]. Available: <https://www.england.nhs.uk/2015/06/patients-hep-c/>.

NHS England, 2018. NHS England sets out plans to be first in the world to eliminate Hepatitis C. Available from: <https://www.england.nhs.uk/2018/01/hepatitis-c-2/> [2018].

Pammolli, F., Magazzini, L. and Riccaboni, M., 2011. The productivity crisis in pharmaceutical R&D. *Nature reviews Drug discovery*, 10 (6), 428.

Philipson, T. and Mechoulan, S., 2003. *Intellectual property & external consumption effects: Generalizations from pharmaceutical markets*. National Bureau of Economic Research.

Razavi, H., Robbins, S., Zeuzem, S., Negro, F., Buti, M., Duberg, A.-S., Roudot-Thoraval, F., Craxi, A., Manns, M. and Marinho, R. T., 2017. Hepatitis C virus prevalence and level of intervention required to achieve the WHO targets for elimination in the European Union by 2030: a modelling study. *The Lancet Gastroenterology & Hepatology*, 2 (5), 325-336.

Razavi, H., Waked, I., Sarrazin, C., Myers, R., Idilman, R., Calinas, F., Vogel, W., Correa, M., Hézode, C. and Lázaro, P., 2014. The present and future disease burden of hepatitis C virus (HCV) infection with today's treatment paradigm. *Journal of viral hepatitis*, 21 (s1), 34-59.

Reekie, W. D., 1978. Price and quality competition in the United States drug industry. *The Journal of Industrial Economics*, 223-237.

Scannell, J. W., Blanckley, A., Boldon, H. and Warrington, B., 2012. Diagnosing the decline in pharmaceutical R&D efficiency. *Nature reviews Drug discovery*, 11 (3), 191.

Schuhmacher, A., Gassmann, O. and Hinder, M. (eds.) 2016. *A review of the pharmaceutical R&D efficiency: costs, timelines, and probabilities*: WILEY-VCH.

Stiglitz, J. E. and Jayadev, A., 2010. Medicine for tomorrow: Some alternative proposals to promote socially beneficial research and development in pharmaceuticals. *Journal of Generic Medicines*, 7 (3), 217-226.

Van Nuys, K., Brookmeyer, R., Chou, J. W., Dreyfus, D., Dieterich, D. and Goldman, D. P., 2015. Broad hepatitis C treatment scenarios return substantial health gains, but capacity is a concern. *Health Affairs*, 34 (10), 1666-1674.

Vernon, J. A., 2005. Examining the link between price regulation and pharmaceutical R&D investment. *Health economics*, 14 (1), 1-16.

Weston, J. F., 1982. A survey of the economics of the pharmaceutical industry with emphasis on economic factors in price differentials. The effectiveness of medicines in containing dental care costs: Impact of innovation, regulation, and quality. *Washington, DC: National Pharmaceutical Council.*

Wiggins, S. N. and Maness, R., 2004. Price Competition in Pharmaceuticals: The Case of Anti-infectives. *Economic Inquiry*, 42 (2), 247-263.

Yin, W., 2008. Market incentives and pharmaceutical innovation. *Journal of Health Economics*, 27 (4), 1060-1077.

Zeng, J., Zhang, J. and Fung, M. K.-Y., 2014. Patent length and price regulation in an R&D growth model with monopolistic competition. *Macroeconomic Dynamics*, 18 (1), 1-22.